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Veterans and Agent Orange

Update 2010

Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Eighth Biennial Update)

Board on the Health of Select Populations

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"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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COMMITTEE TO REVIEW THE HEALTH EFFECTS IN VIETNAM VETERANS OF EXPOSURE TO HERBICIDES (EIGHTH BIENNIAL UPDATE)

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Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **Kristine M. Gebbie,** Adjunct Professor, Flinders University School of Nursing and Midwifery, Adelaide, South Australia. Appointed by the National Research Council and Institute of Medicine, she was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Preface

In 1991, Congress passed Public Law (PL) 102-4, the Agent Orange Act of 1991, to address the uncertainty about the long-term health effects on Vietnam veterans who during their service in Vietnam were exposed to herbicides—mixtures of 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and its contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), picloram, and cacodylic acid. That legislation directed the Secretary of Veterans Affairs to ask the National Academy of Sciences (NAS) to perform a comprehensive evaluation of scientific and medical information regarding the health effects of exposure to Agent Orange, other herbicides used in Vietnam, and the various chemical components of those herbicides, including TCDD. The resulting committee report, *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* (*VAO*), was published by the Institute of Medicine (IOM) in 1994. That report evaluated and integrated the scientific evidence regarding statistical associations between health outcomes and exposure to the herbicides and TCDD on the basis of published material that had accumulated by 1994.

As required by PL 102-4, the Secretary also asked that NAS conduct updates at least every 2 years for 10 years from the date of the first report to review newly available literature and draw conclusions from the overall evidence. The first of the updates, *Veterans and Agent Orange: Update 1996* (*Update 1996*), was published in March 1996. It was followed by *Veterans and Agent Orange: Update 1998* (*Update 1998*) in 1999, *Veterans and Agent Orange: Update 2000* (*Update 2000*) in 2001, *Veterans and Agent Orange: Update 2002* (*Update 2002*) in 2003, and *Veterans and Agent Orange: Update 2004* (*Update 2004*) in 2005.

PL 107-103, the Veterans Education and Benefits Expansion Act of 2001, extended the period for biennial updates to 2014. The first update after the new leg-

islation was *Veterans and Agent Orange: Update 2006* (*Update 2006*), published in 2007, followed by *Veterans and Agent Orange: Update 2008* (*Update 2008*) in 2009. The present report is the third of this second 10-year period of evaluation.

The present update focuses on the relevant scientific studies published from October 1, 2008, through September 30, 2010, that is, after the literature considered in *Update 2008*. To accomplish the review, IOM established a committee of 15 members representing a wide array of expertise to evaluate the newest scientific evidence and to consider it in light of the studies reviewed in *VAO*, *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008*. A link to the experience and expertise of previous committees was provided by recruiting eight members from committees responsible for earlier updates. All committee members were selected because they are experts in their fields, have no conflicts of interest with regard to the matter under study, and have taken no public positions concerning the potential health effects of herbicides in Vietnam veterans or related aspects of herbicide or TCDD exposure. Biographic sketches of committee members and staff appear in Appendix D.

In this second decade of evaluation, the committee sought the most accurate information and advice from the widest possible array of knowledgeable sources for consideration. To be consistent with NAS procedures, the committee met in a series of closed sessions in which members could freely examine, characterize, and weigh the strengths and limitations of the evidence. The committee also convened four open meetings in September, November, and December 2010 and in February 2011 to provide an opportunity for veterans and veterans service organizations, researchers, policy-makers, and other interested parties to present their concerns, review their research, and exchange information directly with committee members. The oral presentations and written statements submitted to the committee are listed in Appendix A. The committee thanks the persons who provided valuable insights into the health problems experienced by Vietnam veterans.

The committee is grateful to Mary Paxton, who skillfully served as study director for this project. The committee also acknowledges the excellent work of IOM staff members Jennifer Cohen, Tia Carter, and Frederick (Rick) Erdtmann. Thanks are also extended to Andrea Cohen, who handled the finances for the project; Norman Grossblatt, who provided editorial skills; and William McLeod, who conducted database searches.

The committee benefited from the assistance of several scientists and researchers who generously lent their time and expertise to give committee members insight into particular issues, provide copies of newly released research, or answer queries about their work. Arnold Schecter, a professor at the University of Texas School of Public Health, discussed research activities concerning herbicide contamination in Vietnam and health of the Vietnamese population. Vaughan Turekian, Chief International Officer of the American Association for the Advancement of Science and its representative to the US–Vietnam Dialogue

Group on Agent Orange–Dioxin, also discussed activities involving the Vietnamese population. Paul Enright, a professor at the Mel and Enid Zuckerman College of Public Health at the University of Arizona, was helpful in answering questions concerning Agent Orange and chronic obstructive pulmonary disease. Yasmin Cypel and Han Kang, Environmental Epidemiology Service of the Department of Veterans Affairs, responded to questions regarding their recent publication concerning the Army Chemical Corps.

Mary K. Walker, *Chair*
Committee to Review the Health Effects
in Vietnam Veterans of Exposure to
Herbicides (Eighth Biennial Update)

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Abbreviations and Acronyms

2,4-D	2,4-dichlorophenoxyacetic acid
2,4,5-T	2,4,5-trichlorophenoxyacetic acid
2,4,5-TCP	2,4,5-trichlorophenol
2,4,5-TP	2-(2,4,5-trichlorophenoxy) propionic acid or Silvex
8-OHdG	8-hydroxy-2′-deoxyguanosine
ACC	Army Chemical Corps
ACS	American Cancer Society
AD	Alzheimer disease
AFHS	Air Force Health Study (also referred to as the "Ranch Hand Study")
AHR	aryl hydrocarbon receptor
AHRE	AHR-responsive element of the canonical DNA recognition motif of the AHR/ARNT complex, also referred to as the dioxin-responsive element (DRE) or the xenobiotic-responsive element (XRE)
AHS	Agricultural Health Study
AIHW	Australian Institute for Health and Welfare
AL	acute leukemia
AL amyloidosis	**a**myloid **l**ight chain form of amyloidosis in which the amyloid in deposits in various organs and tissues consists of antibody light chains
ALL	acute lymphocytic leukemia
ALS	amyotrophic lateral sclerosis (or Lou Gehrig's disease)

AML	acute myeloid leukemia [previously called "acute **myelogenous** leukemia"]
ARNT	aryl hydrocarbon nuclear translocator
BIRLS	VA's Beneficiary Identification Record Locator Subsystem
Blimp1	B lymphocyte maturation protein 1
BMD	bone mineral density
BMI	body-mass index
BWIS	Baltimore–Washington Infant Study
CALUX	chemical-activated luciferase gene expression bioassay, a test for determination of dioxin-like activity in tissue samples
CAS No.	CAS Number is generated by the Chemical Abstracts Service and serves as unique identifier for every chemical
CCR9	chemokine C receptor 9
CD4/CD8 ratio	percentage of T-lymphocytes expressing CD4 antigen (T4 or helper T-cells) to percentage of T-lymphocytes expressing CD8 antigen (T8 or suppressor T-cells), also called T4/T8 ratio
CDC	Centers for Disease Control and Prevention
CHD	coronary heart disease
CI	confidence interval, as defined by lower (LCL) and upper confidence limits (UCL)
CLL	chronic lymphocytic leukemia (which is now regarded as being the same disease as small lymphocytic leukemia [SLL] and designated by some as CLL/SLL)
CNS	central nervous system
COIs	chemicals of interest to VAO series (i.e., TCDD, 2,4,5-T, 2,4-D, picloram, and cacodylic acid)
Con A	concanavalin A
COPD	chronic obstructive pulmonary disease
CSF	cerebrospinal fluid
CT	computed tomography
CVD	cardiovascular disease
CYP---	cytochrome P450 (specific members of this family of metabolizing enzymes are indicted by a number-letter-number suffix)
DDE	*p*,*p*´-diphenyldichloroethene, an environmentally persistent metabolite of the insecticide DDT

dicamba	2-methoxy-3,6-dichlororbenzoic acid, benzoate herbicide with chemical structure related to phenoxy herbicides
dl	dioxin-like
DLC	dioxin-like compound (or chemical)
DMA	dimethyl arsenic acid
DMA^{III}	dimethyl arsenic acid of valency 3
DMA^{V}	dimethyl arsenic acid of valency 5; form of arsenic found in cacodylic acid
DNA	deoxyribonucleic acid
DOD	US Department of Defense
DRE	dioxin-responsive element, which is the recognition motif of the AHR/ARNT complex (also called AHRE or XRE)
DTH	delayed-type hypersensitivity, a cell-mediated immune response
ECG	electrocardiography
EOI	Exposure Opportunity Index, metric of possible Agent Orange exposure of ground troops generated by the Stellman model
EPA	US Environmental Protection Agency
$FEF_{25–75}$	forced midexpiratory flow
FEV_1	forced expiratory volume in 1 second
fg	femtogram (10^{-15} gram)
FSH	follicle-stimulating hormone
FVC	forced vital capacity
g	gram
GBDS	Birth Defects Study
GC/MS	gas chromatography/mass spectrometry
GCT	germ-cell tumor
GERD	gastroesophageal reflux disease
GGT	γ-glutamyltransferase
GI	gastrointestinal
GIS	geographic information system
HbA1c	hemoglobin A1c
HCL	hairy-cell leukemia
HDL	high-density lipoprotein
HepG2	human hepatocarcinoma cell line
HIV	human immunodeficiency virus

HL	Hodgkin lymphoma (previously referred to as Hodgkin's disease [HD] in VAO series)
HpCDD	heptachlorodibenzo-*p*-dioxin, a dioxin congener with seven chlorines
HpCDF	heptachlorodibenzofuran, a furan congener with seven chlorines
HPV	human papilloma virus
HR	hazard ratio
hsp	heat shock protein
HT	hypertension
HxCDD	hexachlorodibenzo-*p*-dioxin, a dioxin congener with six chlorines
HxCDF	hexachlorodibenzofuran, a furan congener with six chlorines
IARC	International Agency for Research on Cancer
ICAM-1	inter-cellular adhesion molecule 1
ICD-#	*International Classification of Diseases*, Revision # (# = version current for records being abstracted)
ICD-#-CM	*International Classification of Diseases*, Revision #, Clinical Modification
ICDO-II	*International Classification of Diseases for Oncology*, 2nd Edition
IFN-γ	interferon-gamma
IHD	ischemic heart disease
IgE	immunoglobulin E
IL-6	interleukin-6 (also called β2-interferon)
IOM	Institute of Medicine
IQR	inter-quartile range
IU	international unit
IUGR	intrauterine growth retardation
JEM	job–exposure matrix
kg	kilogram
L	liter
LDL	low-density lipoprotein
LH	luteinizing hormone
LHCs	lymphohematopoietic cancers
LOD	limit of detection
LPS	lipopolysaccharide

M	molar (concentration in a solution, molecules per volume)
MCF-7	human breast cancer cell line
MCPA	2-methyl-4-chlorophenoxyacetic acid
MCPP	2-(2-methyl-4-chlorophenoxy) propionic acid or Mecoprop
MDS	myelodysplastic syndrome
mg	milligram
MGUS	monoclonal gammopathy of undetermined significance
MI	myocardial infarction
MIH	molar incisor hypomineralization
MIP	macrophage-inflammatory protein
ml	milliliter
MLR	mixed lymphocyte response
MM	multiple myeloma
MMA	monomethyl arsonic acid
MMA^{III}	monomethyl arsonic acid of valency 3
mmHG	millimeters mercury, for blood pressure measurements
MMP	matrix metalloproteinase
MPTP	1-methyl-4-phenyl-1,2,4,6-tetrahydropyridine
MTD	maximum tolerated dose
MRI	magnetic resonance imaging
n	number of study participants
na	not applicable
NAS	National Academy of Sciences
NCI	National Cancer Institute
ndl	not dioxin-like
ng	nanogram (10^{-9} gram)
NHANES	National Health and Nutrition Examination Survey
NHL	non-Hodgkin lymphoma
NIOSH	National Institute for Occupational Safety and Health
NK T-cell	natural killer T-cell
NLS	nuclear-localization signal
NOEL	no-observed-effect level
nr	not reported
NRC	National Research Council
ns	not statistically significant (usually refers to $p < 0.05$)
NTP	National Toxicology Program
NVVRS	National Vietnam Veterans Readjustment Study
OCDD	octachlorodibenzo-*p*-dioxin (1,2,3,4,6,7,8,9-OCDD is the only dioxin congener with eight chlorines)
OFFHS	Ontario Farm Family Health Study

OR	odds ratio
p	p-value, probability of the observed result or one more extreme under null hypothesis
p23	prostaglandin E synthase
PAH	polycyclic aromatic hydrocarbons
PBDD	polybrominated dibenzo-*p*-dioxin
PBDF	polybrominated dibenzofuran
PBPK model	physiologically based pharmacokinetic model
PCB	polychlorinated biphenyl
PCDD	polychlorinated dibenzo-*p*-dioxin
PCDD/Fs	polychlorinated dioxins and furans combined
PCDF	polychlorinated dibenzofuran
PCP	pentachlorophenol
PCT	porphyria cutanea tarda
PD	Parkinson disease
PE	peritoneal endometriosis
PeCDD	pentachlorodibenzodioxin, a dioxin congener with five chlorines
PeCDF	pentachlorodibenzofuran, a furan congener with five chlorines
pg	picogram (10^{-12} gram)
PGE2	prostaglandin E2
PHA	polyhydroxyalkanoate
picloram	4-amino-3,5,6-trichloropicolinic acid
PL	Public Law
PM	proportionate mortality
PMR	proportional mortality ratio
PNS	peripheral nervous system
POP	persistent organic pollutant
ppb	parts per billion = ng/g
ppm	parts per million = µg/g = mg/kg
ppt	parts per trillion = pg/g
PSA	prostate-specific antigen
PSP	Progressive Supranuclear Palsy
PTD	preterm delivery, premature birth at less than 259 days (37 weeks gestation)
PTSD	post-traumatic stress disorder
RA	rheumatoid arthritis
RANTES	**r**egulated on **a**ctivation, **n**ormal **T**-cell–**e**xpressed, and **s**ecreted

RAST	radioallergosorbent
RDD	random-digit dialing
RFP	request for proposals
RH	Ranch Hand, member of Air Force unit primarily responsible for spraying herbicides in Vietnam
RNA	ribonucleic acid
RP	relative prevalence
RR	relative risk (also called "risk ratio")
SCE	sister chromatid exchange
SE	standard error
SEA	Southeast Asia
SEER	NCI's Surveillance, Epidemiology, and End Results
SES	socioeconomic status
SIR	standardized incidence ratio
SLE	systemic lupus erythematosus
SLL	small lymphocytic lymphoma, which is now recognized as a different stage of CLL, rather than a separate disease
SMR	standardized mortality ratio
STS	soft-tissue sarcoma
SWHS	Seveso Women's Health Study
T3	triiodothyronine
T4	thyroxine
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
TCDF	tetrachlorodibenzofuran, a furan congener with four chlorines
TCP	trichlorophenol
TECK	thymus-expressed chemokine
TEF	toxicity equivalency factor, potency of a dioxin-like compound (DLC) relative to TCDD
TEQ	(total) toxic equivalent, or by older usage "toxicity equivalent quotient", i.e., cumulative toxic potency, sum of TEFs for a mixture of PCDDs, PCDFs, and PCBs
tetraCDD	tetrachlorodibenzo-*p*-dioxin, any of the 22 dioxin congeners with four chlorines, including TCDD as defined above
TGF	transforming growth factor
TNF	tumor necrosis factor
Treg	regulatory T cell
TRH	thyrotropin-releasing hormone
TSH	thyroid-stimulating hormone
TTP	time to pregnancy
TWA	time-weighted average

UFW	United Farm Workers of America
UGT	UDP-glucuronosyltranserfase
US	United States
VA	US Department of Veterans Affairs; previously, Veterans Administration
VAO	Veterans and Agent Orange (refers to series of IOM committees and reports; italicized *VAO*, refers to the first comprehensive review published in 1994)
VCAM-1	vascular cell adhesion molecule 1
VES	Vietnam Experience Study
VLDL	very-low-density lipoprotein
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization
XRE	xenobiotic-responsive element, which is the recognition motif of the AHR/ARNT complex (also called DRE or AHRE)

Summary

From 1962 to 1971, the US military sprayed herbicides over Vietnam to strip the thick jungle canopy that could conceal opposition forces, to destroy crops that those forces might depend on, and to clear tall grasses and bushes from the perimeters of US base camps and outlying fire-support bases. Mixtures of 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), picloram, and cacodylic acid made up the bulk of the herbicides sprayed. The herbicide mixtures used were named according to the colors of identification bands painted on the storage drums; the main chemical mixture sprayed was Agent Orange (a 50:50 mixture of 2,4-D and 2,4,5-T). At the time of the spraying, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), the most toxic form of dioxin, was an unintended contaminant generated during the production of 2,4,5-T and so was present in Agent Orange and some other formulations sprayed in Vietnam; it is important to remember that Agent Orange is not synonymous with TCDD or dioxin.

Complaints from returning Vietnam veterans about their own health and that of their children combined with emerging toxicologic evidence of adverse effects of phenoxy herbicides and TCDD in animal studies and some positive epidemiologic studies resulted in sustained controversy. In 1991, because of continuing uncertainty about long-term health effects of the sprayed herbicides in Vietnam veterans, Congress passed Public Law (PL) 102-4, the Agent Orange Act of 1991. That legislation directed the Secretary of Veterans Affairs to ask the National Academy of Sciences (NAS) to perform a comprehensive evaluation of scientific and medical information regarding the health effects of exposure to Agent Orange, other herbicides used in Vietnam, and the various components of those herbicides, including TCDD. The legislation also instructed the Secretary

to ask NAS to conduct updates every 2 years for 10 years from the date of the first report to review newly available literature and draw conclusions from the overall evidence.

In response to the first request, the Institute of Medicine (IOM) convened a committee, whose conclusions IOM published in 1994 in *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* (*VAO*). The work of later committees resulted in the publication of biennial updates (*Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008*) and of focused reports on the scientific evidence regarding type 2 diabetes, acute myeloid leukemia in children, and the latent period for respiratory cancer.

Enacted in 2002, PL 107-103, the Veterans Education and Benefits Expansion Act of 2001, mandated that the *VAO* biennial updates continue through 2014. *Update 2006* was the first report published under that legislation. The current update presents this committee's review of peer-reviewed scientific reports concerning associations between health outcomes and exposure to TCDD and other chemicals in the herbicides used in Vietnam that were published in October 2008–September 2010 and the committee's integration of this information with the previously established evidence database.

CHARGE TO THE COMMITTEE

In accordance with PL 102-4 and PL 107-103, the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Eighth Biennial Update) was asked to "determine (to the extent that available scientific data permit meaningful determinations)" the following regarding associations between specific health outcomes and exposure to TCDD and other chemicals in herbicides used by the military in Vietnam:

A) whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiological methods used to detect the association;
B) the increased risk of disease among those exposed to herbicides during service in the Republic of Vietnam during the Vietnam era; and
C) whether there exists a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease.

The committee notes that, as a consequence of congressional and judicial history, both its congressional mandate and the statement of task are phrased with the target of evaluation being "association" between exposure and health outcomes. The rigor of the evidentiary database needed to support a finding of statistical association is weaker than that needed to establish causality, but posi-

tive findings for any of the aspects of scientific evidence supportive of causality enhance conviction that an observed statistical association is reliable. Such scientific evidence, of course, would include any information assembled in relation to plausible biologic mechanisms as directed in Article C. In accord with its charge, the committee examined outcome measures commonly used to evaluate statistical associations, while assessing the adequacy of control for bias and confounding and the likelihood that an observed association could be explained by chance. Additionally, the committee assessed evidence concerning biologic plausibility derived from laboratory findings in cell-culture or animal models. In particular, associations found to have multiple supportive lines of evidence were interpreted as having stronger scientific support.

In conducting its study, the present committee operated independently of the Department of Veterans Affairs (VA) and other government agencies. The committee was not asked to make and did not make judgments regarding specific cases in which individual Vietnam veterans have claimed injury from herbicide exposure. This report provides scientific information for the Secretary of Veterans Affairs to consider as VA exercises its responsibilities to Vietnam veterans. The committee was not charged to focus on broader issues, such as the potential costs of compensation for veterans or policies regarding such compensation.

In addition to the above charge, the VA made an additional request arising from the decision-making at VA necessitated by the findings of *Update 2008*. The sponsor asked that, when summarizing the evidence available to support the association of a health effect with exposure to the components of the herbicides used by the military in Vietnam, the committee address whether or not all the points that have rather imprecisely become known as the Bradford Hill (1965) "criteria" for causality (strength, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experiment, and analogy) had been satisfied by the information available

COMMITTEE'S APPROACH TO ITS CHARGE

Following the pattern established by prior VAO committees, the present committee concentrated its review on epidemiologic studies to fulfill its charge of assessing whether specific human health effects are associated with exposure to at least one of the herbicides sprayed in Vietnam or to TCDD. The committee also considered controlled laboratory investigations that provided information on whether association between the chemicals of interest and a given effect is biologically plausible.

The VAO committees began their evaluation presuming neither the presence nor the absence of association for any particular health outcome. Over the sequence of reviews, evidence of various degrees of association, lack of association, or persisting indeterminacy with respect to a wide array of disease

states has accrued. For many conditions, however, particularly ones that are very uncommon, any association with the chemicals of interest has remained unaddressed in the medical research literature; for these (unless the condition is logically subsumed under a broader disease category that has been evaluated), the committee remains neutral, abiding by the maxim that "absence of evidence is not evidence of absence."

In accord with Congress's mandated presumption of herbicide exposure for all Vietnam veterans, VAO committees have treated Vietnam-veteran status as a proxy for some herbicide exposure when no more specific exposure information is available. To obtain information potentially relevant to the evaluation of health effects related to herbicide exposure in addition to that available from studies of Vietnam veterans, the committee reviewed studies of other groups potentially exposed to the constituents of the herbicide mixtures used in Vietnam (2,4-D, 2,4,5-T, TCDD, cacodylic acid, and picloram). In addition to retrieving articles identified on the basis of keywords specifying the compounds and chemical classes of interest, literature searches for the earliest reports in the VAO series had been structured to retrieve all studies of several occupational groups, including chemical, agricultural, pulp and paper, sawmill, and forestry workers. To the extent that studies of those workforces were recovered in new searches directed at particular agents of exposure, they were incorporated into the database. Some occupational and environmental cohorts that received exceptionally high exposures (such as the International Agency for Research on Cancer [IARC] and Seveso cohorts discussed in this report) are now well characterized and are producing a stream of informative results. A continuing prospective cohort study of agricultural populations with specific information on the chemicals of interest is also steadily contributing new findings to the database. Most important, the Vietnam veterans themselves are advancing in age and, when studied, are capable of providing substantial information on chronic health conditions directly. As the information in the database on populations with established exposures to the chemicals of interest has grown, the committee has come to depend less on data from studies with nonspecific exposure information and has been able to focus more on findings of studies with refined exposure specificity.

In this update, the committee endeavored to emphasize and clarify the relationship among the succession of publications that have provided ever increasing insight into the health responses of particular exposed populations that have been studied for many years. The information in the results tables for individual health outcomes has grown over eight cycles of revision, but this committee found that the presentation of new findings in update-specific clusters obscured the interdependent nature of many of the studies on a given cohort. Therefore, the findings in the results tables have been rearranged and grouped by study population. In addition, the cohorts themselves have been ordered on these tables to reflect the hierarchical nature of many of these study populations (for example, workers at the Dow plant in Midland, Michigan, are one of several cohorts composing the

National Institute for Occupational Safety and Health cohort, which in turn is one of the many international cohorts making up the IARC cohort). Lastly, the exposure of interest for each cohort has been explicitly noted on the tables to facilitate judgments about when consistency might be expected among populations experiencing the same exposure.

The original legislation, PL 102-4, did not provide a list of specific diseases and conditions suspected of being associated with herbicide exposure. Such a list was developed on the basis of diseases and conditions that had been mentioned in the scientific literature or in other documents identified through the original *VAO*'s extensive literature searches. The *VAO* list has been augmented in response to developments in the literature, requests by VA, and concerns of Vietnam veterans.

The information that the present committee reviewed was identified through a comprehensive search of relevant databases, including databases covering biologic, medical, toxicologic, chemical, historical, and regulatory information. The search of literature published through September 30, 2010, identified more than 6,600 potentially relevant citations. Screening of those retained about 1,300 for closer consideration, and about 65 papers on epidemiologic studies and several score of toxicology studies ultimately contributed new information to this review. Additional information came from veterans and other interested people who testified at public hearings and offered written submissions.

To determine whether there is an association between exposure and a health outcome, epidemiologists estimate the magnitude of an appropriate measure (such as the relative risk or the odds ratio) that describes the relationship between exposure and disease in a defined population or group. In evaluating the strength of the evidence linking herbicide exposure with a particular outcome, the committee considered whether such estimates of risk might be incorrect (because of confounding, chance, or bias related to errors in selection and measurement) or might accurately represent true associations; although they are not required, data supporting biologic plausibility serve to strengthen confidence that an association is not spurious. It has been the practice of all VAO committees to evaluate all studies according to the same criteria and then to weight findings of similar strength and validity equivalently, whether or not the study subjects are Vietnam veterans, when drawing conclusions. The committee recognizes that an absolute conclusion about the absence of association might never be attained, because, as is generally the case in science, studies of health outcomes after herbicide exposure cannot demonstrate that a purported effect is impossible, only that it is statistically improbable.

EVIDENCE REVIEWED BY THE COMMITTEE

The sections below summarize new epidemiologic information evaluated in this update and integrated with that previously assembled. The epidemiologic studies have been divided, both here and in the health-outcome chapters, into

three categories—Vietnam-veteran, occupational, and environmental—depending on the population addressed.

Vietnam-Veterans Studies

Three studies of Vietnam veterans published since *Update 2008* were reviewed by the committee. One study on Army Chemical Corp personnel produced findings related to all cause mortality, while another study on Australian Vietnam veterans evaluated the prevalence of a multitude of self-reported health outcomes, including cancers, circulatory diseases, respiratory diseases, diabetes, and digestive disorders. A third study examined the progression of prostate cancer in a case–control study of veterans with previous Agent Orange exposure.

Occupational Studies

Several occupational studies have been published since *Update 2008*. Recent reports from the Agricultural Health Study examined the incidence of pancreatic cancer, hearing loss, melanoma, thyroid disease, adult onset asthma, myocardial infarction, and rhinitis in private pesticide applicators (farmers), their spouses, and commercial pesticide applicators. The incidence of Parkinson disease (PD) was investigated in an expanded cohort of farmers occupationally exposed to 2,4-D from Washington State and in three newly defined case–control studies assembled from Texas, France, and eight clinics in North America. All cause mortality incidence was reported from two different subcohorts of the IARC cohort. Circulatory diseases and neurologic outcomes were studied in a 40-year follow-up of Czech production workers who were exposed to TCDD during the production of 2,4,5-T.

Environmental Studies

Numerous studies from environmental exposures to the chemicals of interest have been published since *Update 2008*. Reproductive outcomes, including birth weight, birth defects, childhood cancer, neonatal thyroid function, and development of childhood obesity were studied in offspring of mothers exposed to TCDD and other chemicals with dioxin-like biologic activity from incinerator emissions in France, the industrial accident at Seveso, Italy, and dietary intake in Taiwan, Italy, Belgium, the Netherlands, and Japan. Cancer outcomes were evaluated in follow-up studies of residents of Seveso, Italy, farmers and pesticide applicators/users in Canada and the US. Diabetes and conditions associated with metabolic syndrome were assessed in Great Lakes sport-fish consumers, Taiwanese residents near a pentachlorophenol factory, Finnish fisherman, Japanese men and women, and the general US population via the National Health and Nutrition Ex-

amination Survey. New case–control studies examined environmental exposures to the chemicals of interest and endometriosis and Parkinson disease.

THE COMMITTEE'S CONCLUSIONS

Health Outcomes

The present committee weighed the strengths and limitations of the epidemiologic evidence reviewed in this report and in previous VAO reports. Although the studies published since *Update 2008* are the subject of detailed evaluation in this report, the committee drew its conclusions in the context of the entire body of literature. The contribution of recent publications to the evidence database was substantial, but the committee did not weigh them more heavily merely because they were new. Epidemiologic methods and analytic capabilities have improved, but many of the recent studies were also particularly useful for this committee's purpose because they produced results in terms of serum TCDD concentrations or the total amount of exposure from all dioxin-like chemicals. Of course, observations on the health of our population of primary concern, Vietnam veterans, are increasingly informative as they age.

Table S-1 defines four categories of association and gives criteria for assigning health outcomes to them. On the basis of its evaluation of veteran, occupational, and environmental studies, the committee allocated particular health outcomes to categories of relative certainty of association with exposure to the herbicides that were used in Vietnam or to any of their components or contaminants (with no intention of specifying particular chemicals). The committee notes that experimental data related to biologic plausibility of conditions statistically associated with exposure to Agent Orange have gradually emerged since the beginning of this series of VAO reports and that these findings can inform the decisions about how to categorize the degree of association for individual conditions; a footnote to this effect has been added to Table S-1.

The terminology of "early-onset transient peripheral neuropathy" was adopted in *Update 2004* as a replacement for the terminology of "acute and subacute peripheral neuropathy" used in *Update 1996*. *Update 1996*, the first VAO report to find "limited or suggestive evidence of association" with exposure to the chemicals of interest for this health outcome, also noted in the body of the report that this was a "transient" effect. When VA declared this outcome to be presumptively associated with service in Vietnam, its definition included the temporal constraints that symptoms develop shortly after herbicide exposure and that recovery from those symptoms occurs within 2 years of their initial development. Thus, currently qualifying cases are contingent upon when symptoms arise relative to when exposure occurred and that the symptoms are transitory in nature. A thorough review of the existing literature in populations with members

TABLE S-1 Summary of *Eighth Biennial Update* of Findings of Veterans, Occupational, and Environmental Studies Regarding Associations Between Exposure to Herbicides and Specific Health Outcomes[a]

Sufficient Evidence of an Association

Epidemiologic evidence is sufficient to conclude that there is a positive association. That is, a positive association has been observed between exposure to herbicides and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence.[b] For example, if several small studies that are free of bias and confounding show an association that is consistent in magnitude and direction, there could be sufficient evidence of an association. There is sufficient evidence of an association between exposure to the chemicals of interest and the following health outcomes:

Soft-tissue sarcoma (including heart)
* Non-Hodgkin lymphoma
* Chronic lymphocytic leukemia (including hairy cell leukemia and other chronic B-cell leukemias)
* Hodgkin lymphoma
Chloracne

Limited or Suggestive Evidence of an Association

Epidemiologic evidence suggests an association between exposure to herbicides and the outcome, but a firm conclusion is limited because chance, bias, and confounding could not be ruled out with confidence.[b] For example, a well-conducted study with strong findings in accord with less compelling results from studies of populations with similar exposures could constitute such evidence. There is limited or suggestive evidence of an association between exposure to the chemicals of interest and the following health outcomes:

Laryngeal cancer
Cancer of the lung, bronchus, or trachea
Prostate cancer
* Multiple myeloma
* AL amyloidosis
Early-onset peripheral neuropathy (category clarification from *Update 2008*)
Parkinson disease
Porphyria cutanea tarda
Hypertension
Ischemic heart disease
Type 2 diabetes (mellitus)
Spina bifida in offspring of exposed people

Inadequate or Insufficient Evidence to Determine an Association

The available epidemiologic studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association. For example, studies fail to control for confounding, have inadequate exposure assessment, or fail to address latency. There is inadequate or insufficient evidence to determine association between exposure to the chemicals of interest and the following health outcomes that were explicitly reviewed:

Cancers of the oral cavity (including lips and tongue), pharynx (including tonsils), or nasal cavity (including ears and sinuses)
Cancers of the pleura, mediastinum, and other unspecified sites in the respiratory system and intrathoracic organs
Esophageal cancer
Stomach cancer

TABLE S-1 Continued

Colorectal cancer (including small intestine and anus)
Hepatobiliary cancers (liver, gallbladder, and bile ducts)
Pancreatic cancer
Bone and joint cancer
Melanoma
Nonmelanoma skin cancer (basal cell and squamous cell)
Breast cancer
Cancers of reproductive organs (cervix, uterus, ovary, testes, and penis; excluding prostate)
Urinary bladder cancer
Renal cancer (kidney and renal pelvis)
Cancers of brain and nervous system (including eye)
Endocrine cancers (thyroid, thymus, and other endocrine organs)
Leukemia (other than all chronic B-cell leukemias, including chronic lymphocytic leukemia and hairy cell leukemia)
Cancers at other and unspecified sites
Infertility
Spontaneous abortion (other than after paternal exposure to TCDD, which appears *not* to be associated)
Neonatal or infant death and stillbirth in offspring of exposed people
Low birth weight in offspring of exposed people
Birth defects (other than spina bifida) in offspring of exposed people
Childhood cancer (including acute myeloid leukemia) in offspring of exposed people
Neurobehavioral disorders (cognitive and neuropsychiatric)
Neurodegenerative diseases, excluding Parkinson disease
Chronic peripheral nervous system disorders
Hearing loss (newly addressed health outcome)
Respiratory disorders (wheeze or asthma, chronic obstructive pulmonary disease, and farmer's lung)
Gastrointestinal, metabolic, and digestive disorders (changes in hepatic enzymes, lipid abnormalities, and ulcers)
Immune system disorders (immune suppression, allergy, and autoimmunity)
Circulatory disorders (other than hypertension and ischemic heart disease)
Endometriosis
Effects on thyroid homeostasis
Eye problems (newly addressed health outcome)
Bone conditions (newly addressed health outcome)

This committee used a classification that spans the full array of cancers. However, reviews for nonmalignant conditions were conducted only if they were found to have been the subjects of epidemiologic investigation or at the request of the Department of Veterans Affairs. *By default, any health outcome on which no epidemiologic information has been found falls into this category.*

Limited or Suggestive Evidence of *No* Association

Several adequate studies, which cover the full range of human exposure, are consistent in not showing a positive association between any magnitude of exposure to a component of the herbicides of interest and the outcome. A conclusion of "no association" is inevitably limited to the conditions, exposures, and length of observation covered by the available studies. *In addition, the*

continued

TABLE S-1 Continued

possibility of a very small increase in risk at the exposure studied can never be excluded. There is limited or suggestive evidence of *no* association between exposure to the herbicide component of interest and the following health outcomes:

Spontaneous abortion after paternal exposure to TCDD

[a]*Herbicides* indicates the following chemicals of interest: 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD or dioxin), cacodylic acid, and picloram. The evidence regarding association was drawn from occupational, environmental, and veteran studies in which people were exposed to the herbicides used in Vietnam, to their components, or to their contaminants.

[b]Evidence for an association is strengthened by experimental data supporting biologic plausibility, but its absence would not detract from the epidemiologic evidence.

*The committee notes the consistency of these findings with the biologic understanding of the clonal derivation of lymphohematopoietic cancers that is the basis of the World Health Organization classification system.

experiencing early-onset peripheral neuropathy, however, indicated that some individuals continue to manifest neuropathy symptoms long after external exposure has ceased, demonstrating that early-onset peripheral neuropathy is not necessarily a transient condition. Based on this literature, the committee chose to delete the word *transient* to recognize that symptoms of early-onset peripheral neuropathy may be protracted and recovery from those symptoms may be incomplete. This change to the classifications made since the previous update is bolded in Table S-1.

As mandated by PL 102-4, the distinctions among categories are based on statistical association, not on strict causality. The committee was directed to review the scientific data, not to recommend VA policy; therefore, conclusions reported in Table S-1 are not intended to imply or suggest policy decisions. The conclusions are related to associations between exposure and outcomes in human populations, not to the likelihood that any individual's health problem is associated with or caused by the herbicides in question.

This committee gave careful consideration to the request from VA that, in addition to its usual discussion of biologic plausibility, the committee should state the degree to which each of the other "Hill criteria for causality" are satisfied by the existing scientific information. As well known as these standards or those developed by the US Surgeon General when first assessing the health consequences of smoking are, there is in fact no sufficient set of criteria for declaring that causality has been established. In accord with the current thinking of epidemiologists, the committee concluded that adopting a checklist approach would be inappropriate.

Risk in Vietnam Veterans

There have been numerous health studies of Vietnam veterans, but most have been hampered by relatively poor measures of exposure to herbicides or TCDD and by other methodologic problems. In light of those problems, many conclusions regarding associations between exposure to the chemicals of interest and disease have been based on studies of people exposed in various occupational and environmental settings rather than on studies of Vietnam veterans, although studies of health consequences in the maturing veterans themselves have now begun to generate more informative findings. The committee believes that there is sufficient evidence to reach general or qualitative conclusions about associations between herbicide exposure and health outcomes, but the lack of adequate exposure data on Vietnam veterans themselves makes it difficult to estimate the degree of increased risk of disease in Vietnam veterans as a group or individually. Without information on the extent of herbicide exposure of Vietnam veterans and quantitative information about the dose–time–response relationship for each health outcome in humans, estimation of the risks experienced by veterans exposed to the chemicals of interest during the Vietnam War is not possible.

Because of those limitations, only general assertions can be made about risks to Vietnam veterans, depending on the category of association into which a given health outcome has been placed. If there were "limited or suggestive evidence of *no* association" between herbicide exposure and a health outcome, the evidence would suggest no increased risk of the outcome in Vietnam veterans attributable to exposure to the chemicals of interest (at least for the conditions, exposures, and lengths of observation covered by the studies reviewed). Even qualitative estimates are not possible when there is "inadequate or insufficient" evidence of an association. For outcomes categorized as having "sufficient" or "limited or suggestive" evidence of an association with herbicide exposure, the lack of exposure information on Vietnam veterans prevents calculation of precise risk estimates.

The information needed for assigning risk estimates continues to be absent despite concerted efforts to model the exposure of the troops in Vietnam, to measure the serum TCDD concentrations of individual veterans, and to model the dynamics of retention and clearance of TCDD in the human body. Accordingly, several successive VAO committees have stated as a general conclusion that, at least for the present, it was not possible to derive quantitative estimates of any increased risks of various adverse health effects that Vietnam veterans may have experienced in association with exposure to the herbicides sprayed in Vietnam. Given the amount of time that has passed since the Vietnam era, the current committee has concluded that the necessary information to perform such estimation for Vietnam veterans is extremely unlikely ever to become available.

COMMITTEE RECOMMENDATIONS

IOM has been asked to make recommendations concerning the need, if any, for additional scientific studies to resolve continuing scientific uncertainties about the health effects of the herbicides used in Vietnam and their contaminants. Great strides have been made over the past several years in understanding the health effects of exposure to the herbicides used in Vietnam and to TCDD and in elucidating the mechanisms that underlie the effects, but there are still subjects on which increased knowledge could be very useful.

This committee recommends that VA should more actively query its own medical databases to identify potential associations between Vietnam service and specific health outcomes, particularly for those outcomes that are less common. Moreover, if a perceived conflict of interest exists in surveying its own databases, it is recommended that an external advisory group be formed to determine the best mechanism for mining this information so that these medical databases could be available for external study.

The committee for *Update 2008* concluded that it was plausible that exposure to the herbicides sprayed in Vietnam could cause paternally mediated effects in offspring as a result of epigenetic changes, and such potential would most likely be attributable to the TCDD contaminant in Agent Orange. There is a growing body of evidence that TCDD, and also arsenicals, can induce epigenetic changes in animal models, but there remains extremely limited data on the risk of paternal exposure to xenobiotics in general, and the VAO chemicals of interest in particular, resulting in adverse effects on their offspring. Consequently, this committee continues to recommend that laboratory research be conducted to characterize TCDD's potential for inducing epigenetic modifications. Further, the committee recommends development of epidemiologic protocols to address the logistical challenge of determining whether adverse effects are being manifested in the adult children and grandchildren of Vietnam veterans as a result of paternal exposure. The best cohorts for revealing potential associations would be those with known, well-characterized exposure information. Another alternative would be to adopt a case–control approach and explore whether information about Vietnam exposure or specific herbicide exposure could be ascertained in any of the many birth cohorts that have been established in the past several decades. To hone in on a paternal effect, however, it will be necessary to establish that the mothers did not have the opportunity for exposure above background levels to the chemicals of interest.

As in previous years, this committee recommends the pursuit of additional research in toxicology. The development of animal models of various chronic health conditions and their progression would be useful for understanding the possible contributions of the chemicals of interest to compromise the health of aging Vietnam veterans. Specifically, determining the mechanism by which dioxin-like chemicals induce B cell cancers and how this exposure alters the sus-

ceptibility to developing obesity and components of metabolic syndrome would fill important knowledge gaps. Health problems, such as metabolic syndrome, chronic obstructive pulmonary disease (COPD), and measuring meaningful biomarkers of immune/inflammatory disease merit study in human populations.

The committee notes that the earlier investment in studying several exposed populations is now producing useful findings; the National Institute for Occupational Safety and Health, Seveso, Air Force Health Study, and Army Chemical Corps cohorts all merit continuing follow-up or more comprehensive analysis. It is especially important that longitudinal analyses be conducted on cancer, cardiovascular, and reproductive outcomes represented in the complete database assembled in the course of the Air Force Health Study. The committee endorses VA's actions toward restarting the congressionally mandated National Vietnam Veterans Longitudinal Study, derived from the cohort originally studied in the National Vietnam Veterans Readjustment Study.

The committee notes that its recommendations are similar to those offered in previous updates and that there has been little activity in several critical areas. The fate of the assemblage of data and biologic samples from the Air Force Health Study remains unsettled; in the interim, critical integrative analyses such as longitudinal evaluation of the cancer data have not yet been made public, and the unique potential of this resource languishes. It is the committee's conviction that work needs to be undertaken promptly to resolve questions regarding several health outcomes, importantly COPD, tonsil cancer, melanoma, Alzheimer disease, and paternally transmitted effects to their offspring. Creative analysis of VA's own data resources and further work on cohorts that have already been established may well be the most effective way to address those outcomes and to gain a better understanding of the role of herbicide exposure in development of PD in Vietnam veterans.

1

Introduction

The Agent Orange Act of 1991—Public Law (PL) 102-4, enacted February 6, 1991, and codified as Section 1116 of Title 38 of the United States Code—directed the Secretary of Veterans Affairs to ask the National Academy of Sciences (NAS) to conduct an independent comprehensive review and evaluation of scientific and medical information regarding the health effects of exposure to herbicides used during military operations in Vietnam. The herbicides picloram and cacodylic acid were to be addressed, as were chemicals in various formulations containing the herbicides 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). 2,4,5-T contained the contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (referred to in this report as TCDD to represent a single—and the most toxic—congener of the tetrachlorodibenzo-*p*-dioxins [tetraCDDs], also commonly referred to as dioxin). It should be noted that TCDD and Agent Orange are not the same. NAS also was asked to recommend, as appropriate, additional studies to resolve continuing scientific uncertainties and to comment on particular programs mandated in the law. In addition, the legislation called for biennial reviews of newly available information for a period of 10 years; the period was extended to 2014 by the Veterans Education and Benefits Expansion Act of 2001 (PL 107-103).

In response to the request from the Department of Veterans Affairs (VA), the Institute of Medicine (IOM) of the National Academies convened the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. The results of the original committee's work were published in 1994 as *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*, hereafter referred to as *VAO* (IOM, 1994). Successor committees formed to fulfill the requirement for updated reviews produced *Veterans and Agent Orange: Update 1996* (IOM,

1996), *Update 1998* (IOM, 1999), *Update 2000* (IOM, 2001), *Update 2002* (IOM, 2003a), *Update 2004* (IOM, 2005a), *Update 2006* (IOM, 2007), and *Update 2008* (IOM, 2009).

In 1999, VA asked IOM to convene a committee to conduct an interim review of type 2 diabetes; that effort resulted in the report *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes*, hereafter referred to as *Type 2 Diabetes* (IOM, 2000). In 2001, VA asked IOM to convene a committee to conduct an interim review of childhood acute myelogenous leukemia (AML, now preferably referred to as acute myeloid leukemia) associated with parental exposure to any of the chemicals of interest; its review of the literature, including literature available since the review for *Update 2000*, was published as *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Acute Myelogenous Leukemia in the Children of Vietnam Veterans*, hereafter referred to as *Acute Myelogenous Leukemia* (IOM, 2002). In PL 107-103, passed in 2001, Congress directed the Secretary of Veterans Affairs to ask NAS to review "available scientific literature on the effects of exposure to an herbicide agent containing dioxin on the development of respiratory cancers in humans" and to address "whether it is possible to identify a period of time after exposure to herbicides after which a presumption of service-connection" of the disease would not be warranted; the result of that effort was *Veterans and Agent Orange: Length of Presumptive Period for Association Between Exposure and Respiratory Cancer*, hereafter referred to as *Respiratory Cancer* (IOM, 2004).

In conducting their work, the committees responsible for those reports operated independently of VA and other government agencies. They were not asked to and did not make judgments regarding specific cases in which individual Vietnam veterans have claimed injury from herbicide exposure. The reports were intended to provide scientific information for the Secretary of Veterans Affairs to consider as VA exercises its responsibilities to Vietnam veterans. This VAO update and all previous VAO reports are freely accessible on line at the National Academies Press's Website (http://www.nap.edu).

CHARGE TO THE COMMITTEE

In accordance with PL 102-4, the committee was asked to "determine (to the extent that available scientific data permit meaningful determinations)" the following regarding associations between specific health outcomes and exposure to TCDD and other chemicals in the herbicides used by the military in Vietnam:

A) whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiological methods used to detect the association;

B) the increased risk of the disease among those exposed to herbicides during service in the Republic of Vietnam during the Vietnam era; and
C) whether there exists a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease.

The committee notes that, as a consequence of congressional and judicial history, both its congressional mandate and the statement of task are phrased with the target of evaluation being "association" between exposure and health outcomes, although biologic mechanism and causal relationship are also mentioned as part of the evaluation in Article C. As used technically and as thoroughly addressed in a recent report on decision-making (IOM, 2008), the criteria for causation are somewhat more stringent than those for association. The unique mandate of VAO committees to evaluate association, rather than causation, means that the approach delineated in that report is not entirely applicable here. The rigor of the evidentiary database needed to support a finding of statistical association is weaker than that to support causality; however, positive findings for any of the indicators for causality would enhance conviction that an observed statistical association was reliable. In accord with its charge, the committee examined a variety of indicators appropriate for the task, including factors commonly used to evaluate statistical associations, such as the adequacy of control for bias and confounding and the likelihood that an observed association could be explained by chance; and it assessed evidence concerning biologic plausibility derived from laboratory findings in cell-culture or animal models. The full array of indicators examined was used to categorize the strength of the evidence. In particular, associations that manifest multiple indicators were interpreted as having stronger scientific support. Table 1-1 below presents the cumulative findings through *Update 2008* of VAO committees using this approach.

In delivering the charge to the current committee, VA made an additional request arising from the decision-making at VA necessitated by the findings of *Update 2008*. The sponsor asked that the committee, when summarizing the evidence available to support the association of a health effect with exposure to the components of the herbicides used by the military in Vietnam, address whether all the points that have rather imprecisely become known as the "Hill criteria for causality" (Hill, 1965) had been satisfied by the information available. The committee's response to that request can be found Chapter 2 in the section "Evaluation of the Evidence."

Chapter 2 provides details of the committee's approach to its charge and the methods that it used in reaching conclusions.

ISSUES RAISED IN PUBLIC SESSIONS

It has been the practice of VAO committees to conduct open sessions, not only to gather additional information from people who have particular expertise

TABLE 1-1 Summary from *Update 2008* (*Seventh Biennial Update*) of Findings in Occupational, Environmental, and Veterans Studies Regarding the Association Between Specific Health Outcomes and Exposure to Herbicides[a]

Sufficient Evidence of Association

Epidemiologic evidence is sufficient to conclude that there is a positive association. That is, a positive association has been observed between exposure to herbicides and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence.[b] For example, if several small studies that are free of bias and confounding show an association that is consistent in magnitude and direction, there could be sufficient evidence of an association. There is sufficient evidence of an association between exposure to the chemicals of interest and the following health outcomes:

- Soft-tissue sarcoma (including heart)
- Non-Hodgkin's lymphoma
- Chronic lymphocytic leukemia (CLL) (including **hairy cell leukemia and other chronic B-cell leukemias**) (**category clarification since *Update 2006***)
- Hodgkin's disease
- Chloracne

Limited or Suggestive Evidence of Association

Epidemiologic evidence suggests an association between exposure to herbicides and the outcome, but a firm conclusion is limited because chance, bias, and confounding could not be ruled out with confidence.[b] For example, a well-conducted study with strong findings in accord with less compelling results from studies of populations with similar exposures could constitute such evidence. There is limited or suggestive evidence of an association between exposure to the chemicals of interest and the following health outcomes:

- Laryngeal cancer
- Cancer of the lung, bronchus, or trachea
- Prostate cancer
- Multiple myeloma
- AL amyloidosis
- Early-onset transient peripheral neuropathy
- Porphyria cutanea tarda
- **Parkinson's disease (category change from *Update 2006*)**
- Hypertension
- **Ischemic heart disease (category change from *Update 2006*)**
- Type 2 diabetes (mellitus)
- Spina bifida in offspring of exposed people

Inadequate or Insufficient Evidence to Determine Association

The available epidemiologic studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association. For example, studies fail to control for confounding, have inadequate exposure assessment, or fail to address latency. There is inadequate or insufficient evidence to determine association between exposure to the chemicals of interest and the following health outcomes *that were explicitly reviewed*:

- Cancers of the oral cavity (including lips and tongue), pharynx (including tonsils), or nasal cavity (including ears and sinuses)
- Cancers of the pleura, mediastinum, and other unspecified sites within the respiratory system and intrathoracic organs
- Esophageal cancer
- Stomach cancer

TABLE 1-1 Continued

Colorectal cancer (including small intestine and anus)
Hepatobiliary cancers (liver, gallbladder, and bile ducts)
Pancreatic cancer
Bone and joint cancer
Melanoma
Nonmelanoma skin cancer (basal-cell and squamous-cell)
Breast cancer
Cancers of reproductive organs (cervix, uterus, ovary, testes, and penis; excluding prostate)
Urinary bladder cancer
Renal cancer (kidney and renal pelvis)
Cancers of brain and nervous system (including eye)
Endocrine cancers (thyroid, thymus, and other endocrine)
Leukemia (**other than all chronic B-cell leukemias**, including CLL and hairy-cell leukemia)
Cancers at other and unspecified sites
Infertility
Spontaneous abortion (other than for paternal exposure to TCDD, which appears *not* to be associated)[b]
Neonatal or infant death and stillbirth in offspring of exposed people
Low birth weight in offspring of exposed people
Birth defects (other than spina bifida) in offspring of exposed people
Childhood cancer (including acute myeloid leukemia) in offspring of exposed people
Neurobehavioral disorders (cognitive and neuropsychiatric)
Neurodegenerative diseases, excluding Parkinson's disease
Chronic peripheral nervous system disorders
Respiratory disorders (wheeze or asthma, chronic obstructive pulmonary disease, and farmer's lung)
Gastrointestinal, metabolic, and digestive disorders (changes in liver enzymes, lipid abnormalities, and ulcers)
Immune system disorders (immune suppression, allergy, and autoimmunity)
Circulatory disorders (other than hypertension and ischemic heart disease)
Endometriosis
Effects on thyroid homeostasis

This committee used a classification that spans the full array of cancers. However, reviews for nonmalignant conditions were conducted only if they were found to have been the subjects of epidemiologic investigation or at the request of the Department of Veterans Affairs. *By default, any health outcome on which no epidemiologic information has been found falls into this category.*

Limited or Suggestive Evidence of *No* Association

Several adequate studies, which cover the full range of human exposure, are consistent in not showing a positive association between any magnitude of exposure to the chemicals of interest and the outcome. A conclusion of "no association" is inevitably limited to the conditions, exposures, and length of observation covered by the available studies. *In addition, the possibility of a very small increase in risk at the exposure studied can never be excluded.* There is limited or suggestive evidence of *no* association between exposure to the chemicals of interest and the following health outcome:

continued

TABLE 1-1 Continued

Spontaneous abortion and paternal exposure to TCDD

[a]*Herbicides* indicates the following chemicals of interest: 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, or dioxin), cacodylic acid, and picloram. The evidence regarding association was drawn from occupational, environmental, and veteran studies in which people were exposed to the herbicides used in Vietnam, to their components, or to their contaminants.

[b]Evidence of an association can be strengthened by experimental data supporting biologic plausibility, but its absence would not detract from the epidemiologic evidence.

on points that arise during deliberations but especially to hear from individual Vietnam veterans and others concerned about aspects of their health experience that may be service-related. The present committee was pleased by the response to its invitation, which had been circulated by VA, to the primary such session held in Chicago. Open sessions were held at the first four of the committee's five meetings, and the agendas are presented in Appendix A.

A summary of the topics raised at the open sessions and the committee's responses to them follows.

First Meeting, Washington, DC

- **Autoimmune conditions,** particularly mixed connective tissue disease: There is a paucity of evidence from human studies on herbicide exposure and immunologic responses, and what little there is evaluates biomarkers rather than disease states that have an immunologic etiology. The present committee conducted a comprehensive review of the available information, which is addressed in Chapter 6 on immune effects.
- Exposure to Agent Orange during **Vietnam-era service on Guam:** Evaluating where herbicide exposure may have occurred is not within the scope of this committee's charge.

Second Meeting, Chicago

- Coverage of all forms of parkinsonism in VA's recognition of **Parkinson disease** as a condition presumptively associated with service in Vietnam.
- Health problems in **children and grandchildren** of Vietnam veterans: Chapter 8 addresses evidence related to the possibility that the exposure of Vietnam veterans has adverse consequences for their progeny.
- **Thyroid disease:** The existing evidence on disruption of thyroid homeostasis is discussed in Chapter 11. As is the case for immune effects, the available information focuses on biomarkers of perturbation rather than on clinical

conditions. A considerable amount of research has addressed exposure during gestation and nursing, which is not relevant to the experience of Vietnam veterans themselves; the possible consequences of maternal exposure are discussed in Chapter 8.

- **Myelodysplastic syndromes** as forms of leukemia: The International Classification of Diseases has regarded these myeloid neoplasms as having uncertain or unknown behavior, so they cannot be defined as malignant or benign. No epidemiologic studies have looked at this end point with exposure specificity that meets VAO criteria for inclusion, although recently some work has been done on exposure to the broad classification of pesticides in general. In any event, when myelodysplastic syndromes progress into unquestionable malignancies, they become AML, on which there is inadequate or insufficient evidence of association with herbicides (see Chapter 7).
- Vietnam veterans may have experienced **multiple potentially harmful exposures** in addition to herbicide exposure (particularly, exposure to the benzene-containing **petroleum products** used as dispersants for the herbicides and the extensively used **insecticides**): Addressing interactions or synergies of other substances with the several components of these herbicides is beyond the scope of the committee's charge. People are continually exposed to many chemicals, whose possible adverse effects might be exacerbated by exposure to other agents. The number of pairs that could be addressed is enormous, and the number would rise exponentially if triads and larger combinations were considered. There is a vast toxicologic literature on petroleum products and their constituents (for example, see *Gulf War and Health: Volume 3—Fuel, Combustion Products, and Propellants* [IOM, 2005b]) and on the various chemical families of insecticides (see also, *Gulf War and Health: Volume 2—Insecticides and Solvents* [IOM, 2003b]).

Third Meeting, Albuquerque

- **Glioblastomas:** The available evidence concerning cancers of the brain and herbicide exposure is discussed in Chapter 7.
- Evidence from the **Vietnamese population:** After a thorough search of the literature and consultation with US scientists who have attempted to establish collaborative relationships with Vietnamese scientists, the committee concludes that there has been virtually no epidemiologic study of the Vietnamese population that followed the standards of Western protocols. In the interest of increasing scientific understanding, such research would be desirable. Investigations of reproductive outcomes associated with the chronic environmental exposure of men and women occurring now, however, would not be particularly informative about the time-limited exposure experience of predominantly male US veterans.

Fifth Meeting, Phoenix

- **Alzheimer disease,** especially of early onset: The limited available evidence on an association of Alzheimer disease and herbicide exposure is discussed in Chapter 9.

CONCLUSIONS OF PREVIOUS VETERANS AND AGENT ORANGE REPORTS

Health Outcomes

VAO, *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Type 2 Diabetes*, *Acute Myelogenous Leukemia*, *Respiratory Cancer*, *Update 2006*, and *Update 2008* contain detailed reviews of the scientific studies evaluated by the committees and their implications for cancer, reproductive and developmental effects, neurologic disorders, and other health effects.

The original *VAO* committee addressed the statutory mandate to evaluate the association between herbicide exposure and a given health effect by assigning each of the health outcomes under study to one of four categories on the basis of the epidemiologic evidence reviewed. The categories were adapted from the ones used by the International Agency for Research on Cancer in evaluating evidence of the carcinogenicity of various substances (IARC, 1977). Successor VAO committees adopted the same categories.

The question of whether the committee should be considering statistical association rather than causality has been controversial. In legal proceedings that predate passage of the legislation mandating the VAO series of reviews, *Nehmer v United States Veterans Administration* (712 F. Supp. 1404, 1989) found that

> the legislative history, and prior VA and congressional practice, support our finding that Congress intended that the Administrator predicate service connection upon a finding of a significant statistical association between dioxin exposure and various diseases. We hold that the VA erred by requiring proof of a causal relationship.

The committee believes that the categorization of strength of evidence as shown in Table 1-1 is consistent with that court ruling. In particular, the ruling does not preclude the consideration of the factors usually assessed in determining a causal relationship (Hill, 1965; IOM, 2008) as indicators of the strength of scientific evidence of an association. In accord with the court ruling, the committee was not seeking proof of a causal relationship, but any information that supports a causal relationship, such as a plausible biologic mechanism as specified in Article C of the charge to the committee, would also lend credence to the reliability of an observed association. Understanding of causal relationships is the ultimate objective of science, while the committee's goal of assessing statistical

association is an intermediate (less well-defined) point along a continuum that culminates in causality.

The categories, the criteria for assigning a particular health outcome to a category, and the health outcomes that have been assigned to the categories in past updates are discussed below. Table 1-1 summarizes the conclusions of *Update 2008* regarding associations between health outcomes and exposure to the herbicides used in Vietnam or to any of their components or contaminants. That integration of the literature through September 2008 served as the starting point for the current committee's deliberations. It should be noted that the categories of association concern the occurrence of health outcomes in human *populations* in relation to chemical exposure; they do not address the likelihood that any *individual's* health problem is associated with or caused by the chemicals in question.

Health Outcomes with Sufficient Evidence of an Association

In this category, a positive association between herbicides and the outcome must be observed in epidemiologic studies in which chance, bias, and confounding can be ruled out with reasonable confidence. The committee regarded evidence from several studies that satisfactorily addressed bias and confounding and that show an association that is consistent in magnitude and direction as sufficient evidence of an association. Experimental data supporting biologic plausibility strengthen evidence for an association, but are not a prerequisite.

The original *VAO* committee found sufficient evidence of an association between exposure to herbicides and three cancers—soft-tissue sarcoma, non-Hodgkin lymphoma, and Hodgkin lymphoma—and two other health outcomes, chloracne and porphyria cutanea tarda (PCT). After reviewing all the literature available in 1995, the committee responsible for *Update 1996* concluded that the statistical evidence still supported that classification for the three cancers and chloracne but that the evidence of an association with PCT warranted its being placed in the category of limited or suggestive evidence of an association with exposure. No changes were made in this category in *Update 1998* or *Update 2000*.

As the committee responsible for *Update 2002* began its work, VA requested that it evaluate whether chronic lymphocytic leukemia (CLL) should be considered separately from other leukemias. That committee concluded that CLL could be considered separately and, on the basis of the epidemiologic literature and the etiology of the disease, placed CLL in the "sufficient" category. In response to a request from VA, the committee for *Update 2008* affirmed that hairy-cell leukemia belonged in the category of sufficient evidence of an association with the related conditions CLL and the lymphomas.

Health Outcomes with Limited or Suggestive Evidence of an Association

In this category, the evidence must suggest an association between exposure to herbicides and the outcome considered, but the evidence can be limited by

the inability to rule out chance, bias, or confounding confidently. The coherence of the full body of epidemiologic information, in light of biologic plausibility, is considered when the committee reaches a judgment about association for a given outcome. Because the VAO series has four herbicides and TCDD as agents of concern whose profiles of toxicity are not expected to be uniform, apparent inconsistencies can be expected among study populations that have experienced different exposures. Even for a single exposure, a spectrum of results would be expected, depending on the power of the studies and other design factors.

The committee responsible for *VAO* found limited or suggestive evidence of an association between exposure to herbicides and three categories of cancer: respiratory cancer (after individual evaluations of laryngeal cancer and of cancers of the trachea, lung, or bronchus), prostate cancer, and multiple myeloma. The *Update 1996* committee added three health outcomes to the list: PCT, acute and subacute peripheral neuropathy (after *Update 2004* called early-onset transient peripheral neuropathy), and spina bifida in children of veterans. Transient peripheral neuropathies had not been addressed in *VAO*, because they are not amenable to epidemiologic study. In response to a VA request, however, the *Update 1996* committee reviewed those neuropathies and based its determination on case histories. A combination of a 1995 analysis of birth defects among the offspring of veterans who served in Operation Ranch Hand and results of earlier studies of neural-tube defects in the children of Vietnam veterans (published by the Centers for Disease Control and Prevention) led the *Update 1996* committee to distinguish spina bifida from other reproductive outcomes and to place it in the "limited or suggestive evidence" category. No changes were made in this category in *Update 1998*.

After the publication of *Update 1998*, the committee responsible for *Type 2 Diabetes*, on the basis of its evaluation of newly available scientific evidence and the cumulative findings of research reviewed in previous VAO reports, concluded that there was limited or suggestive evidence of an association between exposure to the herbicides used in Vietnam or the contaminant TCDD and type 2 diabetes (mellitus). The evidence reviewed in *Update 2000* supported that finding. The committee responsible for *Update 2000* reviewed the material in earlier reports and the newly published literature and determined that there was limited or suggestive evidence of an association between exposure to herbicides used in Vietnam or the contaminant TCDD and AML in the children of Vietnam veterans. After release of *Update 2000*, researchers in one of the studies that it reviewed discovered an error in the published data. The committee for *Update 2000* was reconvened to re-evaluate the previously reviewed and new literature regarding AML, and it produced *Acute Myelogenous Leukemia*, which reclassified AML in children from "limited or suggestive evidence of an association" to "inadequate or insufficient evidence to determine an association."

After reviewing the data reviewed in previous VAO reports and recently published scientific literature, the committee responsible for *Update 2006* determined

that there was limited or suggestive evidence of an association between exposure to the herbicides used in Vietnam or the contaminant TCDD and hypertension. AL amyloidosis was also moved to the category of "limited or suggestive evidence of an association" primarily on the basis of its close biologic relationship with multiple myeloma.

With a bit more consistent epidemiologic data augmented by increased understanding of mechanisms arising from new toxicologic research, the committee for *Update 2008* was able to resolve the *Update 2006* committee's lack of consensus and moved ischemic heart disease into this category, joining another cardiovascular condition, hypertension. New studies of Parkinson disease with positive findings for association with the specific herbicides of interest were deemed to move the evidence to the category of limited or suggestive.

Health Outcomes with Inadequate or Insufficient Evidence to Determine an Association

By default, any health outcome is in this category before enough reliable scientific data accumulate to promote it to the category of sufficient evidence or limited or suggestive evidence of an association or to move it to the category of limited or suggestive evidence of *no* association. In this category, available studies may have inconsistent findings or be of insufficient quality or statistical power to support a conclusion regarding the presence of an association. Such studies might have failed to control for confounding or might have had inadequate assessment of exposure.

The cancers and other health effects so categorized in *Update 2004* are listed in Table 1-1, but several health effects have been moved into or out of this category since the original *VAO* committee reviewed the evidence then available. Skin cancer was moved into this category in *Update 1996* when inclusion of new evidence no longer supported its classification as a condition with limited or suggestive evidence of *no* association. Similarly, the *Update 1998* committee moved urinary bladder cancer from the category of limited or suggestive evidence of *no* association to this category; although there was no evidence that exposure to herbicides or TCDD is related to urinary bladder cancer, newly available evidence weakened the evidence of *no* association. The committee for *Update 2000* had partitioned AML in the offspring of Vietnam veterans from other childhood cancers and put it into the category of suggestive evidence; but a separate review, as reported in *Acute Myelogenous Leukemia*, found errors in the published information and returned it to this category with other childhood cancers. In *Update 2002*, CLL was moved from this category to join Hodgkin and non-Hodgkin lymphomas in the category of sufficient evidence of an association.

The committee responsible for *Update 2006* removed several cancers (of the brain, stomach, colon, rectum, and pancreas) from the category of limited or suggestive evidence of *no* association into this category because of some changes

in evidence since they were originally placed in the "*no* association" category but primarily because that committee had concerns about the lack of information on all five chemicals of interest and each of these cancers.

Health Outcomes with Limited or Suggestive Evidence of *No* Association

The original *VAO* committee defined this category for health outcomes for which several adequate studies covering the "full range of human exposure" were consistent in showing *no* association with exposure to herbicides at any concentration and had relatively narrow confidence intervals. A conclusion of "*no* association" is inevitably limited to the conditions, exposures, and observation periods covered by the available studies, and the possibility of a small increase in risk related to the magnitude of exposure studied can never be excluded. However, a change in classification from inadequate or insufficient evidence of an association to limited or suggestive evidence of *no* association would require new studies that correct for the methodologic problems of previous studies and that have samples large enough to limit the possible study results attributable to chance.

The original *VAO* committee found a sufficient number and variety of well-designed studies to conclude that there was limited or suggestive evidence of *no* association between the exposures of interest and a small group of cancers: gastrointestinal tumors (colon, rectum, stomach, and pancreas), skin cancers, brain tumors, and urinary bladder cancer. The *Update 1996* committee removed skin cancers and the *Update 1998* committee removed urinary bladder cancer from this category because the evidence no longer supported a conclusion of *no* association. The *Update 2002* committee concluded that there was adequate evidence to determine that spontaneous abortion is *not* associated with paternal exposure specifically to TCDD; the evidence on this outcome was deemed inadequate for drawing a conclusion about an association with maternal exposure to any of the chemicals of interest or with paternal exposure to any of the chemicals of interest other than TCDD. No changes in this category were made in *Update 2000* or *Update 2004*. The *Update 2006* committee removed brain cancer and several digestive cancers from this category because of concern that the overall paucity of information on picloram and cacodylic acid made it inappropriate for those outcomes to remain in this category.

Determining Increased Risk in Vietnam Veterans

The second part of the committee's charge is to determine, to the extent permitted by available scientific data, the increased risk of disease among people exposed to herbicides or the contaminant TCDD during service in Vietnam. Previous reports pointed out that most of the many health studies of Vietnam veterans were hampered by relatively poor measures of exposure to herbicides

or TCDD and by other methodologic problems. Most of the evidence on which the findings regarding associations are based, therefore, comes from studies of people exposed to TCDD or herbicides in occupational and environmental settings rather than from studies of Vietnam veterans. The committees that produced *VAO* and the updates found that the body of evidence was sufficient for reaching conclusions about statistical associations between herbicide exposures and health outcomes but that the lack of adequate data on Vietnam veterans themselves complicated consideration of the second part of the charge.

The evidence of herbicide exposure among various groups studied suggests that although some had documented high exposures (such as participants in Operation Ranch Hand and Army Chemical Corps personnel), most Vietnam veterans had lower exposures to herbicides and TCDD than did the subjects of many occupational and environmental studies. Individual veterans who had very high exposures to herbicides, however, could have risks approaching those described in the occupational and environmental studies.

Estimating the magnitude of risk of each particular health outcome among herbicide-exposed Vietnam veterans requires quantitative information about the dose–time–response relationship for the health outcome in humans, information on the extent of herbicide exposure among Vietnam veterans, and estimates of individual exposure. Committees responsible for *VAO* and the updates have concluded that in general it is impossible to quantify the risk to veterans posed by their exposure to herbicides in Vietnam. Statements to that effect were made for each health outcome in *VAO* (IOM, 1994) and in every update through *Update 2004*. The committee responsible for *Update 2006* chose to eliminate the repetitive restatements in favor of the following general conclusion: "At least for the present, it is not possible to derive quantitative estimates of the increase in risk of various adverse health effects that Vietnam veterans may have experienced in association with exposure to the herbicides sprayed in Vietnam." The committee responsible for *Update 2008* and the current committee have opted to retain the modification in the formatting of the health-outcomes sections.

After decades of research, the challenge of estimating the magnitude of potential risk posed by exposure to the compounds of interest remains intractable. The requisite information is still absent despite concerted efforts to reconstruct likely exposure by modeling on the basis of records of troop movements and spraying missions (Stellman and Stellman, 2003, 2004; Stellman et al., 2003a,b), to measure serum TCDD in individual veterans (Kang et al., 2006; Michalek et al., 1995), and to model the pharmacokinetics of TCDD clearance (Aylward et al., 2005a,b; Cheng et al., 2006b; Emond et al., 2004, 2005, 2006). There is still uncertainty about the specific agents that may be responsible for a particular health effect. Even if one accepts an individual veteran's serum TCDD concentration as the optimal surrogate for overall exposure to Agent Orange and the other herbicide mixtures sprayed in Vietnam, not only is the measurement nontrivial but the hurdle of accounting for biologic clearance and extrapolating to the proper

timeframe remains. The committee therefore believes that it is very unlikely that additional information or more sophisticated methods are going to become available that would permit any sort of quantitative assessment of Vietnam veterans' increased risks of particular adverse health outcomes attributable to exposure to the compounds associated with herbicide spraying in Vietnam.

Existence of a Plausible Biologic Mechanism or Other Evidence of a Causal Relationship

Toxicologic data form the basis of the committee's response to the third part of its charge—to determine whether there is a plausible biologic mechanism or other evidence of a causal relationship between herbicide exposure and a health effect. A separate chapter summarizes toxicologic findings on the chemicals of concern. In updates before *Update 2008*, a considerable amount of detail had been provided about individual newly published toxicology studies; the current committee concurs with the decision made by the last committee that it would be more informative for the general reader to provide integrated toxicologic profiles for the chemicals of interest by interpreting the underlying experimental findings. When there are specific toxicologic findings pertinent to a particular health outcome, they are discussed in the chapter reviewing the epidemiologic literature on that condition. The current committee has endeavored to refine this approach to make the chapter on toxicologic information more accessible to lay readers and more illuminating about its relevance to epidemiologic findings.

In *VAO* and updates before *Update 2006*, this topic has been discussed in the conclusions section for each health outcome after a statement of the committee's judgment about the adequacy of the epidemiologic evidence of an association of that outcome with exposure to the chemicals of interest. As *Update 2006* noted, the degree of biologic plausibility itself influences whether the committee perceives positive findings to be indicative of a pattern or the product of statistical fluctuations. To provide the reader with a more logical sequence, the committee responsible for *Update 2006* placed the biologic-plausibility sections between the presentation of new epidemiologic evidence and the synthesis of all the evidence, which in turn leads to the ultimate statement of the committee's conclusion. The current committee supports that change and has continued to group the sections that way.

ORGANIZATION OF THIS REPORT

The remainder of this report is organized in 11 chapters. Chapter 2 briefly describes the considerations that guided the committee's review and evaluation of the scientific evidence. Chapter 3 addresses exposure-assessment issues. Chapter 4 summarizes the toxicology data on the effects of 2,4-D, 2,4,5-T and

its contaminant TCDD, cacodylic acid, and picloram; the data contribute to the biologic plausibility of health effects in human populations. Chapter 5 has two roles with respect to the epidemiologic information that constitutes the core of the committee's deliberations. First, the tables in the opening section identify the relevant new epidemiologic literature published in this update period, indicating the health outcomes reported upon and whether a previously study population has been revisited. The second portion of Chapter 5 provides a cumulative overview of the study populations that have generated findings (in some instances, in the form of dozens of separate publications) reviewed in the VAO report series. In addition to showing where the new literature fits into this compendium of publications on Vietnam veterans, occupational cohorts, environmentally exposed groups, and case–control study populations, the latter part of this chapter includes description and critical appraisal of the design, exposure assessment, and analysis approaches used.

The committee's evaluation of the epidemiologic literature and its conclusions regarding associations between the exposures of interest and particular health outcomes are presented in the several subsequent chapters. In this update, the committee has broken out two new chapters from the chapter on "other health effects." A chapter on immunologic effects (Chapter 6) now precedes the chapter on cancer (Chapter 7). The new chapter addresses reasons for what might be perceived as a discrepancy between clear immunotoxicity in animal studies and a paucity of epidemiologic studies with such findings. Its placement reflects the committee's belief that immunologic changes may constitute an intermediary mechanism in the generation of more distinct clinical conditions discussed in the following chapters. As in *Update 2008*, Chapter 8, on reproductive and developmental effects, places more emphasis on problems that might be manifested later in the lives of veterans' children or even in later generations. Chapter 9 addresses neurologic disorders. Early-onset peripheral neuropathy is a condition long recognized as a response to herbicide exposure that is manifested shortly after exposure but unlikely to be a response that arises for the first time decades after exposed people leave Vietnam; the discussion of evidence on this short-term response has been taken from Chapter 9 and placed in Appendix B, with the information on chloracne and porphyria cutanea tarda, which are also short-term responses presumptively associated with herbicide exposure. Chapter 10 consists of a set of conditions related to cardiovascular and metabolic effects that have also been excised from the "other health outcomes" chapter. Chapter 11 now contains the residual "other health outcomes": respiratory disorders, gastrointestinal problems, thyroid homeostasis and other endocrine disorders, and new sections on eye problems and bone conditions.

A summary of the committee's findings and its research recommendations are presented in Chapter 12.

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[1]Throughout the report the same alphabetic indicator following year of publication is used consistently for the same article when there were multiple citations by the same first author in a given year. The convention of assigning the alphabetic indicator in order of citation in a given chapter is not followed.

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2

Evaluating the Evidence

This chapter outlines the approach used by the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Eighth Biennial Update) and its predecessors to evaluate the available scientific evidence. A more complete description is found in Chapter 5 of *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*, hereafter referred to as *VAO* (IOM, 1994).

CHOICE OF HEALTH OUTCOMES

As discussed in Chapter 1, the committee was charged with summarizing the strength of the scientific evidence of associations between exposure to various herbicides and contaminants during service in the Vietnam War and individual diseases or other health outcomes. Public Law 102-4, which mandated the committee's work, however, did not specify particular health outcomes suspected of being associated with herbicide exposure. Such a list of outcomes was developed on the basis of diseases and conditions addressed in the scientific literature identified through the original *VAO*'s extensive literature searches. The list has been amended in the VAO updates in response to new publications, to requests from the Department of Veterans Affairs (VA) and various veterans' service organizations, and to concerns of Vietnam veterans and their families. Comments received at public hearings and in written submissions from veterans and other interested persons have been valuable in identifying issues to be pursued in greater depth in the scientific literature.

The VAO committees began their evaluation by presuming neither the presence nor the absence of an association between exposure and any particular health outcome. Over the series of reviews, evidence of various degrees of association,

lack of association, or persistent indeterminacy with respect to a wide array of disease states has accrued. For many conditions, however, particularly ones that are very uncommon, associations with the chemicals of interest have remained unaddressed in the medical research literature; for these, the committee remains neutral on the basis of the understanding that "absence of evidence is not evidence of absence."

IDENTIFICATION OF RELEVANT LITERATURE

Mixtures of 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), picloram, and cacodylic acid made up the bulk of the herbicides sprayed in Vietnam. At the time of the spraying, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, one form of dioxin) was an unintended contaminant from the production of 2,4,5-T and so was present in Agent Pink, Agent Green, Agent Purple, Agent Orange, and Agent Orange II, which all contained 2,4,5-T. It is important to note that TCDD and Agent Orange are not the same. Databases have been searched for the names of those compounds, their synonyms and abbreviations, and their Chemical Abstracts Service (CAS) numbers. The evidence indicates that a single protein, the aryl hydrocarbon receptor (AHR), mediates essentially all the toxicity of TCDD, so *aryl hydrocarbon receptor* also was used as a keyword, as were *dioxin*, *Agent Orange*, and *Vietnam veteran*.

One of the herbicides used in Vietnam was cacodylic acid, or dimethylarsinic acid of valency 5 (DMA^V), an organic form of arsenic. In addition to being synthesized as a herbicide, DMA^V is a metabolite of inorganic arsenic exposure in humans. DMA^V was long thought to be a biologically inactive metabolite, but evidence suggests that methylated forms such as MMA^{III} (Aposhian et al., 2000), and perhaps DMA^{III} and DMA^V (Cohen et al., 2006), might be responsible for some of the adverse effects of inorganic arsenic. The committee carefully reconsidered that evidence but again determined that it does not support a conclusion that exposure to cacodylic acid (DMA^V) would be expected to result in the same adverse health effects as would exposure to toxic concentrations of inorganic arsenic. Therefore, as in prior VAO reports, the literature on the health effects of inorganic arsenic was not considered here. Further details on the effects of inorganic arsenic can be found in *Arsenic in Drinking Water* (NRC, 1999) and *Arsenic in Drinking Water: 2001 Update* (NRC, 2001). For cacodylic acid and picloram, the search terms were the chemical names, synonyms, and CAS numbers of the herbicides.

This report concentrates on the evidence published after the completion of work on *Veterans and Agent Orange: Update 2008* (IOM, 2009). Relevant new contributions to the literature made during the period October 1, 2008–September 30, 2010, were sought. The information that the committee used was compiled from a comprehensive electronic search of public and commercial databases—biologic, medical, toxicologic, chemical, historical, and regulatory—that pro-

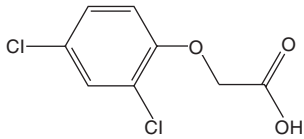
vide citations of the scientific literature. In addition, the reference lists of some review and research articles, books, and reports were examined for potentially relevant articles. As noted above, the terms used in the search strategy included the chemical names, synonyms, and CAS numbers of the specific chemicals of interest—2,4-D, 2,4,5-T, TCDD, cacocylic acid, and picloram (see Figure 2-1 for chemical structures and CAS numbers)—and the more generic terms involved with this project: *Vietnam veteran*, *Agent Orange*, *aryl hydrocarbon receptor*, *dioxin*, *herbicide*, and *phenoxy*. Results on other specific phenoxy herbicides are also of interest: 2-methyl-4-chlorophenoxyacetic acid (MCPA) and 2-(2-methyl-4-chlorophenoxy) propionic acid (MCPP or Mecoprop) for 2,4-D and 2-(2,4,5-trichlorophenoxy) propionic acid (2,4,5-TP or Silvex) for 2,4,5-T (see Figure 2-1); although the benzoate herbicide dicamba (2-methoxy-3,6-dichlorobenzoic acid) is not always categorized with the phenoxy herbicides, it has structural similarities with this class, and measures of its association with various adverse health outcomes have been factored into the evidence. Because some polychlorinated biphenyls (PCBs) and polychlorodibenzofurans (PCDFs) have dioxin-like biologic activity, studies of populations exposed to PCBs or PCDFs were reviewed when results were presented in terms of TOTSL toxic equivalents (TEQs). Findings related only to exposure to the diverse chemical families of pesticides were considered too nonspecific for inclusion in the evidence database used to draw conclusions about associations. (An ancillary analysis conducted during preparation of *Update 2008* determined that the term *pesticide* did not identify any relevant citation that was not picked up by more specific terms, and so it was eliminated from the searches conducted for the current update, and this reduced the number of extraneous hits to be culled.)

(With the structural representation at hand in Figure 2-1, the committee will respond to an assertion it has heard repeatedly from individual Vietnam veterans that "benzene is contained in TCDD." Indeed, the two rings at the ends of the three-ring structure constituting the basic structure of dioxin compounds, to which chlorine molecules or other chemical radicals can be attached, do have the molecular structure of a single benzene molecule and "dibenzo-dioxin" in TCDD's chemical name does mean the molecule is indeed a benzene-substituted dioxane. The benzene ring structure is a basic building block of a vast number of organic compounds, both industrial [such as polyaromatic hydrocarbons, the phenoxy herbicides, picloram, and PCBs] and natural [such as estradiol, a hormone present in both men and women]. However, the biologically active compound benzene does not emerge from dioxin, whose three-ring structure is extremely stable and very resistant to metabolism.)

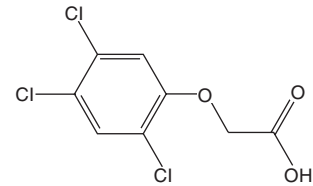
Because they are the target population of the charge to the VAO committees, studies of Vietnam veterans (serving in any of the armed forces, American or otherwise) have always been accorded considerable weight in the committees' deliberations, whether or not estimation of exposure to herbicide-related substances has been attempted. Characterization of exposure in studies of the

Phenoxy Herbicides

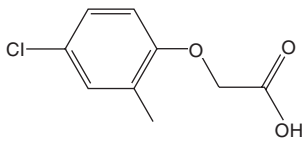
2,4-D [94-75-7]



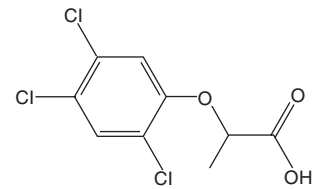
2,4,5-T [93-76-5]



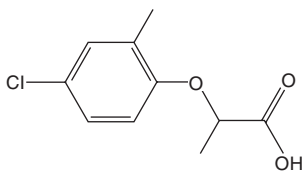
MCPA [94-74-6]



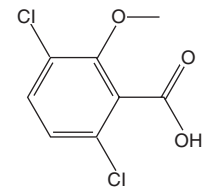
Silvex [93-72-1]



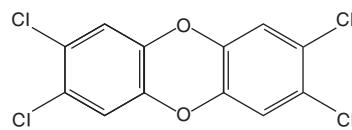
MCPP [93-65-2]



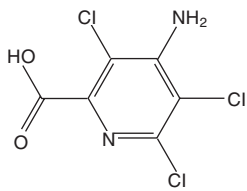
Dicamba [1918-00-9]



2,3,7,8-TCDD [1746-01-6]



Picloram [1918-02-1]



Cacodylic Acid [75-60-5]

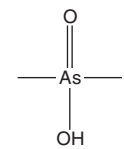


FIGURE 2-1 Chemical structures and CAS numbers for specific chemicals of interest.

veterans was extremely uncommon at the time of the original *VAO* report, and the Vietnam veterans' own ages were still below the ages at which many chronic illnesses are manifested. Consequently, the original committee made extensive efforts to consider several groups known or thought to have potentially higher and better-characterized exposure to TCDD or phenoxy herbicides than Vietnam veterans themselves—both occupational exposure (as of chemical-production, paper and pulp, sawmill, tannery, waste-incinerator, railroad, agricultural, and forestry workers) and environmental exposure (as of residents of Seveso, Times Beach, Quail Run, and Vietnam).

Successive committees have been able to concentrate more on studies that explicitly addressed the exposures specified in the charge. Some occupational and environmental cohorts that received exceptionally high exposures (such as the International Agency for Research on Cancer and Seveso cohorts) are now well characterized and producing a stream of informative results. The Agricultural Health Study, a continuing prospective cohort study of agricultural populations with specific information on the chemicals of interest, is also now contributing a steady stream of information to the database. Most important, the Vietnam veterans themselves are advancing in age and when studied are capable of directly providing substantial information on chronic health conditions and, in some study populations, information related to serum TCDD concentrations. The committee for *Update 2006* decided that exhaustive searches on job titles, occupations, or industries to identify additional study populations with possible, but not specifically characterized, exposure to the chemicals of interest were no longer an efficient means of augmenting the evidence database, in that they are more likely to retrieve citations with information about a health outcome at the expense of considerable uncertainty about exposure.

The previous and current committees followed the *Update 2006* committee's practice of more circumscribed searching. As the information in the database on populations that had established exposure to the chemicals of interest has grown, VAO committees have become less dependent on data from studies with nonspecific exposure information and have been able to focus more on findings of studies with refined exposure specificity. In recognition of the more pivotal role that findings drawn directly from Vietnam veterans were able to play in its decisions, the committee for *Update 2008* reordered its consideration of populations. For each health outcome, studies of Vietnam veterans, the target population of the VAO series, are addressed first and then occupational and environmental studies.

It is well accepted that any TCDD or herbicide effect may be diluted somewhat in studies of Vietnam veterans because some of the veterans may not have been exposed or may have been exposed only at low concentrations. The problem is exacerbated in studies in which exposure is defined in terms of occupation (even on the basis of a full job history). Exploratory studies based on linking to a one-time statement of occupation (for example, on a death certificate or in a census) are thought to be of little use even when a job–exposure matrix is

used to "convert" standardized job codes to specific exposures. Not only is there uncertainty about whether all members of the sample have been exposed to one of the chemicals of interest unless detailed personal monitoring and industrial-hygiene work have been performed but for most occupational categories there is considerable certainty that the workers were exposed to many other potentially toxic agents. Thus, such studies may well minimize the effects of exposure to TCDD or the herbicides of interest while yielding misleading indications of health problems resulting from other exposures.

The search strategy was devised to ensure that abstracts of all potentially relevant articles were subjected to closer screening, but it also resulted in the identification of a large number of nonrelevant studies. The searches produced in excess of 6,600 "hits," including some studies that were identified more than once. It was evident from the abstracts of most of the cited articles that they did not address health effects in association with exposure to the chemicals of interest; for example, many of the cited studies investigated the efficacy of herbicides in killing weeds. All studies that discussed health effects were considered if the search-related information (title, abstract, and keywords) indicated that any of the herbicides of interest (or any of their components) may have been investigated. For each of the more than 1,300 potentially relevant citations ultimately identified, a copy of the entire article was obtained online and reviewed more thoroughly by the committee for inclusion in its report. For the present update, very few documents of interest had to be retrieved as hard copies from library sources.

In large part, included reports are peer-reviewed journal articles, but generally available and formally published government studies (particularly those investigating health effects in Vietnam veterans) are also included under the presumption that they have been carefully reviewed. In practice, the articles are generally in English, but the committee obtained translations for crucial ones that were not in English, as in the case of reports of a study of Korean veterans of the Vietnam War (Kim HA et al., 2003; Kim JS et al., 2003) when *Update 2004* was produced. For the present update, in an effort to determine whether the results of epidemiologic studies of the Vietnamese population had been published in foreign-language publications, a search of non-English journals was conducted on this topic; no additional literature of this sort was identified.

TCDD, the 2,3,7,8-chlorinated congener of dioxin, is the most potent of the polychlorinated dibenzo-*p*-dioxins (PCDDs), dibenzofurans, and biphenyls, so it is presumed to be most problematic of the dioxin-like chemicals contaminating the phenoxy herbicides used in Vietnam. However, our concern is not limited to that congener. In nonlaboratory settings—for example, epidemiologic studies—exposures occur not only to TCDD but to mixtures of dioxins, dibenzofurans, and PCBs, which vary in their degree of chlorination. The concept of toxic equivalency has been developed primarily to permit overarching estimation of oral exposure and risk from certain environmentally persistent chemicals with structural similarities to PCDDs and PCDFs that bind the AHR, induce the same spectrum

of effects, and bioacumulate in the food chain (van den Berg et al., 2006). A toxicity equivalency factor (TEF) is an estimate of the dioxin-like potency of an individual congener relative to the toxicity of TCDD. TEQs are often used to estimate the cumulative toxic potency of mixtures as the sum of TEFs weighted by the concentrations of the corresponding congeners in the mixture; this total is denoted as the mixture's TEQ in terms of dioxin-like activity. That approach is often taken in epidemiologic studies that focus on PCBs. Many epidemiologic studies of PCBs were recovered in the literature search although they were not specifically sought. Because dioxin-like and non–dioxin-like PCB congeners are found together in environmental mixtures and are known to mediate toxicity by various mechanisms, the relative contribution of dioxin-like PCBs to an individual health outcome can be difficult to determine. Therefore, evidence from epidemiologic studies of PCB exposure was retained only for results reported for specific dioxin-like congeners or in terms of TEQs.

The committee for *Update 2008* investigated what pesticides are used in greenhouses and determined that greenhouse workers are not likely to be exposed to herbicides, particularly those of interest for VAO committee deliberations (Czarnota, 2004; Neal, 2006; University of Connecticut, 2006). Results on such populations (Abell et al., 2000, on fertility; Hansen et al., 1992, on cancer in female workers) were retroactively excluded from the evidence database considered in *Update 2008*, and no new citations for studies of such workers have been retained.

More than 60 articles on epidemiologic studies and several score of toxicology studies contributed new information to the present update. New evidence on each health outcome was reviewed in detail. The committee's conclusions, however, are based on the accumulated evidence, not just on recently published studies. In a considerable number of instances over the course of the VAO reports, single study populations have generated multiple entries for a given health outcome. The past procedure has been to enter new results into the summary results tables in groups corresponding to successive updates, so it has been difficult to recognize which findings are based on the experience of the same set of people.

For the present update, the committee adopted a major change in the formatting of the tables of cumulative results for the health outcomes in an effort to make the interrelationships more evident for its own deliberations and for the reader. The practice followed in previous VAO updates of inserting the findings from new publications at the beginning of the sections on veteran, occupational, and environmental studies, thereby creating chronologic bands of studies reviewed in an individual update, has been replaced with a presentation of results by study population. The reported findings on a given condition from a particular study population have been gathered and presented in reverse chronologic order so that the most mature set of statistics appears first. In many instances, this will represent the most informative set of data, the set that has the greatest power to demonstrate an adverse effect in this population. For some health problems,

particularly those common in old age, the toxic effect associated with an external factor may be to make a disease manifest itself sooner. In such situations, the evidence of an association with an exposure may consist of a wave of diagnoses in younger people, and the prevalence will equalize with that of the control group as the populations age. The committee therefore decided that it could not retain only the most recent findings when considering the experience of a given study population.

The cohorts themselves have been ordered in the tables to reflect the overarching cohorts of which they are a subgroup. And, the exposure of interest for each cohort is explicitly noted in the tables to facilitate judgments about when consistency might be expected among populations that experience the same exposure. That should minimize misapprehensions that there are inconsistencies if two excellent studies of groups exposed to different chemicals of interest have incongruent findings.

Primary findings are the components of the evidence that the committee endeavors to integrate in drawing its conclusions; reanalyses (without the incorporation of additional information), pooled analyses, reviews, and so on, may be discussed in conjunction with primary results or in synthesis sections for a given health outcome, but they are not themselves part of the evidence dataset.

COMMITTEE'S APPROACH

The committee's general approach to the evaluation of scientific evidence corresponds closely with the approach developed by the original *VAO* committee as delineated in detail in Chapter 5 of *VAO*. The committee had three specific tasks: to determine whether there is a statistical association between exposure to the herbicides used in Vietnam and health outcomes, to determine the increase in risk of effects among Vietnam veterans, and to determine whether plausible biologic mechanisms provide support for a causal relationship with a given health outcome.

Statistical Association

The issues in determining whether a statistical association exists are detailed in Chapter 5 of *VAO*. The committee found that the most relevant evidence came from epidemiologic studies—investigations in which large groups of people are studied to identify an association between exposure to a chemical of interest and the occurrence of particular health outcomes.

Epidemiologists estimate associations between exposure and outcome in a specific population or group by using such measures as relative risk, standardized mortality ratio, and odds ratio. Those measures indicate the magnitude of a difference in the rate of an outcome between two populations. For example, if the rate in an exposed population is twice the rate in a nonexposed population, the

relative risk, or rate ratio, is 2. Similarly, if the odds of a health outcome are 1:20 in an exposed population but 1:100 in a nonexposed population, the odds ratio is 5. In this report, both *relative risk* (also called *risk ratio*) and *odds ratio* are used to represent the association between exposure and adverse outcome. Both measures are often reported in prospective cohort studies. Case–control studies usually report odds ratios, and cannot report relative risk because the base rate in the control group is usually not available in these studies. However, it is possible for case–control studies to provide estimates for relative risk if ancillary information on the base rate is available (Hsieh et al., 1985; Langholz, 2010). For rare diseases with low rates for both the exposed group and the control group, odds is approximately identical to risk, therefore an odds ratio is approximately identical to a relative risk (that is,

$$odds = risk / [1 - risk],$$

so that when *risk* is close to zero, [1 − *risk*] is close to one, and therefore *odds* will be close to *risk*). An estimated relative risk or odds ratio greater than 1 indicates a positive association (that is, it is more likely that the outcome will be seen in exposed people than in nonexposed people), whereas a relative risk or odds ratio between 0 and 1 indicates a negative or inverse association (that is, the outcome is less likely in exposed people). A relative risk or odds ratio of 1 suggests the absence of association, which is usually the null hypothesis to be tested. A statistically significant association is one that would be unlikely to occur by chance (that is, if the null hypothesis is true). (Chapters 6–11 contain tables of results abstracted from the studies providing evidence about individual health outcomes. Because the distinction between *risk* and *odds* is of little consequence in the deliberations of VAO committees, the column labeled "Estimated Risk" presents these findings without specifying the precise nature of the reported statistic.)

Determining whether an estimated association between an exposure and an outcome represents a real relationship requires careful scrutiny because there can be more than one explanation for an estimate. *Bias* is a distortion of the measure of association that results from flawed selection in the assembly of the study population or from error in measurement of studied characteristics. *Confounding* is a distortion of the measure of association that results from failure to recognize or account for some factor related both to exposure and to outcome. *Chance* is the degree to which an estimated association might vary randomly among different samples of the population studied. The width of a *confidence interval* is used to quantify the likely statistical variability of an exposure–disease association, but it does not incorporate quantification of distortions that may arise from the systematic problems mentioned above. Even when a relative risk or standardized mortality ratio substantially exceeds 1, a conclusion regarding increased risk must be qualified when the confidence interval is wide. In drawing its conclusions, the committee examined the quantitative estimates of association and evaluated the

potential influences of bias, confounding, and chance. In integrating the findings of various studies, the committee considered the degree of statistical significance associated with every estimated risk (a reflection of the magnitude of the observed effect and the power of the study designs) rather than simply tallying the "significant" and "nonsignificant" outcomes as dichotomous items of evidence. The committee also considered whether controlled laboratory investigations provide information consistent with the chemicals' of interest being associated with a given effect and perhaps causally linked to it.

In pursuing the question of statistical association, the committee recognized that an absolute conclusion about the absence of association is unattainable. As in science generally, studies of health effects associated with herbicide exposure cannot demonstrate that a purported effect is impossible or could never occur, only that it is statistically improbable. Any instrument of observation, even an excellent epidemiologic study, is limited in its resolving power. In a strict technical sense, therefore, the absence of an association between even one chemical and a health outcome cannot be proved. Convincingly demonstrating the lack of a particular effect of all five of the compounds of interest simultaneously would be a daunting effort, especially in light of the paucity of information concerning picloram and cacodylic acid. The present committee therefore endorses the decision by the committee for *Update 2006* to reclassify several types of cancer that had been classified since *VAO* (1994) as having "suggestive evidence of *no* association" with "exposure to herbicides."

Interaction or synergism among the chemicals of interest or with other agents is another theoretical concern. The committee was not charged with attributing effects to specific chemicals of interest, and joint effects among them should be adequately identified by the committee's approach. The number of combinations of the chemicals with other agents that might be problematic is virtually infinite. Real-life experience, as investigated with epidemiologic studies, effectively integrates any results of exposure to a target substance over all other possibly detrimental or mitigating exposures that a population might have. It may not be possible to partition contributions of the chemicals of interest from those of all other factors quantitatively, but, to the extent that the possibility of confounding influences can be appraised, the committee will have achieved its objective.

Increased Risk in Vietnam Veterans

When all the available epidemiologic evidence has been evaluated, it is presumed that Vietnam veterans are at increased risk for a specific health outcome if there is evidence of a positive association between one or more of the chemicals of interest and the outcome. The best measure of potency for the quantification of risk to veterans would be the rate of the outcome in exposed Vietnam veterans compared with the rate in nonexposed veterans, adjusted for the degree to which any other factors that differ between exposed and nonexposed veterans might

influence those rates. A dose–response relationship established in another human population suitably adjusted for such factors would be similarly suitable.

It is difficult to quantify risk when exposures of a population have not been measured accurately. Recent serum TCDD concentrations are available only on subgroups enrolled in the Air Force Health Study (AFHS) (the Ranch Hand and Southeast Asia comparison subjects) and from VA's study of deployed and nondeployed members of the Army Chemical Corps. Pharmacokinetic models, with their own set of assumptions, must be applied to extrapolate from contemporary readings to obtain presumably accurate estimates of original exposure of Vietnam-era veterans. The absence of reliable measures of exposure of Vietnam veterans to the chemicals of interest limits the committee's ability to quantify risks of specific diseases in this population.

Although serum TCDD measurements in only a small portion of Vietnam-era veterans are available, the observed distributions of these most reliable measures of exposure make it clear that they cannot be used as a standard to partition veterans into discrete exposure groups, such as service on Vietnamese soil, service in the Blue Water Navy, and service elsewhere in Southeast Asia. For example, many TCDD values observed in the comparison group from the AFHS exceeded US background levels and overlapped considerably with those of the Ranch Hand subjects.

As explained in Chapter 1, the committee for *Update 2006* decided to make a general statement about its continuing inability to address that aspect of its charge quantitatively rather than to reiterate a disclaimer in the concluding section for every health outcome, and the present committee has retained that approach.

Plausible Biologic Mechanisms

Chapter 4, "Information Related to Biologic Plausibility" and previously denoted as "Toxicology," details the experimental basis of assessment of biologic plausibility or the extent to which an observed statistical association in epidemiologic studies is consistent with other biologic or medical knowledge. Does the observation of a particular health effect make sense on the basis of what is known about how the chemicals in question act at the tissue, cellular, or molecular level? The relationship between a particular exposure and a specific human health outcome is addressed in the context of research on the effects of the chemicals on biologic systems and of evidence from animal studies.

Chapter 4 presents an integrated toxicity profile of each of the chemicals of interest without providing detailed commentary on each possibly relevant toxicology article published in the update period. Experimental information pertinent to a particular health outcome is now presented immediately after the epidemiologic evidence on that outcome in the "Biologic Plausibility" sections of the individual health outcomes (Chapters 6–11).

A positive statistical association between an exposure and an outcome does not necessarily mean that the exposure is the cause of the outcome. Data from toxicology studies may support or conflict with a hypothesis that a specific chemical can contribute to the occurrence of a particular disease. Many toxicology studies are conducted with laboratory animals so that variables, including the amount and duration of exposure, can be controlled precisely. Studies that use isolated cells in culture also can elucidate how a chemical alters cellular processes. The objectives of those toxicology studies are to determine what toxic effects are observed at different exposure concentrations and to identify the mechanisms by which the effects are produced. Ultimately, the results of the toxicology studies should be consistent with what is known about the human disease process to support a conclusion that the development of the disease was influenced by an exposure.

Animal studies and in vitro studies with human cells and cell lines do provide important links to understanding underlying biochemical mechanisms associated with toxicity induced by xenobiotics (exogenous chemicals). In some cases, however, toxic effects are observed in animal studies that are not detected in humans. There are many potential factors that may contribute to differences between controlled animal studies and effects observed in humans. The following are among the most important:

- **Physiologic differences.** Laboratory animals are not miniature humans. Depending on the biologic process under investigation, a particular test species may match the human system more closely and so be a better experimental model.
- **Magnitude of exposures.** In general, the TCDD exposure used for animal studies has been many orders of magnitude higher than Vietnam veterans are likely to have received during military service.
- **Duration of exposure.** Although TCDD is a persistent organic pollutant, animal studies seldom examine chronic low-level exposure that occurs over a period of many months or even years.
- **Timing of exposure.** It is well known that many organ systems are highly susceptible to xenobiotic exposure during critical stages of development, such as during gestation; the response of some systems (such as the immune system) may also depend on the timing of exposure to antigens relative to the timing of exposure to xenobiotics such as TCDD.
- **Other genetic susceptibilities.** The etiologies of most diseases in humans and in animals are likely to be under the influence of numerous genes and to involve complex gene-by-environment interactions, and preliminary evidence suggests that TCDD can induce epigenetic modifications to an organism's DNA that may alter future expression of the genome.
- **Sex differences.** There are well-known differences in susceptibility to

xenobiotic exposures between male and female animals, some of which are modified by sex steroids; there are probably other reasons for sex differences.

- **Prior and recurring exposures to multiple sources.** Humans are exposed to xenobiotics from multiple sources throughout their lifetime.
- **Complex mixtures.** Most xenobiotic exposures occur in complex mixtures; the makeup of these mixtures can greatly influence the ultimate toxic effects; in addition to dietary modulation of response to other exposures in both humans and animals, human metabolism is further perturbed by dietary supplements, prescription and over-the-counter pharmaceuticals, and other factors (such as cigarette-smoking or ambient pollution).
- **Stress.** Stress of known or unknown origin is a well-known modifier of human disease responses (such as immune responses); stress is an ever-present variable that is difficult to assess or control for in epidemiologic studies because there is substantial individual variation in response to stress (Cohen et al., 2007).

The absence of evidence of biologic plausibility from toxicology studies, however, does not rule out the possibility of a biologic relationship. In fact, cases in which the epidemiologic evidence is strong but toxicologic support is lacking often drive new toxicology research.

As noted in *VAO*, not only is information on biologic plausibility one of the primary elements in the oft-cited list of factors that has rather imprecisely become known as the Bradford Hill (1965) "criteria" for causality (discussed in more detail at the end of this chapter) but insights about biologic processes inform whether an observed pattern of statistical association might be interpreted as the product of more than error, bias, confounding, and chance. The committee used toxicologic information in that fashion and placed the information before its synthesis and conclusion to provide readers with a more coherent argument for its ultimate conclusion about the adequacy of the available evidence to support the existence of a particular association.

EVALUATION OF THE EVIDENCE

Associations between exposures to the chemicals of interest and specific health outcomes are determined through an analysis of available epidemiologic studies that is informed by an understanding of the toxicology of the chemicals and their exposure pathways. In reaching conclusions, VAO committees consider the nature of the exposures, the nature of the health outcomes, the populations exposed, and the quality of the evidence examined. Some specific issues that this and prior committees have considered are addressed below.

Human Studies

The committee reviewed studies of Vietnam veterans and of other populations that might have been exposed to the chemicals of interest. The other populations factored into the committee's evaluation included cohorts of workers in chemical production and agriculture and populations residing near sites of environmental contamination. The committee believes that studies of such nonveteran subjects can help in the assessment of whether the chemicals of interest are associated with particular health outcomes. As noted above in describing the literature search, studies of nonveteran subjects were identified because one of the chemicals of interest was specified by the original researchers as presenting a possible toxic exposure rather than on the basis of occupational definitions. Some of the studies provide stronger evidence about health outcomes than do studies of veterans because exposures were measured sooner after occurrence and were more thoroughly characterized than has been the case in most studies of veterans. Furthermore, in the studies of workers in chemical-production plants, the magnitude and duration of exposure to the chemicals were generally greater, so the likelihood that any possible health consequence would be manifested was greater. The studies were often large enough to examine health risks among groups of people with different levels of exposure, so dose–response relationships could be investigated. The general practice of VAO committees has been to evaluate all studies, whether or not their subjects were Vietnam veterans, according to the same criteria in determining the strength and validity of findings. Because the subjects of studies of Vietnam veterans are the concern of the legislation that mandated the present review, however, demonstrations of increased incidence of particular health outcomes among them are of unquestionable pertinence in drawing conclusions.

The committee has concluded that it would be inappropriate to use quantitative techniques, such as meta-analysis, to combine individual study results into a single summary measure of statistical association. The committee reached that conclusion because of the many differences among studies in definitions of exposure, health outcomes considered, criteria for defining study populations, correction for confounding factors, and degree of detail in reporting results. The appropriate use of meta-analysis requires more methodologic consistency among studies, especially in the definition of exposure, than is present in the literature reviewed by the committee (Egger et al., 2002; Petitti, 2000). A detailed discussion of the results of individual studies in appropriate categories (Vietnam-veteran, occupational, or environmental exposure; and exposure to Agent Orange or equivalent dioxin-contaminated phenoxy herbicides, to dioxin, to phenoxy herbicides without dioxin contamination, to cacodylic acid, or to picloram) with a thorough examination of each study's strengths and weaknesses is fully informative without making unfounded assumptions of homogeneity.

In general, VAO committees have not considered case reports, case series, or

other published studies that lacked control or comparison groups. An exception was made, however, for early-onset peripheral neuropathy. Individual case reports were reviewed because the rapid appearance and frequently transient nature of the condition impose methodologic constraints that might have precluded the application of standard epidemiologic techniques.

Because any effect of Agent Orange in individuals or groups of veterans is evaluated in terms of disease or medical outcome, attention to disease classification was important to the committee in assembling pertinent data from various investigations related to a particular outcome before integrating the information. The researchers who conducted the studies reviewed by the committee faced the same challenge in interpreting the available documentation when assigning diagnostic labels to given subjects and then grouping the labels for analysis.

Pathologists, clinicians, and epidemiologists use several classification systems, including the *International Classification of Diseases* (ICD); the *International Classification of Diseases, 9th Revision* (ICD-9), *Clinical Modification* (ICD-9-CM), and the *International Classification of Diseases for Oncology*. The 10th revision of ICD (ICD-10) is currently used to classify mortality information. Most of the subjects investigated in the studies cited in this update were diagnosed under earlier systems, and most of the articles report results in accordance with ICD-9 if they use ICD codes at all, so the committee has also used ICD-9. ICD codes are a hierarchic system for indicating type of disease and site. For example, ICD-9 162 specifies cancers of the lung, trachea, or bronchus; 162.2, cancer of a main bronchus; 162.3, cancer of an upper lobe; 162.4, cancer of a middle lobe, and 162.5, cancer of a lower lobe.

For a patient to receive a correct cancer diagnosis, careful staging of the extent of disease is necessary, and a biopsy of the tissue must be analyzed with microscopy, often with special immunohistochemical stains, to confirm a clinical impression. Many of the epidemiologic studies reviewed by this committee did not use the ICD approach to classification of disease and relied instead on clinical impression alone. Death-certificate diagnoses are notoriously inaccurate if the certificates are completed by medical officers who are not familiar with the decedents' medical history (Smith Sehdev and Hutchins, 2001). Self-reported diagnoses, which are obtained from survey questionnaires, often are partially or completely inaccurate; for instance, a patient may report having been treated for stomach cancer although the correct diagnosis was gastric adenocarcinoma, gastric lymphoma, pancreatic cancer, large bowel cancer, or peritoneal cancer.

Many epidemiologic studies report disease outcome by organ system. For instance, the term *digestive system* may be used for conditions that are benign or malignant and that affect the esophagus, stomach, liver, pancreas, small bowel, large bowel, or rectum. Therefore, if a report indicated that a cohort has an increased incidence of digestive system cancer, it would be unclear whether the association was attributable to excess cases of esophageal, gastric, hepatic, pancreatic, or intestinal cancers or to some combination thereof. Such generalization

is complicated by the fact that the cause of cancer may differ between anatomic sites. For instance, there are strong associations between gastric cancer and *Helicobacter pylori* infection, between smoking and squamous cell carcinoma of the esophagus, and between chronic hepatitis B infection and hepatic cancer. Furthermore, a single site may experience a carcinogenic response to multiple agents.

The committee recognizes that outcome misclassification is a possibility when recording of a diagnosis with a specific ICD code is used as the means of entering an observation into an analysis, but this system has been refined over many decades and is virtually universally used and understood, in addition to being exhaustive and explicit. Therefore, this and previous VAO committees have opted to use the ICD system as an organizing tool. Although the groupings of cancer sites for which conclusions about association have been presented may correspond more closely to National Institute for Occupational Safety and Health or National Cancer Institute Surveillance Epidemiology and End Results categories (see Appendix B), the underlying ICD codes provide the most exactitude. In this report, ICD codes appear almost exclusively in the introductory sections of health-outcome discussions (particularly for cancers) to specify precisely what outcome the committee is addressing and, when possible, in the results table to indicate exactly what the primary researchers believed that they were investigating. (See Appendix B for cancer groupings with corresponding ICD-9 and ICD-10 codes.)

Rare diseases, such as hairy cell leukemia and tonsil cancer, are difficult to study because it is hard to accumulate enough cases to permit analysis. Often, the result is that observed cases are included in a broader, less specific category. Thus, epidemiologic data may not be available for assessing whether a particular rare disease is associated with Agent Orange exposure. In some instances, such as chronic lymphocytic leukemia and AL amyloidosis, VAO committees have reached conclusions on the basis of the data available and the etiology of the disease. Through systematic application of the hierarchic nature of the ICD coding system, committees intend to draw, for every type of cancer, an explicit conclusion about the adequacy of available evidence to support an association between herbicide exposure and that type of cancer. For nonmalignant conditions, however, the diversity of disease processes involved makes the use of broad ICD ranges less useful, but, because VAO committees could not possibly address every rare nonmalignant disease, they do not draw explicit conclusions about diseases that are not discussed. Thus, the category of "inadequate or insufficient evidence to determine an association" is the default or starting point for any health outcome; if a condition or outcome is not addressed specifically, it will be in this category.

The committee is aware of the concerns of some veterans about the role of herbicide exposure in the occurrence of multiple health outcomes, such as multiple cancers, in a given person. Little research has been done to address whether the rate of concurrence is greater than would be expected by chance.

Simultaneous analysis of multiple health outcomes could potentially provide more insight into whether the chemicals of interest cause multiple health effects, into competing risks between various health outcomes, and into the interactive effects of health outcomes; but addressing health conditions individually has remained challenging.

VAO committees wanted to be clear in indicating what evidence is factored into their conclusions. The practice in the VAO reports has been to augment the results table for a given health outcome with any additional publications considered in the current update in the categories of Vietnam-veteran, occupational, or environmental studies. Inclusion of sequential sets of results from follow-ups of a study population has the potential to create the appearance of a greater weight of evidence than is warranted, so *Update 2006* and *Update 2008* used italicized citations in results tables to indicate that results had been superseded. The current committee did not want to convey the notion that earlier findings were of no importance. In an effort to get a comprehensive and comprehensible picture of the history of each study population, the current committee decided to abandon the sequential entries by update that had been the format for the result tables since *Update 1996*. The new format adopted for the results tables is a refinement of the cohort-based approach introduced in *Update 2006* for cardiovascular diseases. To facilitate the reader's locating the discussion of the characteristics of particular study populations and the attributes of the publications based on them, the order of studies in the results tables corresponds to their presentation in Chapter 5. The main categorization of veteran, occupational, and environmental studies has been retained in both instances.

An issue related to evidence evaluation that was of concern for the *Update 2006* committee was the evidence category of "*no* association." That committee determined that a conclusion of *no* association would require substantive evidence of such a lack of effect of each of the chemicals of interest. Given the paucity of information that exists for cacodylic acid and picloram, that conclusion would seem suspect even if substantial evidence uniformly supported a finding of *no* association both with exposure to the phenoxy herbicides and with exposure to TCDD. The *Update 2008* and current committees concurred in that determination and adopted a similar approach to the placement of health outcomes in this category.

Exposure Assessment

Much of the evidence that VAO committees have considered has been drawn from studies of populations that were not in Vietnam during the period when Agent Orange and other herbicides were used as defoliants. The most informative of those studies were well-documented investigations of occupational exposures to TCDD or specific herbicides, such as 2,4-D and 2,4,5-T. In many other studies, TCDD exposure was combined with exposures to an array of "dioxin-like"

compounds, and the herbicides were often analyzed as members of a functional class; this is less informative for the committee's purpose than individual results on a specific compound. In the real-world situations investigated in epidemiologic studies, exposure to multiple possibly toxic chemicals is the rule rather than the exception; for example, farmers and other agricultural populations are likely to be exposed to insecticides, fungicides, and herbicides. In such studies, the committee looked for evidence of health effects that are associated with the specific compounds in the defoliants used in Vietnam and sought consideration of and adjustment for other possibly confounding exposures.

The quality of exposure information in the scientific literature reviewed by this and previous VAO committees spans a broad range. Some studies relied on interviews or questionnaires to determine the extent and frequency of exposure. Such self-reported information generally carries less weight than would more objective measures of exposure. The strength of questionnaire-based information as evidence of exposure is enhanced to the extent that the information can be corroborated or validated by other sources. Written records of chemical purchase or production can provide one type of objective information. Even more useful are scientific measurements of exposure. In some occupational studies, for example, workers wear air-sampling instruments that measure the concentration of a contaminant in each worker's breathing zone. Measurement of chemicals or their products in biologic specimens, such as blood and urine, can provide reliable indications of exposure for specific periods. Studies that categorize exposure from well-documented environmental sources of contaminants can be useful in the identification of exposed populations, but their results may be inaccurate if people with different magnitudes of exposure are assigned to the same general category of exposure. Studies that explore environmental exposure and disease frequency in regional populations (such as states and counties) are known as ecologic studies. Most ecologic studies are considered preliminary or "hypothesis-generating" studies because they lack information on exposure and disease on an individual basis and are unable to address potential confounding factors.

Chapter 3 of this update addresses issues of exposure estimation in more detail. The agent of interest may be assessed with various degrees of specificity. For instance, any of the four herbicides in question could be individually measured, and phenoxy herbicides would be a useful broader category for 2,4,5-T and 2,4-D; but a report of findings in terms simply of "herbicides" is only on the margin of being informative, and results stated in terms of "pesticides" are too vague to be useful. For a given chemical of interest, the measure of exposure may be increasingly imprecise—for example, concentrations in target tissue, serum concentrations, cumulative exposure, possible exposure, and so on down to merely a report of service in a job or industry category. Those approaches can address complexities in specificity, duration, and intensity of exposure with various degrees of success. All may provide some information about association with a chemical of interest, but this committee has determined that investigation

of associations between an exposure of concern and most health outcomes has reached the stage where some characterizations of exposure are too nonspecific to promote insight. For health outcomes with very little evidence, a somewhat looser criterion would apply so that no possible signal of an association would be overlooked.

Animal and Mechanistic Studies

Animal models used as surrogates for the study of a human disease must reproduce, with some degree of fidelity, the manifestations of the disease in humans. However, a given effect of herbicide exposure in an animal species does not necessarily establish its occurrence in humans. In addition to possible species differences, many factors affect the ability to extrapolate from results of animal studies to health effects in humans. Animals used in experimental studies are most often exposed to purified chemicals, not to mixtures. Even if herbicide formulations or mixtures are used, the conditions of exposure might not realistically reproduce human exposures that occur in the field. Furthermore, Vietnam veterans were exposed to other agents—such as tobacco smoke, insecticides, therapeutics, drugs, diesel fumes, and alcohol—that may increase or decrease the ability of chemicals in herbicides to produce a particular adverse health outcome. Few, if any, studies either in humans or in experimental animals have examined those interactions.

As discussed in Chapter 4, TCDD is thought to be responsible for many of the toxic effects of the herbicides used in Vietnam. Attempts to establish correlations in the effects of TCDD between experimental systems and humans are particularly problematic because of known species-, sex-, and outcome-specific differences in susceptibility to TCDD toxicity. Some data indicate that humans might be more resistant than are other species to TCDD's toxic effects (Ema et al., 1994; Moriguchi et al., 2003); other data suggest that, for some outcomes, human sensitivity could be the same as or greater than that of some experimental animals (DeVito et al., 1995). Differences in vulnerability may also be affected by variations in the rate at which TCDD is eliminated from the body (see Chapter 4 for details on the toxicokinetics of TCDD), although susceptibility is generally thought be an inherent biological response.

It is important to account for TCDD's mode of action in considering species and strain differences. There is a consensus that most of or all the toxic effects of TCDD involve interaction with the AHR, a protein that binds TCDD and certain other aromatic hydrocarbons with high affinity. Formation of an active complex involving the intracellular receptor, the ligand (the TCDD molecule), and other proteins is followed by interaction of the activated complex with specific sites on DNA. That interaction can alter the expression of genes involved in the regulation of cellular processes. The development of mice that lack the AHR has helped to establish a definitive association between the AHR and TCDD-mediated toxicity.

The affinity of TCDD for the AHR is species- and strain-specific, and responses to binding of the receptor vary among cell types and developmental stages. In addition, genetic differences in the properties of the AHR are known in human populations, as they are in laboratory animals, so some people are at intrinsically greater or less risk for the toxic effects of TCDD.

Although studying AHR biology in transformed human cell lines minimizes the inherent error associated with species extrapolations, caution must be exercised because it is still not clear to what extent toxicity is affected by the transformation itself or by the conditions under which cell lines are cultured in vitro. Furthermore, humans have AHR with differing affinities for dioxin, and thus a single transformed human cell line will not accurately reflect the responses observed across the entire human population.

Publication Bias

Some studies are more likely to be published than others. That is the concept of publication bias, which has been documented in biomedical research (Song et al., 2000; Stern and Simes, 1997). Most commonly, bias can be introduced when studies whose hypotheses are supported by statistically significant results or that are otherwise deemed favorable by their authors are selectively submitted for publication. In addition, papers with "interesting findings" may be of more interest to journal editors and reviewers and thus be more likely to be accepted for publication after submission. Conversely, "negative" studies, in which the hypotheses being tested are not supported by the study findings, often go unpublished. Investigators employed by industry may be inhibited from submitting findings that have potential legal or economic ramifications.

Thus, conclusions about associations between exposure and outcome that are based solely on published results could be subject to bias. Despite that, the committee does not believe that its conclusions have been unduly affected by publication bias, for two reasons: the extensive publicity surrounding the possibility of health effects associated with the herbicides used in Vietnam has created considerable pressure to publish all findings on the subject, and the many published studies assembled and reviewed contain among their results the full range of possible statistical associations, from convincingly negative through indeterminate to strongly positive.

Role of Judgment

This committee's process of reaching conclusions about statistical associations involved more than a formulaic application of quantitative procedures to the assembled evidence. First, the committee had to assess the relevance and validity of individual reports. Then, it had to evaluate the possible influences of measurement error, selection bias, confounding, and chance on the reported results.

Next, the committee integrated all the evidence within and among diverse fields of research. Finally, the conclusions drawn were based on consensus within the committee. Those aspects of the committee's review required thoughtful consideration of alternative approaches at several points and could not be accomplished by adherence to a narrowly prescribed formula.

The realized approach, as described here, has been determined to a large extent by the nature of the exposures, of the health outcomes, and of the resulting evidence available for examination; therefore, it has evolved in the course of the work of this and previous VAO committees. The quantitative and qualitative procedures underlying this review have been made as explicit as possible, but ultimately the conclusions about association expressed in this report are based on the committee's collective judgment. The committee has endeavored to express its judgments as clearly and precisely as the data allowed.

In delivering the committee its charge for this update, VA's representative requested that the committee delineate, for health outcomes found to have some evidence supporting statistical association, how well each of the factors that have rather imprecisely become known as the Hill (1965) "criteria" for causality have been satisfied. Having a scientific perspective on the extent to which these factors, in addition to biologic plausibility, were met would help facilitate the Secretary in making a policy decision concerning a presumptive relationship of any new health outcome to exposure to the herbicides used by the military in Vietnam.

The committee is uniformly and strongly of the opinion that execution of a checklist of the Hill criteria would not be an appropriate approach for fulfilling its charge. The list of issues that Hill discussed are not a definitive set of factors to be addressed in evaluating whether a collection of evidence supports causality. The nine aspects of a statistical association noted by Hill (1965)—strength, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experiment, and analogy—as contributing to a finding of causality vary in the importance that might be assigned to them, but none is sufficient, and only temporality (that the cause precede the effect) is necessary. Philosophers of science have established that a set of sufficient criteria for causality does not exist (Rothman and Greenland, 1998). Citing Weed and Gorelick (1996) and Holman et al. (2001), Rothman et al. (2008) noted that "epidemiologists have *not* agreed on a set of causal criteria or on how to apply them [emphasis in orginal]. . . . The typical use of causal criteria is to make a case for a position for or against causality that has been arrived at by other, unstated means." The establishment of causality is not an absolute or discrete (or necessarily permanent) state. The Hill criteria have often been used as a point of reference in addressing the subject of causation in evaluating possible environmental harms, but even in theoretical and optimal circumstances scientists have not derived a definitive algorithm for recognizing causality. The extent to which a relationship is judged to be causal entails many *subjective* elements involving the universe of information considered and the weight accorded to each evidentiary component considered.

Furthermore, with regard to chronic diseases, causality is rarely limited to a single factor.

For those reasons, the present VAO committee has not adopted the suggestion to perform what would be in effect a checklist approach to distilling evidence concerning underlying causality for any observed statistical association between a human health effect and exposure to the components of the herbicides sprayed in Vietnam. The committee interprets its charge to be to summarize the scientific evidence for consideration by the Secretary, whose role is to make the policy decision of whether a contribution by herbicide exposure to the occurrence of an adverse health effect is likely enough to merit recognition as a presumptive condition.

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[1]Throughout this report, the same alphabetic indicator after year of publication is used consistently for a given reference when there are multiple citations by the same first author in a given year. The convention of assigning the alphabetic indicators in order of citation in a given chapter is not followed.

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3

Exposure to the Herbicides Used in Vietnam

Assessment of human exposure is a key element in addressing two of the charges that guide the work of this committee. This chapter first presents background information on the military use of herbicides in Vietnam from 1961 to 1971 with a review of our knowledge of exposures of those who served in Vietnam and of the Vietnamese population to the herbicides and to the contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, which is referred to in this report as TCDD (and commonly referred to as dioxin) and is the most toxic congener of the tetrachlorodibenzo-*p*-dioxins. It then reviews several key methodologic issues in human population studies; disease latency, possible misclassification based on exposure, and exposure specificity required for scientific evaluation of studies. Further discussion is presented to underscore the difficulties of assessing exposure in the complex environment that characterized Vietnam during the period of interest.

Exposure of human populations can be assessed in a number of ways, including use of historical information, questionnaires and interviews, measurements in environmental media, and measurements in biologic specimens. Researchers often rely on a mixture of qualitative and quantitative information to derive such estimates (Armstrong et al., 1994; Checkoway et al., 2004). The most basic approach compares members of a presumably exposed group with the general population or with a nonexposed group; this method of classification offers simplicity and ease of interpretation. A more refined method assigns each study subject to an exposure category—such as high, medium, or low exposure—and calculates disease risk for each group separately and compares it with the risk for a reference or nonexposed group; this method can identify the presence or absence of an exposure–response trend. In some cases, more detailed information is avail-

able for quantitative exposure estimates that can be used to construct what are sometimes called exposure metrics. The metrics integrate quantitative estimates of exposure intensity (such as chemical concentration in air or extent of skin contact) with exposure duration to produce an estimate of cumulative exposure. Exposure also can be assessed by measuring chemicals and their metabolites in human tissues. Such biologic markers of exposure integrate absorption from all exposure routes, but their interpretation requires knowledge of pharmacokinetic processes. All those exposure-assessment approaches have been used in studies of Vietnam veterans.

MILITARY USE OF HERBICIDES IN VIETNAM

Military use of herbicides in Vietnam took place from 1962 through 1971. Tests conducted in the United States and elsewhere designed to evaluate defoliation efficacy were used to select specific herbicides (IOM, 1994; Young and Newton, 2004). Four compounds were used in the herbicide formulations in Vietnam: 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), 4-amino-3,5,6-trichloropicolinic acid (picloram), and dimethylarsinic acid (cacodylic acid). The chemical structures of those compounds are presented in Chapter 2 (Figure 2-1). The herbicides were used to defoliate inland hardwood forests, coastal mangrove forests, cultivated lands, and zones around military bases. In 1974, a National Resource Council committee estimated the amount of herbicides sprayed from helicopters and other aircraft by using records gathered from August 1965 through February 1971 (NRC, 1974). That committee calculated that about 18 million gallons (about 68 million liters) of herbicide was sprayed over about 3.6 million acres (about 1.5 million hectares) in Vietnam in that period. The amount of herbicides sprayed on the ground to defoliate the perimeters of base camps and fire bases and the amount sprayed by Navy boats along river banks were not estimated.

A revised analysis of spray activities and exposure potential of troops emerged from a study overseen by a committee of the Institute of Medicine (IOM, 1997, 2003a,b). That work yielded new estimates of the amounts of military herbicides used in Vietnam from 1961 through 1971 (Stellman et al., 2003a). The investigators reanalyzed the original data sources that were used to develop herbicide-use estimates in the 1970s and identified errors that inappropriately removed spraying missions from the dataset. They also added new data on spraying missions that took place before 1965. Finally, a comparison of procurement records with spraying records found errors that suggested that additional spraying had taken place but gone unrecorded at the time. The new analyses led to revision of estimates of the amounts of the agents applied, as indicated in Table 3-1. The new research effort estimated that about 77 million liters were applied, about 9 million liters more than the previous estimate.

TABLE 3-1 Military Use of Herbicides in Vietnam (1961–1971)

Code Name	Chemical Constituents[a]	Concentration of Active Ingredient[a]	Years Used[a]	Amount Sprayed	
				VAO Estimate[b]	Revised Estimate[a]
Pink	60% *n*-butyl ester 40% isobutyl ester of 2,4,5-T	961–1,081 g/L acid equivalent	1961, 1965	464,817 L (122,792 gal)	50,312 L sprayed; 413,852 L additional on procurement records
Green	*n*-butyl ester of 2,4,5-T	—	1961, 1965	31,071 L (8,208 gal)	31,026 L on procurement records
Purple	50% *n*-butyl ester of 2,4-D, 30% *n*-butyl ester of 2,4,5-T, 20% isobutyl ester of 2,4,5-T	1,033 g/L acid equivalent	1962–1965	548,883 L (145,000 gal)	1,892,733 L
Orange	50% *n*-butyl ester of 2,4-D, 50% *n*-butyl ester of 2,4,5-T	1,033 g/L acid equivalent	1965–1970	42,629,013 L (11,261,429 gal)	45,677,937 L (could include Agent Orange II)
Orange II	50% *n*-butyl ester of 2,4-D, 50% isooctyl ester of 2,4,5-T	910 g/L acid equivalent	After 1968	—	Unknown; at least 3,591,000 L shipped
White	Acid weight basis: 21.2% triisopropanolamine salts of 2,4-D, 5.7% picloram	By acid weight, 240 g/L 2,4-D, 65 g/L picloram	1966–1971	19,860,108 L (5,246,502 gal)	20,556,525 L
Blue powder	Cacodylic acid (dimethylarsinic acid) sodium cacodylate	Acid, 65% active ingredient; salt, 70% active ingredient	1962–1964	—	25,650 L
Blue aqueous solution	21% sodium cacodylate + cacodylic acid to yield at least 26% total acid equivalent by weight	Acid weight, 360 g/L	1964–1971	4,255,952 L (1,124,307 gal)	4,715,731 L
Total, all formulations	—	—	—	67,789,844 L (17,908,238 gal)	76,954,766 L (including procured)

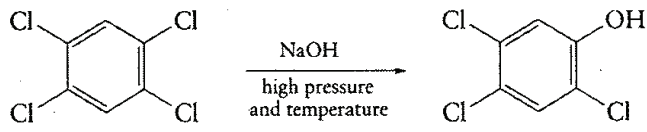
[a]Based on Stellman et al. (2003a).
[b]Based on data from MRI (1967), NRC (1974), and Young and Reggiani (1988).

Herbicides were identified by the color of a band on 55-gal shipping containers and were called Agent Pink, Agent Green, Agent Purple, Agent Orange, Agent White, and Agent Blue. Agent Green and Agent Pink were used in 1961 and 1965, and Agent Purple in 1962–1965. Agent Orange was used in 1965–1970, and a slightly different formulation (Agent Orange II) probably was used after 1968. Agent White was used in 1966–1971. Agent Blue was used in powder form in 1962–1964 and as a liquid in 1964–1971. Agent Pink, Agent Green, Agent Purple, Agent Orange, and Agent Orange II all contained 2,4,5-T and were contaminated to some extent with TCDD. Agent White contained 2,4-D and picloram. Agent Blue (powder and liquid) contained cacodylic acid. The chlorinated phenoxy acids 2,4-D and 2,4,5-T persist in soil for only a few weeks; picloram is much more stable, persisting in soil for years; and cacodylic acid is nonvolatile and stable in sunlight (NRC, 1974). More details on the herbicides used are presented in the initial IOM report, Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam (*VAO*; IOM, 1994).

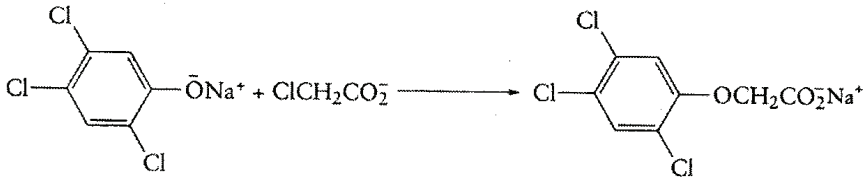
TCDD IN HERBICIDES USED IN VIETNAM

TCDD is formed during the manufacture of 2,4,5-T in the following manner: trichlorophenol (2,4,5-TCP), the precursor for the synthesis of 2,4,5-T, is formed by the reaction of tetrachlorobenzene and sodium hydroxide (Figure 3-1a); 2,4,5-T is formed when 2,4,5-TCP reacts with chloroacetic acid (Figure 3-1b); small amounts of TCDD are formed as a byproduct of the intended main reaction (Figure 3-1b) when a molecule of 2,4,5-TCP reacts with the tetrachlorobenzene stock (Figure 3-1c) instead of with chloroacetic acid. For each step in the reaction, a chlorine atom is replaced with an oxygen atom, and this leads to the final TCDD molecule (NRC, 1974). In the class of compounds known as polychlorinated dibenzo-*p*-dioxins (PCDDs), 75 congeners can occur, depending on the number and placement of the chlorine atoms. Cochrane et al. (1982) noted that TCDD had been found in pre-1970 samples of 2,4,5-TCP. Other PCDDs—2,7-dichloro-dibenzo-*p*-dioxin and 1,3,6,8-tetrachloro-dibenzo-*p*-dioxin—were measured in the same samples. The concentration of TCDD in any given lot of 2,4,5-T depended on the manufacturing process (FAO/UNEP, 2009; Young et al., 1976).

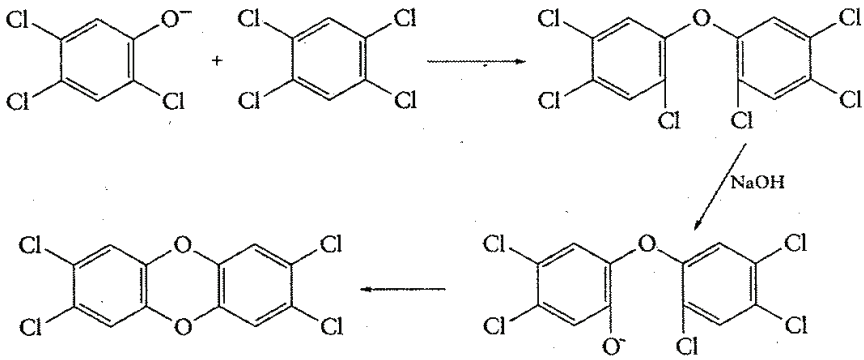
The manufacture of 2,4-D is a different process: its synthesis is based on dichlorophenol, a molecule formed from the reaction of phenol with chlorine (NZIC, 2009). Neither tetrachlorobenzene nor trichlorophenol is formed during this reaction, so TCDD is not normally a byproduct of the manufacturing process. However, other, less toxic PCDDs have been detected in pre-1970 commercial-grade 2,4-D (Cochrane et al., 1982; Rappe et al., 1978; Tosine, 1983). Cochrane et al. (1982) found multiple PCDDs in isooctyl ester, mixed butyl ester, and dimethylamine salt samples of 2,4-D. It has also been noted that cross-contamination of 2,4-D by 2,3,7,8-TCDD occurred in the operations of at least one major manufacturer (Lilienfeld and Gallo, 1989).



a. Trichlorophenol, the precursor for the synthesis of 2,4,5-T, is formed by the reaction of tetrachlorobenzene and sodium hydroxide (NaOH).



b. The herbicide 2,4,5-T is formed when a reactive form of trichlorophenol (2,4,5-trichlorophenoxide) reacts with chloroacetic acid.



c. TCDD is formed when a molecule of trichlorophenol reacts with its own precursor, tetrachlorobenzene. Two intermediate steps are shown in this diagram. At each step, an oxygen–carbon bond forms as a chlorine atom is released. This reaction does not occur in the synthesis of 2,4-D, because the precursors with adjacent chlorines are not used in its production.

FIGURE 3-1 TCDD formation during 2,4,5-T production.

TCDD concentrations in individual herbicide shipments were not recorded but were known to vary from batch to batch and between manufacturers. TCDD concentrations in stocks of Agent Orange remaining after the conflict, which either had been returned from South Vietnam or had been procured but not shipped, ranged from less than 0.05 ppm to almost 50 ppm and averaged 2–3 ppm in two sets of samples (NRC, 1974; Young et al., 1978). Comparable manufacturing standards for the domestic use of 2,4,5-T in 1974 required that TCDD not be present at over 0.05 ppm (NRC, 1974).

Data from Young and Gough were originally used to estimate the amount of TCDD in the various herbicide formulations (Gough, 1986; Young, 1992; Young et al., 1978). Young et al. (1978) estimated that Agent Green, Agent Pink, and Agent Purple—used early in the program (through 1965)—contained 16 times the mean TCDD content of the formulations used in 1965–1970, whereas mean TCDD concentrations in Agent Pink and Agent Green were estimated at 66 ppm. Gough (1986) estimated that about 167 kg of TCDD was sprayed in Vietnam over a 6-year period.

Later analysis by researchers at Columbia University benefited from access to military spray records that had not been available earlier and has resulted in substantial revisions of the estimates (Stellman et al., 2003a). The investigators were able to incorporate newly found data on spraying in the early period of the war (1961–1965) and to document that larger volumes of TCDD-containing herbicides were used in Vietnam than had been estimated previously. They also found the earlier estimates of TCDD contamination in the herbicide formulations to be low, noting that the original estimates were based on samples at the lower end of the distribution of concentration. They concluded that the mean TCDD concentration in Agent Orange was closer to 13 ppm than to the earlier estimate of 3 ppm. They therefore proposed 366 kg of TCDD as a plausible estimate of the total amount of TCDD applied in Vietnam during 1961–1971.

EXPOSURE OF VIETNAM VETERANS

Determination of exposures of US military personnel who served in Vietnam has been perhaps the greatest challenge in the study of health effects associated with herbicides and TCDD. Some military personnel stationed in cities or on large bases may have received little or no herbicide exposure, whereas troops who moved through defoliated areas soon after treatment may have been exposed through soil contact, drinking water, or bathing. Reliable estimates of the magnitude and duration of such exposures are not possible in most cases, given the lack of contemporaneous chemical measurements, the lack of a full understanding of the movement and behavior of the defoliants in the environment, and the lack of records of individual behaviors and locations. Consequently, most studies have focused on populations that had well-defined tasks that brought them into contact with the agents. It is believed that the subjects of those studies, primarily Air

Force personnel involved in fixed-wing aircraft spraying activities (often referred to as Operation Ranch Hand) and members of the US Army Chemical Corps (ACC), may have also had among the highest exposures. As described below, exposures of ground troops are difficult to define, so this group has not been as intensely studied. In accord with Congress's mandated presumption of herbicide exposure of all Vietnam veterans, VAO committees have treated Vietnam-veteran status as a proxy for some herbicide exposure when no more specific exposure information is available.

Exposure of Herbicide Handlers

Military personnel who came into direct contact with the herbicidal chemicals through mixing, loading, spraying, and clean-up activities had relatively high exposures to them. The US Environmental Protection Agency refers to such personnel as pesticide handlers and provides special guidance for preventing or minimizing their exposure during those activities in its worker-protection standard for pesticides (EPA, 1992). The number of US military personnel who handled herbicides directly is not known precisely, but two groups have been identified as high-risk subpopulations among veterans: Air Force personnel involved in Operation Ranch Hand and members of the ACC who used hand-operated equipment and helicopters to conduct smaller-scale operations, including defoliation around special-forces camps; clearing the perimeters of airfields, depots, and other bases; and small-scale crop destruction (NRC, 1980; Thomas and Kang, 1990; Warren, 1968). Additional units and individuals handled or sprayed herbicides around bases or lines of communication; for example, Navy river patrols were reported to have used herbicides to clear inland waterways, and engineering personnel used herbicides to remove underbrush and dense growth in constructing fire-support bases. The latter groups have not been the subject of epidemiologic studies. The herbicides used in Vietnam were not considered to present an important human health hazard at that time, so few precautions were taken to prevent exposure of personnel (GAO, 1978, 1979); that is, military personnel did not typically use chemical-protective gloves, coveralls, or protective aprons, so substantial skin exposure almost certainly occurred in these populations in addition to exposure by inhalation and incidental ingestion (such as by hand-to-mouth contact).

The Air Force personnel who participated in Operation Ranch Hand were the first Vietnam-veteran population to receive special attention with regard to herbicide exposure. In the Air Force Health Study (AFHS), job and work history, biomarkers, and health outcomes of members of this Ranch Hand cohort were contrasted with Air Force personnel who had served elsewhere in Southeast Asia during the Vietnam era. The AFHS began in 1979 (IOM, 2006). The exposure index initially proposed relied on military spray records for the TCDD-containing herbicides (Agent Orange, Agent Purple, Agent Pink, and Agent Green), which also helped to identify the members of the cohort. The subjects were further char-

acterized by military occupation, and exposure in the cohort and the comparison group was evaluated through measurement of TCDD in blood (serum) samples drawn in 1987 or later. A general increase in serum TCDD was detected in people whose jobs involved more frequent handling of herbicides, but there was no clear demarcation between the distributions of serum TCDD concentrations in the Ranch Hand subjects and those in the comparison group (AFHS, 1991). Several methods for estimating herbicide exposure of members of the cohort were developed on the basis of questionnaires and focused on such factors as number of days of skin exposure, percentage of skin area exposed, and the concentration of TCDD in the different herbicidal formulations (Michalek et al., 1995). Most recent analyses of the AFHS data have relied on serum TCDD concentration as the primary exposure metric for epidemiologic classification (Kern et al., 2004; Michalek et al., 2001, 2003; Pavuk et al., 2003). IOM has issued a comprehensive review of the AFHS with recommendations for the use of the extensive data collected in the project (IOM, 2006).

Members of the ACC performed herbicide-spraying operations on the ground and by helicopter and were thereby involved in the direct handling and distribution of Agent Orange and other herbicides in Vietnam. They were identified for detailed study of health effects related to herbicide exposure only in the late 1980s (Thomas and Kang, 1990). An initial feasibility study recruited Vietnam veterans and nondeployed Vietnam-era veterans from within the ACC (Kang et al., 2001). Blood samples collected from 50 Vietnam veterans in 1996 showed an association between those who reported spraying herbicides and higher serum TCDD concentrations; this finding was confirmed in a follow-up study of a larger fraction of the cohort (Kang et al., 2006).

Exposure of Ground Troops

In light of the widespread use of herbicides in Vietnam for many years, it is reasonable to assume that many military personnel were inadvertently exposed to the chemicals of concern. Surveys of Vietnam veterans who were not part of the Ranch Hand or ACC groups have indicated that 25–55% believe that they were exposed to herbicides (CDC, 1989a). That view has been supported by government reports (GAO, 1979) and reiterated by veterans and their representatives in testimony to the VAO committees over the past several years.

Numerous attempts were made in the 1980s to characterize herbicide exposures of people who served as ground troops in Vietnam (CDC, 1988; Erickson et al., 1984; NRC, 1982; Stellman and Stellman, 1986; Stellman et al., 1988). The efforts combined self-reports of contact with herbicides or military service records with aerial-spray data to produce an "exposure opportunity index" (EOI). For example, Erickson et al. (1984) created five exposure categories based on military records to examine the risks of birth defects among the offspring of veterans. Those studies were conducted carefully and provided reasonable estimates

based on available data, but no means of testing the validity of the estimates were available at the time.

The search for a validation method led to the development of exposure biomarkers in veterans. Initial studies measured concentrations of dioxin in adipose tissue of veterans (Gross et al., 1984; Schecter et al., 1987). A study sponsored by the New Jersey Agent Orange Commission was the first to link dioxin concentrations in adipose tissue to dioxin concentrations in blood (Kahn et al., 1988). At the same time, the Centers for Disease Control (now the Centers for Disease Control and Prevention) undertook what came to be called the Agent Orange Validation Study, measuring TCDD in the serum portion of blood from a relatively large sample of Vietnam veterans and veterans who served elsewhere during the Vietnam era (CDC, 1989b). The study did not find a statistically significant difference in mean serum TCDD concentrations between the groups. A review of a preliminary report of the work by an advisory panel established through IOM concluded that the long lag between exposure and the serum measurements (about 20 years) called into question the accuracy of exposure classification based on serum concentrations. The panel concluded that estimates based on troop locations and herbicide-spraying activities might be more reliable indicators of exposure than serum measurements (IOM, 1987).

The report of the first *VAO* committee (IOM, 1994) proposed further work on exposure reconstruction and development of a model that could be used to categorize exposures of ground troops. The committee cautioned that serum TCDD measurements not be regarded as a "gold standard" for exposure, that is, as a fully accurate measure of herbicide exposure. Efforts to develop exposure-reconstruction models for US Vietnam veterans are discussed later in this chapter.

One other effort to reconstruct exposure has been reported by researchers in the Republic of Korea who developed an exposure index for Korean military personnel who served in Vietnam (Kim et al., 2001, 2003). The exposure index was based on herbicide-spray patterns in military regions in which Korean personnel served during 1964–1973, time–location data on the military units stationed in Vietnam, and an exposure score derived from self-reported activities during service. The researchers were not successful in an attempt to validate their exposure index with serum dioxin measurements.

Exposure of Personnel Who Had Offshore Vietnam Service

US Navy riverine units are known to have used herbicides while patrolling inland waterways (IOM, 1994; Zumwalt, 1993), and it is generally acknowledged that estuarine waters became contaminated with herbicides and dioxin as a result of shoreline spraying and runoff from spraying on land. Thus, military personnel who did not serve on land were among those exposed to the chemicals during the Vietnam conflict. In recent years, concern about dioxin exposure via drinking water has arisen among personnel who served offshore but within the territorial

limits of the Republic of Vietnam on ships that converted seawater to drinking water through distillation. Since the last VAO update, NAS convened the Blue Water Navy Vietnam Veterans and Agent Orange Exposure Committee to address that specific issue; its recently released report (IOM, 2011) found that information to determine the extent of exposure experienced by Blue Water Navy personnel was inadequate, but that there were possible routes of exposure.

EXPOSURE OF THE VIETNAMESE POPULATION

As summarized by Constable and Hatch (1985), Vietnamese researchers have made a number of attempts to characterize the herbicide exposure of residents of Vietnam in the process of trying to assess adverse reproductive outcomes. Some compared residents of the South with residents of the unsprayed North, and others endeavored to compare South Vietnamese people who lived in sprayed and unsprayed villages, as determined by observed defoliation. For evaluating reproductive outcomes, pregnancy outcomes of North Vietnamese women married to veterans who served in South Vietnam were compared with those of women whose husbands had not. In some cases, records of herbicide spraying have been used to refine exposure measurements. In assessing infant mortality, Dai et al. (1990) considered village residents to have been exposed if a herbicide mission had passed within 10 km of the village center and further classified exposure by length of residence in a sprayed area and the number of times that the area reportedly had been sprayed.

A small number of studies have provided information on TCDD concentrations in Vietnamese civilians exposed during the war (Schecter et al., 1986, 2002, 2006). Dwernychuk et al. (2002) emphasized the need to evaluate dioxin contamination around former air bases in Vietnam. They collected environmental and food samples, human blood, and breast milk from residents of the Aluoi Valley of central Vietnam. The investigators identified locations where relatively high dioxin concentrations remained in soil or water systems. Soil dioxin concentrations were particularly high around former airfields and military bases where herbicides were handled. Fish harvested from ponds in those areas were found to contain high dioxin concentrations. More recently, Dwernychuk (2005) elaborated on the importance of "hot spots" as important locations for future studies and argued that herbicide use at former US military installations was the most likely cause of the hot spots. The Bien Hoa Air Base, considered a hot spot because of the use of chemical defoliants around the base, was the focus of a study examining dioxin contamination in soils in Vietnam (Mai et al., 2007). The study found high soil concentrations but did not involve estimation of the exposure of people who lived in the vicinity of the bases.

Since *Update 2008*, there has been an increase in the number of publications reporting mostly environmental concentrations of dioxins in various areas throughout Vietnam (Brodsky et al., 2009; Feshin et al., 2008; Hatfield

Consultants, 2009a,b,c; Nhu et al., 2009; Saito et al., 2010). Taken as a whole, those studies suggest a pervasive exposure to dioxins—not limited to hot spots—through environmental media throughout the country more than a half-century after they were initially deposited.

The above studies are not directly relevant to this committee's task, but they may prove useful in future epidemiologic studies of the Vietnamese population and in the development of risk-mitigation policies.

MODELS FOR CHARACTERIZING HERBICIDE EXPOSURE

IOM, following up on the recommendations contained in the original *VAO* report (IOM, 1994), issued a request for proposals seeking individuals and organizations to develop historical exposure-reconstruction approaches suitable for epidemiologic studies of herbicide exposure of US veterans during the Vietnam War (IOM, 1997). The request resulted in the project Characterizing Exposure of Veterans to Agent Orange and Other Herbicides in Vietnam. The project was carried out under contract by a team of researchers in Columbia University's Mailman School of Public Health. The Columbia University project integrated various sources of information concerning spray activities and information on location of military units assigned to Vietnam, all compiled into a database, to generate individualized estimates of the exposure potential of troops serving in Vietnam (Stellman and Stellman, 2003).

"Mobility-factor" analysis, a new concept for studying troop movement, was developed for use in reconstructing herbicide-exposure histories. The analysis is a three-part classification system for characterizing the location and movement of military units in Vietnam. It comprises a mobility designation (stable or mobile), a distance designation (usually in kilometers) to indicate how far a unit might travel in a day, and a notation of the modes of travel available to the unit (by air, by water, or on the ground by truck, tank, or armored personnel carrier). A mobility factor was assigned to every unit that served in Vietnam.

The data were combined into a geographic information system (GIS) for Vietnam. Herbicide-spraying records were integrated into the GIS and linked with data on military-unit locations to permit estimation of individual exposure-opportunity scores. The results are the subject of reports by the contractor (Stellman and Stellman, 2003) and the Committee on the Assessment of Wartime Exposure to Herbicides in Vietnam (IOM, 2003a,b). A summary of the findings on the extent and pattern of herbicide spraying (Stellman et al., 2003a), a description of the GIS for characterizing exposure to Agent Orange and other herbicides in Vietnam (Stellman et al., 2003b), and an explanation of the exposure-opportunity models based on that work (Stellman and Stellman, 2004) have been published in peer-reviewed journals. The publications have argued that it is feasible to conduct epidemiologic investigations of veterans who served as ground troops during the Vietnam War. IOM later issued a report that examined the feasibility

of using the Agent Orange Reconstruction Model developed by Columbia University (IOM, 2008). The report concluded that "despite the shortcomings of the exposure assessment model in its current form and the inherent limitations in the approach, the committee agreed that the model holds promise for supporting informative epidemiologic studies of herbicides and health among Vietnam veterans and that it should be used to conduct studies."

A different perspective has been put forth by Young and colleagues in a series of papers (Young et al., 2004a,b). They have argued that ground troops had little direct contact with herbicide sprays and that TCDD residues in Vietnam had low bioavailability. Those conclusions were based on analyses of previously unpublished military records and environmental-fate studies. They have also argued that direct exposures of ground troops were relatively low because herbicide-spraying missions were carefully planned, and spraying occurred only when friendly forces were not in the target area.

Since *Update 2008*, a pair of industry-sponsored papers that used a mathematical model of herbicide dispersion and deposition from aerial spraying concluded that actual ground deposition of Agent Orange was many orders of magnitude lower than that predicted by previous exposure estimations proposed for use in evaluating ground-troop health effects (Ginevan et al., 2009a,b). The new papers first undertook a quantitative evaluation of the Stellman EOI model (Stellman and Stellman, 2004; Stellman et al., 2003a,b) recommended for possible use in an epidemiologic evaluation of ground troops by IOM (2008). The new evaluation revealed frequent and substantial inconsistencies in the calculated EOI based in part on the use of a central equation "contrary to a large body of pesticide exposure assessment practice," the general imprecision of spray-flight path records, the use of 1.2-km^2 exposure cells in the model, and "unknown computational errors" in the model. The analyses demonstrated unexpected and unexplained 1,000-fold differences in model output for sample flight paths that appear to be in all respects equivalent. The authors propose the use of the AgDRIFT Tier III model as a more accurate and appropriate estimator of ground-troop potential exposures. That model uses a combination of standard Lagrangian and Gaussian techniques in combination with empirically derived information, such as aerosol penetration through a forest canopy, to estimate ground-level exposure. The AgDRIFT Tier III model is purportedly validated and used by the US Forest Service to plan aerial application of various agents to forests. The AgDRIFT model predicts a much smaller area of impact under the spray path and Agent Orange concentrations lower by several orders of magnitude than the EOI estimates for the same set of sample flight paths. That effect is particularly pronounced at points distant from the spray path; the AgDRIFT model predicts Agent Orange exposures up to 20 orders of magnitude lower than the EOI model at a point 4 km away from the flight-path centerline. Finally, the authors point out that the use of any exposure model for ground troops will be severely limited by the imprecision of spatial and temporal measures of troop movements.

Exposure assessment of human populations is difficult. It is most reliable in situations in which there is a single or predominant source of contamination or a single route of exposure that occurs over a short period, such as the atomic bomb studies used to assess the health effects of radiation exposure. Accurate and reliable assessment is far more problematic in situations with multiple dispersed sources of contamination or multiple routes of exposure that occur over an extended period many years in the past. Exposure-assessment studies for the Ranch Hand and ACC cohort studies approach the former scenario in their relative simplicity and ease. Nonetheless, attempts to quantify exposures to date, even at the level of serum biomarkers of exposure, have been less than satisfactory. In the case of ground troops, which more nearly approaches the latter scenario, few studies have characterized exposure beyond "in-theater" vs "not-in-theater" comparisons. Considerable work has been done by National Academies committees and others to develop ground-troop exposure assessments based on numbers, patterns, and timing of aerial spray missions combined with troop-location information.

Although previously recommended by earlier VAO committees, the Stellman model has not yet been applied in a study evaluating the health of ground troops. The focus on aerial spraying as the primary exposure, however, may be misplaced. To ascribe a health effect to an exposure in an epidemiologic study accurately, one must account for *all* sources and routes of exposure—a concept now popularly termed total exposure assessment. In the Vietnam theater, there were undoubtedly multiple sources and routes of TCDD exposure of ground troops other than being directly under an aerial-spray mission. The relative magnitudes of those sources and whether the aerial spray route predominated are unknown and now probably unknowable. For instance, troops in the field commonly collected drinking water from streams. Some of those streams are still highly polluted with TCDD. Although the ultimate source of the TCDD in the streams may have been aerial spraying, the concentration of TCDD in the water would not necessarily be correlated with spray mission exposure estimates and could conceivably far exceed the "direct exposure" estimates, depending on the terrain, rainfall, timing of water collection, and other unknown factors. The dynamic nature of TCDD released into the environment is largely unknown quantitatively, so an exposure assessment that accounts for all sources of TCDD exposure is impossible. In addition, an assessment of total exposure must include an understanding of coexposures that could confound TCDD exposure analyses or otherwise directly account for an observed health effect. Studies have not factored coexposures into health risk estimates.

METHODOLOGIC ISSUES IN EXPOSURE ASSESSMENT

Analyses of Vietnam-veteran studies have been an important source of information for understanding associations between the herbicides used in Vietnam and specific health outcomes, but, as discussed in Chapter 2, the committee has

extended its review of the scientific literature to other populations in which exposure could be estimated with greater accuracy. Those populations are discussed in detail in Chapter 5. We focus here on several key methodologic issues that complicate development of accurate estimates of exposure of the Vietnam-veteran population and the other study populations discussed in this report: the latent period between exposure and disease, exposure misclassification, and exposure specificity.

Latency

The temporal relationship between exposure and disease is complex and often difficult to define in studies of human populations. Many diseases do not appear immediately after exposure. Cancer, for example, might not appear for many years after exposure. The time between a defined exposure period and the occurrence of disease is often referred to as a latent period (IOM, 2004). Exposures can be brief (sometimes referred to as acute exposures) or protracted (sometimes referred to as chronic exposures). At one extreme, an exposure can be the result of a single event, as in an accidental poisoning. At the other extreme, a person exposed to a chemical that is stored in the body may continue to experience "internal exposure" for years even if exposure from the environment has ceased. The definition of the proper timeframe for duration of exposure constitutes a challenge to exposure scientists.

Misclassification

Exposure misclassification in epidemiologic studies can affect estimates of risk. A typical situation is in a case–control study in which the reported measurement of exposure of either group or both groups can be misclassified. The simplest situation to consider is one in which the exposure is classified into just two levels, for example, ever vs never exposed. If the probability of exposure misclassification is the same in cases and controls (that is, nondifferential), it can be shown that the estimated association between disease and exposure is biased toward the null value; in other words, one would expect the true association to be stronger than the observed association. However, if the probability of misclassification is different between cases and controls, bias in the estimated association can occur in either direction, and the true association might be stronger or weaker than the observed association.

The situation in which exposure is classified into more than two levels is somewhat more complicated. Dosemeci et al. (1990) have demonstrated that in that situation the slope of a dose–response trend is not necessarily attenuated toward the null value even if the probability of misclassification is the same in the two groups of subjects being compared; the observed trend in disease risk across the several levels of exposure may be either an overestimate or an underestimate

of the true trend in risk. Greenland and Gustafson (2006) have discussed the effect of exposure misclassification on the statistical significance of the result, demonstrating that if one adjusts for exposure misclassification when the exposure is represented as binary (for example, ever vs never exposed), the resulting association is not necessarily more significant than in the unadjusted estimate. That result remains true even though the observed magnitude of the association (for example, the relative risk) might be increased.

Specificity

Incorporation of findings of studies of persons exposed to components of the herbicides sprayed in Vietnam requires some decisions about their relative contributions to the VAO project's evidentiary database. Only a few herbicidal chemicals were used as defoliants during the Vietnam conflict: esters and salts of 2,4-D and 2,4,5-T, cacodylic acid, and picloram in various formulations. Many scientific studies reviewed by the committee report exposures to broad categories of chemicals rather than to those specific chemicals. The categories are presented in Table 3-2 with their relevance to the committee's charge. The information in Tables 3-2 and 3-3 represents the committee's current thinking with respect to their relevance and has helped to guide its evaluation of epidemiologic studies. Earlier VAO committees did not address the issue of exposure specificity in exactly this manner. The committee for *VAO* and the first several updates gave more weight to results based solely on job title (for example, "farmer" with no additional information) than have the committees for the last three updates but entirely excluded findings from the Yusho and Yucheng polychlorinated biphenyl (PCB) poisonings, whereas recent committees have factored in results that are now more commonly expressed in terms of individual dioxin-like PCB congeners.

Many studies have examined the relationship between exposure to "pesticides" and adverse health outcomes, and others have used the category of "herbicides" without identifying specific chemicals. A careful reading of a scientific report often reveals that none of the chemicals of interest (those used in Vietnam, as delineated above) contributed to the exposures of the study population, so such studies could be excluded from consideration. But in many cases, the situation is more ambiguous. For example, reports that define exposure in the broad category of "pesticides" with no further information have little relevance to the committee's charge to determine associations between exposures to herbicides used in Vietnam and adverse health outcomes. Reports that define exposure in the more restricted category of "herbicides" are of greater relevance but are of little value unless it is clear from additional information that exposure to one or more of the herbicides used in Vietnam occurred in the study population—for example, if the published report indicates that the chemicals of interest were among the pesticides or herbicides used by the study population, the lead author of a published

TABLE 3-2 Current Committee Guidance for the Classification of Exposure Information in Epidemiologic Studies That Focus on the Use of Pesticides or Herbicides, and Relevance of the Information to the Committee's Charge to Evaluate Exposures to 2,4-D and 2,4,5-T (Phenoxy Herbicides), Cacodylic Acid, and Picloram

Specificity of Exposure Reported in Study	Additional Information	Relevance to Committee's Charge
Pesticides	Chemicals of interest were not used, or there was no additional information	Not relevant
	Chemicals of interest were used	Limited relevance
Herbicides	Chemicals of interest were not used	Not relevant
	There was no additional information	Limited relevance
	Chemicals of interest were used	Relevant
Phenoxy herbicides	—	Highly relevant
2,4-D or 2,4,5-T	—	Highly relevant
Cacodylic acid[a]	—	Highly relevant
Picloram	—	Highly relevant

[a]None of the epidemiologic studies reviewed by the committee to date has specified exposure to cacodylic acid.

TABLE 3-3 Current Committee Guidance for the Classification of Exposure Information in Epidemiologic Studies That Focus on Exposure to Dioxin-like Chemicals and Relevance of the Information to the Committee's Charge

Specificity of Exposure Reported in Study	Additional Information	Relevance to Committee's Charge
Dioxin-like chemicals	Exposure to PCBs or polychlorinated dibenzofuron (PCDF)	Limited relevance
Dioxin-like chemicals	Results expressed in terms of (total) toxic equivalents (TEQs) or concentrations of individual congeners recognized as having dioxin-like activity[a]	Highly relevant
TCDD or mixture of PCDDs	Established on the basis of environmental sampling or work histories	Highly relevant
TCDD or mixture of PCDDs	Concentrations in tissues of a subset of participants (preferably soon after exposure)	Very highly relevant
TCDD or mixture of PCDDs	Concentrations in tissues of individual participants (preferably soon after exposure)	Most informative

[a]The values of toxic equivalency factors for individual dioxin-like chemicals, which are weighted by concentration and summed to derive TEQs are presented in Table 4-2.

report has been contacted and has indicated that the chemicals of interest were among the chemicals used, the chemicals of interest are used commonly for the crops identified in the study, or the chemicals of interest are used commonly for a specific purpose, such as removal of weeds and shrubs along highways.

Among the various chemical classes of herbicides that have been identified in published studies reviewed by the committee, phenoxy herbicides, particularly 2,4-D and 2,4,5-T, are directly relevant to the exposures experienced by US military forces in Vietnam. On the basis of the assumption that compounds with similar chemical structure may have analogous biologic activity, information on the effects of other chemicals in the phenoxy herbicide class—such as Silvex, 2-methyl-4-chlorophenoxyacetic acid, 2-(2-methyl-4-chlorophenoxy) propionic acid (Mecoprop), and dicamba—has been factored into the committee's deliberations with somewhat less weight. The very few epidemiologic findings on exposure to picloram or cacodylic acid have been regarded as highly relevant. The committee has decided to include many studies that report on unspecified herbicides in their health-effects sections, and their results have been entered into the health-outcome–specific tables; however, these studies tend to contribute little to the evidence considered by the committee. The many studies that provide chemical-specific exposure information are believed to be far more informative for the committee's purposes.

A similar issue arises in the evaluation of studies that document exposure to dioxin-like compounds. Most "dioxin" studies reviewed by the committee have focused on TCDD, but TCDD is only one of a number of PCDDs. The committee recognizes that in real-world conditions exposure to TCDD virtually never occurs in isolation and that there are hundreds of similar compounds to which humans might be exposed, including other PCDDs, polychlorinated dibenzofurans (PCDFs), and PCBs. Exposure to TCDD is almost always accompanied by exposure to one or more of the other compounds. The literature on the other compounds, particularly PCBs, has not been reviewed systematically by the committee unless TCDD was identified as an important component of the exposure or the risks of health effects were expressed in terms of toxicity equivalent quotients (TEQs), which are the sums of toxicity equivalency factors for individual dioxin-like compounds as measured by activity with the aryl hydrocarbon receptor (AHR). The committee took that approach for two reasons. First, exposure of Vietnam veterans to substantial amounts of the other chemicals, relative to exposure to TCDD has not been documented. Second, the most important mechanism for TCDD toxicity involves its ability to bind to and activate the AHR. Many of the other chemicals act by different or multiple mechanisms, so it is difficult to attribute toxic effects after such exposures specifically to TCDD. Furthermore, people's environmental exposures to dioxin-like chemicals and their non–dioxin-like counterparts are to mixtures of components that tend to be correlated, so it is not surprising that specific chemicals measured in a person's serum also tend to be correlated; this means that it will be difficult for epidemiologic

studies to attribute any observed association to a particular chemical configuration (Longnecker and Michalek, 2000). Analyses in terms of TEQs circumvent that problem to some extent.

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4

Information Related to Biologic Plausibility

The committee reviewed all relevant experimental studies of 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), 4-amino-3,5,6-trichloropicolinic acid (picloram), dimethylarsinic acid (DMA, also called cacodylic acid), and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) that have been published since *Update 2008* (IOM, 2009) and has incorporated the findings, when it was appropriate, into this chapter or into the biologic-plausibility sections of Chapters 6–11 when they are of consequence for particular health outcomes. For each substance, this chapter includes a review of toxicokinetic properties, a brief summary of the toxic outcomes investigated in animal experiments, and a discussion of underlying mechanisms of action as illuminated by in vitro studies. In addition, the final section of this chapter presents two newly emerging subjects of molecular and biologic science that provide novel insight into potential mechanisms of xenobiotic-induced disease and may increase the biologic plausibility of the toxic actions of herbicides sprayed in Vietnam.

Establishment of biologic plausibility through laboratory studies strengthens the evidence of a cause–effect relationship between herbicide exposure and health effects reported in epidemiologic studies and thus supports the existence of the less stringent relationship of association, which is the target of this committee's work. Experimental studies of laboratory animals or cultured cells allow observation of effects of herbicide exposure under highly controlled conditions, which is difficult or impossible to achieve in epidemiologic studies. Such conditions include frequency and magnitude of exposure, exposure to other chemicals, preexisting health conditions, and genetic differences between people, all of which can be controlled in a laboratory animal study.

Once a chemical contacts the body, it begins to interact through the processes

of absorption, distribution, metabolism, and excretion. Those four biologic processes characterize the disposition of a foreign substance that enters the organism. Their combination determines the concentration of the chemicals in the body and how long each organ is exposed to it and thus influences its toxic or pharmacologic activity.

Absorption is the entry of a substance into an organism, normally by uptake into the bloodstream via mucous surfaces, such as the intestinal walls of the digestive tract during ingestion. Low solubility, chemical instability in the stomach, and inability to permeate the intestinal wall can all reduce the extent to which a substance is absorbed after being ingested. The solubility of a chemical in fat and its hydrophobicity influence the pathways by which it is absorbed and its relative potential to be metabolized (structurally transformed) and ultimately whether it persists in the body or is excreted. Absorption is a critical determinant of a chemical's bioavailability, that is, the fraction of it that reaches the systemic circulation. In addition to ingestion routes of exposure experienced by free-ranging humans are inhalation (entry via the airways) and dermal exposure (entry via the skin). Animal studies may involve additional routes of exposure that are not ordinarily encountered by humans, such as intravenous or intraperitoneal injection, in which a chemical is injected into the bloodstream or abdominal cavity, respectively.

Distribution refers to the travel of a substance from the site of entry to the tissues and organs where they will have their ultimate effect or be sequestered. Distribution takes place most commonly via the bloodstream.

Metabolism is the breaking down that all substances begin to experience as soon as they enter the body. Most metabolism of foreign substances takes place in the liver by the action of a number of enzymes, including cytochrome P-450s, which catalyze the oxidative metabolism of many chemicals. As metabolism occurs, the initial (parent) chemical is converted to new chemicals called metabolites, which are often more water-soluble (polar) and thus more readily excreted. When metabolites are pharmacologically or toxicologically inert, metabolism deactivates the administered dose of the parent chemical, reducing its effects on the body. Metabolism may activate a chemical to a metabolite that is more potent or more toxic than it is.

Excretion, also referred to as elimination, is the removal of substances or their metabolites from the body, most commonly in urine or feces. The relative rate of excretion of a chemical from the body is often limited by the rate of metabolism of the parent chemical into more water soluble, readily excreted metabolites. Excretion is often incomplete, especially in the case of chemicals that resist metabolism, and incomplete excretion results in the accumulation of foreign substances that can adversely affect biologic functions.

The routes and rates of absorption, distribution, metabolism, and excretion of a toxic substance collectively are termed toxicokinetics (or pharmacokinetics). Those processes determine the amount of a particular substance or metabolite that reaches specific organs or cells and that persists in the body. Understanding the toxicokinetics of a chemical is important for valid reconstruction of exposure

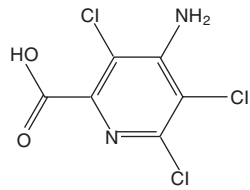
of humans and for assessing the risk of effects of a chemical. The principles involved in toxicokinetics are similar among chemicals, although the degree to which different processes influence the distribution depends on the structure and other inherent properties of the chemicals. Thus, the lipophilicity or hydrophobicity of a chemical and its structure influence the pathways by which it is metabolized and whether it persists in the body or is excreted. The degree to which different toxicokinetic processes influence the toxic potential of a chemical depends on metabolic pathways, which often differ among species. For that reason, attempts at extrapolation from experimental animal studies to human exposures must be extremely careful.

Many chemicals were used by the US armed forces in Vietnam. The nature of the substances themselves was discussed in more detail in Chapter 6 of the original *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* (*VAO*) report (IOM, 1994). Four herbicides documented in military records were of particular concern and are examined here: 2,4-D, 2,4,5-T, picloram, and cacodylic acid. This chapter also examines TCDD, the most toxic congener of the tetrachlorodibenzo-*p*-dioxins (tetraCDDs), also commonly referred to as dioxin, a contaminant of 2,4,5-T, because its potential toxicity is of concern. Considerably more information is available on TCDD than on the herbicides themselves. Other contaminants present in 2,4-D and 2,4,5-T are of less concern. Except as noted, the laboratory studies of the chemicals of concern used pure compounds or formulations; the epidemiologic studies discussed in later chapters often tracked exposures to mixtures.

PICLORAM

Chemistry

Picloram (Chemical Abstracts Service Number [CAS No.] 1918-02-1; see chemical structure in Figure 4-1) was used with 2,4-D in the herbicide formulation Agent White, which was sprayed in Vietnam. It is also used commonly in Australia in a formulation with the trade name Tordon 75D®. Tordon 75D



4-amino-3,5,6-trichloropicolinic acid

FIGURE 4-1 Structure of picloram.

contains several chemicals, including 2,4-D, picloram, a surfactant diethyleneglycolmonoethyl ether, and a silicone defoamer. A number of studies of picloram used such mixtures as Tordon or other mixtures of 2,4-D and picloram that are similar to Agent White.

Toxicokinetics

The original *VAO* committee reviewed studies of the toxicokinetics of picloram. Studies of animals showed rapid absorption through the gastrointestinal tract and rapid elimination of picloram as the unaltered parent chemical in urine. Nolan et al. (1984) examined the toxicokinetics of picloram in six healthy male volunteers who were given single oral doses of 0.5 or 5.0 mg/kg and a dermal dose of 2.0 mg/kg. Picloram was rapidly absorbed in the gavage study and rapidly excreted unchanged in urine. More than 75% of the dose was excreted within 6 hours, and the remainder with an average half-life of 27 hours. On the basis of the quantity of picloram excreted in urine in the skin study, the authors noted that only 0.2% of the picloram applied to the skin was absorbed. Because of its rapid excretion, picloram has low potential to accumulate in humans.

In general, the literature on picloram toxicity continues to be sparse. Studies of humans and animals indicate that picloram is rapidly eliminated as the parent chemical. Studies of animals have indicated that picloram is sparingly toxic at high doses.

Toxicity Profile

The original *VAO* committee reviewed studies of the carcinogenicity, genotoxicity, acute toxicity, chronic systemic toxicity, reproductive and developmental toxicity, and immunotoxicity of picloram. In general, there is limited evidence on cancer in some rodent models but not in other species (NCI, 1978). In those studies, there was some concern that contaminants in the picloram (in particular, hexachlorobenzene) might be responsible for the carcinogenicity. Thus, picloram has not been established as a chemical carcinogen.

There is also no evidence, on the basis of studies conducted by the Environmental Protection Agency (EPA, 1988c), that picloram is a genotoxic agent. Picloram is considered a mild irritant; erythema is seen in rabbits only at high doses. The available information on the acute toxicity of picloram is also paltry. Some neurologic effects—including hyperactivity, ataxia, and tremors—were reported in pregnant rats exposed to picloram at 750 or 1,000 mg/kg (Thompson et al., 1972).

Chronic Systemic Toxicity

Several studies have reported various effects of technical-grade picloram on the livers of rats. In the carcinogenicity bioassay conducted by Stott and col-

leagues (1990), treatment-related hepatomegaly, hepatocellular swelling, and altered tinctorial properties in the central regions of the liver lobules were noted in the groups exposed at 60 and 200 mg/kg per day. In addition, males and females exposed at the high dose had higher liver weights than controls. The no-observed-effect level (NOEL) was 20 mg/kg per day, and the lowest observed-effect level was 60 mg/kg per day for histologic changes in centrilobular hepatocellular tissues. According to the Environmental Protection Agency (EPA), hexachlorobenzene (at 197 ppm) was probably not responsible for the hepatic effects (EPA, 1988c). Gorzinski and colleagues (1987) also reported a dose-related increase in liver weights, hepatocellular hypertrophy, and changes in centrilobular tinctorial properties in male and female F344 rats exposed to picloram at 150 mg/kg per day and higher in the diet for 13 weeks. In a 90-day study, cloudy swelling in the liver cells and bile duct epithelium occurred in male and female F344 rats given 0.3% or 1.0% technical picloram in the diet (EPA, 1988c). Hepatic effects have also been reported in dogs exposed to picloram: increased liver weights were reported in beagles that received 35 mg/kg per day or more in the diet for 6 months (EPA, 1988c). No other effects of chronic exposure to picloram have been reported.

Reproductive and Developmental Toxicity

The reproductive toxicity of picloram was evaluated in a two-generation study; however, too few animals were evaluated, and no toxicity was detected at the highest dose tested, 150 mg/kg per day (EPA, 1988c). Some developmental toxicity was produced in rabbits exposed to picloram by gavage at 400 mg/kg per day on days 6–18 of gestation. Fetal abnormalities included single-litter incidences of forelimb flexure, fused ribs, hypoplastic tail, and omphalocele (John-Greene et al., 1985). Some maternal toxicity was observed at that dose, however, and EPA concluded on the basis of the low-litter incidence of the findings that the malformations were not treatment-related (EPA, 1988c). No teratogenic effects were produced in the offspring of rats given picloram by gavage at up to 1,000 mg/kg per day on days 6–15 of gestation, although the occurrence of bilateral accessory ribs was significantly increased (Thompson et al., 1972).

Immunotoxicity

Studies of the potential immunotoxicity of picloram included dermal sensitization and rodent immunoassays. In one study, 53 volunteers received nine 24-hour applications of 0.5 mL of a 2% potassium picloram solution on the skin of both upper arms. Each volunteer received challenge doses 17–24 days later. The formulation of picloram (its potassium salt) was not a skin sensitizer or an irritant (EPA, 1988c). In a similar study, a 5% solution of picloram (M-2439, Tordon 101 formulation) produced slight dermal irritation and a sensitization response in 6 of the 69 volunteers exposed. When the individual components of

M-2439—picloram, triisopropanolamine (TIPA) salt, and 2,4-D TIPA salt—were tested separately, no sensitization reaction occurred (EPA, 1988c). Tordon K+, but not technical-grade picloram, was also found to be a skin sensitizer in guinea pigs (EPA, 1988c). CD1 mice exposed to Tordon 202C (94% 2,4-D and 6% picloram) had no consistent adverse effects on antibody responses (Blakley, 1997), but the lack of a consistent response may be due to the fact that CD1 mice are outbred.

Mechanisms

No well-characterized mechanisms of toxicity for picloram are known.

CACODYLIC ACID

Chemistry

Arsenic (As) is a naturally occurring element that exists in a trivalent form (As^{+3} or As^{III}) and a pentavalent form (As^{+5} or As^{V}). The As^{III} in sodium arsenite is generally considered to be the most toxic—see Figure 4-2 for chemical structures of selected arsenic-containing compounds.

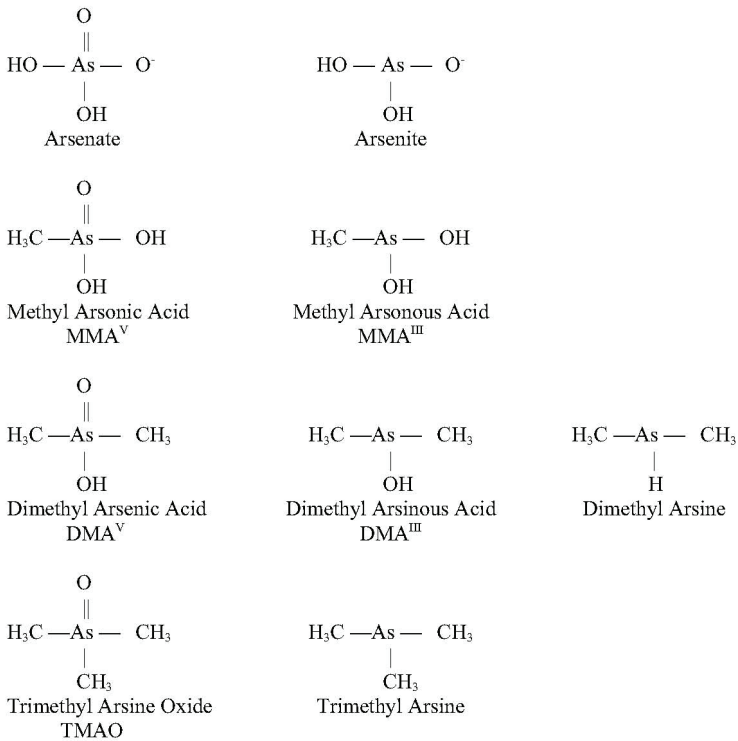


FIGURE 4-2 Structures of selected arsenic-containing compounds.

Arsenic is commonly present in drinking-water sources associated with volcanic soils and can reach high concentrations (over 50 ppb). Numerous human health effects have been attributed to drinking-water exposure, particularly bladder, skin, and lung cancers and vascular diseases.

Arsenic exists in both inorganic and organic (methylated) forms and is readily metabolized in humans and other species. Inorganic arsenic can be converted to organic forms. While organic forms can be converted into inorganic forms by microorganisms in the soil, there is no evidence that this can occur in humans or other vertebrate species (Cohen et al., 2006). Cacodylic acid (CAS No. 75-60-5) has a valence of +5 and is commonly referred to as dimethylarsinic acid (DMA^V). Cacodylic acid, disodium methanearsonate, and monosodium methanearsonate are herbicides that EPA approved for use in the United States, where they are occasionally applied on golf courses and large open spaces. Cacodylic acid was the form of arsenic used in Agent Blue, one of the mixtures used for defoliation in Vietnam; DMA^V made up about 30% of Agent Blue. Agent Blue was chemically and toxicologically unrelated to Agent Orange, which consisted of phenoxy herbicides contaminated with dioxin-like compounds. As shown in Figure 4-3, DMA^{III} and DMA^V, as well as monomethyl arsonic acid (MMA^{III} and MMA^V) are metabolic products of exposure to inorganic arsenic. Methylation of inorganic arsenic used to be considered a detoxification process associated with increased excretion (Vahter and Concha, 2001). However, some of the methylated metabolic intermediates, especially MMA^{III}, have been found to be more toxic

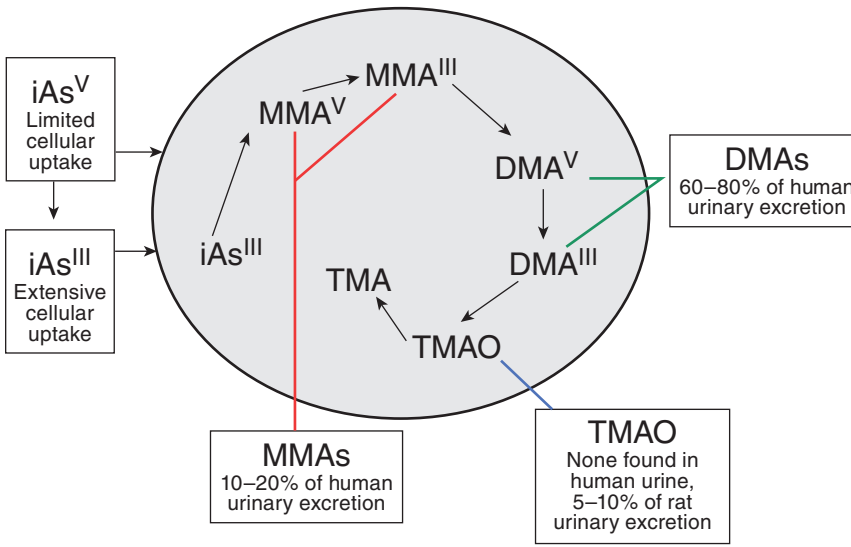


FIGURE 4-3 General pathways of arsenic metabolism after exposure to inorganic arsenic (iAs).
SOURCE: Adapted with permission from Cohen et al., 2006.

than the parent sodium arsenite (Aposhian et al., 2000). The methylation pathway of inorganic arsenic results in the formation of pentavalent DMA (DMA^V) and trivalent DMA (DMA^{III}).

The committee contemplated the relevance of animal data following exposure to inorganic arsenic, where DMA^V is formed endogenously, vs data following direct exposure to exogenous DMA^V, as would have been the form of arsenic to which Vietnam veterans were potentially exposed. It has not been established, nor can it be inferred, that the observed effects of exposure to inorganic arsenic are caused by endogenous formation of DMA^V. Furthermore, recent studies would suggest that there is an increased incidence of cancer in individuals that generate less DMA^V endogenously (Huang SK et al., 2008). Finally, because there is no evidence that DMA is demethylated to inorganic arsenic in humans or other animals (Cohen et al., 2006), the committee chose to not consider the literature on inorganic arsenic in this report. The reader is referred to *Arsenic in Drinking Water* (NRC, 1999a) and *Arsenic in Drinking Water: 2001 Update* (NRC, 2001). Thus, the committee only considered and reviewed those toxicological studies in which animals were directly exposed to DMA^V.

Toxicokinetics

The metabolism and disposition of DMA^V has recently been reviewed (Cohen et al., 2006; Suzuki et al., 2010). In general, DMA^V is rapidly excreted mostly unchanged in the urine of most animal species after systemic exposure. However, rats are unique in that a small percentage (10%) of DMA^V binds to hemoglobin in red blood cells and that leads to a longer half-life in blood (Cui et al., 2004; Suzuki et al., 2004). The binding of DMA^V to hemoglobin is 10 times higher in rats than in humans (Lu et al., 2004). Chronic exposure of normal rat hepatocytes to DMA^V resulted in reduced uptake over time and in acquired cytotoxic tolerance (Kojima et al., 2006); the tolerance was mediated by induction of glutathione-*S*-transferase activity and of multiple-drug–resistant protein expression. Adair et al. (2007) recently examined the tissue distribution of DMA in rats after dietary exposure for 14 days and found that it was extensively metabolized to trimethylated forms that may play a role in toxicity.

Recently, a physiologically based pharmacokinetic model (PBPM) for intravenous and ingested DMA^V has been developed on the basis of mouse data (Evans et al., 2008). Similar models have been developed for humans on the basis of exposure to inorganic arsenic (El-Masri and Kenyon, 2008), but these models have limited utility in considering the toxicity of DMA^V exposures that are relevant to Vietnam veterans.

Toxicity Profile

This section discusses the toxicity associated with organic forms of arsenic, most notably DMA^V because it is the active ingredient in Agent Blue. The toxic-

ity of inorganic arsenic is not considered relevant to veteran exposures to Agent Blue.

Neurotoxicity

Kruger et al. (2006) found that DMA^{III} and DMA^{V} significantly attenuated neuronal ion currents through *N*-methyl-D–aspartate receptor ion channels whereas only DMA^{V} inhibited ion currents through α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. The data suggest that those methylated forms of arsenic may have neurotoxic potential.

Immunotoxicity

Previous studies have shown that a low concentration of DMA^{V} (10^{-7} M) could increase proliferation of human peripheral blood monocytes after their stimulation with phytohemagglutinin whereas it took a high concentration (10^{-4} M) to inhibit release of interferon-γ. This suggested that immunomodulatory effects of DMA^{V} are concentration-specific (Di Giampaolo et al., 2004).

Genotoxicity and Carcinogenicity

Both DMA^{III} and DMA^{V} are genotoxic, increasing oxidative stress and causing DNA damage. Gómez et al. (2005) demonstrated that DMA^{III} induced a dose-related increase in DNA damage and oxidative stress in Jurkat cells. DMA^{III} was considerably more potent than DMA^{V} in inducing DNA damage in Chinese hamster ovary cells (Dopp et al., 2004), and this was associated with a greater uptake of DMA^{III} into the cells. An additional study showed that DMA^{V} is poorly membrane-permeable, but when forced into cells by electroporation it can induce DNA damage (Dopp et al., 2005). Gene-expression profiling of bladder urothelium after chronic exposure to DMA^{V} in drinking water showed significant increases in genes that regulate oxidative stress (Sen et al., 2005), while hepatic gene-expression profiling showed that DMA^{V} exposure induced changes consistent with oxidative stress (Xie et al., 2004). In vivo, DMA^{V}-induced proliferation of the urinary bladder epithelium could be attenuated with the antioxidant *N*-acetylcysteine (Wei et al., 2005).

Both DMA^{III} and DMA^{V} are also carcinogenic. Cancer has been induced in the urinary bladder, kidneys, liver, thyroid glands, and lungs of laboratory animals exposed to high concentrations of DMA. In a 2-year bioassay, rats exposed to DMA^{V} developed epithelial carcinomas and papillomas in the urinary bladder and nonneoplastic changes in the kidneys (Arnold et al., 2006). Similarly, Wang et al. (2009) found that DMA^{V} exposure in drinking water given to F344 rats resulted in a change in the urinary bladder epithelium, but there were no changes in DNA repair capacity. In another study, Cohen et al. (2007a) exposed F344 rats to DMA^{V}

in the diet for 2 years and found an increase in bladder tumors; they postulated that trimethylated forms of arsenic may be responsible for bladder cancer in rats. In the mouse lung, DMA^V acted act as a tumor initiator (Yamanaka et al., 2009) and as a tumor promoter (Mizoi et al., 2005). Additionally, DMA^V can act as a complete carcinogen inducing lung tumors in susceptible strains of mice, including those with deficient DNA repair activity (Hayashi et al., 1998; Kinoshita et al., 2007). Yamanaka et al. (2009) suggest that DMA^{III} can act as a tumor promoter through the formation of a DMA^{III} radical after reduction of DMA^V.

Mechanisms

Oxidative stress is a common theme that runs through the literature on the mechanisms of action of arsenic, particularly with regard to cancer in animals, although some studies have suggested that methylated arsenicals (MMA^{III} and DMA^{III}) can induce mutations in mammalian cells at concentrations below those required to produce oxidative stress after in vitro exposures (Klein et al., 2008). Recent studies have shown that mice deficient in DNA-repair enzymes associated with oxidative stress are highly susceptible to formation of tumors, particularly lung tumors, induced by DMA^V (Kinoshita et al., 2007). The chemical reaction of arsenicals with thiol groups in sensitive target tissues, such as red blood cells and kidneys, may also be a mechanism of action of organic arsenicals (Naranmandura and Suzuki, 2008).

The variation in the susceptibility of various animal species to tumor formation caused by inorganic and organic arsenic is thought to depend heavily on differences in metabolism and distribution. Thus, genetic differences may play an important role. Numerous investigators are examining potential human susceptibility factors and gene polymorphisms that may increase a person's risk of cancer and other diseases induced by arsenicals. Several such studies have been undertaken (Aposhian and Aposhian, 2006; Hernandez et al., 2008; Huang SK et al., 2008; Huang YK et al., 2008; McCarty et al., 2007; Meza et al., 2007; Steinmaus et al., 2007, 2010), but it is not yet possible to identify polymorphisms that may contribute to a person's susceptibility to DMA-induced cancer or tissue injury.

PHENOXY HERBICIDES: 2,4-D AND 2,4,5-T

Chemistry

2,4-D (CAS No. 94-75-7) is an odorless and, when pure, white crystalline powder (Figure 4-4); it may appear yellow when phenolic impurities are present. The melting point of 2,4-D is 138°C, and the free acid is corrosive to metals. It is soluble in water and in a variety of organic solvents (such as acetone, alcohols, ketones, ether, and toluene). 2,4,5-T (CAS No. 93-76-5) is an odorless, white to light-tan solid with a melting point of 158°C. 2,4,5-T is noncorrosive and is

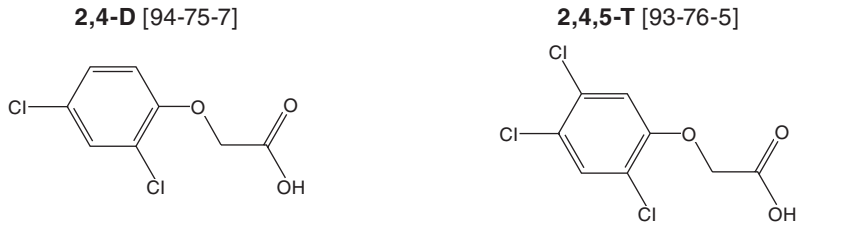


FIGURE 4-4 Structures of 2,4-D and 2,4,5-T.

soluble in alcohol and water. It reacts with organic and inorganic bases to form salts and with alcohols to form esters.

Uses of 2,4-D and 2,4,5-T

2,4-D has been used commercially in the United States since World War II to control the growth of broadleaf plants and weeds on range lands, lawns, golf courses, forests, roadways, parks, and agricultural land and remains today a widely used herbicide approved for use by the European Union and the US EPA. Formulations include 2,4-D amine and alkali salts and esters, which are mobile in soil and easily absorbed through the leaves and roots of many plants. Like 2,4-D, 2,4,5-T was developed and marketed as a herbicide during World War II. However, the registration for 2,4,5-T was canceled by EPA in 1978 when it became clear that it was contaminated with TCDD during the manufacturing process. It is recognized that the production of 2,4-D also involves the generation of some dioxin contaminants, even some with dioxin-like activity, but the fraction of TCDD is comparatively very small, as illustrated in Chapter 4.

The herbicidal properties of 2,4-D and 2,4,5-T are related to their ability to mimic the plant growth hormone indole acetic acid. They are selective herbicides in that they affect the growth of only broadleaf dicots (which include most weeds) and do not affect monocots, such as wheat, corn, and rice.

Toxicokinetics

Several studies have examined the absorption, distribution, metabolism, and excretion of 2,4-D and 2,4,5-T in animals and humans. Data on both compounds are consistent among species and support the conclusion that absorption of oral or inhaled doses is rapid and complete. Absorption through the skin is much lower but may be increased with the use of sunscreens or alcohol (Brand et al., 2002; Pont et al., 2004). After absorption, 2,4-D and 2,4,5-T are distributed widely in the body but are eliminated quickly, predominantly in unmetabolized form in urine (Sauerhoff et al., 1977). Neither 2,4-D nor 2,4,5-T is metabolized to a great

extent in the body although 2,4,5-trichlorophenol and 2,4-dichlorophenol have been identified as trace metabolites in urine. The half-life in humans after single doses of 2,4-D or 2,4,5-T has been estimated to be about 18–23 hours (Gehring et al., 1973; Kohli et al., 1974; Sauerhoff et al., 1977; WHO, 1984). Hines et al. (2003) found that concentrations of 2,4-D and its metabolites in the urine of herbicide applicators were consistent with 2,4-D urinary half-life estimates of 13–40 hours in humans.

Toxicity Profile

The toxicity database on 2,4-D is extensive (http://toxnet.nlm.nih.gov/ (search on "2,4-D"; accessed April 21, 2011), whereas the data available on the toxicity of purified 2,4,5-T, independent of its contamination by TCDD, are sparse. TCDD is much more toxic than 2,4,5-T, and much of the toxicity attributed to 2,4,5-T in early studies was later shown to be caused by the TCDD contaminant. The following summary therefore focuses on 2,4-D toxicity, and information on pure 2,4,5-T is added when it is available.

After a single oral dose, 2,4-D is considered to produce moderate acute toxicity with an LD_{50} (dose lethal to 50% of exposed animals) of 375 mg/kg in rats, 370 mg/kg in mice, and from less than 320 to 1,000 mg/kg in guinea pigs. Rats and rabbits have dermal LD_{50}s of 1,500 mg/kg and 1,400 mg/kg, respectively. 2,4,5-T itself also produces moderate acute toxicity, with oral LD_{50}s of 389 mg/kg in mice and 500 mg/kg in rats. Death from acute poisoning with 2,4-D or 2,4,5-T has been attributed to the ability of the chemicals to uncouple oxidative phosphorylation, a vital process used by almost all cells in the body as the primary means of generating energy. After exposure to high doses, death due to multiple organ failure can occur rapidly. Studies in rats, cats, and dogs indicate that the central nervous system is the principal target organ for acute 2,4-D toxicity in mammals and suggest that the primary site of action is the cerebral cortex or the reticular formation (Arnold et al., 1991; Dési et al., 1962a,b). Neurotoxicity in humans is the predominant effect of acute inhalation and oral exposure to 2,4-D; symptoms include stiffness of arms and legs, incoordination, lethargy, anorexia, stupor, and coma. 2,4-D is also an irritant of the gastrointestinal tract, causing nausea, vomiting, and diarrhea.

Chronic exposure to 2,4-D at relatively high concentrations has been shown to produce a variety of toxic effects, including hepatic and renal toxicity, neurotoxicity, and hematologic changes. A NOEL of 2,4-D of 1 mg/kg was identified for renal toxicity in rats (Hazleton Laboratories America, 1987). The reproductive toxicity of 2,4-D is limited to reduced survival and decreased growth rates of offspring of mothers fed high doses during pregnancy and was associated with maternal toxicity. However, even at high exposures, 2,4-D did not affect fertility and did not produce teratogenic effects in the offspring. The purity of 2,4,5-T has been shown to influence its reproductive toxicity; TCDD contamination increases

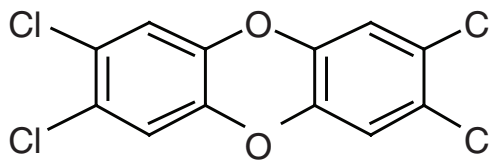
its fetotoxic effects and induces teratogenic effects. Immunotoxicity of 2,4-D has been reported in a small number of studies. At high doses that produced clinical toxicity, suppression of the antibody response was observed, whereas other measures of immune function were normal. The immunotoxicity of 2,4,5-T has not been evaluated in laboratory animals.

The carcinogenicity of 2,4-D or 2,4,5-T has been studied in rats, mice, and dogs after exposure in their food, direct placement in their stomachs, or exposure of their skin. All the studies had negative results except one that found an increased incidence of brain tumors in male rats, but not female rats, that received the highest dose of 2,4-D. The occurrence of malignant lymphoma in dogs kept as pets was reported to be higher when owners reported that they used 2,4-D on their lawns than when they did not (Hayes et al., 1991, 1995), but detailed reanalysis did not confirm this finding (Kaneene and Miller, 1999). A controlled study using dogs exposed to 2,4-D in the laboratory had negative results. Timchalk (2004) suggested that dogs are not relevant for comparative evaluation of human health risk attributable to 2,4-D exposure, because they excrete 2,4-D less efficiently than rats or humans. 2,4-D is not metabolized to reactive intermediates capable of interacting with DNA, and the evidence supports the conclusion that 2,4-D is not a carcinogen.

TCDD

Chemistry

TCDD is a polychlorinated dibenzo-*p*-dioxin that has a triple-ring structure consisting of two benzene rings connected by an oxygenated ring (Figure 4-5); chlorine atoms are attached at the 2, 3, 7, and 8 positions of the benzene rings. The chemical properties of TCDD include a molecular weight of 322, a melting point of 305–306°C, a boiling point of 445.5°C, and a log octanol–water partition coefficient of 6.8 (National Toxicology Program substance profile). It is very lipophilic or fat-soluble and is virtually insoluble in water (19.3 ng/L) but soluble in organic solvents, such as benzene and acetone. It has been suggested that volatilization of dioxin from water may be an important mechanism of transfer from



2,3,7,8-tetrachlorodibenzo-*p*-dioxin

FIGURE 4-5 Chemical structure of TCDD.

the aqueous to the atmospheric phase (EPA, 2004); however, because of its very low water solubility, most TCDD is bound to sediments and particulate matter.

Toxicokinetics

The absorption, distribution, metabolism, and excretion of TCDD have been extensively studied in humans and a number of other animal models in the last 25 years. Given the plethora of data, this section only highlights and summarizes key findings. A more exhaustive review may be found at http://www.epa.gov/ncea/pdfs/dioxin/nas-review.

TCDD is absorbed into the body rapidly but is eliminated very slowly. Because it is very lipophilic, resistant to metabolism, and very slowly eliminated, the concentration of TCDD in the lipid fraction of blood serum is thought to be in dynamic equilibrium with that in the lipid fraction in other tissue compartments. Thus, the lipid-adjusted blood serum concentration of TCDD is used to estimate total body burdens; at high TCDD concentrations, however, the liver sequesters some of the dioxin so that lipid adjustment ignoring hepatic fraction would underestimate total body burden. Exposure of humans to TCDD is thought to occur primarily via the mouth, skin, and lungs. In laboratory animals, oral administration of TCDD has been shown to result in absorption of 50–93% of the administered dose (Nolan et al., 1979; Rose et al., 1976). Similarly, a study performed in a 42-year-old man found that 87% of the oral dose was absorbed (Poiger and Schlatter, 1986). Dermal absorption appears to be dose-dependent, with lower absorption occurring at higher doses (Banks and Birnbaum, 1991). Studies performed in vitro with isolated humans indicate that human skin may be more resistant to absorption (Weber, 1991).

After ingestion and gastrointestinal absorption, TCDD associates primarily with the lipoprotein fraction of the blood and later partitions into the cellular membranes and tissues (Henderson and Patterson, 1988). TCDD is distributed to all compartments of the body; the amounts differ from organ to organ, but most studies indicate that the primary disposition of TCDD is in the liver and adipose tissues. For example, in a human volunteer, it was found that at 135 days after ingestion, 90% of TCDD was in fat (Poiger and Schlatter, 1986); in the rhesus monkey, TCDD is very persistent in adipose tissue (Bowman et al., 1989). The disposition and elimination of TCDD depend on the tissue examined, the time that has elapsed since exposure, total exposure, and other factors. For example, the concentration of cytochrome P450 1A2 (CYP1A2) (Poland et al., 1989) in the liver is increased by TCDD. Direct binding of TCDD to CYP1A2 is thought to result in sequestration of TCDD in the liver and to inhibit its distribution to other tissues. The importance of CYP1A2 concentrations for the toxic actions of TCDD has also been demonstrated in several laboratory situations; for instance, CYP1A2-knockout mice were more susceptible than wild-type mice to TCDD immunotoxicity (Smialowicz et al., 2008) and maternal hepatic CYP1A2 was

found to sequester TCDD and protect mouse fetuses against TCDD-induced teratogenesis (Dragin et al., 2006). In addition, distribution of TCDD is age-dependent, as shown by studies in which young animals displayed the highest concentration of TCDD in the liver and older animals the highest concentrations in kidneys, skin, and muscle (Pegram et al., 1995). Finally, the rate of elimination of TCDD, particularly after low exposures, depends heavily on the amount of adipose tissue mass (Aylward et al., 2005a; Emond et al., 2005, 2006).

In laboratory animals, TCDD is metabolized slowly. TCDD is eliminated primarily in feces as both the parent chemical and its more polar metabolites. However, elimination appears to be dose-dependent; at low doses, about 35% of the administered dose of TCDD was detected in the feces; at higher doses, about 46% was observed (Diliberto et al., 2001). The dose-dependent occurrence of TCDD metabolites in the feces is thought to be due to increased expression of metabolizing enzymes at higher doses and hepatic sequestration making dioxins more available for metabolism. A measure of elimination is half-life, which is defined as the time required for the plasma concentration or the amount of a chemical in the body to be reduced by one-half. The half-life of TCDD in humans varies with body-mass index (BMI), age, sex, and concentration in the body and has been found to vary from 0.4 to more than 10 years (Table 4-1).

Milbrath et al. (2009) conducted a comprehensive review of studies that reported the congener-specific elimination rates of TCDD and related compounds and analyzed the relationships between the apparent half-lives of these compounds as a function of age, body fat, smoking status, and breastfeeding. Infants (under 2 years old) have a reported half-life of 0.4 years (Leung et al., 2006), and adults a half-life of 7.2 years (Milbrath et al., 2009). As people age, the rapid growth results in a dilution effect, resulting in shorter half-lives. Aging also results in an increase and a redistribution of body fat and a redistribution of lipophilic chemicals that alters their rate of elimination (Van der Molen et al., 1996). Human studies of the

TABLE 4-1 Estimates of TCDD Half-Life in Humans and Animals

Reference	Half-Life[a]	Confidence Interval	Comment
Human studies:			
Leung et al., 2006	0.4 year		Breastfed infants, 0–1 year after exposure
Kumagai and Koda, 2005	1.1–2.3 years		Adult male, incinerator workers, 0–1.3 years after exposure
Aylward et al., 2005a	< 3 years		Calculated for exposures at more than 10,000 pg/g of serum lipid
	> 10 years		Calculated for exposures at less than 50 pg/g of serum lipid

TABLE 4-1 Continued

Reference	Half-Life[a]	Confidence Interval	Comment
Flesch-Janys et al., 1996	7.2 years		Adult males, Boehringer cohort
Geusau et al., 2002	1.5 years[b]		Adult female, severe exposure, 0–3 years after exposure
	2.9 years[b]		Adult female, severe exposure, 0–3 years after exposure
Michalek et al., 2002	0.34 year[b]		Adult males, Seveso cohort, 0–3 months after exposure
	6.9 years		Adult males, Seveso cohort, 3–16 years after exposure
	9.8 years		Adult females, Seveso cohort, 3–16 years after exposure
	7.5 years		Adult males, Ranch Hands, 9–33 years after exposure
Needham et al., 1994	7.8 years	7.2–9.7 years	Adults, Seveso cohort
Pirkle et al., 1989	7.1 years	5.8–9.6 years	Adult males, Ranch Hands, 9–23 years after exposure
Milbrath et al., 2009	7.2 years		Reference half-life for 48.7-year-old
Sorg et al., 2009	15.4 months		Victor Yushchenko: TCDD at 108,000 ppt lipid
Animal studies:			
Neubert et al., 1990	73.7 days	60.9–93.8 days	Monkeys, single injection
DeVito and Birnbaum, 1995	15 days		Mice, female B6C3F1
Gasiewicz et al., 1983	11 days[c]		Mice, C5BL/6J
	24.4 days[c]		Mice, DBA/2J
	12.6 days[c]		Mice, B6D2F1/J
Koshakji et al., 1984	20 days		Mice, male ICR/Ha Swiss
Hurst et al., 1998	8 days		Rats, Long-Evans, excretion from liver
Pohjanvirta and Tuomisto, 1990	21.9 days		Rats, male Han/Wistar, resistant strain
Viluksela et al., 1996	20.2 days		Rats, Long-Evans, TurkuAB strain
	28.9 days[d]		Rats, Long-Evans, Charles River strain
Weber et al., 1993	16.3 ± 3.0 days		Rats, male Sprague-Dawley

[a]Half-lives of TCDD in humans based on measurement of TCDD in serum samples.

[b]Shorter half-lives measured in humans during first months after exposure or in severely contaminated persons consistent with nonlinear elimination predicted by physiologically-based pharmacokinetic (PBPK) models (for example, Carrier et al., 1995). Greater half-life in females attributed to greater BMI index.

[c]Total cumulative excretion of ^{3}H-TCDD-derived radioactivity.

[d]Attributed to differences in dilution due to different growth rates.

Ranch Hand cohort have consistently found a similar relationship of increasing half-life of TCDD with increasing BMI (Michalek and Tripathi, 1999; Michalek et al., 1992, 1996). Smoking and breastfeeding are associated with promoting elimination of TCDD and, in the case of breastfeeding, exposing infants through breast milk. Polycyclic aromatic hydrocarbons (PAHs) in cigarette smoke are capable of inducing CYP1A1, 1A2, and 1B1, which in turn may increase the rate of metabolism and later elimination of TCDD. A 30% decrease in TCDD half-life has been associated with smoking (Flesch-Janys et al., 1996).

Special Case of the Poisoning of Victor Yushchenko In 2004, Victor Yushchenko, a candidate for the presidential election in Ukraine, was poisoned with TCDD, which led to severe chloracne and a blood serum concentration of 108,000 ppt (pg/g lipid wt), which is about 50,000 times greater than that in the general population at the time. The incident provided an opportunity to assess the toxicokinetics of TCDD after what was apparently a single very large acute exposure. Serum and fat analysis of TCDD supports the first-order elimination half-life of 15.4 months in that person, and the similar decay curves confirmed that TCDD was in equilibrium between serum lipids and subcutaneous fat (Sorg et al., 2009). That is much shorter than the 7.2-year reference half-life reported by Milbrath et al. (2009) and supports the dose-dependent elimination of TCDD, which is associated with induction of potential TCDD-metabolizing enzymes (CYP1A1, 1A2, and 1B1) in very high TCDD exposures. Two metabolites of TCDD (2,3,7-trichloro-8-hydroxydibenzo-*p*-dioxin and 1,3,7,8-tetrachloro-2-hydroxydibenzo-*p*-dioxin) were detected in feces, serum, and urine but not in fat and skin. Over a 12-month period, about 38% of the TCDD-derived material was eliminated as metabolites (95% in feces, 5% in urine) and 62% eliminated as parent chemical. The metabolite:TCDD ratio in the blood serum was about one-fiftieth of that in the feces; this supports the conclusion that the metabolites were not originally ingested with TCDD. The very slow metabolism of TCDD has been previously reported in laboratory animal models (Gasiewicz et al., 1983; Olson, 1986; Olson et al., 1980; Poiger and Schlatter, 1979), but this is the first report of metabolism in humans. It is also noteworthy that the structures of the human metabolites are the same as previously reported in the rat and dog (Poiger et al., 1982; Sawahata et al., 1982).

In light of the variables discussed above and the effect of differences in physiologic states and metabolic processes, which can affect the mobilization of lipids and possibly of compounds stored in them, complex physiologically-based pharmacokinetic (PBPK) models have been developed to integrate exposure dose with organ mass, blood flow, metabolism, and lipid content to predict the movement of toxicants into and out of each organ. A number of recent modeling studies have been performed in an effort to understand the relevance of animal experimental studies to exposures that occur in human populations (Aylward et al., 2005a,b; Beaudouin et al., 2010; Emond et al., 2005).

Toxicity Profile

Administration of TCDD to laboratory animals affects many tissues and organs. The effects of TCDD in laboratory animals have been observed in a number of species (rats, mice, guinea pigs, hamsters, monkeys, cows, and rabbits) after the administration of a variety of doses and after periods that represent acute (less than 24 hours), subchronic (1 day to 3 months), and chronic (more than 3 months) exposures. Some differences are observed in the different species, particularly with respect to their degree of sensitivity, but in general the effects observed are qualitatively similar. Relatively high exposures of TCDD affect a variety of organs and result in organ dysfunction and death. Different animal species vary widely in lethal toxicity of TCDD; the oral LD_{50} of the chemical varies from 1 µg/kg (guinea pigs) to 5,000 µg/kg (hamsters). There is up to a 5,000-fold interspecies variability in the acute lethal potency of TCDD observed in mature guinea pigs, rats, and hamsters. The developing fetus, however, is uniquely vulnerable to gestational TCDD exposure, and there is only about a 10-fold variability in fetal lethal potency in these species (Kransler et al., 2007; Peterson et al., 1993; Poland and Knutson, 1982). A characteristic of TCDD exposure is a wasting syndrome with loss of adipose and muscle tissue and severe weight loss, although the specific mechanisms of lethality remain unknown. In most rodents, exposure to TCDD affects the liver, as indicated by hepatic enlargement, the presence of hepatic lesions, and impaired hepatic function. The thymus is also sensitive. Finally, in both humans and nonhuman primates, TCDD exposure results in chloracne and associated dermatologic changes. As will be discussed in more detail in Chapters 6–11, studies performed in animal models have indicated that exposure to TCDD adversely affects the heart, the skin, and the immune, endocrine, and reproductive systems and increases the incidence of cancers of the liver, skin, thyroid, adrenal cortex, hard palate, nasal turbinates, tongue, and respiratory and lymphatic systems (ATSDR, 1998; Birnbaum, 1994; Huff et al., 1994; Knerr and Schrenk, 2006). When TCDD has been administered to pregnant animals, birth defects such as cleft palate, malformations of the reproductive organs of the male and female progeny, and abnormalities in the cardiovascular, pulmonary, and nervous systems have been observed.

Administration of TCDD to laboratory animals and cultured cells affects enzymes, hormones, and receptors. In addition to adversely affecting the ability of specific organs to fulfill their normal physiologic roles, TCDD has been found to alter the function and expression of essential proteins. Some of the proteins are enzymes, specialized proteins that increase the rates of chemical reactions and aid in the body's ability to convert chemicals into different molecules. The metabolism of foreign chemicals often changes their biologic properties, increasing their polarity (water solubility) and thus promoting the elimination of the metabolites. The enzymes that are most affected by TCDD are ones that act on or metabolize

xenobiotics and hormones. Xenobiotics are chemicals (drugs and environmental contaminants) that are not expected to be present in the body, and hormones are made by the body and serve as chemical messengers that transport a signal from one cell to another. Among the enzymes affected by TCDD, the best studied is CYP1A1, which metabolizes xenobiotics. In laboratory animals, exposure to TCDD commonly results in an increase in the CYP1A1 present in most tissues; CYP1A1 therefore is often used as a marker of TCDD exposure. Related enzymes, which are also increased with TCDD exposure, include CYP1B1 and CYP1A2, which with CYP1A1 are capable of biotransforming procarcinogens to potentially mutagenic and carcinogen metabolites.

Other enzymes that are affected by TCDD are ones that metabolize hormones, such as thyroid hormones, retinoic acid, testosterone, estrogens, and adrenal steroids. Those hormones transmit their signals by interacting with specific proteins called receptors and in this manner initiate a chain of events in many tissues of the body. For example, binding of the primary female sex hormone, estrogen, to the estrogen receptor promotes the formation of breasts and the thickening of the endometrium and regulates the menstrual cycle. Exposure to TCDD can increase the metabolism of estrogen and thus leads to a decrease in the amount of estrogen available for binding and activating the estrogen receptor. The ultimate effect of TCDD is an interference with all the bodily functions that are regulated by estrogens. Similarly, the actions of TCDD on the adrenal steroids can adversely affect their ability to regulate glucose tolerance, insulin sensitivity, lipid metabolism, obesity, vascular function, and cardiac remodeling. In addition to changing the amount of hormone present, TCDD has been found to interfere with the ability of receptors to fulfill their role in transmitting hormone signals. Animal models have shown that exposure to TCDD can increase the amounts of enzymes in the body and interfere with the ability of hormones to activate their specific hormone receptors. Those actions of TCDD on enzymes and hormone receptors are thought to underlie, in part, observed developmental and reproductive effects and cancers that are hormone-responsive.

TCDD alters the paths of cellular differentiation. The broad spectrum of TCDD effects on hormone and growth factor systems, cytokines, and other signal-transducer pathways indicates that TCDD is an extremely powerful growth dysregulator (Birnbaum, 1994). Research performed primarily in cultured cells has shown that TCDD can affect the ability of cells to undergo such processes as proliferation, differentiation, and apoptosis. During the proliferative process, cells grow and divide. When cells are differentiating, they are undergoing a change from less specialized to more specialized. Cellular differentiation is essential for an organism to mature from a fetal to an adult state. In the adult, proper differentiation is required for normal functions of the body, for example, in maintaining a normally responsive immune system. Processes of controlled cell death, such as apoptosis, are similarly important during development of the fetus and are nec-

essary for normal physiologic functions in the adult. Apoptosis is a way for the body to eliminate damaged or unnecessary cells. The ability of a cell to undergo proliferation, differentiation, and apoptosis is tightly controlled by an intricate network of signaling molecules that allows the body to maintain the appropriate size and number of all the specialized cells that form the fabric of complex tissues and organs. Disruption of that network that alters the delicate balance of cell fate can have severe consequences, including impairment of the function of the organ because of the absence of specialized cells. Alternatively, the presence of an excess of some kinds of cells can result in the formation and development of tumors. Thus, the ability of TCDD to disrupt the normal course of a specific cell to proliferate, differentiate, or undergo apoptosis is thought to underlie (at least in part) its adverse effects on the immune system and the developing fetus and its ability to promote the formation of some cancers.

Mechanism

TCDD binds and activates the aryl hydrocarbon receptor (AHR) in the cells of virtually every tissue in the body. The ability of TCDD to bind to the AHR with high affinity is considered to be necessary, but not sufficient, to produce the wide array of adverse effects associated with TCDD exposure. The pathologic responses associated with exposure to TCDD are thought to be due to binding to and activation of the AHR and later alterations in the expression of TCDD-regulated genes and to altered signaling of biologic pathways that interact with the AHR signal-transduction mechanism (Poland and Knutson, 1982; Safe, 1990; Schmidt and Bradfield, 1996; Whitlock, 1990).

The AHR functions as a ligand-activated nuclear transcription factor. On binding of agonists (ligands), such as TCDD, the AHR forms a heterodimer with a structurally related protein called AHR nuclear translocator (ARNT). The dimeric complex binds to core DNA sequences called xenobiotic-responsive elements (XREs) or dioxin-responsive elements (DREs) in the promotor region of responsive genes and enhances the transcription of those genes. Many of the AHR-regulated genes encode drug-metabolizing enzymes, such as CYP1A1, CYP1A2, CYP1B1, and a variety of phase II conjugating enzymes. Although the up-regulation of these proteins is a sensitive biomarker of exposure to TCDD, which in part contributes mechanistically to some of the adverse effects of TCDD, the tissue-, species-, time-, and dose-specific modulation (increase and decrease) of many genes is thought to contribute to the wide array of toxic responses to TCDD exposure (Boverhof et al., 2006; Ovando et al., 2006, 2010; Perdew, 2008; Puga et al., 2009).

AHR Signaling Pathway

As depicted in Figure 4-6, in the absence of bound ligand, the inactive AHR is retained in the cytoplasm of the cell in a complex consisting of two molecules

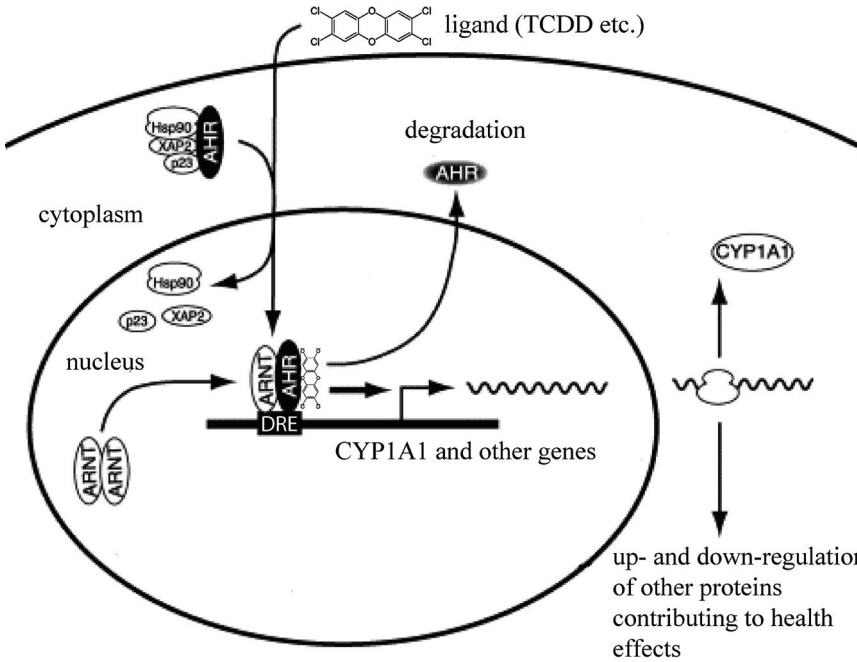


FIGURE 4-6 Mechanism of gene induction and repression after AHR activation by TCDD.

of the heat-shock protein hsp90, one molecule of prostaglandin E synthase 3 (p23) (Kazlauskas et al., 1999), and one molecule of the immunophilin-like protein hepatitis B virus X-associated protein 2 (XAP2) (Petrulis et al., 2003), previously identified as AHR-interacting protein (Ma and Whitlock, 1997) and AHR-activated 9 (Carver and Bradfield, 1997). The hsp90 dimer–p23 complex plays multiple roles in the protection of the AHR from proteolysis, maintaining it in a conformation that makes it accessible to ligand binding at the same time that it prevents the premature binding of ARNT (Carver et al., 1994; Pongratz et al., 1992; Whitelaw et al., 1993). XAP2 interacts with the carboxyl terminus of hsp90 and with the AHR nuclear-localization signal (NLS), a short amino acid domain that targets the receptor for interaction with nuclear-transport proteins. Binding of XAP2 blocks such interaction, preventing the inappropriate trafficking of the receptor into the nucleus (Petrulis et al., 2003).

Binding of ligand (such as TCDD) induces the release of XAP2 and the exposure of the NLS and leads to the binding of nuclear-import proteins and translocation of the cytosolic complex into the nucleus (Davarinos and Pollenz, 1999; Song and Pollenz, 2002). Once in the nucleus, chaperones and cochaperones

dissociate from the AHR, allowing the binding of ARNT (Hoffman et al., 1991; Probst et al., 1993). The activated AHR–ARNT heterodimeric complex is then capable of directly or indirectly interacting with DNA by binding to recognition sequences in the regulatory region of responsive genes (Dolwick et al., 1993; Probst et al., 1993).

The canonical DNA recognition motif of the AHR–ARNT complex is referred to as the AHR-responsive element (AHRE, also referred to as the DRE or the XRE). This element is found in the promoter region of AHR-responsive genes and contains the core sequence 5′-GCGTG-3′ (Shen and Whitlock, 1992), which is part of a more extensive consensus-binding sequence, 5′-T/GNGCGTGA/CG/CA-3′ (Lusska et al., 1993; Yao and Denison, 1992). The AHR–ARNT complex binds to the AHRE core sequence in such a manner that ARNT binds to 5′-GTG-3′ and AHR binds to 5′-TC/TGC-3′ (Bacsi et al., 1995; Swanson et al., 1995). A second type of element, termed AHRE-II, 5′-CATG(N6)C[T/A]TG-3′, has been shown to be capable of acting indirectly with the AHR–ARNT complex (Boutros et al., 2004; Sogawa et al., 2004). The end result of the process is the recruitment of the transcriptional machinery associated with RNA polymerase II and the initiation of differential changes in the expression of the genes bearing the AHR–ARNT recognition motif. Many of the genes code for proteins responsible for detoxification reactions directed at the elimination of the ligand. Research suggests that posttranslational modifications in histone proteins may modify the response (Hestermann and Brown, 2003; Schnekenburger et al., 2007).

In addition to the widely accepted view that the actions of TCDD are mediated by binding of the activated AHR–ARNT dimer to DREs on DNA, which results in altered gene expression (Figure 4-6), more recent studies suggest that a "nongenomic" pathway within the cytoplasm also contributes to the toxic effects of TCDD, as reviewed by Matsumura (2009). The TCDD-mediated activation of AHR within the cytoplasm does not involve binding to ARNT or DNA and appears to contribute to rapid inflammatory responses associate with TCDD (Sciullo et al., 2008). In several cell lines, activation of protein kinase C (PKC) and the subsequent activation of the serine phosphorylated form of cytosolic phospholipase A2 (cPLA2) takes place within 15 minutes of TCDD exposure (Dong and Matsumura, 2008; Park et al., 2007). It is proposed that within the cytoplasm, TCDD-mediated activation of AHR leads to a rapid increase in intracellular Ca^{2+}, activation of PKC, cPLA2, Src tyrosine kinase, and activation of pro-inflammatory proteins, such as cyclooxygenase (COX-2) (Matsumura, 2009). This pathway and other alternative mechanisms of TCDD-mediated AHR activation have also been reviewed by Perdew (2008).

AHR Physiology

The vertebrate AHR is presumed to have evolved from its counterpart in invertebrates, in which it serves a ligand-independent role in normal develop-

ment processes. The ancestral function of the AHR appears to be the regulation of specific aspects of embryonic development, it having acquired the ability to bind xenobiotic compounds only during vertebrate evolution (Hahn, 2001). The invertebrate AHR also functions as a transcription factor and binds to the same dimerization partner (ARNT) and DNA-response elements as the vertebrate protein, but it does not respond to any of the environmental ligands recognized by the vertebrate receptor. Instead, it regulates diverse developmental processes that are independent of exogenous ligand exposure, such as neuronal differentiation during worm development in *Caenorhabditis elegans* (Huang et al., 2004; Qin and Powell-Coffman, 2004) or normal morphogenesis of legs, antennae, and bristles in *Drosophila melanogaster* (Adachi-Yamada et al., 2005). In developing vertebrates, the AHR seems to play a role in cellular proliferation and differentiation and, in keeping with this role in invertebrates, also has a developmental role in craniofacial, renal, and cardiovascular morphogenesis (Birnbaum et al., 1989; Fernandez-Salguero et al., 1997; Lahvis et al., 2005). Other potential functional roles of the AHR include reproduction, innate immunity, tumor suppression, and blood-pressure regulation (Fujii-Kuriyama and Kawajiri, 2010).

The clearest adaptive physiologic response to AHR activation is the induction of xenobiotic-metabolizing enzymes involved in detoxification of toxic ligands. Evidence of that response, which was described above, was first observed in conjunction with the induction of *Cyp1a1*, which resulted from exposure to polycyclic aromatic hydrocarbons (PAHs) or TCDD and was directly related to activation of the AHR signaling pathway (Israel and Whitlock, 1983, 1984). Because of the presence of the AHRE motif in their gene promoters, other metabolizing genes were tested and found to be induced by AHR ligands, and this led to the identification of a so-called AHR gene battery of phase I and phase II detoxification genes that code for the drug-metabolizing enzymes CYP1A1, CYP1A2, CYP1B1, NQO1, ALHD3A1, UGT1A2, and GSTA1 (Nebert et al., 2000). Presumably, vertebrates have evolved those enzymes to detect a wide array of foreign, potentially toxic chemicals, represented in the wide variety of substrates that the AHR is able to bind to and whose biotransformation and elimination it is able to facilitate.

A potential complication of the adaptive responses elicited by AHR activation is the induction of a toxic response. Toxicity may result from the adaptive response itself if the induction of metabolizing enzymes results in the production of toxic metabolites. For example, the PAH benzo[a]pyrene (B[a]P), an AHR ligand, induces its own metabolism and detoxification by the AHR-dependent signaling mechanism described earlier but paradoxically becomes bioactivated to a toxic metabolite in several tissues by metabolism that depends on CYP1A1 and CYP1B1 enzymatic activity (Harrigan et al., 2004). A second potential source of AHR-mediated toxicity may be aberrant changes in global gene expression beyond those observed in the AHR gene battery. The global changes in gene expression may lead to deleterious changes in cellular processes and physiology.

Microarray analysis has proved invaluable in understanding and characterizing that response (Boverhof et al., 2006; Martinez et al., 2002; Ovando et al., 2006, 2010; Puga et al., 2000, 2004; Vezina et al., 2004).

It is clear that the AHR is an essential component of the toxicity of dioxin and of dioxin-like chemicals (DLCs). Homozygous deletion of the AHR in mice leads to a phenotype that is resistant to the toxic effects of TCDD and to the carcinogenic effects of B[a]P (Fernandez-Salguero et al., 1996; Lahvis and Bradfield, 1998; Schmidt et al., 1996). AHR knockout mice, however, have other phenotypic effects, including reduced liver size, hepatic fibrosis, and cardiovascular abnormalities. Hence, it is likely that dioxin has effects that are due to disruption of endogenous AHR functions and that are unrelated to the intrinsic toxicity of some of its ligands.

Definition of Dioxin-like Compounds, the Toxic Equivalence Factor, and Toxic Equivalents

TCDD has the highest affinity for the AHR, but many other chemicals have dioxin-like properties: they have similar chemical structures, have similar physiochemical properties, and cause a common battery of toxic responses because of their relatively high affinity for the AHR. Because of their hydrophobic nature and resistance to metabolism, these chemicals persist and bioaccumulate in fatty tissues of animals and humans. Although there are several hundred polychlorinated, polybrominated, and mixed polychlorinated/brominated dibenzo-*p*-dioxins, dibenzofurans, and biphenyls, only a relatively small number of congeners of these chemical classes display dioxin-like activity. Only 17 polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans with chlorine at the 2, 3, 7, and 8 positions and a few of the coplanar polychlorinated biphenyls (PCBs) that are often measured in environmental samples are recognized as being DLCs. In the context of risk assessment, these polychlorinated dibenzo-*p*-dioxins, polychlorinated dibenzofurans, and PCBs are commonly found as complex mixtures when detected in environmental media and biologic tissues or when measured as environmental releases from specific sources. That complicates the human health risk assessment that may be associated with exposures to varied mixtures of DLCs. To address the problem, the concept of toxic equivalence has been elaborated by the scientific community, and the toxic equivalence factor (TEF) has been developed and introduced to facilitate risk assessment of exposure to those chemical mixtures. On the most basic level, TEFs compare the potential toxicity of each DLC found in a mixture with the toxicity of TCDD, the most toxic member of the group. The procedure involves assigning individual TEFs to the DLCs on the basis of in vivo and in vitro potency relative to TCDD, which is assigned a TEF of 1.0. The DLCs have been assigned TEFs ranging from 0.00001 to 1.0 by the World Health Organization (WHO) (van den Berg et al., 2006, as summarized in Table 4-2, below). When several chemicals are present in

TABLE 4-2 World Health Organization Toxicity Equivalency Factors (TEFs) for Dioxin-like Chemicals (values revised as of 2005)

Chemical	TEF
Chlorinated dibenzo-*p*-dioxins	
2,3,7,8-TCDD	1.0
1,2,3,7,8-PeCDD	1.0
1,2,3,4,7,8-HxCDD	0.1
1,2,3,6,7,8-HxCDD	0.1
1,2,3,7,8,9-HxCDD	0.1
1,2,3,4,6,7,8-HpCDD	0.01
OctoCDD	0.0003
Chlorinated dibenzofurans	
2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDF	0.03
2,3,4,7,8-PeCDF	0.3
1,2,3,4,7,8-HxCDF	0.1
1,2,3,6,7,8-HxCDF	0.1
1,2,3,7,8,9-HxCDF	0.1
2,3,4,7,8,9-HxCDF	0.1
1,2,3,4,6,7,8-HpCDF	0.01
1,2,3,4,7,8,9-HpCDF	0.01
OctoCDF	0.0003
Non-*ortho*-substituted PCBs	
PCB 77—3,3′,4,4′-tetraCB	0.0001
PCB 81—3,4,4′,5-tetraCB	0.0003
PCB 126—3,3′,4,4′,5-pentaCB	0.1
PCB 169—3,3′,4,4′,5,5′-hexaCB	0.03
Mono-*ortho*-substituted PCBs	
PCB 105—2,3,3′,4,4′-pentaCB	0.00003
PCB 114—2,3,4,4′,5-pentaCB	0.00003
PCB 118—2,3′,4,4′,5-pentaCB	0.00003
PCB 123—2′,3,4,4′,5-pentaCB	0.00003
PCB 156—2,3,3′,4,4′,5-hexaCB	0.00003
PCB 157—2,3,3′,4,4′,5′-hexaCB	0.00003
PCB 167—2,3′,4,4′,5,5′-hexaCB	0.00003
PCB 189—2,3,3′,4,4′,5,5′-heptaCB	0.00003

ABBREVIATIONS: CB, chlorinated biphenyl; CDD, chlorinated dibenzo-*p*-dioxin; CDF, chlorinated dibenzofuran; PCB, polychlorinated biphenyl; TEF, toxicity equivalency factor.
SOURCE: Adapted from van den Berg et al., 2006.

a mixture, the toxicity of the mixture is estimated by multiplying the TEF of each DLC in the mixture by its mass concentration and summing the products to yield the TCDD toxic equivalents (TEQs) of the mixture. In that approach to assess dioxin-like activity of a complex real-world mixture of DLCs, an environmental or biologic specimen with a 100-ppt (parts per trillion; 100 pg/g) TEQ is toxicologically equivalent to 100-ppt TCDD. There are two accepted specialized methods for assessing the DLCs in a complex biologic or environmental specimen,

one involving analytic chemistry that quantifies specific DLCs (high-resolution gas chromatography-mass spectroscopy) and the other involving a reporter-gene biologic screen that assesses dioxin-like activity due to binding to the AHR in a transformed cell line (CALUX, EPA method 4435). Epidemiologic studies discussed in this and other updates assess exposure by reporting the specific concentration of TCDD in a specimen or by expressing dioxin-like activity in a complex mixture in units of TEQs.

Carcinogenic Classification of TCDD

EPA and the International Agency for Research on Cancer (IARC), a branch of WHO, have defined criteria to classify the potential carcinogenicity of chemicals on the basis of the weight of scientific evidence from animal, human, epidemiologic, mechanistic, and mode-of-action studies. EPA classified TCDD as a "probable human carcinogen" in 1985 and as "carcinogenic to humans" in a 2003 reassessment. In 1998, the IARC panel of experts concluded that the weight of scientific evidence supported the classification of dioxin as a class I carcinogen, that is, as "carcinogenic to humans." Four years later, the US National Toxicology Program upgraded its classification to "known to be a human carcinogen." In 2006, a panel of experts convened by the National Research Council to evaluate the EPA reassessment concluded that TCDD was "likely to be carcinogenic to humans." That designation reflected the revised EPA *Guidelines for Carcinogen Risk Assessment* made public in 2005.

Genotoxicity

Genotoxicity describes a deleterious action that affects the integrity of a cell's DNA. Genotoxic substances are known to be potentially mutagenic or carcinogenic. Although TCDD is carcinogenic in humans and laboratory animals, it is generally classified as nongenotoxic and nonmutagenic (Wassom et al., 1977). There is no evidence of covalent binding of TCDD or its metabolites to DNA (Poland and Glover, 1979). TCDD does interact with DNA through a receptor-mediated pathway that involves the initial binding of TCDD to the AHR, binding of the activated receptor complex to DREs on DNA and later alterations in expression of TCDD-regulated genes, and altered signaling of biologic pathways that interact with the AHR signal-transduction mechanism (Poland and Knutson, 1982; Safe, 1990; Schmidt and Bradfield, 1996; Whitlock, 1990). TCDD, 2,4,5-T, and 2,4-D were not mutagenic in *Salmonella typhimurium* with or without the addition of liver metabolic-activation enzymes (Blevins, 1991; Mortelmans et al., 1984). TCDD-induced cytogenetic damage in laboratory mice showed no increase in the frequencies of sister-chromatid exchanges, chromosomal aberrations, or micronuclei in bone marrow cells of either C57Bl/6J or DBA/2J mice after administration of a single high dose TCDD up to 150 µg TCDD/kg (Meyne et al., 1985). TCDD did not alter the frequency or spectrum of mutations in male

and female Big Blue transgenic rats (Thornton et al., 2001). There is one report of a positive result with TCDD in a test that measured induction of chromosomal deletions resulting from intrachromosomal recombination in mouse embryos in vivo (Schiestl et al., 1997).

In summary, the vast majority of studies did not detect mutagenic activity of TCDD in a variety of in vitro and in vivo short-term tests.

Other Toxic Outcomes of Dioxin Exposure

Chloracne is a signature effect of high exposure to TCDD and DLCs for some species and for humans who are sensitive.

There is an extensive body of evidence from experimental studies in animal-model systems that TCDD, other dioxins, and several DLCs are immunotoxic (Kerkvliet, 2009). Although the available evidence on dioxin immunotoxicity in humans is scant, mechanistic considerations support the notion that chemical alterations of immune function would cause adverse health outcomes because of the critical role that the immune system plays in general protection—fighting off infection and eliminating cancer cells at early stages. Because of those considerations, these chemicals are potential immunotoxicants.

Similarly, reproduction and embryonic development clearly are targets of TCDD, other dioxins, and DLCs; it is found consistently that the adverse effects are more prevalent during fetal development than in the adult. Although data on those effects in humans have been practically nonexistent, some good data is now emerging on the developmental impacts of DLCs in human (Mocarelli et al., 2008). Human and animal studies have revealed other potential health outcomes including cardiovascular disease, hepatic disease, thyroid dysfunction, lipid disorders, neurotoxicity, and metabolic disorders, such as diabetes.

A number of effects of TCDD exposure in vitro appear to be independent of AHR-mediated transcription and in at least one instance perhaps independent of AHR. Guo et al. (2004) showed that TCDD induced expression of transforming growth factor-α and other genes involved in extracellular matrix deposition in cells from mice with homozygous ablation of the *Ahr* gene. Studies also have shown that TCDD can mobilize calcium from intracellular sources and increase calcium imported from the culture medium (Puga et al., 1995). Mitochondrial oxidative stress has also been shown to be induced in relation to calcium mobilization (Senft et al., 2002). Calcium mobilization by TCDD may have an important effect on signal-transduction mechanisms that control gene expression, inasmuch as several proto-oncogenes, such as *c-fos*, are activated by calcium changes.

Summary of Biologic Plausibility That TCDD Induces Adverse Effects in Humans

Mechanistic studies in vitro and in laboratory animals have characterized the biochemical pathways and types of biologic events that contribute to adverse

effects of exposure to TCDD. For example, much evidence indicates that TCDD acting via the AHR in partnership with ARNT alters gene expression. Receptor binding may result in release of other cytoplasmic proteins that alter the expression or activity of other cell-regulatory proteins. Mechanistic studies also indicate that many other cellular-component proteins contribute to the gene-regulatory effect and that the response to TCDD exposure involves a complex interplay between genetic and environmental factors. Comparative data from animal and human cells in vitro and from tissues suggest a strong qualitative similarity among species in response to TCDD, and this further supports the applicability to humans of the generalized model of initial events in response to dioxin exposure. Biochemical and biologic responses to TCDD exposure are considered adaptive or simply reflective of exposure and not adverse in themselves if they take place within the normal homeostatic ranges of an organism. However, they may exceed normal physiologic boundaries or constitute early events in a pathway that leads to damage to sensitive members of the population. In the latter case, the response is toxic and would be expected to cause an adverse health effect. Those generalizations set the ground rules for the concept of *biologic plausibility*, which relies on extrapolation from animals studies to human risks and on the *precautionary principle*, which bases decision-making on minimizing exposure if the precise nature or magnitude of the potential damage that a substance may cause in humans is uncertain.

LIMITATIONS OF EXTRAPOLATING LABORATORY STUDIES TO HUMAN RESPONSES

In some instances, toxic responses identified in laboratory animal and cell-culture studies are not detected in epidemiologic studies after human exposure to the same chemicals. Although animal and cell-culture studies provide important links to understanding of biochemical mechanisms associated with toxicity induced by xenobiotics, many factors must be considered in extrapolating these results to human disease and disease progression. The following are key factors that might limit the ability of laboratory studies to predict human responses completely and accurately.

Magnitude and Duration of Exposure

In many instances, animal and cell-culture studies are conducted at higher exposures and for shorter durations than what typically occurs in human exposures. For example, the concentrations of TCDD used in animal studies can be many times higher than in the TCDD exposures of Vietnam veterans during their military service. In addition, TCDD is a persistent organic pollutant, and this results in human exposure that occurs over a lifetime, whereas animal studies seldom examine chronic low-level exposure that occurs over a period of many months or years. Animal studies that establish a measurement of body

burden over a specific time interval provide the best potential for extrapolation to humans.

Timing of Exposure

Many organ systems are more susceptible to xenobiotic exposure during critical stages of development, differentiation, or function—such as during gestation or when faced with another external challenge (for example, antigens, smoking, dietary salt, and fat)—than at other times. Therefore, the response of some systems (such as immune or cardiovascular systems) may depend on the timing of exposure relative to the other challenges.

Exposure Composition

Most animal and cell-culture studies are conducted with exposure to single chemicals or a well-defined mixture, but most human exposures occur in complex mixtures from multiple sources.

Difference in AHR Affinity

The binding affinity of AHR for TCDD differs between species (discussed in Okey et al., 2005). Many strains of mice used for toxicologic study harbor a high-affinity AHR allele (AHR^b) and exhibit increased sensitivity to hepatic CYP1A induction, immunosuppression, birth defects, and other responses relative to other mouse strains that carry the low-affinity allele (AHR^d). That simple allelic difference in AHR affinity has not been observed in humans, and TCDD-binding affinity of the AHR found in most humans more closely resembles the low-affinity mouse AHR^d allele. Nonetheless, Nebert et al. (2004) reported that some individuals have TCDD-binding affinity that is 12 times higher than other individuals. Thus, although humans are generally considered less sensitive based on an AHR with a low TCDD-binding affinity, this assumption may not apply to all individuals.

Complex Disease Etiology

The etiology of human diseases is highly influenced by genetics, environmental factors, and gene–environment interactions; these factors can be protective as well as deleterious. In addition to the chemical of interest, environmental factors commonly influencing human responses include diet, prescription and over-the-counter pharmaceuticals, cigarette-smoking, and even stress. Stress produced via known or unknown sources is a well-known modifier of human disease responses (for example, immune and cardiovascular responses). Furthermore, stress is an ever-present variable that is difficult to assess or control for in epidemiologic studies because there is substantial individual-to-individual variation in

response to stress (Cohen et al., 2007b). In contrast, laboratory studies are often conducted with inbred strains of animals under tightly controlled experimental conditions and thus may underestimate or overestimate the potential contribution of a single chemical exposure to disease development.

Sex Differences

There are well-known differences in susceptibility to xenobiotic exposures between male and female animals, some of which are modified by sex steroids. And there are probably additional reasons for sex differences.

EMERGING SUBJECTS IN DISEASE ETIOLOGY

The final section of this chapter presents two newly emerging subjects of molecular and biologic science that provide novel insight into potential mechanisms of disease etiology: epigenetics and developmental immunotoxicity (DIT). It is anticipated that these developing areas of disease etiology may represent important considerations for future committees when evaluating the biologic plausibility of clinical disease associated with exposure to herbicides sprayed in Vietnam.

Epigenetics

Epigenetics consists of mechanisms regulating gene expression that are independent of changes in DNA sequence and mitotically stable; that is, they will be replicated when a cell divides (Skinner et al., 2010). The epigenetic marks on DNA are maintained every time the cell divides and are needed to maintain the identity and function of the cell type.

The history of epigenetics began in the 1940s when Conrad Waddington coined the term *epigenetics* to describe environment–gene interactions that alter biologic traits (Waddington, 1940, 1953, 1956). It was not until the 1970s that the first molecular epigenetic factor was described: DNA methylation, the chemical addition of a methyl group to DNA (Holliday and Pugh, 1975). In the 1980s, the role of DNA methylation in modifying gene expression—turning genes on and off—was established (Chen and Riggs, 2005). In the 1990s, the chemical modification of histone proteins associated with DNA also was shown to modify gene expression and represented the second molecular epigenetic mechanism (Turner, 1998). In the early 2000, various small noncoding RNA molecules were shown to regulate DNA activity (Sato et al., 2011). Around 2005, the first mapping of genome-wide epigenetic marks (epigenomes) was conducted (Pokholok et al., 2005).

Today, the processes recognized as epigenetic mechanisms are various forms of DNA alkylation (Chen and Riggs, 2005; Holliday and Pugh, 1975), histone

modification (Turner, 1998), alterations in chromatin structure (Murr, 2010), and modulation of expression by some small RNA molecules (Valeri et al., 2009). DNA methylation is the addition of a methyl group onto specific nucleotides. In mammals, this occurs at cytosine nucleotides that are adjacent to guanine nucleotides. Methylation of DNA can alter the expression of the adjacent gene, particularly if methylation has occurred in the promoter of the gene. Other forms of DNA alkylation that have been seen less frequently are hydroxymethylation and adenylation. Histones are the proteins that bind and form complex structures with DNA called nucleosomes. Chemical modifications of the histones, such as methylation and acetylation, can alter histone structure and modify gene expression, particularly if the histone modification has occurred in the promoter of the gene (Turner, 1998). The coiling or twisting of the DNA–histone complexes creates a structure called chromatin, and the structure of the chromatin can alter gene expression. The most recently recognized epigenetic factor is small noncoding RNA molecules that can associate with mRNA and regulate gene expression. The interaction of all these epigenetic processes creates the epigenome, and the epigenome has a critical role in regulating gene expression independently of changes in DNA sequence (Skinner et al., 2010).

Environmental epigenetics involves the ability of environmental factors—such as nutrition, toxicants, and stress—to alter epigenetic programming. Thus, epigenetics provides a molecular mechanism by which environmental factors can influence disease etiology (Jirtle and Skinner, 2007; Szyf, 2007). The role of epigenetics in disease etiology has been shown for cancer and a number of other diseases (Skinner et al., 2010). In addition, environmental factors at critical times of development have the ability to alter epigenetic programming and to cause changes in gene expression (Skinner et al., 2010). A relevant example is that in vitro treatment of preimplantation embryos with TCDD alters the DNA methylation of imprinted genes (Wu et al., 2004). That in turn affects the functions and development of cells, tissues, and biologic systems. It is well established that early-life exposures or environmental influences are associated with the onset of disease much later in life (Barker et al., 2010). Thus, an early developmental alteration in the epigenome provides a molecular mechanism whereby adult diseases can have a developmental basis.

Epigenetic transgenerational inheritance involves the ability of the environment to promote a permanent alteration in the germ line that is transmitted to later generations (Skinner et al., 2010). The process requires exposures at very critical times of development of the germ line when epigenetic programming is being established. This type of epigenetic inheritance between generations can affect disease etiology and other biologic phenomena.

In summary, the ability of epigenetic mechanisms to regulate gene expression might underlie the ability of xenobiotic exposure to contribute to disease development and the potential for offspring to inherit effects of the disrupted epigenetic processes.

Developmental Immunotoxicity

A second emerging field in biologic science that may provide insight into the mechanism of xenobiotic-induced disease is the disruption of the developing immune system by xenobiotic exposure or DIT. The developing immune system is among the most sensitive physiologic targets of prenatal and childhood environmental insult. The sensitivity is due, in part, to the novel processes of gene rearrangement, somatic-cell selection, and immune-cell distribution that are required to produce a security system that can effectively protect not only the child but also the aging adult against external challenges without itself producing immune-mediated chronic disease. To produce that security system, the maturation of the immune system needs a critical series of steps that produce highly specialized immune cells that are capable of self vs nonself recognition and are tailored to the specialized functional environments of different tissues and organs (such as brain, lungs, skin, liver, gastrointestinal tract, and reproductive tract). A disruption of immune development can place the integrity of the organism at risk.

Among the known risk factors for DIT are such chemicals as heavy metals, some pesticides, such industrial solvents as trichloroethylene, and PCBs. The adverse outcomes of DIT may become apparent soon after exposure or can emerge much later in life. Often, childhood or adult infections can trigger the appearance of DIT-associated immune problems that were established earlier in life (Dietert, 2009). DIT-induced alterations can also contribute to myriad health problems related to dysfunction or pathology in virtually any tissue or organ. Chemicals, drugs, infectious agents, and physical and emotional stressors can synergize to increase the risk of DIT. Not everyone is at an identical risk for DIT. People who have particular genotypes may be at increased risk for specific chemical-induced DIT on the basis of heritable factors that affect metabolism or immune vulnerability.

The heightened sensitivity of the developing immune system is due to the existence of critical developmental windows of vulnerability during which environmental interference with key steps of immune maturation can change the entire course of immune development and result in later-life immune dysfunction and increased risk of disease. The events programmed for these critical developmental windows have several basic features:

- They are necessary, usually one-time events of early development, with no equivalents in adults.
- They lock in building blocks upon which additional maturational events rely.
- If they do not occur both on time and efficiently, the ramifications are usually profound, prolonged, and irreversible.

Examples of critical windows of immune vulnerability and the chemicals that can cause disruptions have been described in several reviews (Dietert and

Dietert, 2008; Dietert and Piepenbrink, 2006; Dietert et al., 2000; Holsapple et al., 2003; Landreth, 2002) and include

- The process of the seeding of immune cells to tissues where they become resident populations.
- The selection process of thymocytes in the thymus.
- The maturation of macrophage populations in the lung, in the brain, and elsewhere.
- The maturation of dendritic cells to provide balanced immune responses.
- The initial development, expansion, and seeding to the periphery of t-regulatory cell populations.

The increased sensitivity of the fetal, neonatal, and juvenile immune systems compared with the immune system of an adult can be manifested as a sensitivity to lower doses of chemical exposure than doses that affect the adult, a greater persistence of the immune problems that follow exposure than are seen in adults, a broader array of immune problems than are experienced by adults, and greater likelihood that a second later-life chemical exposure or environmental stressor will trigger an unexpected immune problem.

It is important to note that disruption of immune maturation is not the only route for DIT. Early-life chemical exposure may affect the status of genes (the epigenome) in such a way that their pattern of expression in later life is affected and thereby alter immune functional capacity. Such changes in gene status that affect immune status could occur in the exposed generation (for people exposed in utero or during childhood), or they could carry through one or more additional generations as a result of true epigenetic alterations.

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[1]Throughout this report, the same alphabetic indicator after year of publication is used consistently for a given reference when there are multiple citations by the same first author in a given year. The convention of assigning the alphabetic indicator in order of citation in a given chapter is not followed.

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5

Epidemiologic Studies: Compendium of New Publications and Background on Multiple Referenced Populations

The continuing effort to evaluate and integrate epidemiologic studies pertinent to possible health effects of the chemicals of interest—2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), 4-amino-3,5,6-trichloropicolinic acid (picloram), and cacodylic acid (dimethyl arsenic acid or DMA)—has involved the review of thousands of publications over successive updates, *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*, hereafter referred to as *VAO* (IOM, 1994), *Veterans and Agent Orange: Update 1996* (IOM, 1996), *Update 1998* (IOM, 1999), *Update 2000* (IOM, 2001), *Update 2002* (IOM, 2003a), *Update 2004* (IOM, 2005), *Update 2006* (IOM, 2007), and *Update 2008* (IOM, 2009), and three shorter more focused VAO reports: *Herbicide/Dioxin Exposure and Type 2 Diabetes*, hereafter referred to as *Type 2 Diabetes* (IOM, 2000), *Herbicide/Dioxin Exposure and Acute Myelogenous Leukemia in the Children of Vietnam Veterans*, hereafter referred to as *Acute Myelogenous Leukemia* (IOM, 2002), and *Length of Presumptive Period for Association Between Exposure and Respiratory Cancer*, hereafter referred to as *Respiratory Cancer* (IOM, 2004).

The first part of this chapter tabulates epidemiologic publications that appeared in the period from October 1, 2008 (the closing date for inclusion in *Update 2008* [IOM, 2009]), through September 30, 2010, as a compendium of new information on human health outcomes considered by the present committee. In this chapter and later chapters, epidemiologic studies are organized into three categories according to the populations being studied: Vietnam veterans, occupational populations other than Vietnam veterans, and nonoccupational populations affected by environmental exposures. Within each population, various study de-

signs (most important, cohort, case–control, and cross-sectional) have strengths and weaknesses (see Chapter 2) that influence their potential to contribute evidence considered in the health-outcomes chapters.

The second part of this chapter provides design information on populations that are the subjects of multiple references in this and earlier VAO reviews, including new studies of populations that have been studied previously and studies of new populations with multiple health outcomes, to avoid repeating design information in multiple health-outcomes chapters. (The design information on studies of new populations that involve single health outcomes is provided in the various health-outcomes chapters.) For presentation of the background information, the study populations are arranged into the categories based on whether they are composed of Vietnam veterans, occupationally exposed workers, or environmentally exposed individuals or were assembled according to a case–control approach focused on particular health outcomes.

In addition to reviewing studies involving exposures to the specific chemicals of interest listed previously, this and earlier VAO committees have also considered studies that examined compounds chemically related to the herbicides used in Vietnam, such as 2-(2-methyl-4-chlorophenoxy) propionic acid, hexachlorophene, and chlorophenols, particularly 2,4,5-trichlorophenol. Some publications did not indicate the specific herbicides to which study participants were exposed or the magnitude of exposure; those limitations were considered when the committee weighed the relevance of each publication, as detailed in Chapter 2. The committee also considers studies of exposure to polychlorinated biphenyls (PCBs) and other dioxin-like compounds (DLCs) informative if their results were reported in terms of TCDD toxic equivalents (TEQs) or concentrations of specific congeners of DLCs. Available details of exposure assessment and use of the resulting data in analyses are discussed in Chapter 3, which follows the same sequence to categorize study populations.

NEW EPIDEMIOLOGIC PUBLICATIONS

The new epidemiologic publications reviewed by the committee for this update are listed in Tables 5-1, 5-2, and 5-3. The conditions listed in the "Health Outcomes reported" column are indicative of the chapters in which the new publications are considered. Note, however, that studies assessing the occurrence of various cancers following exposure scenarios temporally comparable to exposure during military service are discussed in Chapter 7, which addresses cancer outcomes in the veterans themselves. Studies of childhood cancers in relation to parental exposure to the chemicals of interest are discussed in Chapter 8, which addresses possible adverse effects in the veterans' offspring. Cancer studies that consider only childhood exposure are not considered relevant to the committee's charge.

TABLE 5-1 Publications Reporting a Single Health Outcome in New Populations

Author	Study Design	Exposure Measure(s) Having Results	Health Outcome Reported	Study Population
Studies of Vietnam Veterans				
Shah et al., 2009	Case–control	Reported as "previous agent orange exposure"	Progression of prostate cancer	Veterans with radical prostatectomies examined at 1 of 5 VA Healthcare facilities; health data culled from the SEARCH database
Occupational Studies				
Dhillon et al., 2008	Case–control	Occupational and environmental exposures, including 2.4-D, 2,4,5-T, Silvex	PD	Individuals, ≥ 50 yrs of age, diagnosed with PD and living in eastern TX
Elbaz et al., 2009	Case–control	Herbicides, phenoxys	PD	PD patients (18–75 yrs of age) who applied for free healthcare for agriculture workers or related occupations in France
Lo et al., 2010	Case–control	Herbicides (unspecified)	Colorectal carcinoma	Egyptian cases and hospital-matched controls
Tanner et al., 2009	Case–control	2,4-D	PD	Consecutively eligible PD patients recruited from 8 US movement disorder clinic
Environmental Studies				
Aronson et al., 2010	Case–control	POPs (dl PCBs 118 and 156) in serum	Prostate cancer	Male clinic patients (50–80 yrs of age) who visited 1 of 5 urologists from 1997 through 1999 in Kingston, Ontario
Chang et al., 2010	Cross-sectional	TEQs	Type 2 diabetes (insulin resistance and pancreatic β-cell function	Residents living near a deserted PCP factory in Tainan City, Taiwan
Cok et al., 2010	Case–control	Organochlorine pesticides and PCB (including dl-PCB 118) in adipose tissue	Infertility	Adipose taken from fertile and infertile men during surgical procedures in Turkey

TABLE 5-1 Continued

Author	Study Design	Exposure Measure(s) Having Results	Health Outcome Reported	Study Population
Cornelis et al., 2009	Case–control	Herbicides—undefined	Bladder cancer	Application of GIS to agricultural pesticide use to a bladder cancer study
Dai and Oyana, 2008	Ecologic	Dioxin levels in soil (ppt–TEQ)	Breast cancer	Breast cancer incidence and residential proximity to dioxin-contaminated areas (GIS study)
Dallaire et al., 2009	Cross-sectional	Dl PCBs (including PCB 105, 118, 156, ~170, ~180)	Thyroid function	Random sample of Inuit population of Québec, Canada
Darnerud et al., 2010	Case–control	TEQs for dioxin/furans and mono-ortho PCBs	Thyroid hormone levels	Swedish mother–child pairs (1996–1999); analysis of breast milk maternal pre-birth serum, and child's serum
Dhooge et al., 2010	Cross-sectional	Dl PCB 118 in serum	BMI	Random sampling of Flemish adults (50–65 yrs of age) and adolescents residing in study area
Farooq et al., 2010	Case–control	Pesticide use for "weeds"	Breast cancer	Self-reported residential pesticide use in and around New York City, NY
Giordano et al., 2010	Case–control	Serum levels of dl PCB 118 and non-dl PCBs	Hypospadias	Hypospadic children and controls recruited from 2 hospitals in Rome, Italy (September 2005–May 2007)
Hodgson et al., 2008	Cohort	TEQs for PCBs (including dl PCBs 105, 118, 156, 157, 167)	Bone mineral density	Baltic adults (60–81 yrs of age)
Konishi et al., 2009	Prospective cohort	Dioxins, furans, dl PCBs, TEQ (1998 and 2006) in maternal serum	Birth weight	Pregnant women recruited (July 2002–October 2005) in Sapporo, Japan
Krüger et al., 2008	Cohort	Dioxin-like serum activity of lipophilic POPs	Chromosome activity in sperm	European and inuit men; subset of INUENDO study

continued

TABLE 5-1 Continued

Author	Study Design	Exposure Measure(s) Having Results	Health Outcome Reported	Study Population
Kuscu et al., 2009	Ecologic	TEQ in soil	MIH	Elementary school children from industrialized and nonindustrialized areas in Turkey
Laisi et al., 2008	Case–control	PCDD/F and PCB TEQs in breast milk	MIH	Mothers and children with cleft palates born 1995–1999 and control children in Finland
Maluf et al., 2009	Case–control	Herbicides or pesticides (agricultural or home use)	AA	LATIN case–control study; compared exposures for the previous 30–365 days for AA patients and controls
Niskar et al., 2009	Case–control	Serum level congeners of dioxin, furans, and PCBs	Endometriosis	Patients at a reproductive medicine clinic in Atlanta, GA
Porpora et al., 2009	Case–control	Serum TEQs	Endometriosis	Italian women undergoing laparoscopy for endometriosis or other benign gynecologic condition
Rull et al., 2009	Case–control	Chlorinated phenol—including 2,4-D, MCPA, MCPP, diclofop-methyl	ALL	Northern California Childhood Leukemia Study—Residential proximity (within a half-mile) of pesticide application
Shim et al., 2009	Case–control	Residential or occupational exposure to herbicides	Childhood brain cancer (astrocytomas and primitive neuroectodermal tumors)	Atlantic Coast Childhood Brain Cancer Study; maternal report of parental pesticide exposure in 2 yrs prior to birth
Tawara et al., 2009	Cohort	TEQs (TCDD and other dl-congeners, total TEQ)	Birth size	Mother-infant pairs from Hokuriku District, Japan (an area with high coastal fish consumption)
Turyk et al., 2009	Cross-sectional	POPs (including dl-PCBs 118, 167)	Diabetes	Great Lakes sport-fish consumers

TABLE 5-1 Continued

Author	Study Design	Exposure Measure(s) Having Results	Health Outcome Reported	Study Population
Verhulst et al., 2009	Prospective birth cohort	Gestational exposure; cord blood levels of PCBs, including dl 118	BMI (first 3 yrs of life)	Mother-infant pairs recruited from maternity wards throughout Flanders, Belgium (September 2002–February 2004)
Vidal et al., 2009	Case–control	Herbicide use for gardening	Progressive supranuclear palsy (a Parkinsonian syndrome)	In or outpatients from 5 large Parkinson disorder centers in France
Vlajinac et al., 2010	Case–control	Herbicides	PD	Newly diagnosed PD patients in Belgrade, Serbia (January 2001–November 2005)
Waller et al., 2010	Case–control	2,4-D	Gastroschisis (abdominal hernia)	Live-born singleton infants with gastroschisis identified from Washington State birth certificates and US Geological Survey databases
Ward et al., 2009	Case-control	Residential carpet dust (including dl-PCBs 105, 118, 170, 180)	ALL	Northern CA Childhood Leukemia Study; analysis ALL and contents of residential carpet dust
Zhang et al., 2010	Case–control	TEQs from cord blood	Thyroid hormone homeostasis	Electronic-waste recycling community in China
Zota et al., 2010	Case–control	Pesticide use for “lawn care” or “indoor or outdoor plant care”	Breast cancer	Cape Cod Breast Cancer and Environment Study—use of household cleaners by Cape Cod residents

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; AA, aplastic anemia; AHR, aryl hydrocarbon receptor; ALL, acute lymphocyte leukemia; BMI, body mass index; dl, dioxin-like; GIS, geographic information system; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MIH, molar incisor hypomineralization; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin; PCDF, polychlorinated dibenzofuran; PD, Parkinson disease; PE, peritoneal endometriosis; POP, persistent organic pollutants; SEARCH, Shared Equal Access Research Cancer Hospital; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEQ, (total) toxic equivalent; VA, Department of Veterans Affairs.

TABLE 5-2 Publications on Multiple Health Outcomes in New Study Populations

Author	Study Design	Exposure Measures(s) Having Results	Health Outcome(s) Reported	Study Population
Occupational Studies				
Orsi et al., 2009	Case–control	Pesticides, herbicides (phenoxys)	HL, NHL, MM, lymphoproliferative syndrome (including CLL, hairy cell leukemia)	French, male patients with lymphoid neoplasms (18–75 yrs of age) and matched controls
Environmental Studies				
Halldorsson et al., 2009	Cohort	dl activity in maternal serum	Birth weight and development at 6 months	Danish National Birth Cohort; women (25–35 yrs of age) chosen according to their intake of fatty fish

ABBREVIATIONS: CLL, chronic lymphocytic leukemia; dl, dioxin-like; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; MM, multiple myeloma.

Publications Reporting a Single Health Outcome in New Populations

New publications reporting a single health outcome in populations not studied previously are listed in Table 5-1 with an indication of the outcomes. Descriptions and critiques of the designs of these studies are provided in the sections of the report that discuss the results on the particular health outcomes.

Publications Reporting Multiple Health Outcomes in New Populations

New publications reporting multiple health outcomes in populations not studied previously are listed in Table 5-2, with a list of outcomes that were investigated. Comprehensive discussions of the designs of these studies are presented in the second part of this chapter, organized according to the type of study population. The results, with comments related to their reliability or limitations, appear in the appropriate outcome-specific sections of Chapters 6–11.

New Publications on Previously Studied Populations

A number of long-term studies of populations exposed to the chemicals of interest are of particular importance to the VAO project. The disease experiences of those populations are updated with the passage of time. Placing each new publication in its historical context helps the committee to combine the evidence

TABLE 5-3 Publications on Previously Studied Populations

Author	Study Design	Exposure Measure(s) Having Results	Health Outcome(s) Reported	Study Population
Studies of Vietnam Veterans				
Cypel and Kang, 2010	Retrospective cohort	Service in Vietnam during Vietnam War	Mortality through 2005 from all causes; all cancers; cancers (oral/pharynx, digestive, respiratory, prostate, testicular, skin, brain, lymphopoietic [leukemia]), diabetes, circulatory (HT, cerebrovascular), respiratory (pneumonia, influenza, COPD), digestive (cirrhosis of liver)	ACC veterans who handled/sprayed herbicides in Vietnam vs non-Vietnam veteran peers or US men
O'Toole et al., 2009	Longitudinal cohort	Service in Vietnam during Vietnam War	Prevalence of neoplasms (melanoma, prostate), thyroid, diabetes, lipids, eye, ear, circulatory (HT, IHD, cerebrovascular), respiratory disorders, digestive disorders, RA (also much investigation of PTSD and other psych problems)	Interviewed sample of Australian Vietnam veterans vs results of general population on National Health Survey
Occupational Studies				
Andreotti et al., 2009	Cohort	2,4-D	Pancreatic cancer	AHS (private and commercial applicators and spouses)

continued

TABLE 5-3 Continued

Author	Study Design	Exposure Measure(s) Having Results	Health Outcome(s) Reported	Study Population
Boers et al., 2010	Cohort	Chlorophenoxy herbicides	Follow-up mortality (1955–2006) from stomach, pancreas, lung, prostate, bladder, and kidney cancers; melanoma, NHL, leukemia, endocrine/blood diseases, nervous system, IHD, other heart disease, cerebrovascular, respiratory diseases, digestive diseases, (genitourinary diseases)	Subcohort of IARC cohort (Netherlands)
Collins et al., 2009a,b	Cohort	TCDD, PCP, PCDD, 2,4,5-T	Mortality from cancers—all and specific, diabetes, cerebrovascular, IHC, respiratory disorders, digestive disorders	Subcohort of NIOSH (Dow Chemical, Midland, Michigan plant workers)
Crawford et al., 2008	Cohort	Herbicides, including 2,4-D, 2,4,5-T, 2,4,5-TP	Hearing loss	AHS (licensed pesticide applicators)
Dennis et al., 2010	Cohort	Herbicides, including 2,4-D, 2,4,5-T, 2,4,5-TP	Melanoma	AHS (licensed, male pesticide applicators)
Firestone et al., 2010	Case–control	2,4-D occupational exposure	PD	Expansion of Firestone et al. (2005) adding cases newly diagnosed 2003–2006 to those diagnosed 1992–2002 at University of Washington

TABLE 5-3 Continued

Author	Study Design	Exposure Measure(s) Having Results	Health Outcome(s) Reported	Study Population
Goldner et al., 2010	Cohort	2,4-D, 2,4,5-T	Thyroid disease	AHS (female spouses of private applicators)
Hoppin et al., 2009	Cohort	2,4-D, 2,4,5-T, 2,4,5-TCP, dicamba	Adult-onset asthma	AHS and Agricultural Cohort Consortium
Landgren et al., 2009	Cohort	2,4-D, dicamba	MGUS	AHS (licensed, male pesticide applicators)
McBride et al., 2009a,b	Cohort	2,4,5-T, phenoxy herbicides, picloram	Mortality (cancers—all and specific, diabetes, cardiovascular disease, respiratory disorders)	Subcohort of IARC cohort (New Zealand)
Mills et al., 2009	Cohort	2,4-D, 2,4,5-T, 2,4,5-T	Myocardial infarction (mortality and incidence) and long-term pesticide use	AHS (licensed, male pesticide applicators)
Pelclová et al., 2009	Cohort	2,4,5-T	Neurological status, arterial plaques, diabetes, lipids, HT, IHD	Czech 2,4,5-T workers—40 yr follow-up
Slager et al., 2009	Cohort	2,4-D	Rhinitis	AHS (commercial pesticide applicators [male and female])
Environmental Studies				
Colt et al., 2009	Case–control	TEQs, ndl PCB 180, α-chlordane in serum or dust	NHL	NCI–SEER Study—newly diagnosed NHL patients (20 to 74 yrs of age) at 4 SEER registries

continued

TABLE 5-3 Continued

Author	Study Design	Exposure Measure(s) Having Results	Health Outcome(s) Reported	Study Population
Cordier et al., 2010	Cohort	Emissions from municipal solid waste incinerators	Urinary tract birth defects	Rhone-Apes, France residents living near waste incinerator
Eskenazi et al., 2010	Cohort	Serum concentrations of TCDD	Time to pregnancy	SWHS (20 yr follow-up in Seveso women 0–40 yrs of age at time of the accident)
Ha et al., 2009	Cross-sectional	Dioxins, furans, dl PCBs	Newly diagnosed HT	NHANES (1999–2002)
Lee et al., 2008	Cross-sectional	Serum concentrations of PCDDs, PCDFs, dl and non-dl PCBs, including dl PCBs 74, 118, 126, 156, 169	PN	NHANES (1999–2002)
McDuffie et al., 2009	Case–control	"pesticides" in article; listed in *Update 2002* as phenoxyherbicides, 2,4-D, and Mecoprop	HL, NHL, MM, STS	Cross-Canada Study of Pesticides and Health
Ng et al., 2010	Case–control	Organochlorines (including dl PCBs 105, 118, 156)	NHL	Canadian NHL patients (20–70 yrs of age); follow-on to Spinelli et al., 2007
Pesatori et al., 2008	Case–control	Serum concentrations of TCDD	Incidence cases of pituatary adenomas	Seveso population (1976–1996); incidence cases identified by hospital discharge records

TABLE 5-3 Continued

Author	Study Design	Exposure Measure(s) Having Results	Health Outcome(s) Reported	Study Population
Pesatori et al., 2009	Cohort	Serum concentrations of TCDD	Cancer incidence (all and specific)	Seveso, 20 yr follow-up (men and women from Zones A, B and R)
Ruder et al., 2009	Case–control	Pesticides—undefined	Gliomas	Upper Midwest Health Study—residing on a farm at ≥ 18 yrs of age and potential exposure to crops, livestock, and farm tasks
Schreinemachers, 2010	Cross-sectional	2,4-D	Urinary 2,4-D (recent exposure), lipids, glucose metabolism	NHANES III (1988–1994)
Su et al., 2010	Cohort	PCDD, PCDF, and PCB cogeners, TEQ	Growth and thyroid function	Taiwanese mother–child pairs (5 yr follow-up), assessed development by gender and level of exposure
Turunen et al., 2008	Cohort	TCDD, PCBs, TEQs	Mortality (all causes, specific cancers, IHD, cerebrovascular disease)	Finnish fisherman and their wives vs national rates
Uemura et al., 2009	Cross-sectional	TEQs (total and PCDDs, PCDFs, and dl PCBs)	Metabolic syndrome (BMI, HT, triglycerides, HDL, cholesterol, diabetes)	Stratified sample of Japanese men and women 15–73 yrs of age

continued

TABLE 5-3 Continued

Author	Study Design	Exposure Measure(s) Having Results	Health Outcome(s) Reported	Study Population
Viel et al., 2008b	Ecologic	Dioxin emissions from municipal solid-waste incinerators	NHL	NHL cases identified through a population-based cancer registry and living in vicinity of a solid-waste incinerator

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DB, 2-(2,4-dichlorophenoxy) butyric acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TP, 2-(2,4,5-trichlorophenoxy) propionic acid; ACC, Army Chemical Corps; AHS, Agricultural Health Study; BMI, body mass index; COPD, chronic obstructive pulmonary disease; HDL, high-density lipoprotein; HL, Hodgkin lymphoma; HT, hypertension; IARC, International Agency for Research on Cancer; IHD, ischemic heart disease; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; NCI, National Cancer Institute; ndl, not dioxin-like; NHANES, National Health and Nutrition Examination Survey; NHL, non-Hodgkin lymphoma; NIOSH, National Institute of Occupational Safety and Health; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin; PCDF, polychlorinated dibenzofuran; PN, peripheral neuropathy; PTSD, post-traumatic stress disorder; RA, rheumatoid arthritis, SEER, NCI's Surveillance, Epidemiology, and End Results; STS, soft-tissue sarcoma; SWHS, Seveso Women's Health Study; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEQ, (total) toxic equivalent.

across publications appropriately, taking into consideration the interdependence among related publications. Such clusters of studies are useful in describing the course of a population's response to an exposure, and joint consideration of an entire body of research on a population may yield insight into relationships with potential confounding factors.

Many cohorts potentially exposed to the chemicals of interest have been monitored periodically, including the cohorts of the International Agency for Research on Cancer (IARC), the National Institute for Occupational Safety and Health (NIOSH), and the National Cancer Institute (NCI); residents of Seveso; and Ranch Hand and Army Chemical Corps (ACC) personnel. For the sake of completeness, the discussions of specific health outcomes and the associated cumulative-results tables in Chapters 6–11 include references to publications discussed in previous VAO reports and to new publications. In drawing its conclusions, the committee combined the evidence in new publications and the evidence synthesized in the most recent update (*Update 2008*), taking into account the interdependence among related publications.

Individual researchers who belong to research consortia evaluating cohorts in large multicenter studies (such as the IARC and NCI cohort studies) sometimes publish reports based on the subsets of study participants that they themselves

are monitoring. The VAO committees take into consideration all reports that have been published, including those based on entire cohorts and those based on subcohorts. In drawing its conclusions, the committee considered both types of studies, taking into consideration the interdependence among related studies. In particular, some subcort studies provide more data than studies of entire cohorts, such as individual serum TCDD concentrations and personal information that can be used to adjust for confounders of concern. Furthermore, even when analyses based on an entire cohort would include data on a subcohort as a subset, reports on the subcohort might provide additional information on the consistency of the relationships among subcohorts, such as whether there are important subcohort-by-exposure interaction effects, when these issues were not considered in the full-cohort studies.

Many of the cohorts that have contributed to the cumulative findings of the VAO committees are no longer being followed; however, the cohorts' histories are briefly recapitulated in the body of this report. Additional background information can be found in earlier reports in this series.

The new publications on previously studied populations are listed in Table 5-3. These new publications are reviewed in the context of the history of publications on the same populations to take into account the fact that they are not presenting entirely new evidence but rather enhancing the picture that has been emerging over many years.

STUDY POPULATIONS: PREVIOUSLY ADDRESSED OR HAVING MULTIPLE HEALTH OUTCOMES

One-time reports on given study populations that addressed only single health outcomes are not discussed in the rest of this chapter. In the sections below, we present study design information on populations of Vietnam veterans, occupational cohorts, and environmentally exposed groups that have been reported on repeatedly, often for many health outcomes, and on case–control studies that have generated multiple publications relevant to the VAO series.

In drawing its conclusions, the committee synthesized the evidence from studies that have been conducted over time, taking into account the interdependence among related studies. In particular, if new results are updating or expanding previously studied populations or concern a subset of original study populations, this synthesis considers redundancy among studies while recognizing that separately reported information can impart new relevance to other data on a study population. The design information provided in the rest of this chapter links repeated studies and clarifies their interdependence.

The rest of this chapter also provides design information or studies involving multiple health outcomes to avoid repetition in the health-outcome chapters (Chapters 6–11). Some of the populations have been studied previously and reviewed in previous VAO publications (thus these populations are multiple ref-

erenced both over time and across health outcomes), while some have not been addressed in other VAO publications. Detailed descriptions of many of the study populations can be found in Chapter 2 of the original *VAO* report, and the criteria for inclusion were discussed in Appendix A of that report. Details of exposure assessment in individual studies are presented in the present chapter, whereas generic issues of exposure assessment are discussed in Chapter 3 with the special challenges involved in characterizing and reconstructing the herbicide exposures of Vietnam veterans.

In this update, the committee adopts a major change in the formatting of the tables of cumulative results on the health outcomes, which was aimed at making relationships among publications more evident for its own deliberations and for the reader. The prior practice was to insert findings from new publications in the results tables at the beginning of the sections on veteran, occupational, and environmental studies and so create bands of studies reviewed in individual updates. Now, however, the reported findings on a given condition from a particular study population from all VAO reports are gathered and presented in reverse chronologic order to provide the full history of the study of each endpoint in each group studied. Within the three general types of exposure, the order of the study populations in the newly formatted tables roughly reflects the degree of importance attributed to the information generated, and studies of subgroups are presented after those on an overarching cohort. For example, when first reported (Saracci et al., 1991), the original IARC Cohort of Phenoxy Herbicide Workers was composed of 20 cohorts from 10 countries that had been studied separately. When mortality of those workers was followed up (Kogevinas et al., 1997), they were augmented with 16 additional cohorts, 4 German study populations and 14 groups of workers studied separately at US manufacturing facilities, which together comprise the independently studied NIOSH cohort. To simplify the location of underlying information on study populations, the discussion of them in this chapter follows the order in which their findings are presented in the result tables for each health outcome.

The section below on Vietnam veterans covers studies conducted in the United States by the Air Force, the Centers for Disease Control and Prevention (CDC), the Department of Veterans Affairs (VA), the American Legion, and individual states; it also covers studies of Australian and South Korean Vietnam veterans. The section "Occupational Studies" covers studies of workers other than Vietnam veterans exposed occupationally to chemicals of interest, including production workers, agriculture and forestry workers (including herbicide and pesticide applicators), and paper and pulp workers. The section "Environmental Studies" covers studies of populations exposed to the chemicals of interest from nonoccupational sources, including the general population, such as the National Health and Nutrition Examination Survey (NHANES) cohort, and people who had usually high exposures because of industrial sources in their residential neighborhoods, such as residents of Seveso, Italy; southern Vietnam; suburban

Taichung, Taiwan; Chapaevsk, Russia; and Times Beach, Missouri. This chapter ends with a section addressing publications based on repeatedly mentioned case–control study populations; case–control studies assessing Vietnam-veteran status, however, are included in the section on veteran studies, while nested case–control studies are presented in conjunction with the cohorts upon which they were derived.

VIETNAM-VETERAN STUDIES

Studies of Vietnam veterans who might have been exposed to herbicides, including Agent Orange, have been conducted in the United States at the national and state levels and in Australia and Korea. Exposures have been estimated by various means, and health outcomes have been evaluated with reference to various comparison or control groups. This section is organized primarily by research sponsor because it is more conducive to a methodologic presentation of the articles. The specificity of exposure measures spans a wide range from individual exposures of Ranch Hand and ACC personnel, as reflected in serum TCDD measurements, to the use of service in Vietnam as a surrogate for TCDD exposure in some studies.

Several comparison groups have been used for veteran cohort studies: Vietnam veterans who were stationed in areas where herbicide-spraying missions were unlikely to have taken place; Vietnam-era veterans who were in the military at the time of the conflict but did not serve in Vietnam; veterans who served in other wars or conflicts, such as the Korean War and World War II; and various US populations (either state or national).

In all studies of Vietnam veterans (whether or not the study participants are American), the study participants are the target population of the committee's charge, and they are assumed to have a higher probability of exposure to the chemicals of interest than people who did not serve in Vietnam, whether or not their individual exposures are characterized beyond the mere fact that they were deployed to Vietnam.

United States

Air Force Health Study of Operation Ranch Hand Servicemembers

Although, unfortunately, no new reports from the Air Force Health Study (AFHS) were identified in the current literature review, previous reports and findings from the study provided important information that was incorporated into the previous VAO reports and continue to play an important role in the committee's assessment of the overall evidence for the current report. Although the data-gathering phase of this study is complete, the committee remains very interested in seeing additional publications providing longitudinal analysis of the

vast amount of information assembled and making use of the preserved collection of biologic samples

Major defoliation activities in Vietnam were conducted by Air Force personnel as part of Operation Ranch Hand. Veterans who took place in the defoliation activities became the first subpopulation of Vietnam veterans to receive special attention with regard to Agent Orange and have become known as the Ranch Hand cohort within the AFHS. To determine whether exposure to herbicides, including Agent Orange, had adverse health effects, the Air Force made a commitment to Congress and the White House in 1979 to conduct an epidemiologic study of Ranch Hand personnel (AFHS, 1982). Results of biologic-marker studies of Ranch Hand personnel have been consistent with their being exposed, as a group, to TCDD. When the Ranch Hand cohort was classified by military occupation, a general increase in serum TCDD was detected in people whose jobs involved more frequent handling of herbicides (AFHS, 1991a).

The exposure index initially proposed in the AFHS relied on military records of TCDD-containing herbicides (Agent Orange, Agent Purple, Agent Pink, and Agent Green) sprayed as reported in the Herbicide Reporting System (HERBS) tapes for the period starting in July 1965 and on military procurement records and dissemination information for the period before July 1965. In 1991, the exposure index was compared with the results of the Ranch Hand serum-TCDD analysis. The exposure index and the TCDD body burden correlated weakly.

Michalek et al. (1995) developed several indexes of herbicide exposure of members of the Ranch Hand cohort and tried to relate them to the measurements of serum TCDD from 1987 to 1992. Self-administered questionnaires completed by veterans of Operation Ranch Hand were used to develop three indexes of herbicide or TCDD exposure: number of days of skin exposure, percentage of skin area exposed, and the product of the number of days of skin exposure, percentage of skin exposed, and a factor for the concentration of TCDD in the herbicide. A fourth index, which used no information gathered from individual study participants, was calculated by multiplying the volume of herbicide sprayed during a person's tour of duty by the concentration of TCDD in herbicides sprayed in that period and then dividing the product by the number of crew members in each job specialty at the time.

Each of the four indexes tested was significantly related to serum TCDD although the models explained only 19–27% of the variability in serum TCDD concentrations. Days of skin exposure had the highest correlation. Military job classification (non–Ranch Hand combat troops, Ranch Hand administrators, Ranch Hand flight engineers, and Ranch Hand ground crew), which is separate from the four indexes, explained 60% of the variability in serum TCDD. When the questionnaire-derived indexes were applied within each job classification, days of skin exposure added statistical significance, but not substantially, to the variability explained by job alone.

A retrospective matched-cohort study design was used to examine morbid-

ity and mortality; follow-up was scheduled to continue until 2002. Records from the National Personnel Records Center and the US Air Force Human Resources Laboratory were searched and cross-referenced to identify all Ranch Hand personnel (AFHS, 1982; Michalek et al., 1990). A total of 1,269 participants were originally identified (AFHS, 1983). A control population of 24,971 C-130 crew members and support personnel assigned to duty in Southeast Asia (SEA) but not occupationally exposed to herbicides (AFHS, 1983) was selected from the same data sources. Control participants were individually matched for age, type of job (based on Air Force specialty code), and race (white or not white) to control for age-related, educational, socioeconomic-status, and race-related differences in development of chronic disease. To control for many potential confounders related to the physical and psychophysiologic effects of combat stress and the SEA environment, Ranch Hands were matched to control participants who performed similar combat or combat-related jobs (AFHS, 1982). Rank also was used as a surrogate of exposure. Alcohol use and smoking were included in the analysis when they were known risk factors for the outcome of interest.

Ten matches formed a control set for each exposed participant. For the mortality study, the intent was to follow each exposed participant and a random sample of half of each participant's control set for 20 years in a 1:5 matched design. The morbidity component of follow-up consisted of a 1:1 matched design; the first control was randomized to the mortality-ascertainment component of the study. If a control was noncompliant, another control from the matched "pool" was selected; controls who died were not replaced.

The baseline physical examination occurred in 1982, and examinations took place in 1985, 1987, 1992, 1997, and 2002. Morbidity was ascertained through questionnaires and physical examination, which emphasized dermatologic, neurobehavioral, hepatic, immunologic, reproductive, and neoplastic conditions. Some 1,208 Ranch Hands and 1,668 comparison participants were eligible for baseline examination. Initial questionnaire response rates were 97% for the exposed cohort and 93% for the nonexposed; baseline physical-examination responses were 87% and 76%, respectively (Wolfe et al., 1990). Deaths were identified and reviewed by using US Air Force Military Personnel Center records, the VA Beneficiary Identification Record Locator Subsystem (BIRLS), and the Internal Revenue Service database of active Social Security numbers. Death certificates were obtained from the appropriate health departments (Michalek et al., 1990).

Ranch Hands were divided into three categories on the basis of their potential exposure:

- *Low potential.* Pilots, copilots, and navigators. Exposure was primarily through preflight checks and spraying.
- *Moderate potential.* Crew chiefs, aircraft mechanics, and support personnel. Exposure could occur by contact during dedrumming and air-

craft loading operations, onsite repair of aircraft, and repair of spray equipment.

- *High potential.* Spray-console operators and flight engineers. Exposure could occur during operation of spray equipment and through contact with herbicides in the aircraft.

Ostensibly, the AFHS was designed to answer exactly the question that the VAO project is asking, but the realized nature of the "exposed" (Ranch Hand veterans) and "comparison" (SEA veterans) groups and the evolving practices of VAO committees endeavoring to fulfill the intention of their congressional mandate make interpretation less straightforward.

Results have been published for baseline morbidity (AFHS, 1984a) and baseline mortality (AFHS, 1983); the first (1984b), second (1987), third (1992), fourth (1997), and fifth (2002) follow-up examinations (AFHS, 1987, 1990, 1995, 2000, 2005); and the reproductive-outcomes study (AFHS, 1992; Michalek et al., 1998a; Wolfe et al., 1995). Mortality updates have been published for 1984–1986, 1989, and 1991 (AFHS, 1984b, 1985, 1986, 1989, 1991a). An interim technical report updated cause-specific mortality in Ranch Hands through 1993 (AFHS, 1996). Michalek et al. (1998b) and Ketchum and Michalek (2005) reported on 15-year and 20-year follow-up of postservice mortality, respectively, in veterans of Operation Ranch Hand, updating an earlier cause-specific mortality study by Michalek et al. (1990).

Blood samples for determination of serum TCDD concentrations were drawn at the cycle examinations in 1982 from 36 Ranch Hands (Pirkle et al., 1989), in 1987 from 866 Ranch Hands (AFHS, 1991b), in 1992 from 455 Ranch Hands (AFHS, 1995), and in 1997 from 443 Ranch Hands (AFHS, 2000). For veterans whose TCDD was not measured in 1987 but was measured later, the later measurement was extrapolated to 1987 by using a first-order kinetics model with a constant half-life of 7.6 years. Analyses of the serum TCDD readings were included in the report on the 1987 follow-up examination (AFHS, 1991b), and other Ranch Hand publications have addressed the relationship between serum TCDD and reproductive hormones (Henriksen et al., 1996); diabetes mellitus, glucose, and insulin (Henriksen et al., 1997); skin disorders (Burton et al., 1998); infant death (Michalek et al., 1998a); sex ratios (Michalek et al., 1998c); skin cancer (Ketchum et al., 1999); insulin, fasting glucose, and sex-hormone–binding globulin (Michalek et al., 1999a); immunologic responses (Michalek et al., 1999b); diabetes mellitus (Longnecker and Michalek, 2000; Steenland et al., 2001a); cognitive function (Barrett et al., 2001); hepatic abnormalities (Michalek et al., 2001a); peripheral neuropathy (Michalek et al., 2001b); hematologic results (Michalek et al., 2001c); psychologic functioning (Barrett et al., 2003); correlations between diabetes and TCDD elimination (Michalek et al., 2003); thyroid function (Pavuk et al., 2003); cancer incidence (Akhtar et al., 2004; Pavuk et al., 2005); insulin sensitivity (Kern et al., 2004); prostate cancer (Pavuk et al., 2006); serum testos-

terone and risk of benign prostate hyperplasia (Gupta et al., 2006); and diabetes and cancer incidence (Michalek and Pavuk, 2008). All the VAO updates, *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes* (IOM, 2000), and *Veterans and Agent Orange: Length of Presumptive Period for Association Between Exposure and Respiratory Cancer* (IOM, 2004) have discussed reports and papers addressing the cohort in more detail.

The tendency of the AFHS researchers to use differing cutpoints and population definitions for analogous analyses suggests their a posteriori selection in a fashion that influences the results. For example, Michalek and Pavuk (2008) allude to the commonly held assumption that Agent Orange was more heavily contaminated earlier in the war as the motivation for making various temporal partitions in their analyses, but the choices were not consistent. For cancer, 1968 or before was the cutpoint for the "date of service" variable, whereas "days of spraying" were counted through 1967 and the distribution was partitioned at 30 days. For diabetes, however, "date of service" was divided at 1969 or before and "number of days of spraying" was split at 90 days or more, with no specification of the period over which the counting was done.

The AFHS is perceived by many to be the central piece of research for decision-making by the VAO committees, but this study also has important limitations which all VAO committees have had to take into consideration. A recent Institute of Medicine report, *Disposition of the Air Force Health Study* (IOM, 2006), a report undertaken by another IOM committee as the AFHS was approaching the end of its data-gathering phase, described the limitations of the AFHS very effectively and was quoted in extensive detail in *Updates 2006* and *2008*. In summary, the committee recognizes the following features as the primary strengths and limitations of the AFHS:

- The AFHS is one of the most pertinent studies for the VAO reviews, with a study population that was directly exposed to the chemicals of interest in the Vietnam War theater.
- It can be argued that the AFHS population is not representative of the entire population of Vietnam veterans, so the AFHS study findings might not be generalizable to all Vietnam veterans.
- The AFHS might be underpowered for detecting small effects, especially for rare outcomes, because of its relatively small sample size. Therefore, the study's findings are vulnerable to false negatives (failure to detect an important association). However, the underpower problem does not affect the validity for positive findings; these findings are likely to be real, especially if they are repeated over examination cycles.
- For AFHS analyses that used non-AFHS Vietnam veterans as the comparison group, the comparison group might also be exposed to the chemicals of interest, although the exposure is likely to be substantially higher for the AFHS group than for the comparison group. Therefore the com-

parison is not a ideal "exposed vs unexposed" comparison, but rather a "high exposure vs low exposure" comparison. Again, the exposure in the comparison group might also make the study findings vulnerable to false negatives if the exposure differential between the AFHS group and the comparison group is not large enough to allow the association between the exposure and the outcome to be detected. However, this problem does not affect the validity for positive findings.

Army Chemical Corps Cohort

Although the study of members of the US ACC was conducted by VA (whose other research efforts on Vietnam veterans are discussed together below), it is discussed immediately after the AFHS because of the importance that VAO committees have attributed to it. Like the Ranch Hand personnel, members of the ACC were involved directly in handling and distributing herbicides in Vietnam. Because the ACC personnel were expected to have been highly exposed to Agent Orange, VAO committees recommended study of this important group of Vietnam veterans (IOM, 1994) and later encouraged publication of its findings (IOM, 2004). The availability of serum TCDD concentrations in a subset of this cohort of Vietnam veterans has made its findings particularly useful in appraising possible associations with various health outcomes.

These troops performed chemical operations on the ground and by helicopter and were thereby involved in the direct handling and distribution of herbicides in Vietnam. The ACC population was belatedly identified for the study of health effects related to herbicide exposure (Thomas and Kang, 1990). In an extension, Dalager and Kang (1997) compared mortality in veterans of the ACC specialties, including Vietnam veterans and non-Vietnam veterans. Results of an initial feasibility study were reported by Kang et al. (2001). They recruited 565 veterans: 284 Vietnam veterans and 281 non-Vietnam veterans as controls. Blood samples were collected in 1996 from 50 Vietnam veterans and 50 control veterans, and 95 of the samples met CDC standards of quality assurance and quality. Comparison of the entire Vietnam cohort with the entire non-Vietnam cohort showed that the geometric mean TCDD concentrations did not differ significantly ($p = 0.6$). Of the 50 Vietnam veterans sampled, analysis of questionnaire responses indicated that those who reported spraying herbicides had higher TCDD concentrations than did those who reported no spraying activities. The authors concluded that Agent Orange exposure was a likely contributor to TCDD concentrations in Vietnam veterans who had a history of spraying herbicides.

Kang et al. (2006) reported findings from the main study. A health survey of 1,499 Vietnam veterans and 1,428 non-Vietnam veterans was administered by telephone. Exposure to herbicides was assessed by analyzing serum specimens from a sample of 897 veterans for dioxin. Veterans who reported spraying herbicides had significantly higher TCDD serum concentrations than did Vietnam

veterans and other veterans who did not report herbicide spraying. The final analysis compared Vietnam-veteran sprayers with Vietnam-veteran nonsprayers in the entire study population.

Since *Update 2008*, Cypel and Kang (2010) have examined the following mortality outcomes in the ACC personnel through 2005: cancers (oral and pharyngeal, digestive, respiratory, prostate, testicular, skin, brain, and lymphopoietic [leukemia]), diabetes, circulatory (hypertension and cerebrovascular), respiratory (pneumonia, influenza, and chronic obstructive pulmonary disease), and digestive (cirrhosis of the liver). The study compares 2,872 ACC personnel who served in Vietnam with 2,737 ACC personnel who did not serve in Vietnam, using survival analysis that controls for race, age at entry into follow-up, rank, and duration of military service. The study also compares 662 ACC personnel who served in Vietnam who reported spraying herbicides with 811 who did not, controlling for additional covariates obtained in the telephone survey—body mass index (BMI) and smoking status. Both cohorts were also compared with the expected mortality for US males.

The primary strengths and limitations of the ACC studies are similar to those of the AFHS. In addition, the committee is concerned that the findings in Cybel and Kang (2010) regarding respiratory diseases were not adjusted for smoking status, probably an important confounding factor for respiratory diseases, in the analyses based on the entire ACC cohort that compared those who served in Vietnam with those who did not. (The subcohort analyses that compared sprayers with nonsprayers were adjusted for smoking status.)

Centers for Disease Control and Prevention Studies

Surveys of US Vietnam veterans who were not part of the Ranch Hand or ACC groups indicated that 25–55% believed that they were exposed to herbicides (CDC, 1989a; Erickson et al., 1984a,b; Stellman and Stellman, 1986). Several attempts have been made to estimate exposure of Vietnam veterans who were not part of the Ranch Hand or ACC groups. CDC has undertaken a series of studies to examine various health outcomes in Vietnam veterans as directed by Congress in the Veterans Health Programs Extension and Improvement Act of 1979 (Public Law [PL] 96-151) and the Veterans' Health Care, Training, and Small Business Loan Act of 1981 (PL 97-72). *VAO* and *Update 1996* describe those studies in detail. The first was a case–control interview study of birth defects in offspring of men who served in Vietnam (Erickson et al., 1984a,b). In 1983, the US government asked CDC to conduct a study of possible long-term health effects in Vietnam veterans exposed to Agent Orange. The CDC Agent Orange study (CDC, 1985) attempted to classify veterans' service-related exposures to herbicides. That involved determining the proximity of troops to Agent Orange spraying by using military records to track troop movement and the HERBS tapes to locate herbicide-spraying patterns. The CDC birth-defects study developed an exposure-opportunity index to score Agent Orange exposure (Erickson et al., 1984a,b).

In 1987, CDC conducted the Agent Orange Validation Study to test the validity of the various indirect methods used to estimate exposure of ground troops to Agent Orange in Vietnam. The study measured serum TCDD in a nonrandom sample of Vietnam veterans and in Vietnam-era veterans who did not serve in Vietnam (CDC, 1988a). Vietnam veterans were selected for the study on the basis of the number of Agent Orange hits that they were thought to have experienced on the basis of the number of days on which their company was within 2 km and 6 days of a recorded Agent Orange spraying event. Blood samples were obtained from 66% of 646 Vietnam veterans and from 49% of the eligible comparison group of 97 veterans. More than 94% of those whose serum was obtained had served in one of five battalions.

The median serum TCDD in Vietnam veterans in 1987 was 4 ppt (range, under 1 to 45 ppt). Only two veterans had concentrations above 20 ppt. The "low" exposure group consisted of 298 Vietnam veterans, the "medium" exposure group 157 veterans, and the "high" exposure group 191 veterans. The distribution of TCDD measurements was nearly identical with that in the control group of 97 non-Vietnam veterans. The CDC validation study concluded that study participants could not be distinguished from controls on the basis of serum TCDD. In addition, neither record-derived estimates of exposure nor self-reported exposure to herbicides could predict Vietnam veterans with currently high serum TCDD (CDC, 1988a, 1989a). The report concluded that it was unlikely that military records alone could be used to identify a large number of veterans who might have been heavily exposed to TCDD in Vietnam.

Using exposure estimates from the Agent Orange Validation Study, CDC conducted the Vietnam Experience Study (VES), a historical cohort study of the health experience of Vietnam veterans (CDC, 1989b). The study was divided into three parts: physical health, reproductive outcomes and child health, and psychosocial characteristics (CDC, 1987, 1988a,b,c, 1989b). Using VES data, CDC examined postservice mortality (through 1983) in a cohort of 9,324 US Army veterans who served in Vietnam and in 8,989 Vietnam-era Army veterans who served in Korea, Germany, or the United States (Boyle et al., 1987; CDC, 1987). Another study (O'Brien et al., 1991) combined the mortality and interview data to identify all veterans who had non-Hodgkin lymphoma (NHL). To evaluate whether self-reported assessment of exposure to herbicides influences the reporting of adverse health outcomes, CDC designed a study of VES participants (Decoufle et al., 1992). In a follow-up of CDC's VES cohort, Boehmer et al. (2004) reported findings on mortality during 1965–2000.

The serum TCDD measurements in Vietnam veterans also suggested that exposure to TCDD in Vietnam was substantially lower, *on average*, than that of persons exposed as a result of the industrial explosion in Seveso or that of the heavily exposed occupational workers who have been the focus of many of the studies evaluated by the committee. The assessment of *average* exposure does not preclude heavy exposure of subgroups of Vietnam veterans.

CDC undertook the Selected Cancers Study (CDC, 1990a) to investigate the effects of military service in Vietnam and of exposure to herbicides on the health of American veterans, specifically NHL (CDC, 1990b), soft-tissue sarcoma (STS) and other sarcomas (CDC, 1990c), Hodgkin lymphoma (HL; CDC, 1990d), and nasal, nasopharyngeal, and primary liver cancers (CDC, 1990d).

No new publications from the CDC studies were identified for the present review.

Other Department of Veterans Affairs Studies

The ACC discussed above is one of the major studies conducted by VA of Vietnam veterans' exposures to the chemicals of interest. The other VA studies are described below in this section.

Numerous cohort and case–control studies conducted by VA are discussed in detail in previous VAO reports. Among the earliest was a proportionate-mortality study by Breslin et al. (1988). The participants were ground troops who served in the US Army or Marine Corps at any time from July 4, 1965, through March 1, 1973, or veterans who were born in 1934–1957. A list of 186,000 Vietnam-era veterans who served in the Army or Marine Corps and were reported deceased as of July 1, 1982, was assembled from VA's BIRLS; 75,617 names were randomly selected from the list for inclusion in the study. Information extracted from the selected military records included the places, dates, and branch of military service; date of birth; sex; race; military occupation specialty codes; education level; type of discharge; and confirmation of service in Vietnam. Additional information was extracted on veterans who served in SEA, including the first and last dates of service in SEA, the military unit, and the country where the veteran served. For the final sample of 52,253 Army and Marine Corps veterans, cause of death was ascertained from death certificates or Department of Defense Report of Casualty forms for 51,421 men, including 24,235 who served in Vietnam and 26,685 men who did not serve in SEA; 501 deaths were excluded from the final analyses because service in SEA was in a country other than Vietnam or the location of military service was unknown. Each veteran's cause of death was coded by a nosologist who used the 8th revision of the *International Classification of Diseases*.

On the basis of the proportionate-mortality study (Breslin et al., 1988), Burt et al. (1987) conducted a nested case–control study of NHL with controls selected from among the cardiovascular-disease deaths. In a follow-up of the Breslin et al. study, Bullman et al. (1990) compared cause-specific proportionate mortality of 6,668 Army I Corps Vietnam veterans—veterans who served in the northernmost part of South Vietnam in a combat zone designated as Military Region I by the US military—with that of 27,917 Army Vietnam-era veterans who had not served in Vietnam. The study by Bullman et al. included the study population identified by Breslin et al. and an additional 9,555 Army Vietnam-era veteran deaths that were identified after the BIRLS mortality data were extended through

December 31, 1984. Similarly, Watanabe et al. (1991) updated the Vietnam-veteran mortality experience reported by Breslin et al. (1988) by extending the follow-up from January 1, 1982, to December 31, 1984. An additional 11,325 deceased Army and Marine Vietnam-era veterans were identified from the period and included in the study. The study population for Watanabe et al. consisted of 62,068 military veterans, of whom 29,646 served in Vietnam and 32,422 never served in SEA. Proportionate-mortality ratios were calculated for three referent groups: branch-specific (Army and Marine Corps) non-Vietnam veterans, all non-Vietnam veterans combined, and the US male population. A third follow-up proportionate-mortality study (Watanabe and Kang, 1996) using the veterans from Breslin et al. (1988) and Watanabe et al. (1991) included an additional 9,040 randomly selected Vietnam-era veterans who died from July 1, 1984, through June 30, 1988. The final study included 70,630 veterans—33,833 who served in Vietnam and 36,797 who never served in SEA—and the analyses were performed with the same referent groups described previously (Watanabe et al., 1991).

VA also conducted studies that focused on specific health outcomes, using data from VA's Agent Orange Registry (AOR), a computer database containing health information on Vietnam veterans who voluntarily undergo physical examinations at a VA hospital. The AOR was set up in 1978 to monitor Vietnam veterans' health complaints or problems that could be related to Agent Orange exposure during military service in Vietnam. The physical examinations consist of an exposure history, a medical history, laboratory tests, and an examination of body systems most commonly affected by toxic chemicals. As of June 1, 2008, the registry contained information from 506,184 examinations (Agent Orange Review, 2008).

Using early data from the registry, Bullman et al. (1991) examined the risk of posttraumatic stress disorder (PTSD) in a case–control study of veterans who received AOR medical examinations during January 1983–December 1987. The final analyses include 374 PTSD cases and 373 controls whose military records were used to verify Vietnam service, Military Occupational Specialty Codes (MOSCs), primary duties, military branch, dates of Vietnam service, medals, awards, and disciplinary actions for each veteran. Similarly, Bullman et al. (1994) studied the risk of testicular cancer by using the AOR health records of veterans who received Agent Orange medical examinations during March 1982–January 1991. The final analyses in that study included 97 testicular-cancer cases and 311 controls. A surrogate metric for Agent Orange exposure was developed by using branch of service, combat MOSCs, geographic area of service in Vietnam, location of military units in relation to herbicide spray missions, and the length of time between spray missions and military operations in sprayed areas.

Watanabe and Kang (1995) compared postservice mortality in Vietnam veterans in the Marine Corps with that in Vietnam-era marines who did not serve in Vietnam. All study participants were on active duty during 1967–1969 and were followed from their discharge date or from the date of the US military withdrawal from Vietnam until their date of death or December 31, 1991, whichever came

first. The final study population included 10,716 Vietnam and 9,346 non-Vietnam veteran marines.

Kang et al. (1991) conducted a case–control study that compared dioxin and dibenzofuran concentrations in the adipose tissue of 36 Vietnam veterans with those in 79 non-Vietnam veterans and a sample of US men born in 1936–1954. All tissue samples were archived specimens from the US Environmental Protection Agency National Human Adipose Tissue Survey and had been collected by hospitals and medical examiners from men who died from external causes or surgical procedures. Military service—branch of service, MOSC, and geographic service location in Vietnam, if applicable—was researched and verified with military records. Controls were matched by birth year and sample collection year (± 2 years), and the final analyses were adjusted by age and BMI.

Dalager et al. (1991) examined NHL in male Vietnam veterans in a hospital-based case–control study. Study participants were identified via inpatient discharge records from VA medical centers for fiscal years 1969–1985. Cases were identified as having a malignant lymphoma and a birth date during 1937–1954. Controls were identified from VA medical-center discharge records and were matched by hospital, discharge date, and birth date. The location and dates of each veteran's military service were verified by using military records. A surrogate Agent Orange exposure opportunity was also developed for each Vietnam veteran according to branch of service, combat experience, and geographic location of the military unit assignment. The final analysis included 201 cases and 358 controls. Another study by Dalager et al. (1995a) examined the association between HL and Vietnam service. It used the same method as the 1991 Dalager et al. study; the analysis included 283 HL cases and 404 controls.

VA has also evaluated specific health outcomes, including case–control studies of STS (Kang et al., 1986, 1987), testicular cancer (Bullman et al., 1994), and lung cancer (Mahan et al., 1997). It also has conducted a study of self-reported physical health (Eisen et al., 1991) and PTSD (Goldberg et al., 1990) in monozygotic twins who served during the Vietnam era.

VA has examined other outcomes in Vietnam veterans: PTSD (Bullman et al., 1991; True et al., 1988), suicide and motor-vehicle crashes (Bullman and Kang, 1996; Farberow et al., 1990), and tobacco use (McKinney et al., 1997). The studies have been included for completeness, but the outcomes that they address are outside the purview of this committee. *VAO* and *Update 1998* discuss them in detail; most did not deal with exposure to Agent Orange, and exposure to "combat" was evaluated as the risk factor of interest.

Chamie et al. (2008) examined the association between Agent Orange and prostate cancer among northern California Vietnam veterans, using self-reported exposure status (VAO *Update 2008*, p. 318). Since *Update 2008*, Schecter et al. (2009) have commented on that study, stating that the self-report method used in Chamie et al. (2008) "has been shown repeatedly to be unreliable." They noted the possibility that attenuation (underestimation of an association) would result

from the misclassification arising from an unreliable exposure measurement, which would be expected to strengthen the strong positive association observed. They also commented on the exclusion in Chamie et al. (2008) of cases diagnosed before 1998 as a limitation.

Female Vietnam Veterans Although estimates vary, 5,000–7,000 US women are believed to have served in Vietnam after volunteering for military service (Thomas et al., 1991). The vast majority of them served as combat nurses—mostly in the Army Nurse Corps—but some also served with the Women's Army Corps and the Air Force, Navy, and Marine Corps (Spoonster-Schwartz, 1987; Thomas et al., 1991).

In 1986, PL 99-972 was enacted, requiring that an epidemiologic study be conducted to examine long-term adverse health effects in female Vietnam veterans as a result of their exposure to traumatic experiences, exposure to such herbicides as Agent Orange or other chemicals or medications, or any similar experience or exposure during such service. The first study that VA conducted to assess mortality in female Vietnam veterans was by Thomas et al. (1991). No comprehensive record of female personnel who served in Vietnam in 1964–1972 existed, so researchers gathered military service data from each branch of the armed forces to conduct the mortality study through December 31, 1987. Female Army and Navy personnel were identified from morning reports and muster rolls of hospitals and administrative support units where women were likely to have served. Military personnel were identified as female by their names, leaving open the possibility that some women may have been inadvertently excluded from the analysis. Women who served in the Air Force and Marine Corps were identified through military records. The combined roster of all female personnel from the military branches was considered by the researchers to be relatively complete. A comparison group consisted of female veterans who were identified through the same process as the female Vietnam veterans but who had not served in Vietnam during their military service. Demographic information and information on overseas tours of duty, unit assignments, jobs, and principal duties were abstracted from military records. Mortality information was obtained from VA's beneficiary records, the Social Security Administration, the Internal Revenue Service, the National Death Index, and military personnel records. When women whose service in the military fell outside the period of interest, whose records were lacking data, or who served in SEA but not Vietnam were excluded, the analysis included 132 deaths in 4,582 female Vietnam veterans and 232 deaths in 5,324 comparison veterans who served in the military in July 4, 1965–March 28, 1973. Cause-specific mortality was derived for Vietnam veterans and comparison veterans and compared with mortality in US women with adjustment for race, age, and calendar period. Dalager et al. (1995b) updated mortality in the original cohort until December 31, 1991, using the same study protocol as Thomas et al. (1991). After updating of mortality figures and adjustment of the existing cohort on the basis of new information about the study groups based on the inclusion

criteria, 4,586 Vietnam veterans and 5,325 comparison veterans were included in the final analyses (Dalager et al., 1995b).

VA also published studies of pregnancy outcomes and gynecologic cancers—namely, neoplasms of the cervix, uterus, and ovary—in US female Vietnam veterans (Kang et al., 2000a,b). Army veterans were identified from a list obtained by the US Army and Joint Services Environmental Support Group; computerized lists were also provided by the Air Force, Navy, and Marine Corps. Military-service data were abstracted from personnel records. Of 5,230 eligible veterans, 4,390 whose permanent tour of duty included service in Vietnam were alive on January 1, 1992. From a pool of 6,657 potential control participants whose military units did not serve in Vietnam, 4,390 veterans who were alive on January 1, 1992, were randomly selected as controls. After exclusion of 250 veterans and 250 nonveterans who participated in a pilot study, an attempt was made to locate the remaining 4,140 veterans in each group. Various location strategies were used, and fewer than 5% (370) were not located; another 339 were deceased. A full telephone interview was conducted on 6,430; 775 refused (13% of Vietnam veterans and 17% of non-Vietnam veterans), and another 366 completed only a short written questionnaire. A questionnaire was administered on demographic background, general health, lifestyle, menstrual history, pregnancy history, pregnancy outcomes, and military experience, including nursing occupation and combat exposure. Information on pregnancy complications—including smoking, infections, medications, exposure to X rays, occupational history, and exposure to anesthetic gases, ethylene oxide, herbicides, and pesticides—was collected for each pregnancy. In Kang et al. (2000a), the first pregnancy after the beginning of Vietnam service was designated as the index pregnancy of each woman. For the comparison group, the first pregnancy after July 4, 1965, was used as the index pregnancy of each woman. Odds ratios were calculated for reproductive history and pregnancy outcomes. The study analyzed data on 3,392 Vietnam and 3,038 non-Vietnam veterans and on 1,665 Vietnam and 1,912 non-Vietnam veteran index pregnancies. In Kang et al. (2000b), a self-reported history of gynecologic cancers (defined by the authors as cancers of the breast, ovary, uterus, and cervix) was collected. The authors attempted to "retrieve hospital records on all reported cancers as far back as 30 years." Of records successfully found, 99% of the breast cancers and 90% of all cancers were confirmed. The authors did not provide data on validation of the three sites other than breast, but stated that Vietnam status was not associated with verification of outcome.

After the publications by Kang et al. (2000a,b), Congress passed PL 106-419, which provides compensation for children of female Vietnam veterans who are born with birth defects unrelated to an existing familial disorder, to a birth-related injury, or to a fetal or neonatal infirmity with a well-established cause. Eighteen birth defects are covered by the legislation, including cleft lip or palate, congenital heart disease, hypospadias, neural-tube defects, and Williams syndrome. A complete list of covered birth defects can be found in Section 3.815 of the legislation.

Cypel and Kang (2008) conducted a mortality study of female Vietnam veterans and compared their mortality with that in a control group of women who were in military service but did not participate in the Vietnam War. Non-Vietnam veterans were selected randomly from among women who never served in Vietnam and were matched to the Vietnam veterans according to rank and military occupation.

No reports on female Vietnam Veterans have been published since *Update 2008*.

American Legion The American Legion, a voluntary service organization for veterans, conducted a cohort study of the health and well-being of Vietnam veterans who were members. Studies examined physical health and reproductive outcomes, social–behavioral consequences, and PTSD in veterans who had served in SEA and elsewhere (Snow et al., 1988; Stellman JM et al., 1988; Stellman SD et al., 1988). No new studies have been published on the cohort.

State Studies Several states have conducted studies of Vietnam veterans, most of them unpublished in the scientific literature. *VAO* and *Update 1996* reviewed studies of veterans of Hawaii (Rellahan, 1985), Iowa (Wendt, 1985), Maine (Deprez et al., 1991), Massachusetts (Clapp, 1997; Clapp et al., 1991; Kogan and Clapp, 1985, 1988; Levy, 1988), Michigan (Visintainer et al., 1995), New Jersey (Fiedler and Gochfeld, 1992; Kahn et al., 1988, 1992a,b,c), New Mexico (Pollei et al., 1986), New York (Greenwald et al., 1984; Lawrence et al., 1985), Pennsylvania (Goun and Kuller, 1986), Texas (Newell, 1984), West Virginia (Holmes et al., 1986), and Wisconsin (Anderson et al., 1986a,b). No new state studies have been published.

Other US Vietnam-Veteran Studies Additional studies have examined health outcomes that included spontaneous abortion (Aschengrau and Monson, 1989) and late adverse pregnancy outcomes in spouses of Vietnam veterans (Aschengrau and Monson, 1990). After a published study indicated a potential association between testicular cancer in dogs and their service in Vietnam (Hayes et al., 1990), Tarone et al. (1991) conducted a case–control study of testicular cancer in male veterans. *VAO* summarized those studies, and no new studies have been published.

The 1997 Institute of Medicine request for proposals for historical-exposure reconstruction has led to the development of new methods for estimating Vietnam veterans' exposures to Agent Orange. The resulting Columbia University project integrated various sources of information on spraying activities to generate individualized estimates of the exposure potential of troops who served in Vietnam (Stellman and Stellman, 2003). Location data on military units assigned to Vietnam were compiled into a database developed from five primary and secondary sources: the Unit Identification Code list (a reference list of units serving in Vietnam created and used by the Army), a command-post list (division-level data on

command locations of Army personnel), Army Post Office lists (compilations of locations down to and including battalion size and other selected units updated monthly), troop-strength reports (data assembled by the US Military Assistance Command on troop allocations, updated monthly and generally collected on the battalion level), and order-of-battle information (data on command post, arrival and departure dates, and authorized strength of many units). For units that served in the III Corps Tactical Zone during 1966–1969, battalion-tracking data were also available; these are data on the grid coordinate locations of battalion-sized units derived from daily journals, which recorded company locations over 24-hour periods.

Mobility-factor analysis, a new concept for studying troop movement, was developed for use in reconstructing herbicide-exposure histories. The analysis is a three-part classification system for characterizing the location and movement of military units in Vietnam. It comprises a mobility designation (stable, mobile, or elements mobile), a distance designation (usually in a range of kilometers) to indicate how far a unit might travel in a day, and a notation of the modes of travel available to the unit: air, ground (truck, tank, or armored personnel carrier), or water. A mobility factor was assigned to every unit that served in Vietnam.

All those data were combined into a geographic information system (GIS) for Vietnam with a grid resolution of 0.01° latitude and 0.01° longitude. Herbicide-spraying records were integrated into the GIS and linked with data on military-unit locations to permit estimation of exposure-opportunity scores for individuals. The results are the subject of reports by the contractor (Stellman and Stellman, 2003) and the responsible IOM committee (IOM, 2003b,c). A summary of the findings regarding the extent and pattern of herbicide spraying (Stellman et al., 2003a), a description of the GIS for characterizing exposure to Agent Orange and other herbicides in Vietnam (Stellman et al., 2003b), and an explanation of the exposure-opportunity models based on that work (Stellman and Stellman, 2004) have been published in peer-reviewed journals. The publications argue that it is now feasible to conduct epidemiologic investigations of veterans who served as ground troops during the Vietnam War. IOM later issued a report that examined the feasibility of using the Agent Orange Reconstruction Model developed by Columbia University (IOM, 2008). The report concluded that "despite the shortcomings of the exposure assessment model in its current form and the inherent limitations in the approach, the committee agreed that the model holds promise for supporting informative epidemiologic studies of herbicides and health among Vietnam veterans and that it should be used to conduct studies."

A different perspective has been put forth in a series of papers (Young and Newton, 2004; Young et al., 2004a,b) that argue that ground troops had little direct contact with herbicide sprays and that TCDD residues in Vietnam had low bioavailability. Those conclusions were based on analyses of previously unpublished military records and environmental-fate studies. They also argue that ground-troop exposures were relatively low because herbicide-spraying missions were carefully planned and spraying occurred only when friendly forces were

not in the target area. Finally, they note that the GIS-based exposure-opportunity model has not yet been validated through measurement of serum dioxin concentrations in veterans (Young, 2004).

Australia

The Australian government has commissioned studies to investigate health risks to Australian veterans: birth anomalies (Donovan et al., 1983, 1984; Evatt, 1985), death (ADVA, 2005a; CIH, 1984a,b,c; Crane et al., 1997a,b; Evatt, 1985; Fett et al., 1987a,b; Forcier et al., 1987), morbidity (AIHW, 1999, 2000, 2001; CDVA, 1998a,b), cancer (ADVA, 2005b; results supersede those in CDVA, 1998a), and death and cancer in Australian National Service veterans (ADVA, 2005c; results supersede those in CIH, 1984a; Crane et al., 1997b; Fett et al., 1984). Those government-sponsored studies of Australian Vietnam veterans did not characterize the veterans' exposure to the herbicides sprayed in Vietnam beyond the fact that they served on land or in Vietnamese waters during May 23, 1962–July 1, 1973. It is the convention of VAO committees, however, to regard Vietnam veterans in general as being more likely to have received higher exposures to the chemicals of concern than the general public. Nevertheless, it would have been informative to validate that assumption by gathering biomarkers of exposure, such as serum measurements, in a sample of Australian Vietnam veterans.

Update 2000 had moved the occurrence of acute myeloid leukemia (AML) among the offspring of Vietnam veterans in to the limited or suggestive category of association primarily on the basis of findings reported in AIHW (2000), but rescinded in a revised report (AIHW (2001). The reversion of the conclusion on this matter by the committee for *Update 2000* is discussed in the special report (IOM, 2002)

O'Toole et al. (1996a,b,c) described self-reported health status in a random sample from the roster of Australian Army Vietnam veterans. Since *Update 2008*, O'Toole et al. (2009) have published an update for O'Toole et al. (1996a,b,c). The update is a prospective study based on a sample of 1,000 Australian Army Vietnam veterans (both regular enlistment and National Service conscription) selected randomly from an overall population of 57,643 service members deployed to Vietnam. Members of the sample have been sought for interviews twice: 641 responded in wave 1 in 1990–1993 and 450 in wave 2 in 2005–2006, with 391 responding to both waves. The Australian Bureau of Statistics National Health Survey was administered in both waves with collection of additional data on combat experience, PTSD, and general psychiatric status. The specific health outcomes examined include neoplasms (melanoma and prostate cancer); thyroid conditions; diabetes; lipids; eye and ear conditions; and circulatory conditions (hypertension, ischemic heart disease, and cerebrovascular disease). The Vietnam veterans' self-reported health status was compared with responses of the general male Australian population (standardized to the age distribution of the Vietnam veterans) to the Australian National Health Surveys gathered in 1989–1990 and

2004–2005; it is not clear that this instrument was administered to the two groups under comparable conditions. In addition, the survey data obtained from the Vietnam veterans were used to model the relationship between specific health outcomes and various predictors with logistic regression models, but exposure to the herbicides sprayed in Vietnam was not characterized. In Model 1, interview data obtained from the wave 2 cohort were used to fit logistic regression models for each health endpoint to Army service data (type of enlistment, service details [including duration of Vietnam service], conduct and casualty information, pre-enlistment education and employment, and Army psychologic classification test results). In Model 2, interview data obtained from the overlap between wave 1 and wave 2 cohorts were used to fit an expanded model that includes the same Army service data plus wave 1 data (smoking and alcohol status, PTSD, self-reported combat index, and psychiatric diagnoses).

An important limitation in this study is the low rate of response to the wave 2 survey (450 respondents of the original sample of 1,000, 51.4% of those not known to have died). The response rate for the combination of the two surveys is even lower. With such low response rates, the findings from the study are vulnerable to nonresponse bias if the nonrespondents differ from the respondents in important ways. In addition, the use of self-report measures of health conditions used in the study might be of low validity and subject to recall bias. In that the present committee was very skeptical about the reliability of the nearly uniform findings of statistically increased prevelance for nearly 50 health conditions, little attention was given to the modeling efforts.

Korea

Military personnel of the Republic of Korea served in Vietnam during 1964–1973. Kim et al. (2001) attempted to use serum dioxin concentrations to validate an index for estimating group exposure. The study involved 720 veterans who served in Vietnam and 25 veterans who did not. The exposure index was based on Agent Orange spraying patterns in military regions in which Korean personnel served, time–location data on the military units stationed in Vietnam, and an exposure score derived from self-reported activities during service. A total of 13 pooled samples were submitted to CDC for serum dioxin analysis. One analytic sample was prepared from the pooled blood of the 25 veterans who did not serve in Vietnam. The remaining 12 samples were intended to correspond to 12 exposure categories; each was created by pooling blood samples from 60 veterans. The 12 exposure categories ultimately were reduced to four exposure groups, each representing a quartile of 180 Vietnam veterans but characterized by only three serum TCDD measurements.

The paper by Kim et al. (2001) reported highly significant Pearson correlation coefficients and results of multiple logistic-regression analysis. The statistical analyses apparently were based on the assignment of the pooled serum dioxin value to each individual in the exposure group, thereby inflating the true sample

size. The multiple regression analysis evaluated such variables as age, BMI, and consumption of tobacco or alcohol. In a later report on the same exposure groups and serum dioxin data, the authors corrected their analysis (Kim J-S et al., 2003). A correlation was observed between serum dioxin concentrations and ordinal exposure categories, but the correlation was not statistically significant. The authors attributed the lack of statistical significance to the small sample, and they noted that the data exhibited a distinct monotonic upward trend (average serum dioxin concentrations, 0.3, 0.6, 0.62, 0.78, and 0.87 pg/g [lipid-adjusted] for exposure categories 0–4, respectively). The decision to pool blood samples from a large number of persons within each exposure set (Kim et al., 2001) greatly reduced the power of the validation study. Instead of 180 samples in each of the final exposure categories, the pooled analysis produced only three samples in each category. The lipid-adjusted serum TCDD concentrations from the 12 pooled samples from Vietnam veterans ranged from 0.25 to 1.2 pg/g, whereas the single sample from the non-Vietnam veterans contained 0.3 pg/g. The narrow range of results makes the biologic relevance of any differences questionable.

Thus, it appears that there was not a clear separation between Korean Vietnam veterans and non-Vietnam veterans. Furthermore, the range of mean values for the four Vietnam-veteran exposure categories was narrow, and all concentrations were relatively low (less than 1 pg/g). The relatively low serum dioxin concentrations observed in the 1990s in those people are the residual of substantially higher initial concentrations, as has been seen in other Vietnam-veteran groups. However, the concentrations reported in the Korean-veterans study are significantly lower than those reported in American Vietnam veterans in the 1988 CDC Agent Orange Validation Study, which was nonetheless unable to distinguish Vietnam veterans from non-Vietnam veterans on the basis of serum dioxin (CDC, 1988a). The Korean authors were able to construct plausible exposure categories based on military records and self-reporting, but they were unable to validate the categories with serum dioxin measurements.

Epidemiologic studies also looked at immunotoxicologic effects (Kim H-A et al., 2003) and skin and general disease patterns (Mo et al., 2002) in Korean Vietnam veterans who were exposed to Agent Orange during the Vietnam conflict.

No reports on Korean Vietnam veterans have been published since *Update 2004*.

OCCUPATIONAL STUDIES

Several occupational groups in the United States and elsewhere have been exposed to the chemicals of interest. Exposure characterization varies widely in the metric used, the extent of detail, confounding by other exposures, and whether individual, surrogate, or group (ecologic) measures are used. Some studies use job titles as broad surrogates of exposure; others rely on disease-registry data.

The committee reviewed many epidemiologic studies of occupationally exposed groups for evidence of an association between health risks and exposure

to TCDD or to the herbicides used in Vietnam, primarily the phenoxy herbicides 2,4-D and 2,4,5-T. TCDD is an unwanted byproduct of 2,4,5-T production but not of 2,4-D production. Other contaminants, including other dioxins (such as 1,3,6,8-tetrachlorodibenzo-*p*-dioxin) have been reported at low concentrations in 2,4-D, but those identified do not have the toxicity of TCDD (ATSDR, 1998; Huston, 1972; Norström et al., 1979). In reviewing the studies, the committee considered two types of exposure separately: exposure to 2,4-D or 2,4,5-T and exposure to TCDD from 2,4,5-T or other sources. That separation is necessary because some health effects could be associated with exposure to 2,4-D or 2,4,5-T in the absence of substantial TCDD exposure. After recognition of the problem of dioxin contamination in phenoxy herbicides, production conditions were modified to minimize contamination, but use of the products most subject to containing specifically TCDD (2,4,5-T and Silvex) was banned. As a result, study participants exposed to phenoxy herbicides only after the late 1970s would not be assumed to have been at risk for exposure to TCDD.

The distinction is particularly important for workers in agriculture and forestry, including farmers and herbicide appliers, whose exposure is primarily the result of mixing, loading, and applying herbicides. In addition to those occupational groups, the committee considered studies of occupational exposure to dioxins, focusing on workers in chemical plants that produced phenoxy herbicides or chlorophenols, which tend to be contaminated with polychlorinated dibenzo-*p*-dioxins (PCDDs). Waste-incineration workers were also included in the occupation category because they can come into contact with dioxin-like compounds while handling byproducts of incineration. Other occupationally exposed groups included were pulp and paper workers exposed to dioxins through bleaching processes that use chlorinated compounds and sawmill workers exposed to chlorinated dioxins that can be contaminants of chlorophenates used as wood preservatives.

Production Workers

International Agency for Research on Cancer

A multisite study by IARC involved 18,390 production workers and phenoxy herbicide sprayers working in 10 countries (Saracci et al., 1991). The full cohort was established by using the International Register of Workers Exposed to Phenoxy Herbicides and Their Contaminants. Twenty cohorts were combined for the analysis: one each in Australia, Austria, Canada, Finland, and Sweden; two each in Denmark, Italy, the Netherlands, and New Zealand; and seven in the United Kingdom. There were 12,492 production workers and 5,898 sprayers in the full cohort.

Questionnaires were constructed for workers who were manufacturing chlorophenoxy herbicides or chlorinated phenols and for herbicide sprayers and were completed with the assistance of industrial hygienists. Information from

production records and job histories were examined when available. Workers were classified as exposed, probably exposed, with unknown exposure, or non-exposed. The exposed-workers group (n = 13,482) consisted of all those known to have sprayed chlorophenoxy herbicides and all who worked in particular aspects of chemical production. Two subcohorts (n = 416) had no job titles available but worked in chemical-production facilities that were likely to produce TCDD exposure, so they were deemed probably exposed. Workers with no exposure information (n = 541) were classified as "exposure unknown." Nonexposed workers (n = 3,951) were those who had never been employed in parts of factories that produced chlorophenoxy herbicides or chlorinated phenols and had never sprayed chlorophenoxy herbicides.

One study evaluated mortality from STS and malignant lymphoma in people in 10 countries (Kogevinas et al., 1992). A cohort study of cancer incidence and mortality was conducted in 701 women in seven countries who were occupationally exposed to chlorophenoxy herbicides, chlorophenols, and dioxins (Kogevinas et al., 1993). Two nested case–control studies were undertaken with the IARC cohort to evaluate the relationship between STS and NHL (Kogevinas et al., 1995).

An expanded and updated analysis of the IARC cohort was published in 1997 (Kogevinas et al., 1997). The researchers added herbicide-production workers in 12 plants in the United States (the NIOSH cohort) and 4 plants in Germany. The 21,863 workers exposed to phenoxy herbicides or chlorophenols were classified in three categories of exposure to TCDD or higher-chlorinated dioxins: those exposed (n = 13,831), those not exposed (n = 7,553), and those with unknown exposure (n = 479). Several exposure metrics were constructed for the cohort—years since first exposure, duration of exposure (in years), year of first exposure, and job title—but detailed methods were not described. Vena et al. (1998) studied nonneoplasm mortality in the IARC cohorts. *VAO*, *Update 1996, Update 1998*, and *Update 2000* highlight those studies.

No new publications for the IARC cohort were identified for this review.

International Agency for Research on Cancer Subcohorts

In addition to the NIOSH cohort and its component subcohorts (discussed above), several of the other subcohorts that make up the IARC cohort have been evaluated apart from the IARC-coordinated efforts. They include Danish production workers (Lynge, 1985, 1993), British production workers (Coggon et al., 1986, 1991), Dutch production workers (Boers et al., 2010; Bueno de Mesquita et al., 1993; Hooiveld et al., 1998), Austrian production workers (Jäger et al., 1998; Neuberger et al., 1998, 1999), New Zealand production workers (McBride et al., 2009a,b; Smith et al., 1981, 1982; 't Mannetje et al., 2005), and German production workers (Becher et al., 1996; Flesch-Janys, 1997; Flesch-Janys et al., 1995; Manz et al., 1991). The studies of those groups are discussed below.

Flesch-Janys et al. (1995) updated the cohort and added a quantitative exposure assessment based on blood or adipose measurements of PCDDs and polychlorinated dibenzofurans (PCDFs). The authors estimated maximum PCDD and PCDF exposure of 190 workers with a first-order kinetics model, half-lives with an elimination study of 48 workers in the cohort, and background concentrations in the German population. They then regressed the estimated maximum PCDD and PCDF exposures of the workers against the length of time that they worked in each production department in the plant. The working-time weights were then used with work histories of the remainder of the cohort to estimate PCDD and PCDF exposure of each person at the end of that person's exposure. Those values were used to estimate TCDD doses in the population. Becher et al. (1996) conducted an analysis of several German cohorts, including the Boehringer–Ingelheim cohort described above (Kogevinas et al., 1997), a cohort from the BASF Ludwigshafen plant that did not include those involved in a 1953 accident, and cohorts from a Bayer plant in Uerdingen and a Bayer plant in Dormagen. All the plants were involved in production of phenoxy herbicides or chlorophenols. Exposure assessment involved estimates of duration of employment from the start of work in a department where exposure was possible until the end of employment in the plant. Analysis was based on time since first exposure. Hooiveld et al. (1998) updated the mortality experience of production workers in two chemical factories in the Netherlands with known exposure to dioxins: workers in herbicide production, nonexposed production workers, and workers known to have been exposed as a result of an accident that occurred in 1963. On the basis of an assumption of first-order TCDD elimination with an estimated half-life of 7.1 years, measured TCDD concentrations were extrapolated to the time of maximum TCDD exposure of a group of 47 workers. A regression model was then used to estimate, for each cohort member, the effect on estimated maximum TCDD exposure attributable to exposure as a result of the accident, duration of employment in the main production department, and time of first exposure before (or after) 1970. The studies of those groups were discussed in more detail in *VAO*, *Update 1996*, *Update 1998*, *Update 2000*, and *Update 2006*.

Several reports on the Dutch and New Zealand subcohorts of the IARC cohort have been published since *Update 2008*.

Boers et al. (2010) conducted updated analyses based on the third follow-up (1955–2006) of the Dutch subcohort of the IARC cohort, examining cause-specific mortality (from cancer and not from cancer) in 2,106 male workers employed in two manufacturing factories (A and B) that produced and formulated chlorophenoxy herbicides (2,4,5-T at Factory A; 2-methyl-4-chlorophenoxyacetic acid [MCPA], methylchlorophenoxypropionic acid, and 2,4-D at Factory B). The study populations were defined as all workers who worked at Factory A during 1955–1985 or Factory B during 1965–1986. Both cohorts were followed through 2006; this accumulated 65,087 person-years and 567 observed deaths. Sample loss was minimal (less than 1% lost to follow-up, and less than 5%

emigrated). Linkage to death certificates at Statistics Netherlands was used to ascertain cause-specific mortality, including various cancers (stomach, pancreas, lung, melanoma, prostate, bladder, kidney, genitourinary, NHL, and leukemia), endocrine and blood diseases, nervous system diseases, ischemic heart disease and other heart disease, cerebrovascular disease, respiratory diseases, digestive diseases, and genitourinary diseases. Exposure status was classified according to the type of work experience (such as production vs office) and involvement in the 1963 accident at Factory A. TCDD measures taken in 1993 support this exposure classification: the highest mean TCDD concentrations were found in workers who were involved in the 1963 accident (1,841.8 ppt) or who worked in main production (608.2 ppt), whereas concentrations in nonexposed workers were much lower (7.6 ppt). Cox proportional-hazards models, with attained age as the time scale, were used to assess hazard ratios for exposed vs nonexposed workers. Exposure to phenoxy herbicides and dioxins was expected to be different between Factory A and Factory B, so the factories were analyzed separately. Further nested case–control studies were conducted for the Factory A cohort by using all 112 cancer cases and three controls per case matched on age and employment period, the analysis used conditional logistic regression.

McBride et al. (2009a,b), Collins et al. (2009c), and Burns et al. (2010) examined the New Zealand subcohort of the IARC cohort, which comprised employees who worked at the Dow AgroSciences (formerly Ivon Watkins-Dow) plant in New Plymouth that manufactured diverse agrochemical products, including phenoxy herbicides. McBride et al. (2009a) conducted expanded and updated analyses of cause-specific mortality (from both cancer and other conditions) in 1,599 participants who worked at the site at any time from January 1, 1969, to November 1, 1988 (referred to hereafter as the 1988 cohort). McBride et al. (2009b) included 1,754 participants who worked at the site at any time from January 1, 1969, to October 1, 2003 (the 2003 cohort). Both cohorts are followed through 2004. The New Zealand Health Information Service Mortality Collection was used to identify deaths (n = 247 for both cohorts; it appears that there were no deaths among the increment of 155 workers who were in the 2003 cohort but not in the 1988 cohort). Exposure status was classified according to work experience. A subsample of the 1988 cohort participated in a serum dioxin analysis (n = 346, 70% exposed). The results from McBride et al. (2009b) have not been included in the outcome chapters in this report, because the results were diluted by inclusion of a set of workers who had no opportunity for TCDD exposure and no observed deaths.

Collins et al. (2009c) described the group's serum TCDD concentrations overall, and Burns et al. (2010) performed analyses to determine what factors might predict serum TCDD: age, BMI, and employment history were found to be significant determinants. In particular, the exposed group has significantly ($p = 0.03$) higher concentrations (9.9 ppt) than the unexposed group (4.8 ppt); number of years since termination is associated significantly ($p = 0.002$) with

lower TCDD; and serum TCDD is also associated significantly ($p < 0.0001$) with predicted cumulative TCDD exposure based on area-under-the-curve for a pharmacokinetic model of the accumulation and elimination of dioxins. Both studies reported standardized mortality ratios (SMRs) that were derived by using the Occupational Cohort Mortality Analysis Program with the New Zealand population as the reference population and adjusted for age, sex, and calendar age. For the 1988 cohort, SMRs were stratified by exposure status (ever exposed and never exposed) and by predicted cumulative exposure categories. For the 2003 cohort, SMRs were reported for the entire cohort and stratified by employment duration (less than 3 months and at least 3 months) and by latency (15 years and less than 15 years of latency). For the 1988 cohort, proportional-hazards survival analysis was also used to test the association between mortality and predicted cumulative exposure categories.

The New Zealand studies have several important limitations. The sample loss was substantial: 13% were lost to follow-up in both cohorts; and 8% emigrated in the 1988 cohort and 9% in the 2003 cohort. If sample loss was nonrandom, the study findings might be vulnerable to sample selection bias. In addition, the inclusion in the 2003 cohort of the employees hired as recently as 2003 is questionable. It appears that no deaths were observed in the increment between the 1988 cohort and the 2003 cohort (those hired since 1988), presumably because these participants are relatively young. The inclusion of the incremental participants might dilute the power of the study to detect effects of TCDD exposures on health outcomes that require a long latent period; participants who have not yet "matured" through the latent period might be contributing noise rather than signal to the analyses. The committee, therefore, did not give substantial weight to the dose–response findings of McBride et al. (2009b).

National Institute for Occupational Safety and Health

Starting in 1978, an extensive set of data on chemical production workers potentially contaminated with TCDD in 1942–1984 has been compiled by NIOSH. More than 5,000 workers who were involved in production or maintenance at any of 12 companies were identified from personnel and payroll records; 172 additional workers identified previously by their employers as being exposed to TCDD were also included in the study cohort. The employees' possible exposure resulted from working with substances of which TCDD was a contaminant: 2,4,5-T, 2,4,5-trichlorophenol (2,4,5-TCP), 2-(2,4,5-trichlorophenoxy) propionic acid (Silvex, 2,4,5-TP), 2-(2,4,5-trichlorophenoxy) ethyl 2,2-dichloropropionate (Erbon), *o*,*o*-dimethyl *o*-(2,4,5-trichlorophenoxy) phosphorothioate (Ronnel®), and hexachlorophene. The 12 plants involved were large manufacturing sites of major chemical companies, so many of the participants were potentially exposed to many other compounds, some of which could be toxic and carcinogenic. The NIOSH cohort was added to the IARC cohort as of the 1997 publication by Kogevinas et al. (1997).

Exposure status was determined initially through a review of process operating conditions, employee duties, and analytic records of TCDD in industrial-hygiene samples, process streams, products, and waste (Fingerhut et al., 1991). Occupational exposure to TCDD-contaminated processes was confirmed by measuring serum TCDD in 253 cohort members. Duration of exposure, defined as the number of years worked in processes contaminated with TCDD, was used as the primary exposure metric in the study. The use of duration of exposure as a surrogate for cumulative exposure was based on a correlation (Pearson correlation efficient, 0.72) between log-transformed serum TCDD and number of years worked in TCDD-contaminated processes. Duration of exposure of individual workers was calculated from work records, and exposure-duration categories were created: less than 1 year, 1 to less than 5 years, 5 to less than 15 years, and 15 years and longer. In some cases, information on duration of exposure was not available, so a separate metric, duration of employment, was defined as the total time that each worker was employed at the study plant.

Before the first publication of mortality results for the main cohort, the NIOSH Cross-sectional Medical Study gathered comprehensive medical histories, conducted medical examinations, and measured the pulmonary function of workers employed in chemical manufacturing at plants in Newark, New Jersey (1951–1969) and Verona, Missouri (1968–1972). Control participants were recruited from surrounding neighborhoods (Sweeney et al., 1989, 1993). The New Jersey plant manufactured 2,4,5-TCP and 2,4,5-T; the Missouri plant manufactured 2,4,5-TCP, 2,4,5-T, and hexachlorophene. Specific health outcomes were evaluated in the members of this subcohort, including porphyria cutanea tarda (Calvert et al., 1994) and effects on pulmonary function (Calvert et al., 1991), hepatic and gastrointestinal function (Calvert et al., 1992), mood (Alderfer et al., 1992), the peripheral nervous system (Sweeney et al., 1993), and reproductive hormones (Egeland et al., 1994). Sweeney et al. (1996, 1997/1998) reviewed and updated noncancer outcomes, including hepatic function, gastrointestinal disorders, chloracne, serum glucose concentration, hormone and lipid concentrations, and diabetes. The data gathered from the two plants were also examined for cardiovascular effects (Calvert et al., 1998); diabetes mellitus, thyroid function, and endocrine function (Calvert et al., 1999); immune characteristics (Halperin et al., 1998); and cancer incidence (Kayajanian, 2002). Cross-sectional medical surveys reported serum TCDD concentrations and surrogates of cytochrome P450 induction (Halperin et al., 1995) in that cohort. Lawson et al. (2004) studied three birth outcomes—birth weight, preterm delivery, and birth defects—in offspring of the cohort members by comparing serum TCDD concentrations with those in a reference population. TCDD exposures at conception were estimated by using physiologically based pharmacokinetic modeling (Dankovic et al., 1995; Thomaseth and Salvan, 1998).

A follow-up study (Steenland et al., 1999) examined the association between TCDD exposure and cause of death; it examined specific health outcomes, includ-

ing cancer (all and site-specific), respiratory disease, cardiovascular disease, and diabetes. The researchers used a more refined exposure assessment than previous analyses; it excluded workers whose records were inadequate to determine duration of exposure, and this reduced the number of study participants to a subcohort of 3,538 workers (69% of the overall cohort). The exposure assessment for the subcohort was based on a job–exposure matrix (JEM) that assigned each remaining worker a quantitative exposure score for each year of work (Piacitelli and Marlow, 1997).

Steenland et al. (2001a) reanalyzed data from two studies of TCDD and diabetes mellitus: one in the US workers of the NIOSH cohort (Calvert et al., 1999) and one in veterans of Operation Ranch Hand in which the herbicides were sprayed from planes in Vietnam (Henriksen et al., 1997). Another study by Steenland et al. (2001b) included a detailed exposure–response analysis of data on workers at one of the original 12 companies in the cohort study. A group of 170 workers who had serum TCDD greater than 10 ppt, as measured in 1988 in the NIOSH Cross-sectional Medical Study, was identified. The investigators conducted a regression analysis by using the work history of each worker, the exposure score for each job held by each worker, a simple pharmacokinetic model of the storage and excretion of TCDD, and an estimated TCDD half-life of 8.7 years. The pharmacokinetic model allowed calculation of the estimated serum TCDD concentration at the time of last exposure of each worker. Results of the analysis were used to estimate the serum TCDD concentration that was attributable to occupational exposure of all 3,538 workers in the subcohort defined in 1999.

Using exposure data on the NIOSH cohort from Steenland et al. (2001b), Crump et al. (2003) conducted a meta-analysis of dioxin dose–response studies in three occupational cohorts: the NIOSH cohort (Fingerhut et al., 1991), the Hamburg cohort (Flesch-Janys et al., 1998), and the BASF cohort (Ott and Zober, 1996). Bodner et al. (2003) compared mortality in Dow Chemical Company workers with mortality in the NIOSH and IARC cohorts; study details are in the Dow Chemical Company section of this chapter.

Aylward et al. (2005a) applied a concentration- and age-dependent elimination model to the NIOSH cohort data to determine the impact of these factors on estimates of serum TCDD concentrations. The authors found that their model produced a better fit to serum sampling data than first-order models did. Dose rates varied by a factor of 50 among different combinations of input parameters, elimination models, and regression models. The authors concluded that earlier dose-reconstruction efforts may have underestimated peak exposure in these populations. Aylward et al. (2005b) also applied the concentration- and age-dependent elimination model to serial measurements of serum lipid TCDD concentrations in 36 adults in Seveso, Italy, and three adults in Vienna, Austria, who had documented TCDD exposure. They concluded that a large degree of uncertainty is characteristic of back-calculated dose estimates of peak TCDD exposure and recommended that further analyses explicitly recognize the uncertainty.

Since *Update 2008*, Richardson (2010) has used data from the NIOSH cohort (Steenland et al., 1999, 2001a,b) to illustrate the use of person–time logistic regression as an alternative to a proportional-hazards model for survival outcomes. Model parameters fitted using the two methods were nearly identical.

Monsanto

The NIOSH study cohort (Fingerhut et al., 1991) included employees of the Monsanto facility in Nitro, West Virginia, that produced 2,4,5-T in 1948–1969. Zack and Suskind (1980) examined the mortality experience of the 121 men who had chloracne associated with an unintentional release that occurred on March 8, 1949. Other studies considered mortality and other health outcomes in additional workers involved in numerous aspects of 2,4,5-T production at the Monsanto plant (Collins et al., 1993; Moses et al., 1984; Suskind and Hertzberg, 1984; Zack and Gaffey, 1983). The Monsanto studies were discussed in more detail in *VAO*. No additional studies on those participants alone have been published; they have since been followed as part of the NIOSH and IARC cohorts.

Dow Chemical Company

Workers at Dow Chemical Company facilities where 2,4-D was manufactured, formulated, or packaged have been the focus of a cohort analysis since the 1980s (Bond et al., 1988). Several studies of Dow production workers are summarized in *VAO*, *Update 1996*, *Update 1998*, *Update 2002*, and *Update 2004*. Originally, Dow conducted a study of workers engaged in the production of 2,4,5-T (Ott et al., 1980) and one of trichlorophenol (TCP)-manufacturing workers who had chloracne (Cook et al., 1980). Industrial hygienists developed a JEM that ranked employee exposures as low, moderate, or high on the basis of available air-monitoring data and professional judgment. The matrix was merged with employee work histories to assign an estimate of exposure to each job. A cumulative dose was then developed for each of the 878 employees by multiplying the representative 8-hour time-weighted average (TWA) exposure value for each job by the number of years in the job and then adding the products for all jobs. A 2,4-D TWA of 0.05 mg/m_3 was used for low, 0.5 mg/m_3 for moderate, and 5 mg/m_3 for high exposure. The role of dermal exposure in the facilities does not appear to have been considered in the exposure estimates. It is not clear to what extent the use of air measurements alone can provide accurate classification of workers into low-, moderate-, and high-exposure groups. Biologic monitoring of 2,4-D apparently was not included in the study.

Extension and follow-up studies compared potential exposure to TCDD with morbidity (Bond et al., 1983) and potential paternal TCDD exposure with reproductive outcomes (Townsend et al., 1982). Dow employees who had a diagnosis of chloracne or who were classified as having chloracne on the basis of a clinical

description were followed prospectively for mortality (Bond et al., 1987). Large-scale cohort mortality studies of workers exposed to herbicides in several of the plants (Bloemen et al., 1993; Bond et al., 1988; Burns et al., 2001) also were conducted with the same exposure-assessment procedures.

Dow assembled a large cohort at the Midland, Michigan, plant (Bond et al., 1989a; Cook et al., 1986, 1987). Exposure to TCDD in the cohort was characterized on the basis of chloracne diagnosis (Bond et al., 1989b). Within the cohort, a cohort study of women (Ott et al., 1987) and a case–control study of STS (Sobel et al., 1987) were conducted. The Dow cohorts have been followed as part of the NIOSH and IARC cohorts since 1991 and 1997, respectively.

Dow also has conducted a cohort study of its manufacturing workers exposed to pentachlorophenol (PCP) (Ramlow et al., 1996). The exposure assessment evaluated the available industrial-hygiene and process data, including recollections from employees about processes and jobs, information about changes in processes and engineering controls, measurements from surface wipes, and exposure monitoring data from area sampling and personal breathing zones. Jobs in the"flaking/prilling/packaging area" were determined to have higher potential exposure because of dermal exposure to airborne PCP; the industrial-hygiene data suggested a difference of about a factor of 3 between the areas of highest and lowest potential exposure. An estimated exposure-intensity score of 1–3 (from lowest to highest potential exposure intensity) was assigned to each job. Information concerning the use of personal protective equipment was deemed to be unreliable. For each participant, cumulative PCP and TCDD exposure indexes were calculated by multiplying the duration of each exposed job by its estimated exposure intensity and then summing across all exposed jobs.

Bodner et al. (2003) published a 10-year follow-up of the work of Cook et al. (1986), comparing the mortality experience of 2,187 male Dow workers potentially heavily exposed to dioxin before 1983 with that of the NIOSH and IARC cohorts. Dow researchers have published a study of serum dioxin concentrations measured in 2002 in former chlorophenol workers (Collins et al., 2006). Most of the workers in the study were included in the NIOSH and IARC cohorts. The authors used their data to estimate worker exposures at the time of exposure termination by using several pharmacokinetic models. They concluded that their findings were consistent with those of other studies that reported high serum dioxin concentrations in chlorophenol workers after occupational exposures.

Since *Update 2008*, a set of articles following up on cause-specific mortality (both cancer and noncancer) and TCP (Collins et al., 2009a) and PCP (Collins et al., 2009b) workers at the Dow Chemical site in Midland, Michigan, have been published; 196 people belonged in both groups. The cohort of TCP workers with potential exposure specifically to TCDD is one of the eight cohorts in the NIOSH cohort of dioxin-exposed US workers. Collins et al. (2008) presented exposure information on the entire group of workers.

The TCP cohort consists of 1,615 people who worked with TCP or 2,4,5-T

during 1942–1982 and whose vital status was followed from 1942 through 2003; 58,743 person-years were accumulated, and 662 deaths were observed. SMRs for cause-specific mortality in the cohort—with and without the overlap of 196 people with the PCP cohort in Collins (2009b)—were calculated by using the US population as the reference population and using the Occupational Cohort Mortality program. Proportional-hazards survival analysis was also used to assess the association between predicted cumulative TCDD exposure and mortality on the basis of a pharmacokinetic model applied to work-history information (Aylward et al., 2007). Villeneuve and Steenland (2010) raised several concerns about this study, including the need to consider latency of 15–20 years, the need to consider alternative specifications for the dose–response relationship other than the linear specification used, the apparent inconsistency between the nonsignificant dose–response coefficient in Collins et al. (2009a) and the corresponding findings in previous analyses of the NIOSH cohort (Steenland et al., 1999) that included the Dow cohort, and the need for further details about the distribution of estimated cumulative serum concentrations, compared with the measured serum concentrations. Collins et al. (2010) did not provide adequate responses to those concerns.

Collins et al. (2009b) reported a similar study of people who were engaged in the manufacture of PCP from 1937 to 1980 at the same plant as the TCP cohort, with the accrual of years-at-risk starting from the beginning of 1940. Unlike TCP, PCP did not contain TCDD, but it did contain other highly chlorinated dioxin congeners, and 20% of the PCP workers had suffered from chloracne. The cohort was followed for "up to 64 years." Although the date of closure for the follow-up was not provided explicitly, it appears that the cohort was followed through 2003, as were the TCP workers. The cohort consisted of 773 PCP workers; 27,035 person-years were accumulated, and 370 deaths were observed. SMRs for the PCP cohort (with and without the overlap of 196 people with the TCP cohort) were given for cause-specific mortality with the US population as the referent population. Proportional-hazards survival analysis was also used to assess the association between mortality and predicted cumulative exposure as total toxic equivalent to TCDD.

BASF

An accident on November 17, 1953, during the manufacture of TCP at a BASF plant in Germany resulted in extreme exposure of some workers to TCDD. *VAO*, *Update 1996*, *Update 1998*, and *Update 2000* summarized studies of those workers, including a mortality study of persons initially exposed or later involved in cleanup (Thiess et al., 1982), an update and expansion of that study (Zober et al., 1990), and a morbidity follow-up (Zober et al., 1994). In addition, Ott and Zober (1996) and Zober et al. (1997) examined cancer incidence and mortality in workers exposed to TCDD after the accident or during reactor cleanup, maintenance, or demolition.

No studies have been published on those cohorts since *Update 2000*.

Czech Worker Studies

Several studies of Czech workers have been reviewed by VAO committees. The original committee reviewed a 10-year follow-up study of 55 men in Czechoslovakia who were exposed to TCDD during the production of 2,4,5-T (Pazderova-Vejlupková et al., 1981). The exposure occurred because of excessive temperature and pressure in the production process over an extended period (1965–1968) rather than as a consequence of a major release at a single time. More than 80 workers were affected, but the researchers provided little information about those who were not included in the study. Researchers observed several disorders in the workers, including chloracne, metabolic disturbances, abnormal results of glucose-tolerance tests, evidence of a mild hepatic lesion, nervous system focal damage, and psychologic disorders. In a 30-year follow-up, Pelclová et al. (2001, 2002) examined biochemical, neuropsychologic, neurologic, and lipid-metabolism abnormalities in the surviving Czech cohort. Previous VAO committees concluded that there were methodologic problems of selection bias; lack of control for confounding by educational achievement, tobacco use, or alcohol use; the use of self-reported symptoms; and the lack of an objective measure of exposure. In 2004, Pelclová and colleagues (2007) compared vascular function of 15 exposed workers with that of 14 healthy male healthcare workers who had no history of occupational exposure to TCDD. Urban et al. (2007) evaluated the same set of workers, looking at overall health effects. Further details on those studies were given in *Update 2006* and *Update 2008*.

Since *Update 2008*, Pelclová et al. (2009) have reported a new update on the exposed cohort that was based on examination and testing of 11 participants in a follow-up visit in 2008, including internal and neurologic examination, eye fundus examination, TCDD in plasma, thyroid-stimulating hormone (TSH), testosterone and serum lipids, ultrasonography of the carotid artery, nerve-conduction study, electroencephalography, visual-evoked potential, Lanthony test of acquired visual impairment, single-photon emission computer tomography of the brain, neuropsychologic examination (eight consented), and carbohydrate-deficient transferrin (CDT), an index of long-term alcohol consumption. Mean TCDD concentration remained high (274 pg/g blood lipids), with a wide dispersion (53–756) among the 11 participants. Prevalences of health conditions were compared with those in the male population of comparable age. Paired t-tests and F-tests were used to test for changes in assessments obtained repeatedly during follow-up visits; Spearman's rank correlation coefficient was used to test the association between health outcomes (such as color-vision impairment) and risk factors (such as concentrations of TCDD and CDT).

The study continues to have important limitations. With a low retention rate (11 participants of the original cohort of 80), the study findings are vulnerable to nonresponse bias. No description of sample loss was given, even regarding the loss of four participants from the 2004 follow-up reported in Pelclová et al.

(2007). The comparison with the prevalence in the male population of comparable age is important in the interpretation of the study findings; however, no description of the comparison group is given beyond citations to (presumed) its sources.

Other Chemical Plants

Studies have reviewed health outcomes in UK chemical workers exposed to TCDD as a result of an industrial accident in 1968 (Jennings et al., 1988; May, 1982, 1983), 2,4-D production workers in the former Soviet Union (Bashirov, 1969), 2,4-D and 2,4,5-T production workers in the United States (Poland et al., 1971), white men employed at a US chemical plant that manufactured flavors and fragrances (Thomas, 1987), and US chemical workers engaged in the production of PCP, lower-chlorinated phenols, and esters of chlorophenoxy acids (Hryhorczuk et al., 1998). The long-term immunologic effects of TCDD were examined in 11 industrial workers involved in production and maintenance operations at a German chemical factory that produced 2,4,5-T (Tonn et al., 1996), and immunologic effects were studied in a cohort of workers formerly employed at a German pesticide-producing plant (Jung et al., 1998). *VAO*, *Update 1998*, and *Update 2000* detailed those studies. Garaj-Vrhovac and Zeljezić (2002) conducted a study of workers occupationally exposed to a complex mixture of pesticides (atrazine, alachlor, cyanazine, 2,4-D, and malathion) during their production.

Chernyak et al. (2004) reported on serum concentrations of PCDDs, PCDFs, and PCBs in 2003 for firefighters exposured to those chemicals during an industrial fire in 1992 at a cable-manufacturing plant in Shelekhov, Irkutsk, Russia. When expressed as the total toxic equivalent (TEQ), the mean dioxin concentration in the blood of 15 exposed firefighters was 169 pg/g (range, 50–477 pg/g); in the control group of firefighters matched for age and duration of career, the mean concentration was 105 pg/g (range, 27–205 pg/g). A neurologic syndrome—manifested as toxic encephalopathy with organic psychiatric disorders, sensory polyneuropathy, and autonomic limb disorders—has developed in a significant proportion of exposed firefighters; the disability rate in this group is higher than in other firefighters in the same region (Chernyak et al., 2007).

Since *Update 2008*, Chernyak et al. (2009) have reported on the serum concentrations in November 2008 in a random sample of firefighters (13 exposed and 7 not exposed) from the 2003 cohort studied earlier (Chernyak et al., 2004). No firefighter in the sample had a TEQ exceeding 100 pg/g lipid. The mean PCDD and PCDF concentration was similar among groups.

Waste-Incineration Worker Studies

A study of infectious-waste–incineration plant workers in Japan used serum dioxin concentrations to document higher PCDD and PCDF exposures of workers than of controls (Kumagai and Koda, 2005). A second study in Japan examined

the association between serum dioxin concentrations (TEQ values for PCDDs, PCDFs, and coplanar polychlorinated biphenyls) and oxidative DNA-damage markers in municipal-waste–incineration workers (Yoshida et al., 2006).

Researchers in South Korea compared plasma protein concentrations in 31 waste-incineration workers with those in 33 nonexposed participants (Kang et al., 2005). A second Korean study evaluated immunologic and reproductive toxicity (DNA damage and sperm quality) in 31 waste-incineration workers and 84 control participants (Oh et al., 2005). Rather than measuring serum dioxin, both studies inferred dioxin exposure of individual workers on the basis of dioxin concentrations in air and estimated exposures to polycyclic aromatic hydrocarbons by analyzing two urinary metabolites: 1-hydroxypyrene and 2-naphthol.

No studies relevant to the chemicals of interest have been published on waste-incineration workers since *Update 2006*.

Agriculture, Forestry, and Other Outdoor Work

Various methods have been used to estimate occupational exposure of agricultural workers to herbicides or TCDD. The simplest method derives data from death certificates, cancer registries, or hospital records (Burmeister, 1981). Although such information is relatively easy to obtain, it cannot be used to estimate duration or intensity of exposure or to determine whether a worker was exposed to a specific agent. In some studies of agricultural workers, examination of differences between occupational practices has allowed identification of subsets of workers who were likely to have had higher exposures (Hansen et al., 1992; Musicco et al., 1988; Ronco et al., 1992; Vineis et al., 1986; Wiklund and Holm, 1986; Wilklund et al., 1988a). In other studies, county of residence was used as a surrogate for exposure, and agricultural censuses of farm production and chemical use were relied on for characterizing exposure in individual counties (Blair and White, 1985; Cantor, 1982; Gordon and Shy, 1981), exposure was estimated on the basis of the number of years of employment in a specific occupation as a surrogate for exposure duration, or supplier records of pesticide sales were used to estimate exposure or to estimate acreage sprayed to determine the amount used (Morrison et al., 1992; Wigle et al., 1990). Still others used self-reported information on exposure that recounted direct handling of a herbicide, whether it was applied by tractor or hand-held sprayer, and what types of protective equipment or safety precautions were used (Hoar et al., 1986; Zahm et al., 1990). A set of studies validated self-reported information with written records, signed statements, or telephone interviews with co-workers or former employers (Carmelli et al., 1981; Woods and Polissar, 1989).

Forestry and other outdoor workers, such as highway-maintenance workers, are likely to have been exposed to herbicides and other compounds. Exposure of those groups has been classified by using approaches similar to those noted above for agricultural workers, for example, by using the number of years employed, job category, and occupational title.

Agricultural Health Study

The US Agricultural Health Study (AHS) is a prospective investigation of cohorts of private pesticide applicators (farmers), their spouses, and commercial pesticide applicators in Iowa and North Carolina, with a total of 89,658 participants, including 57,311 applicators (82% of those seeking licensing) and 32,347 spouses (75% of all spouses). The applicators are predominantly, but not exclusively, male, and the converse is true for the spouses. It is sponsored by NCI, the Environmental Proctection Agency, and the National Institute of Environmental Health Sciences. Enrollment in the study was offered to applicants for applicator certification in Iowa and North Carolina. The project's website (www.aghealth.org) provides many details about the study, including specification of which pesticides were the subject of information gathered from the enrollment forms and mailed questionnaires (Alavanja et al., 1994).

In phase I (1993–1997), the enrollment form for both commercial (8.6%) and private (largely farmers) applicators asked for the details of use of 22 pesticides (10 herbicides, including 2,4-D; 9 insecticides; 2 fungicides; and 1 fumigant) and yes–no responses as to whether 28 other pesticides (8 herbicides, including 2,4,5-T and Silvex, 2,4,5-TP; 13 insecticides; 4 fungicides; and 3 fumigants) had ever been used.

A subset of 24,034 applicators also completed and mailed back a take-home questionnaire. The questionnaire asked for details about use of the 28 pesticides with yes–no information on the enrollment form and for yes–no responses as to whether 108 other pesticides (34 herbicides, including organic arsenic, which would cover cacodylic acid; 36 insecticides; 29 fungicides; and 9 fumigants) had ever been "frequently" used. Dosemeci et al. (2002) published an algorithm designed to characterize personal exposures of that population. Weighting factors for key exposure variables were developed from the literature on pesticide exposure. This quantitative approach has the potential to improve the accuracy of exposure classification for the cohort but has not yet been used in published epidemiologic studies.

The response rate for the take-home questionnaire, 42%, is rather low. Although no pronounced differences in demographics, medical histories, or farming practices were found between those who completed and did not complete the take-home questionnaire (Tarone et al., 1997), selection bias might compromise the validity of studies based on the questionnaire because of differences that might not have been captured in the enrollment form.

Phase II was a 5-year follow-up conducted in 1999–2003. Computer-assisted telephone interviews (CATIs) were completed by 60,138 participants. The interviews specified "pesticides" in general to include herbicides. They asked about specific pesticides on individual crops; for several crops, only if atrazine or 2,4-D was specified was a participant asked whether it had been used alone or as part of the manufacturer's mixture. A full pesticide list was not posted on the Website with the follow-up questionnaire. In addition, dietary histories were

completed by 35,164 respondents, and buccal cell samples were gathered from 34,810 participants.

The rate of response to the phase II survey, 67% overall and 63% of the original cohort of 55,748 male applicators, is modest and leaves some room for selection bias to compromise the validity of the studies based on this survey.

In Phase III (2005–2010), responses to an updated CATI were provided by 43,426 participants.

Numerous reports on the AHS cohort have been considered in earlier updates. All have developed pesticide-exposure estimates or exposure categories from self-administered questionnaires. Using various subsets of the study population, they have addressed a variety of health outcomes: doctor visits resulting from pesticide exposure (Alavanja et al., 1998), chemical predictors of wheeze (Hoppin et al., 2002), prostate-cancer incidence (Alavanja et al., 2003, 2005), lung-cancer incidence (Alavanja et al., 2004), reproductive effects (Farr et al., 2004, 2006), cancer risk in the 21,375 children of pesticide appliers born in 1975 or later (Flower et al., 2004), mortality (Blair et al., 2005a), morbidity (Blair et al., 2005b), rheumatoid arthritis (De Roos et al., 2005a), breast-cancer incidence (Engel et al., 2005), neurotoxicity of chronic exposure to modest amounts of pesticides (Kamel et al., 2005), and prevalence of wheeze (Hoppin et al., 2006a). Three additional publications have discussed pesticide-use patterns in the population (Hoppin, 2005, Hoppin et al., 2006b; Kirrane et al., 2004; Samanic et al., 2005). The AHS questionnaire collected detailed information regarding herbicide use; 2,4-D was the most commonly reported herbicide. Kamel et al. (2007a) evaluated questionnaire responses from more than 18,000 AHS participants, who listed a variety of neurologic symptoms, including memory and concentration problems. Another study by Kamel et al. (2007b) evaluated Parkinson disease in participants in the AHS. Lee WJ et al. (2007) analyzed incident colorectal cancers diagnosed in AHS participants in 1993–2005. Associations with self-reported exposures to 50 pesticides (including 2,4-D, 2,4,5-T, and 2,4,5-TP) were studied. Samanic et al. (2006) reported on the incidence of all cancers combined and selected individual cancers in male pesticide applicators in the AHS particularly with respect to reported exposures to the benzoic acid herbicide dicamba (3,6-dichloro-2-methoxybenzoic acid). Dicamba was used in combination with other herbicides, such as 2,4-D and Agent Orange. Montgomery and colleagues (2008) discussed the relationship between self-reported incident diabetes and pesticide and herbicide exposure in 31,787 licensed pesticide applicators and their spouses. Saldana and colleagues (2007) reported on the cross-sectional relationship between pesticide and herbicide exposure and a history of gestational diabetes in the wives of licensed applicators. Of 11,273 women asked about their pregnancies closest to enrollment, 506 (4.5%) reported gestational diabetes. Hoppin et al. (2006c) evaluated participants who experienced wheeze, Hoppin et al. (2007a) evaluated farmer's lung (hypersensitivity pneumonitis), Hoppin et al. (2007b) and Valcin et al. (2007) evaluated chronic bronchitis, and Hoppin et al. (2008) evaluated atopic and nonatopic asthma in women.

Since *Update 2008*, several articles have reported on AHS participants' exposures to the VAO chemicals of interest and health outcomes.

Andreotti et al. (2009) conducted a case–control analysis of pancreatic cancer in participants who completed the enrollment form (93 incident cases in 64 applicators and 29 spouses and 82,503 cancer-free controls). Ever use of 24 chemicals and intensity-weighted lifetime days—(lifetime exposure days) × (exposure intensity score)—of 13 chemicals was assessed. Risk estimates were calculated by using unconditional logistic regression for various exposures and controlling for age, smoking, and diabetes.

Hoppin et al. (2009) reported on pesticide use and 127 cases of allergic and 314 cases of nonallergic adult-onset asthma in 19,704 male private applicators at least 20 years old in the AHS who completed both the enrollment form and the take-home questionnaire with full information on smoking, asthma history, age, BMI, and high pesticide-exposure events. The researchers excluded 487 female applicators with 19 cases of asthma because of the small sample. Logistic regression was used to evaluate the association between farming exposures and adult-onset asthma, allowing for separate associations with allergic and nonallergic asthma and adjusting for age, state (Iowa or North Carolina), smoking status (current, past, or never), and BMI. For each of 48 pesticides, exposure status was specified as ever use vs never use. Further exposure–response analyses were conducted with a three-level specification for exposure—never used, median use or less, and greater than median use—according to the distribution for intensity-adjusted days of use for the specific pesticide. As noted previously, the findings from this study might be vulnerable to selection bias due to the low response rate (42%) for the take-home survey.

Mills et al. (2009) reported on the association between lifetime use of 49 pesticides and the incidence and mortality of myocardial infarction (MI) in the AHS cohort; 476 deaths in 54,069 male participants who completed the enrollment form and 839 nonfatal events in 32,024 male participants who completed the phase II telephone interview. Deaths from MI, as either a primary or a contributing cause, were recorded from state and national death records starting at enrollment and going through December 31, 2006. The incidence of nonfatal MI was determined on the basis of a positive response on the 5-year follow-up questionnaire to the question "Has a doctor or other health professional ever told you that you had a heart attack (or myocardial infarction)?" First MIs that occurred after enrollment were counted as incident MIs. Separate analyses for mortality and incidence were conducted by using Cox regression and adjusting for state (North Carolina or Iowa), age, and smoking status (whether or not the participant had smoked 100 cigarettes in his lifetime). The incidence analysis also adjusted for BMI. The analyses were conducted for each pesticide specified as ever used and as lifetime days of exposure. As noted previously, the validity of the findings for the incidence analysis might be compromised because of the modest rate of response to the phase II survey—63% according to the committee's calculation (35,088 respondents among 55,748 in the original cohort), reported as 70% in

Mills et al. (2009). In particular, for incidence analyses reported in Mills et al. (2009), this survey is vulnerable to selection bias due to left truncation, that is, missing participants who died before the survey.

Goldner et al. (2010) examined the association between organochlorine exposure and thyroid disease in 19,529 female spouses in the AHS. The analysis was limited to female spouses of private applicators who completed both the take-home survey in phase I (pesticide use) and the follow-up interview in phase II (thyroid disease) and had complete data on all covariates. Thyroid-disease status (none in 14,486, hyperthyroidism in 369, hypothyroidism in 1,114, and other in 560) was ascertained from self-reported history of physician diagnoses obtained during phase II interviews. Polytomous logistic regression was used to estimate the association between use of herbicides (including 2,4-D and 2,4,5-T and insecticides and thyroid-disease status (with no disease as the reference group) with adjustment for education, age, smoking (never, past, or current), BMI, and hormone-replacement therapy (ever or never). As noted previously, the findings from this study might be vulnerable to selection bias due to the low overall rate of response to the combination of the take-home survey and the follow-up interview.

Dennis et al. (2010) reported on 150 cases of cutaneous melanoma diagnosed after enrollment of pesticide applicators in the AHS who completed both the enrollment form and the take-home questionnaire during phase I, excluding 24,704 who had a cancer diagnosis before enrollment. Cases were identified through linkage to cancer registries, state death registries, and the National Death Index with the cutoff date of December 31, 2005. Dichotomous measures (ever used) were used for arsenic pesticides (lead arsenate and inorganic and organic arsenic). Categorical measures (no, low, or high) based on intensity-weighted lifetime days of exposure were used for other chemicals, including 2,4-D, 2,4,5-T, and 2,4,5-TP. Unconditional logistic regression was used to estimate the association between melanoma and exposure with adjustment for age, sex, and other variables "as indicated" (apparently selection through an unspecified variable selection procedure), including sun exposure, tendency to burn, red hair, and BMI.

Thomas et al. (2010) reported on a monitoring study for 2,4-D and chlorpyrifos exposures in a sample of AHS participants. For 69 2,4-D applicators, geometric mean values were 7.8 and 25 mg/L in preapplication and postapplication urine, respectively ($p < 0.05$ for difference) and 0.37 mg/m^3 in personal air. The estimated amount of dermal absorption through the hands (hand loading) and through total skin surface (body loading) were 0.39 mg and 2.9 mg 2,4-D, respectively; the readings for individual applicators were correlated across these media. Glove use and the mode of application were found to be associated with the degree of exposure.

Slager et al. (2009) reported on current rhinitis among commercial pesticide applicators in the AHS (excluding private applicators, such as farmers). Of the 4,916 commercial pesticide applicators in the full AHS cohort, the 2,245 individuals who had provided information on all the variates in the analysis model constituted the sample for this investigation. Current rhinitis was ascertained

with the following question in the take-home questionnaire: "During the past 12 months have you had a stuffy, itchy, or runny nose?" Exposure to individual pesticides was specified both as a dichotomous measure (ever vs never in the past year) and as a categorical measure (days per year). Logistic regresson was used to estimate the association between exposure and current rhinitis, with adjustment for age, education, and growing up on a farm. As noted previously, the findings from this study might be vulnerable to selection bias due to the low rate of response to the take-home survey (46% among commercial applicators, slightly higher among the entire AHS cohort).

Crawford et al. (2008) reported on hearing loss in white male licensed pesticide applicators in the AHS, considering the hypothesis that some pesticides are neurotoxic and could potentially affect hearing. The study sample consisted of participants who completed the enrollment form and the take-home questionnaire during phase I and the follow-up telephone interview in phase II. Hearing loss was ascertained with the following question in the phase II interview: "Do you have trouble with your hearing in one or both ears (this is without a hearing aid)?" Potential cases of hearing losses attributable to a congenital condition or to infection or injury (determined by responses to survey questions) were excluded. The analysis also excluded participants who reported never using pesticides and excluded nonwhite and female respondents. Of 16,246 participants who completed all three surveys, 14,229 were retained in the final analysis sample. Logistic regression was used to estimate the associatons between exposure and hearing loss with adjustment for state, age, and exposures to noise, solvents, and metals. The overall low rate of response (less than 30%) to the combination of the three surveys raises concerns about the validity of the study findings. The authors argued that there were too few nonwhites and females (1.5% of eligible participants) for analysis. Although it might be reasonable to consider those participants to be too few to be analyzed as subgroups, it is unclear why they needed to be excluded from the main analysis. (Limited analysis for nonwhites is mentioned in the discussion.)

California United Farm Workers of America Study

Mills and Yang (2005) and Mills et al. (2005) analyzed lymphohematopoietic cancer and breast cancer, respectively, in nested case–control studies of Hispanic workers drawn from a cohort of 139,000 Californians who were members of the United Farm Workers of America (UFW). Estimates of exposure to specific pesticides, including 2,4-D, were developed through linkage of the union's job histories with the California Pesticide Use Reporting Database of the state's Department of Pesticide Regulation, which has records of all agricultural applications of pesticides in the state since 1970. Vital status and cancer incidence were ascertained through a probabilistic record linkage to the California Cancer Registry for the period 1988–2001. Mills and Yang (2007) conducted a nested

case–control study of gastric cancer embedded in the UFW cohort and identified cases of gastic cancer newly diagnosed in 1988–2003.

No reports relevant to the chemicals of interest have been published on the California UFW population since *Update 2008*.

Upper Midwest Health Study

The Upper Midwest Health Study (UMHS) was initiated by NIOSH as a population-based case–control study of cancer risk in a nonmetropolitan midwestern US population. Several reports from the study were reviewed in previous updates. Chiu et al. (2004) and Lee WJ et al. (2004a) conducted pooled (combined) analyses of two earlier case–control studies of NHL carried out by the UMHS in Iowa and Minnesota (Cantor et al., 1992) and Nebraska (Zahm et al., 1990). Chiu et al. (2004) examined the association of NHL with agricultural pesticide use and familial cancer, and Lee WJ et al. (2004a, 2006) looked at NHL in asthmatics who reported pesticide exposure. Data from the Nebraska data (Chiu et al., 2006, based on Zahm et al., 1990, 1993) were used to identify whether subtypes of NHL had a higher risk. Specifically, tissue samples were analyzed according to the presence of a specific chromosomal translocation (t[14;18] [q32;q21]); only 172 of 385 cases were included. Researchers evaluated farm pesticide exposure in men (Ruder et al., 2004) and women (Carreon et al., 2005) in Iowa, Michigan, Minnesota, and Wisconsin in relation to gliomas as part of the UMHS. Two studies focused on pesticide use and the risk of adenocarcinomas of the stomach and esophagus (Lee WJ et al., 2004b) and the risk of gliomas (Lee WJ et al., 2005). Cases were white Nebraska residents over 21 years old who were identified from the Nebraska Cancer Registry and matched to controls drawn from an earlier study by Zahm et al. (1990). Ruder et al. (2006) published a follow-up study to Ruder et al. (2004) evaluating gliomas in UMHS participants. The new analyses provided no evidence of greater use of pesticides in cases than in controls, and there was no breakdown of specific agents.

Since *Update 2008*, Ruder et al. (2009) have published a new follow-up study to Ruder et al. (2004, 2006); findings were similar, and there was no breakdown by specific agents.

Ontario Farmers

The Ontario Farm Family Health Study (OFFHS) has produced several reports on exposure to phenoxyacetic acid herbicides, including 2,4-D. A study of male pesticide exposure and pregnancy outcome (Savitz et al., 1997) developed an exposure metric based on self-reports of mixing or application of crop herbicides, crop insecticides, and fungicides; livestock chemicals; yard herbicides; and building pesticides. Study participants were asked whether they participated in those activities during each month, and their exposure classifications were based

on activities in 3-month periods. Exposure classification was refined with answers to questions about use of protective equipment and specificity of pesticide use.

A related study included analysis of 2,4-D residues in semen as a biologic marker of exposure (Arbuckle et al., 1999a). The study began with 773 potential participants, but only 215 eventually consented to participation. Of the 215, 97 provided semen and urine samples for 2,4-D analysis.

The OFFHS also examined pregnancy outcomes of stillbirth, gestational age, and birth weight (Savitz et al., 1997) and the effect of exposure to pesticides, including 2,4-D, on time to pregnancy (Curtis et al., 1999) and on the risk of spontaneous abortion (Arbuckle et al., 1999b, 2001). About 2,000 farm couples participated in the study. Exposure information was pooled from interviews with husbands and wives to construct a history of monthly agricultural and residential pesticide use. Exposure classification was based on a yes–no response for each month. Data on such variables as acreage sprayed and use of protective equipment were collected but were not available in all cases. Other studies have used herbicide biomonitoring in a subset of the population to evaluate the validity of self-reported predictors of exposure (Arbuckle et al., 2002). Assuming that the presence of 2,4-D in urine was an accurate measure of exposure and that the results of the questionnaire indicating 2,4-D use were more likely to be subject to exposure-classification error (that is, assuming that the questionnaire results were less accurate than the results of urinalysis), the questionnaire's prediction of exposure, compared with the urinary 2,4-D concentrations, had a sensitivity of 57% and a specificity of 86%. In multivariate models, pesticide formulation, protective clothing and gear, application equipment, handling practice, and personal-hygiene practice were valuable as predictors of urinary herbicide concentrations in the first 24 hours after application was initiated.

Additional publications have reported results from the cohort and were included in previous updates. Urinary concentrations of 2,4-D and MCPA were measured in samples from farm applicators (Arbuckle et al., 2005) and from women who lived on Ontario farms (Arbuckle and Ritter, 2005). Indirect sources of herbicide exposure of farm families were evaluated through wipe sampling of surfaces and drinking-water samples (Arbuckle et al., 2006). Weselak et al. (2008) examined occupational exposures and birth defects in the offspring of OFFHS participants. Spouses completed questionnaires that requested the history of pesticide use on the farm. Pregnancies resulting in birth defects were reported by the female study participants. All birth defects were combined for study analyses, and exposure was examined by pesticide class, family, and active ingredient for two 3-month periods—before and after conception.

No reports on the OFFHS relevant to the chemicals of interest have been published since *Update 2008*.

Mortality Study of Male Canadian Farm Operators

The mortality study of Canadian male farm operators evaluated the risk to farmers of death and of specific health outcomes: NHL (Morrison et al., 1994; Wigle et al., 1990), prostate cancer (Morrison et al., 1992), brain cancer (Morrison et al., 1993), multiple myeloma (Semenciw et al., 1993), leukemia (Semenciw et al., 1994), and asthma (Senthilselvan et al., 1992).

No reports on relevant health outcomes have been published on participants in the study since *Update 1996*.

Swedish Cancer-Environment Registry

The Swedish Cancer-Environment Registry (CER) linked the cancer cases entered in the Swedish Cancer Registry with the records of people who responded to the 1960 and 1970 national censuses, which had obtained data on current occupation. The resulting database has been used in studies that evaluated cancer mortality and farm work (Wiklund, 1983); STS and malignant lymphoma in agricultural and forestry workers (Wiklund and Holm, 1986; Wiklund et al., 1988a); and the risk of NHL, HL, and multiple myeloma in relation to occupational activities (Eriksson et al., 1992).

No new studies using the Swedish CER that are relevant to the chemicals of interest have been published since the original *VAO* report.

Farmers of Italian Piedmont

Corrao et al. (1989) evaluated cancer incidence in farmers licensed to spray pesticides in Italy's southern Piedmont region. In a continuation of that study, Torchio et al. (1994) reported on the mortality experience of a cohort of 23,401 male farmers in the Piedmont area from the time they registered to use agricultural pesticides (1970–1974) through 1986. That area is characterized by higher use of herbicides, particularly 2,4-D and MCPA, than the rest of the country. The cohort was partitioned into people who lived near arable land, those who lived near woodlands, and those who lived near mixed-use land; separate results were reported for the first two groups.

No reports on this cohort have been published since 1994.

Other Studies of Agricultural Workers

Studies of proportionate mortality were conducted in Iowa farmers (Burmeister, 1981) and male and female farmers in 23 states (Blair et al., 1993). Cancer mortality in a cohort of rice growers in the Novara Province of northern Italy was investigated (Gambini et al., 1997), and cancer incidence in Danish gardeners was studied (Hansen et al., 1992). Lerda and Rizzi (1991) studied the incidence of sperm abnormalities in Argentinian farmers. Ronco et al. (1992)

studied mortality in Danish farmers and the incidence of specific types of cancer in Italian farmers. The utility of the findings was limited by their being the largely unanalyzed products of linking each country's cancer registry with census records to garner information on recent occupation. Brain, lymphatic, and hematopoietic cancers have been studied in Irish agricultural workers (Dean, 1994). Kristensen et al. (1997) tested whether cancers or birth defects were increased in the offspring of Norwegian farmers who worked on farms with pesticide use documented by agricultural censuses. Faustini et al. (1996) evaluated the immune, neurobehavioral, and lung function of residents in an agricultural area of Saskatchewan, Canada, and focused on immunologic changes in 10 farmers who mixed and applied commercial formulations that contained chlorophenoxy herbicides. Mandel et al. (2005) reported results of urinary biomonitoring of farm families in Minnesota and South Carolina as a part of CropLife America's Farm Family Exposure Study. Fritschi et al. (2005) used a computer-assisted telephone interview and occupational histories reviewed by an industrial hygienist to estimate exposures to phenoxy herbicides in an Australian study. Curwin et al. (2005) measured 2,4-D concentrations in urine and hand-wipe samples to characterize exposures of farmers and nonfarmers in Iowa.

Other studies of the agricultural use of pesticides have not provided specific information on exposure to 2,4-D, TCDD, or other compounds relevant to Vietnam veterans' exposure (Bell et al., 2001a,b; Chiu et al., 2004; Duell et al., 2001; Garry et al., 2003; Gorell et al., 2004; Hanke et al., 2003; van Wijngaarden et al., 2003).

A series of papers from a workshop focused on methods of assessing pesticide exposure in farmworker populations (Arcury et al., 2006; Barr et al., 2006a,b; Hoppin et al., 2006b; Quandt et al., 2006). They provide a helpful review of current methodologic issues in exposure science for those populations but do not address the chemicals of interest directly.

Hansen et al. (2007) evaluated cancer incidence from May 1975 through 2001 in an occupational cohort of Danish Union of General Workers identified among men working in 1973; their cancer incidence from 1975 to 1984 was reported by Hansen et al. (1992).

Forestry Workers

Studies have been conducted in forestry workers potentially exposed to the types of herbicides used in Vietnam. A cohort mortality study examined men employed at a Canadian public utility (Green, 1987, 1991), a Dutch study of forestry workers exposed to 2,4,5-T investigated the prevalence of acne and hepatic dysfunction (van Houdt et al., 1983), a study evaluated cancer incidence in a group of New Zealand forestry workers (Reif et al., 1989), and a study examined mortality and cancer incidence in a cohort of Swedish lumberjacks (Thörn et al., 2000). No reports on forestry workers have been published since 2000.

Other Studies of Herbicide and Pesticide Applicators

Studies of commercial herbicide applicators are relevant because they can be presumed to have had sustained exposure to herbicides. However, because they also are likely to have been exposed to a variety of other compounds, assessment of individual or group exposure to specific phenoxy herbicides or TCDD is complicated. Some studies have attempted to measure applicators' exposure on the basis of information from work records on acreage sprayed or on the number of days of spraying. Employment records also can be used to extract information on which compounds are sprayed.

One surrogate indicator of herbicide exposure is the receipt of a license to spray. Several studies have specifically identified licensed or registered pesticide and herbicide applicators (Blair et al., 1983; Smith et al., 1981, 1982; Swaen et al., 1992; Wiklund et al., 1988b, 1989a,b). Individual estimates of the intensity and frequency of exposure were rarely reported in the studies that the committee examined, however, and many applicators were known to have applied many kinds of herbicides, pesticides, and other substances. In addition, herbicide spraying is generally a seasonal occupation, and information is not always available on possible exposure-related activities during the rest of the year.

Several studies have evaluated various characteristics of herbicide exposures: type of exposure, routes of entry, and routes of excretion (Ferry et al., 1982; Frank et al., 1985; Kolmodin-Hedman and Erne, 1980; Kolmodin-Hedman et al., 1983; Lavy et al., 1980a,b; Libich et al., 1984). Those studies appear to have shown that the major route of exposure is dermal absorption, with 2–4% of the chemical that contacts the skin being absorbed into the body during a normal workday. Air concentrations of the herbicides were usually less than 0.2 mg/m^3. Absorbed phenoxy acid herbicides are virtually cleared within 1 day, primarily through urinary excretion. Typical measured excretion was 0.1–5 mg/day in ground crews and lower in air crews.

A study of 98 professional turf sprayers in Canada developed new models to predict 2,4-D dose (Harris et al., 2001). Exposure information was gathered from self-administered questionnaires. Urine samples were collected throughout the spraying season (24-hour samples on 2 consecutive days). Estimated 2,4-D doses were developed from the data and used to evaluate the effect of protective clothing and other exposure variables.

Only one study has provided information on serum TCDD concentrations in herbicide applicators. Smith et al. (1992) analyzed blood from nine professional spray applicators in New Zealand who first sprayed before 1960 and were spraying in 1984. The duration of spraying varied from 80 to 370 months. Serum TCDD was 3–131 ppt on a lipid basis (mean, 53 ppt). The corresponding value for age-matched controls was 2–11 ppt (mean, 6 ppt). Serum TCDD was correlated positively with the number of months of professional spraying.

Several additional cohorts of herbicide and pesticide applicators have been assessed for health outcomes: cancer mortality in Swedish railroad workers

(Axelson and Sundell, 1974; Axelson et al., 1980), mortality in pesticide applicators in Florida (Blair et al., 1983), general and cancer mortality and morbidity in Finnish men who applied 2,4-D and 2,4,5-T (Asp et al., 1994; Riihimaki et al., 1982, 1983), cancer in pesticide and herbicide applicators in Sweden (Dich and Wiklund, 1998; Wiklund et al., 1987, 1988b, 1989a,b), mortality from cancer and other causes in Dutch male herbicide applicators (Swaen et al., 1992, 2004), cancer mortality in Minnesota highway-maintenance workers (Bender et al., 1989), birth defects in the offspring of Minnesota pesticide applicators (Garry et al., 1994, 1996a,b), lung-cancer morbidity in male agricultural plant-protection workers in the former German Democratic Republic who spent a portion of their work year in applying pesticides (Barthel, 1981), mortality and reproductive effects in British Columbia sawmill workers potentially exposed to chlorophenate wood preservatives used as fungicides (Dimich-Ward et al., 1996; Heacock et al., 1998; Hertzman et al., 1997), and cancer in pesticide users in Iceland (Zhong and Rafnsson, 1996). 't Mannetje et al. (2005) evaluated a study population that included herbicide production workers and is a subcohort of the IARC cohort, which was discussed earlier in the section on production workers. Details of the studies' designs and results are included in previous VAO studies.

No studies relevant to the chemicals of interest have been published on herbicide or pesticide applicators since *Update 2006*.

Paper, Pulp, and Sawmill Cohorts

Workers in the paper and pulp industry can be exposed to TCDD and other dioxins that can be generated by the bleaching process during the production and treatment of paper and paper products. In the past, workers in sawmills might have been exposed to pentachlorophenates, which are contaminated with higher-chlorinated PCDDs (Cl_6–Cl_8), or to tetrachlorophenates, which are less contaminated with higher-chlorinated PCDDs. Wood is dipped into those chemical preservatives and then cut and planed in the mills. Most exposure is dermal, but some exposure can occur by inhalation (Hertzman et al., 1997; Teschke et al., 1994).

VAO described studies of pulp and paper-mill workers potentially exposed to TCDD and various health outcomes, including general mortality in workers at five mills in Washington, Oregon, and California (Robinson et al., 1986); cancer incidence in male paper workers in Finland (Jappinen and Pukkala, 1991); respiratory health in a New Hampshire mill (Henneberger et al., 1989); and cause-specific mortality in white men employed in plants identified by the United Paperworkers International Union (Solet et al., 1989). *Update 2000* described studies of cancer risk in workers in the Danish paper industry (Rix et al., 1998) and oral-cancer risk in occupationally exposed workers in Sweden (Schildt et al., 1999). *Update 2006* reviewed a multinational study of cancer mortality (McLean et al., 2006) in 60,468 paper and pulp industry workers exposed to chlorinated

organic compounds during employment during 1920–1996; this collaboration led by IARC was composed of cohorts in 11 countries, had follow-up through 1990 to 1996 (depending on the country), and used a JEM to estimate individual cumulative exposure to 27 agents, including TCDD.

Since *Update 2008*, McLean et al. (2009) have studied serum dioxin concentrations in 94 former sawmill workers in New Zealand who were classified as exposed (n = 71) and nonexposed (n = 23) according to their work history. In addition, the serum dioxin test results from 23 former sawmill workers from Sawmill Workers Against Poisons (SWAP) were provided to the study. A semiquantitative estimate of exposure intensity was also developed by using a PCP exposure algorithm that incorporated the participants' job titles and specific work tasks; mixing of PCP solutions, cleaning sludge, and spraying. Serum concentrations of PCDDs and PCDFs were analyzed; the total TEQ was calculated by using the WHO-TEFs (Van den Berg et al., 2006). Mean concentrations in exposed workers were higher than those in the nonexposed: 1,2,3,6,7,8-HxCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD concentrations were 2–3 times higher, and WHO-TEQ about 40% higher (13.67 pg/g vs 9.56 pg/g). The congener profiles in serum were consistent with those in PCP solutions, and dioxin concentrations increased with both employment duration and estimated exposure intensity. The averages in the SWAP members were 2–3 times those in the exposed study participants (37.74 pg/g).

ENVIRONMENTAL STUDIES

Industrial accidents have led to the evaluation of long-term health effects in neighboring nonworker populations of exposure to fairly high concentrations of the chemicals of interest. Effects on residents around normally performing industrial operations, such as waste incinerators, and even on people exposed only to "background" concentrations have also been studied.

People's environmental exposures to dioxin-like chemicals and their non–dioxin-like counterparts are to mixtures of components that tend to correlate, so it is not surprising that specific chemicals measured in a person's serum also tend to correlate; this collinearity means that it will be difficult for epidemiologic studies to attribute any observed association to a particular chemical configuration (Longnecker and Michalek, 2000). Analyses in terms of TEQs circumvent that problem to some extent.

Seveso, Italy

Among the largest industrial accidents that have resulted in environmental exposure to TCDD was one in Seveso, Italy, on July 10, 1976, that was caused by an uncontrolled reaction during TCP production. The degree of TCDD contamination in the soil has been used extensively as a means of imputing expo-

sures of members of the population. Three areas were defined on the basis of soil sampling: Zone A (n = 556), the most heavily contaminated, from which all residents were permanently evacuated within 20 days; Zone B (n = 3,920), an area of lower contamination that all children and women in the first trimester of pregnancy were urged to avoid during daytime; and Zone R (n = 26,227), a region with some contamination in which consumption of local crops was prohibited (Bertazzi et al., 1989a,b). The sample sizes differ among follow-up studies, presumably because of migration; the sample sizes given above were reported in Bertazzi et al. (1989b).

Data on serum TCDD concentrations in Zone A residents have been presented by Mocarelli et al. (1990, 1991) and by CDC (1988d). In the 10 residents who had severe chloracne, TCDD concentrations were 828–56,000 ppt of lipid weight. In 10 without chloracne, TCDD concentrations were 1,770–10,400 ppt. TCDD was undetectable in all control participants but one. The highest of those concentrations exceeded any that had been estimated at the time for TCDD-exposed workers on the basis of backward extrapolation and a half-life of 7 years. Data on nearby soil concentrations, number of days that a person stayed in Zone A, and whether local food was consumed were considered in evaluating TCDD. That none of those data correlated with serum TCDD suggested strongly that the important exposure was from fallout on the day of the accident. The presence and degree of chloracne did correlate with TCDD. Adults seemed much less likely than children to develop chloracne after acute exposure, but surveillance bias could have affected that finding. Recent updates (Bertazzi et al., 1998, 2001) have not changed the exposure-assessment approach.

A number of studies of the Seveso population have used lipid-adjusted serum TCDD concentrations as the primary exposure metric (Baccarelli et al., 2002; Eskenazi et al., 2002a,b, 2003a, 2004; Landi et al., 2003). Fattore et al. (2003) measured current air concentrations of PCDDs in Zones A and B and compared them with measurements in a control area near Milan. The authors concluded that release from PCDD-contaminated soil did not add appreciably to air concentrations in the Seveso study area. Finally, Weiss et al. (2003) collected breast milk from 12 mothers in Seveso to compare TCDD concentrations with those in a control population near Milan. The investigators reported that the TCDD concentrations in human milk from mothers in Seveso were twice as high as those in controls. The authors concluded that breastfed children in the Seveso area were likely to have higher body burdens of TCDD than children in other areas.

Several cohort studies have been conducted on the basis of the exposure categories. Seveso residents have had long-term follow-up of their health outcomes, especially cancer. Bertazzi and colleagues conducted 10-year mortality follow-up studies of adults and children who were 1–19 years old at the time of the accident (Bertazzi et al., 1989a,b, 1992), 15-year follow-up studies (Bertazzi et al., 1997, 1998), and a 20-year follow-up study (Bertazzi et al., 2001). Pesatori et al. (1998) also conducted a 15-year follow-up study to update noncancer mortality. The

25-year follow-up assessed vital status through 2001 of residents ("present") in the Seveso area and reference territory at the time of the Seveso accident and of immigrants and newborns ("non-present") in the 10 years thereafter (Consonni et al., 2008). Cause-specific mortality was determined for each zone and compared with that in the comparison cohort and adjusted for presence at the accident, sex, period, age, and time since the Seveso accident.

In addition to a 2-year prospective controlled study of workers potentially exposed to TCDD during cleanup of the most highly contaminated areas after the accident (Assennato et al., 1989a), studies have examined specific health effects associated with TCDD exposure in Seveso residents: chloracne, birth defects, spontaneous abortion, and crude birth and death rates (Bisanti et al., 1980); the distribution of chloracne in Seveso children (Caramaschi et al., 1981); compounds in the blood and urine of children who had chloracne (Mocarelli et al., 1986); chloracne and peripheral nervous system conditions (Barbieri et al., 1988); dermatologic and laboratory tests in a group of the children with chloracne and compared with results in a group of controls (Assennato et al., 1989b); health status and TCDD concentrations in chloracne cases and noncases recruited previously by Landi et al. (1997, 1998) and followed by Baccarelli et al. (2005a); hepatic-enzyme–associated conditions (Ideo et al., 1982, 1985); abnormal pregnancy outcomes (Mastroiacovo et al., 1988); cytogenetic abnormalities in maternal and fetal tissues (Tenchini et al., 1983); neurologic disorders (Boeri et al., 1978; Filippini et al., 1981); cancer (Bertazzi et al., 1993; Pesatori et al., 1992, 1993); sex ratio of offspring who were born in Zone A (Mocarelli et al., 1996); breast cancer (Warner et al., 2002); immunologic effects (Baccarelli et al., 2002); aryl hydrocarbon receptor–dependent (AHR-dependent) pathway and toxic effects of TCDD in humans (Baccarelli et al., 2004); effects of TCDD-mediated alterations in the AHR-dependent pathway in people who lived in Zones A and B (Landi et al., 2003); and NHL-related t(14;18) translocation prevalence and frequency in dioxin-exposed healthy people in Seveso (Baccarelli et al., 2006). Baccarelli et al. (2005b) reviewed statistical strategies for handling nondetectable readings or readings near the detection limit in dioxin-measurement datasets. They recommended that a distribution-based multiple-imputation method be used to analyze environmental data when substantial proportions of observations have nondetectable readings.

Baccarelli et al. (2008) reported on crude sex ratios, birth weight, and neonatal thyroid function for all births in 1994–2005 to women who were less than 18 years old at the time of the Seveso accident. Mocarelli et al. (2008) investigated TCDD's effects on reproductive hormones and sperm quality in a comparison of 135 men who were exposed to TCDD by the 1976 Seveso accident with 184 healthy men who were not exposed to TCDD or who lived in the Seveso contamination zones. Both groups were divided into three categories that reflected their ages at the time of the Seveso accident: infancy to prepuberty (1–9 years), puberty (10–17 years), and adulthood (18–26 years).

Since *Update 2008*, several reports on the Seveso cohort have been published. Pesatori et al. (2008) investigated the incidence of pituitary tumors in the Seveso population (804 in Zone A, 5,941 in Zone B, and 38,624 in Zone C) compared with the reference population in the surrounding, noncontaminated area (232,745). The hospital discharge-registration system of the Lombardy Region (where the study area is) was used to identify incident cases of pituitary adenoma during 1976–1996. All relevant medical records were reviewed to confirm the diagnoses for each case. Risk ratios and 95% confidence intervals were estimated by using Poisson regression and adjusting for age, sex, and calendar period and an assumed 10-year latent period for dioxin effects.

Pesatori et al. (2009) reported on cancer incidence in a 20-year follow-up of the Seveso cohort covering the period 1977–1996. The study included all participants, 0–74 years old who lived in the study area (723 in Zone A, 4,821 in Zone B, 31,643 in Zone R, and 181,574 in the reference zone) at the time of the accident. Participants who moved outside the study area were traced with a success rate of more than 99% (Consonni et al., 2008). Emigration was homogeneous among zones and ranged from 4.7% to 6.7%. The difference in exposure among zones was corroborated by soil TCDD measurements, serum concentrations of TCDD, and TEQs. In the absence of a regionwide cancer registry, incident cancer cases were ascertained from the 120-hospital network of the Lombardy region. Original medical records were examined to identify true cases, to retrieve diagnoses as accurately as possible, and to determine the actual dates of occurrence. The study covered malignant tumors at any site, and benign tumors of liver, bladder, and central nervous system first diagnosed after the date of the accident. For cohort members who were not hospitalized or who emigrated outside Lombardy, cancer cases were identified solely from death certificates, thereby missing nonfatal incident cases. Risk ratios and 95% confidence intervals for Zones A, B, and R vs the reference zone were derived by using Poisson regression and adjusting for sex, age, and period.

Seveso Women's Health Study

Several studies have used data from the Seveso Women's Health Study (SWHS) to evaluate the association between individual serum TCDD and reproductive effects in women who resided in Seveso at the time of the accident in 1976. The study group consisted of 981 volunteers who were between infancy and 40 years old at the time of the accident, who had resided in Zone A or B, and for whom adequate serum remained from the samples collected shortly after the explosion. The stored samples were used for new TCDD analyses with improved analytic techniques that became available in recent years.

As part of the SWHS, Eskenazi et al. (2001) tested the validity of exposure classification by zone. Investigators measured serum TCDD in samples collected in 1976–1980 from 601 residents (97 in Zone A and 504 in Zone B). A question-

naire that the women completed in 1996–1998 included age, chloracne history, animal mortality, consumption of homegrown food, and location at the time of the explosion. Participants did not know their TCDD concentrations at the time of the interview, but most knew their zones of residence. Interviewers and TCDD analysts were blinded to participants' zones of residence. Zone of residence explained 24% of the variability in serum TCDD. Addition of the questionnaire data improved the regression model, explaining 42% of the variability. Those findings demonstrate a significant association between zone of residence and serum TCDD, but much of the variability in TCDD concentration is still unexplained by the models.

Previously reviewed studies had examined associations between serum TCDD and menstrual cycle (Eskenazi et al., 2002a), endometriosis (Eskenazi et al., 2002b), pregnancy outcome (Eskenazi et al., 2003a), age at exposure of female Seveso residents (Eskenazi et al., 2004), age at menarche and age at menopause (Eskenazi et al., 2005), and age at menarche in women who were premenarcheal at the time of the explosion (Warner et al., 2004). Warner et al. (2005) compared a chemical-activated luciferase-gene expression bioassay with an isotope-dilution high-resolution gas-chromatography–high-resolution mass-spectrometry assay to measure PCDDs, PCDFs, and PCBs in serum of 78 women who resided near Seveso to determine average total dioxin-like TEQs; similar results were obtained with the two methods. Eskenazi et al. (2007) and Warner et al. (2007) examined the incidence of fibroids and ovarian function, respectively, in SWHS participants. Eskanazi et al. (2007) excluded women who had received a diagnosis of fibroids before 1976, leaving a total of 956 women for analysis. Fibroids were ascertained in 634 women by self-report, medical records, and ultrasonography. Analyses were adjusted for confounding by parity, family history of fibroids, age at menarche, current BMI, smoking, alcohol consumption, and education. Warner et al. (2007) studied menstrual function in SWHS participants who were 20–40 years old and not taking oral contraceptives; the evaluations included ultrasonography (96 women), serum hormone concentrations (87 women), and the occurrence of ovulation (203 women).

Since *Update 2008*, Eskenazi et al. (2010) have examined the relationship between serum TCDD around the time of the accident and time to pregnancy (TTP) in 472 SWHS participants who had attempted pregnancy since the accident. In addition to other eligibility criteria for SWHS, participants were eligible for this study if they were newborn to 40 years old at the time of the accident. Nine women were excluded because of fertility-related problems, leaving 463 eligible women in the analysis sample. The main analysis was restricted to the 278 women who delivered live births that were not the results of contraceptive failure. Alternative analyses included various subsamples excluded in the main analysis.

TTP for the first postaccident pregnancy was determined from responses in interviews conducted in 1996–1998 to the question "How many months did it take to become pregnant? In other words, for how many months had you been

having sexual intercourse without doing anything to prevent pregnancy?" Women whose TTP was 12 months or more were classified as infertile.

Initial serum TCDD concentrations at the time of the accident were measured in stored samples from 444 participants (431 collected in 1976 or 1977 and 13 collected in 1978–1981). For 19 participants with insufficient stored samples, new samples were collected in 1996 or 1997. For the 27 women with detectable post-1977 TCDD measurements, TCDD was back-extrapolated to 1976 by using the Filser Model (Kreuzer et al., 1997).

Initial serum TCDD concentrations were extrapolated to the time when each woman initiated her attempt to become pregnant; Kreuzer et al. (1997) used a toxicokinetic model for women 16 years old or younger at the time of the accident, and Pirkle et al. (1989) used a first-order kinetic model that assumed a 9-year half-life.

The association between serum TCDD and TTP was assessed by using a Cox proportional-hazards model to estimate the fecundability odds ratios (ORs) and 95% confidence intervals. The association between serum TCDD and infertility was assessed by using multiple logistic regression. Both models were adjusted for maternal age, maternal smoking in the year before conception, parity, menstrual-cycle irregularity, oral contraceptive use in the year before attempt, paternal age near the time of conception, and history of reproductive and endocrine conditions, including pelvic infection and thyroid or urogenital problems. A variety of sensitivity analyses were conducted to investigate the consistency of study findings and to check for possible bias.

Initial serum TCDD and expolated serum TCDD were specified as continuous variables on the logarithmic scale and as categorical variables.

National Health and Nutrition Examination Survey

In the early 1960s, the CDC National Center for Health Statistics began the National Health and Nutrition Examination Survey (NHANES) program as a means of monitoring and assessing the health and nutritional status of people of all ages living in the United States. In 1999, the survey became a continuous program that has a changing focus on a variety of health and nutrition measurements to meet emerging needs. A rich variety of data—demographic and socioeconomic data, dietary information and medical, dental, and physiologic assessments; and serum concentrations of persistent organic pollutants (POPs), including specific congeners of dioxins, furans, and PCBs—are collected through in-person interviews, health examinations, and blood samples obtained from a nationally representative sample of adults and children in the noninstitutionalized US population. Information obtained from NHANES data is used to determine prevalences of diseases, to assess nutritional status, and to establish national standards of height, weight, and blood pressure. Researchers also conduct analyses of the NHANES

data for epidemiologic studies and health-science research on serum concentrations of various compounds in association with various health outcomes.

NHANES data from 1999–2002 were used to evaluate cardiovascular disease (Ha et al., 2007) and hypertension (Everett et al., 2008a,b). Lee D-H et al. (2006, 2007a,b,c) used data from the same years to evaluate several health outcomes, including diabetes, the metabolic syndrome, insulin resistance, and arthritis. Turyk et al. (2007) analyzed NHANES data from 1999–2002 and 2001–2002 to evaluate associations with thyroid hormone concentrations. Since *Update 2008*, several new publications have used NHANES data in reporting on associations between the chemicals of interest and various health outcomes.

Lee et al. (2008) examined the associations between serum concentrations of POPs and the prevalence of peripheral neuropathy and poor glycemic control (A1C ≥ 7.0%) in NHANES 1999–2002 participants who were at least 40 years old and had diabetes or impaired fasting glucose. Peripheral neuropathy is ascertained on the basis of one or more insensate sites on the foot. Diabetes is ascertained on the basis of high plasma glucose (≥ 126 mg/dL fasting or ≥ 200 mg/dL nonfasting) or on the basis of whether a person is taking insulin or an oral antidiabetes agent. Although 49 POPs were measured, analysis was restricted to 25 POPs of which at least 60% of study participants had detectable concentrations: three PCDDs, four PCDFs, five dioxin-like PCBs, seven dioxin-unlike PCBs, and six organochlorine (OC) pesticides. Logistic regresson was used to determine the OR between each outcome (peripheral neuropathy or poor glycemic control) and each exposure to POP subclass with adjustment for age, sex, race or ethnicity, poverty, duration of diabetes, hypertension (yes or no), BMI, cigarette-smoking (never, former, or current), cotinine concentration, alcohol consumption, leisure-time physical activity (vigorous, moderate, or none), and A1C (neuropathy only). For each POP subclass, a cumulative measure was derived by summing the rank scores among individual compounds that belonged to the subclass; the cumulative measure was then categorized into tertiles. Additional analyses were conducted for individual compounds by using the correlation coefficient between the rank score for each compound and each outcome with adjustment for the same covariates listed above.

Ha et al. (2009) examined the association between serum concentrations of POPs and the prevalence of newly diagnosed hypertension in NHANES 1999–2002 adult participants 40 years old or older. After exclusion of 444 patients known to be hypertensive irrespective of antihypertensive medication, 165 diabetic patients, and 49 subjects for whom blood pressure values were missing, the final sample size was 524. Participants were considered to have hypertension if their systolic blood pressure was 140 mmHg or higher or if their diastolic blood pressure was 90 mmHg or higher. The analysis was restricted to 21 POPs of which at least 60% of study participants had detectable concentrations: three PCDDs, three PCDFs, five dioxin-like PCBs, six dioxin-unlike PCBs, and four OC pesticides. The discrepancy from Lee et al. (2008) in the

number of POPs detected is probably due to the difference in the samples used. For each POP, participants whose serum concentrations were below the limit of detection were regarded as the reference group; participants who had detectable concentrations were categorized into quartiles. A cumulative measure for each POP subclass was derived by summing the category numbers (0 for nondetectable, 1 for detectable below the first quartile, and so on up to 4 for above the third quartile) of individual compounds belonging to the subclass. The summary values were again categorized into quartiles. Logistic regression was used to derive adjusted ORs, which were stratified by sex and adjusted for age, race or ethnicity, poverty-income ratio, BMI, cigarette-smoking (never, former, or current), cotinine, alcohol consumption, and leisure-time physical activity (vigorous, moderate, or none).

Schreinemachers (2010) examined the association in healthy adults between exposure to 2,4-D, as indicated by its presence in urine, and biomarkers that are linked to the pathogenesis of acute MI and type 2 diabetes, namely, serum high density lipoprotein (HDL), triglycerides, total cholesterol minus HDL, insulin, C-peptide, plasma glucose, and TSH. Study participants, 20–59 years old, were selected from a subset of the NHANES III (1988–1994) sample. The study sample is regarded as a convenient sample rather than a representative sample of the US population because volunteers were recruited without a formal statistical sampling procedure. Among 1,338 candidate participants for the study, 375 were excluded because of missing data on urinary 2,4-D, and 236 were excluded on the basis of study exclusion criteria: history of congestive heart failure, heart attack, diabetes, thyroid disease, lupus, or cancer; a white blood cell count over 12×10^9 per liter, C-reactive protein over 10 mg/dL, or glycosylated hemoglobin (HbA1c) over 8%. Among the remaining 727 study participants, urinary 2,4-D was detectable in 102 (14%), with concentrations of 1–28 mg/dL. The outcome variables were compared between participants with and without detectable urinary 2,4-D by using Wilcoxon's rank-sum test. Further analysis was conducted with linear regression, and the outcome variables were transformed to a logarithmic scale. The linear-regression models included the following explanatory variables: 2,4-D (binary), HDL (continuous, log-transformed, and included in all models except when HDL itself was the dependent variable), urinary creatinine (continuous, log-transformed), sex, age, BMI, race or ethnicity, and smoking (none, past, and active). Alcohol consumption, education, household income, and hours of fasting before a blood sample was drawn were also checked for their effects on the regression coefficient for uninary 2,4-D. The analyses were conducted on the final study sample of 727 and on two subsamples that were expected to be more susceptible: participants who had HbA1c above the median (5.1%) of the total sample, and participants who had thyroxine at or below the median (8.5 µg/dL) of the total sample.

Castorina et al. (2010) compared metabolites of current-use pesticides and other precursor compounds in 538 women from the Center for the Health As-

sessment of Mothers and Children of Salinas (CHAMACOS) cohort with those in 342 pregnant women from NHANES 1999–2002. CHAMACOS (Eskenazi et al., 2003b) is a longitudinal birth cohort study investigating the effect of in utero and postnatal environmental exposures on the health of children who live in the Salinas Valley of Monterey County, California. The study enrolled 601 pregnant women from September 1999 to November 2000 in six prenatal clinics in the largely agricultural Salinas area. Women were eligible if they were no more than 20 weeks into gestation, were at least 18 years old, were qualified to receive poverty-based government health insurance, and planned to continue receiving prenatal care at a participating clinic. Personal interviews were conducted during which information on demographics, household characteristics, health, and occupation of CHAMACOS participants was collected. Two interviews were conducted shortly after enrollment (mean, 13 weeks of gestation; SD, 5.2 weeks), and later in the second trimester (mean, 26 weeks of gestation; SD, 2.6 weeks) by bilingual (English and Spanish), bicultural study staff. At each prenatal interview, spot urine samples were collected from CHAMACOS participants and analyzed for metabolites, including organophosphorus, organochlorine compounds, pyrethroid pesticides, herbicides, and ethylene bisdithiocarbamate fungicides.

Of the 601 study participants, adequate urine samples with valid creatinine concentrations were collected from 538 (90%) at the first sampling point and 481 (80%) at the second. In addition, pesticide-use data were extracted from the California pesticide use reporting dataset and geocoded into square-mile units. NHANES reported concentrations of current-use pesticide metabolites measured in spot urine collected from representative samples of the US population stratified by age, sex, and racial or ethnic group (Barr et al., 2005; CDC, 2004). The NHANES comparison group consisted of 342 pregnant women 15–50 years old, a subset of the 3,048 US residents 6–59 years old who had metabolite concentrations measured in urine samples during NHANES testing in 1999 and 2002. The public-release versions of the NHANES datasets, including demographic information and metabolite data, were used for the analyses. No sample weights were applied to the NHANES data. Descriptive analyses were conducted on the CHAMACOS and NHANES cohorts. Metalobites concentrations were compared between the two cohorts using a Wilcoxon rank-sum test and quantile regression at the 95th percentile adjusted for demographic variables, including age, current smoking (yes or no), ethnicity, and socioeconomic status. Analysis of variance (ANOVA) was used to compare differences in detection frequency.

Vietnamese Studies

Various epidemiologic studies have been conducted in the Vietnamese population exposed to the spraying that occurred during the Vietnam conflict. In a review paper, Constable and Hatch (1985) summarized the unpublished results of studies conducted by researchers in Vietnam. They also examined nine reports

that focused primarily on reproductive outcomes (Can et al., 1983a,b; Huong and Phuong, 1983; Khoa, 1983; Lang et al., 1983a,b; Nguyen, 1983; Phuong and Huong, 1983; Trung and Chien, 1983). Vietnamese researchers later published results of four additional studies: two on reproductive abnormalities (Phuong et al., 1989a,b), one on mortality (Dai et al., 1990), and one on hepatocellular carcinoma (Cordier et al., 1993). Ngo et al. (2006) published a meta-analysis that addressed an association between exposure to Agent Orange and birth defects and covered some reports reviewed previously in Constable and Hatch (1985), some new Vietnam studies, and studies on US and Australian veterans who served in Vietnam.

The committee has been interested in recent assessments of contaminant levels in Vietnam attributable to storage, distribution, and spraying of herbicides by the US military during the Vietnam War, but none has explored association between the concentrations measured and health outcomes.

Dioxins and PCBs were among organochlorines measured by Schecter et al. (2003) in food samples gathered in 2002 around Bien Hoa City, Vietnam, about 32 km north of Ho Chi Minh City (formerly Saigon). Bien Hoa City is known as a dioxin "hot spot," with a substantial leak of more than 5,000 gal of Agent Orange at the nearby Bien Hoa air base about 30 years before the study. Marked increases in TCDD concentrations and TEQs were found in ducks, chickens, and fish, but not in pork or beef. The study concluded that food appeared to be responsible for the increase in TCDD in residents of Bien Hoa City, even though the original Agent Orange contamination occurred 30–40 years before sampling.

Hansen et al. (2009) studied serum concentrations of organochlorines (including dioxin-like PCBs 118, 126, 156, and 169) in delivering women in two communities in southern Vietnam: Nha Trang, a coastal city about 450 km northeast of Ho Chih Minh City, and Dien Khanh, a rural district about 10 km inland from Nha Trang. Of 246 women delivering infants from May to July 2005, 94 in Nha Trang and 95 in Dien Khanh met the studies residence requirements, agreed to participate, and provided a blood specimen. Mean concentrations of the ordinarily prevelant non–dioxin-like PCB 153 were 0.15 µg/L in Nha Trang and 0.10 µg/L in Dien Khanh, while other PCB congeners were low in both communities. Age and parity were the most important predictors of plasma concentrations for all compounds, while community of residence was also predictive for PCB 153. Correlations with the health status of mothers or children were not reported.

Nhu et al. (2009) examined the correlations of dioxin concentrations in soil, sediment, and breast milk in an area in Vietnam that had been sprayed with herbicide during the war, Cam Chinh commune in Quang Tri province, and a control site that was not sprayed, Cam Phuc commune in Ha Tinh province. Soil and sediment samples were taken randomly throughout Cam Chinh commune and analyzed for PCDDs and PCDFs. Spatial distribution of PCDDs and PCDFs was estimated by using lognormal kriging (Saito and Goovaerts, 2000). Breast-milk samples were taken from lactating mothers 20–40 years old who lived in

two communes (86 in Cam Chinh commune and 71 in Cam Phuc commune) in September 2002–July 2003. The participants were also interviewed to collect information on personal habits, such as smoking, alcohol drinking, contraceptive-drug use, history of pesticide contact, disease history, number of pregnancies, age at each pregnancy, and reason for pregnancy failure, if applicable. The mean dioxin concentrations in soil and breast milk in the sprayed area were significantly higher than those in the nonsprayed area. There were no significant correlations between the estimated dioxin concentrations in soil obtained with the kriging method and those in breast milk. Again, no results were presented with respect to the health status of mothers or infants.

Taiwanese Mother-and-Child-Studies

A prospective study of healthy Tiawanese mothers and their children recruited during the mothers' pregnancy is underway to study the associations between exposures to PCDDs, PCDFs, and PCBs and health outcomes (Chao et al., 2004; Su et al., 2010; Wang et al., 2004, 2005). The study enrolled pregnant women who had no clinical complications, were 25–35 years old, and delivered in the period December 1, 2000–November 30, 2001, in a medical center in suburban Taichung in central Taiwan, where a solid-waste incinerator is located. Participants completed a questionnaire concerning maternal age, occupation, disease history, cigarette-smoking, alcohol consumption, dietary habits, and baby's stature. Biologic samples (including placenta, umbilical-cord blood, mother's venous blood, and breast milk) were collected for analysis of PCDDs, PCDFs, and PCBs. A total of 610 women were enrolled (80% of those invited). The placenta was collected and the questionnaire completed for 430 participants. Of those, 250 provided sufficient venous blood for the chemical analyses. Of the 250, 175 provided adequate breast-milk samples. Wang et al. (2004) reported on PCDDs, PCDFs, and PCBs in the biologic samples and correlations among specimens. Chao et al. (2004) reported on PCDDs, PCDFs, and PCBs in breast milk and the cumulative dose derived for infants exclusively breastfed vs those formula-fed.

Wang et al. (2005) examined the association between in utero exposure to PCDDs, PCDFs, and PCBs and thyroid and growth hormones in the newborns. Hormone concentrations were compared between infants with high vs low dioxin/PCB TEQ (above vs below the median) and between females (n = 62) and males (n = 57), using a two-sample t-test or the Mann-Whitney U test (when the distribution deviates significantly from the normal distribution assumed for the t-test). Spearman's correlation was used to evaluate the association between hormone concentrations and PCDD, PCDF, and PCB concentrations. Further analyses were carried out with stepwise multivariate regression analysis to adjust for age and other covariates selected through the stepwise selection procedure. Wang et al. (2006) examined the association between PCDDs, PCDFs, and PCBs measured in the placenta samples and estrogens and metabolites measured in using mothers'

blood samples, using Pearson correlations, linear and quadratic regressions, and multivariate regression analyses.

Su et al. (2010) reported on 2-year and 5-year follow-ups of the mother–child pairs in Wang et al. (2005). Children's anthropomorphic measures were obtained, including height, weight, BMI, head circumference, chest girth, bone age, and the ratio between bone age and chronologic age. Thyroid, sex hormone, and growth factor concentrations were measured in venous blood samples obtained from children whose mothers' serum PCDD and PCDF TEQs were available. The anthropomorphic measures and thyroid, sex hormone, and growth factor concentrations were compared by sex (29 and 14 males at years 2 and 5, respectively, and 41 and 27 females at years 2 and 5) and pooled across sexes and those with high vs low in utero PCDD and PCDF concentrations (≥ 15 vs < 15 pg-TEQ/g of lipid) were compared with a two-sample t-test or (when not normally distributed) a Wilcoxon rank-sum test. Further analyses were conducted with multiple regression and stepwise selection for detecting factors that might affect the growth or hormone concentrations.

Chapaevsk, Russia

Several studies in the Samara region of Russia have identified the Middle Volga Chemical Plant (also known as SZVH or Khimprom) in Chapaevsk, about 950 km southeast of Moscow, as a major source of TCDD pollution (Revazova et al., 2001; Revich et al., 2001). From 1967 to 1987, the plant produced γ-hexachlorocyclohexane (lindane) and its derivatives. Since then, it has produced various crop-protection products. Dioxins have been detected in air, soil, drinking water, and cow's milk in the region, but no description of air-, soil-, or water-sampling methods was given. The number of samples analyzed was small for some media (two drinking-water samples, seven breast-milk samples pooled from 40 women, and 14 blood samples) and unreported for others (air, soil, and vegetables). Higher concentrations of dioxin were found around the center of Chapaevsk than in outlying areas. That conclusion was based primarily on concentrations measured in soil: 141 ng TEQ/kg of soil less than 2 km from the plant compared with 37 ng TEQ/kg of soil 2–7 km from the plant and 4 ng TEQ/kg of soil 7–10 km from the plant. Concentrations outside the city (10–15 km from the plant) were about 1 ng TEQ/kg. The publications also compared measurements in Chapaevsk with those in other Russian cities that had industrial facilities. The highest TCDD concentrations observed in Chapaevsk nearest the plant were higher than the maximum concentrations reported by four other studies referred to in the articles. Residence in the city of Chapaevsk was used as a surrogate for exposure in the epidemiologic analyses, and no attempt has been made to create exposure categories based on residential location in the city or on occupational or lifestyle factors that might have influenced TCDD exposure.

Akhmedkhanov et al. (2002) sampled 24 volunteers in the same population

for lipid-adjusted serum dioxin concentrations. Residents living within 5 km of the plant had higher concentrations than those who lived farther from the plant. It was not clear whether the analysis included adjustments for age, BMI, or education, all of which are significant predictors of dioxin concentration.

Several new studies of the Chapaevsk cohort have been published since *Update 2008*. The Russian Children's Study (Burns et al., 2009) enrolled 499 peripubertal boys (8–9 years old) in Chapaevsk from 2003 to 2005, using the townwide health-insurance information system. No rationale was given for the exclusion of girls from the study. Children were excluded if they were institutionalized (for example, living in orphanages), if birth or family history information was missing, if they were of Azerbaijani nationality (which impacted their likelihood of relocating during the study period), or if they had a chronic illness that could affect childhood growth and development. Eligible boys were given a physical examination and provided blood samples for dioxin and PCB analyses. Nurse-administered health, lifestyle, and dietary questionnaires were completed by the participants and their mothers or guardians. Serum samples below the limit of detection (LOD) were assigned a value equal to the LOD divided by the square root of 2. Dioxin and PCB congeners were grouped into summary measures: lipid-adjusted serum concentration of total PCDDs/PCDFs/coplanar PCBs (C-PCBs), lipid-adjusted serum 1998 and 2005 TEQs, and lipid-adjusted serum concentration of total PCBs. General linear-regression models were used to assess associations of serum dioxins, furans, and PCBs (transformed to a logarithmic scale) with anthropometric, demographic, lifestyle, geographic, and dietary covariates.

Humblet et al. (2010) reported on predictors of serum dioxin, furans, and PCBs in 492 mothers of children enrolled in the Russian Children's Study. Seven mothers had sibling pairs in the study, and this accounted for the difference between the sizes of samples of mothers and children. Serum samples from 446 mothers were collected and analyzed for dioxin, furans, and PCBs, grouped into total PCDDs, total PCDFs, total C-PCBs, total mono-*ortho* polychlorinated biphenyls (M-PCBs), total PCBs, non–dioxin-like PCBs, total PCDD TEQs, total PCDF TEQs, total C-PCB TEQs, total M-PCB TEQs, and total TEQs. The median total PCB concentrations and total TEQs were 260 ng/g of lipid and 25 pg TEQ/g of lipid, respectively. A health and lifestyle questionnaire was administered by a nurse to collect data on reproductive, medical, residential, and occupational histories, including distance from plant and employment at plant; socioeconomic measures, such as household income and education; lifestyle information, such as duration of gardening, farming, and smoking; height, weight, and prepregnancy weight for the enrolled child (from which current and prior BMI and percentage change in BMI since pregnancy were derived); and frequency of maternal consumption of various food categories. Multivariate regression models were used to assess predictors of serum dioxins, furans, and PCBs, using a variable selection procedure that selected candidate predictor variables according to their statistical

significance, except four variables that were included because of a priori interest irrespective of their statistical significance: employment at SVZH and consumption of oily foods, fish, and local dairy products.

Times Beach and Quail Run Cohorts

Several reports have provided information on environmental exposure to TCDD in the Times Beach area of Missouri (Andrews et al., 1989; Patterson et al., 1986), one of the incidents that heightened concerns about the health effects of dioxin. In 1971, TCDD-contaminated sludge from a hexachlorophene-production facility was mixed with waste oil and sprayed in various community areas for dust control. Soil contamination in some samples exceeded 100 ppb. Among the Missouri sites with the highest soil TCDD concentrations was the Quail Run mobile-home park. Residents were considered exposed if they had lived in the park for at least 6 months during the time when contamination occurred (Hoffman et al., 1986).

Among 51 exposed participants, 87% had adipose-tissue TCDD concentrations below 200 ppt; however, TCDD concentrations in seven of the 51 were 250–750 ppt. Among 128 nonexposed control participants, adipose-tissue TCDD ranged from undetectable to 20 ppt (median, 6 ppt). On the basis of a 7-year half-life, it is calculated that two study participants would have had adipose-tissue TCDD near 3,000 ppt at the time of the last exposure (Andrews et al., 1989).

Several studies evaluated health effects potentially attributable to exposure (Evans et al., 1988; Hoffman et al., 1986; Stehr et al., 1986; Stehr-Green et al., 1987; Stockbauer et al., 1988; Webb et al., 1987). Those studies were reviewed in *VAO*; no further work on these cohorts has been published.

Other Environmental Studies

Numerous other environmental studies were reviewed in *VAO* and previous updates.

Reproductive outcomes related to environmental exposure to the chemicals of interest were studied in Oregon (EPA, 1979); Arkansas (Nelson et al., 1979); Iowa and Michigan (Gordon and Shy, 1981); New Brunswick, Canada (White et al., 1988); Skaraborg, Sweden (Jansson and Voog, 1989); and Northland, New Zealand (Hanify et al., 1981).

Additional outcomes of environmental exposure to the chemicals of interest were studied for STSs and connective-tissue cancers in Midland County, Michigan (Michigan Department of Public Health, 1983); NHL in Yorkshire, England (Cartwright et al., 1988); adverse health effects after an electric-transformer fire in Binghamton, New York (Fitzgerald et al., 1989); lymphomas and STSs in Italy (Vineis et al., 1991); cancer in Finland (Lampi et al., 1992); early-onset Parkinson disease (PD) in Oregon and Washington (Butterfield et al., 1993);

neuropsychologic effects in Germany (Peper et al., 1993); mortality and cancer incidence in two cohorts of Swedish fishermen whose primary exposure route was assumed to be diet (Svensson et al., 1995); immunologic effects of prenatal and postnatal exposure to PCB or TCDD in Dutch infants from birth to the age of 18 months (Weisglas-Kuperus et al., 1995); effects of inhalation exposure to TCDD and related compounds in wood preservatives on cell-mediated immunity in German day-care center employees (Wolf and Karmaus, 1995); skin cancer in Alberta, Canada (Gallagher et al., 1996); immunologic effects in hobby fishermen in the Frierfjord in southeastern Norway (Lovik et al., 1996); HL, NHL, multiple myeloma, and acute myeloid leukemia in various regions of Italy (Masala et al., 1996); NHL, HL, and chronic lymphocytic leukemia in a rural Michigan community (Waterhouse et al., 1996); cancer mortality in four northern wheat-producing states (Schreinemachers, 2000); mortality and incinerator dioxin emissions in municipalities in Japan (Fukuda et al., 2003); prevalence of hypertension in Taiwanese who lived near municipal-waste incinerators (Chen HL et al., 2006); and adverse pregnancy outcomes in Japan on the basis of maternal residence at the time of birth (Tango et al., 2004).

Combustion records in the Zeeburg area of Amsterdam in the Netherlands were used as a surrogate for exposure to dioxins in a study of orofacial clefts (ten Tusscher et al., 2000). Location downwind or upwind of an incineration source was used to define exposed and reference groups for the study. A study of STS in the general population was conducted in the vicinity of Mantua in northern Italy (Costani et al., 2000). Several industrial facilities are in Mantua, and residential proximity to them was presumed to result in increased TCDD exposure, but TCDD was not measured in the environment or in human tissues.

A study of dioxin exposure pathways in Belgium focused on long-time residents of the vicinity of two municipal-waste incinerators (Fierens et al., 2003a). Residents near a rural incinerator had significantly higher serum dioxin concentrations than a control group (38 vs 24 TEQ pg/g of lipid). Concentrations in people who lived near the incinerators increased proportionally with intake of local-animal fat. A second study (Fierens et al., 2003b) measured dioxin body burden in 257 people who had been environmentally exposed, with the object of determining whether dioxin and PCB exposures were associated with type 2 diabetes and endometriosis. No difference in body burden was found between women who had endometriosis and women in a control group, but the risk of type 2 diabetes was significantly higher in those who had higher body burdens of dioxin-like compounds and of PCBs. Another study of the correlation between dioxin-like compounds in Italian and Belgian women and the risk of endometriosis used measurements of TCDD and other dioxins in blood (De Felip et al., 2004). There was no difference in body burden between women who had endometriosis and a control group, but serum-dioxin concentrations were substantially higher in the Belgian controls than in a similar group in Italy (45 vs 18 TEQ pg/g of lipid, respectively).

Bloom et al. (2006) measured serum dioxin in New York sport fishermen as part of a study of thyroid function. A methodologic study by Petreas et al. (2004) found generally high correlations between concentrations of dioxins and related compounds in breast and abdominal fat in the same woman; this suggested that they could be used interchangeably in epidemiologic studies. The same study, however, also found that adjusting concentrations according to lipid content rather than weight of the fat samples is important because of the presence of nonlipid components in the samples.

Karouna-Renier et al. (2007) examined health effects related to dioxins and furans in soil at a Superfund site in Pensacola, Florida, contaminated by operations at a wood-treating company that operated from 1942 to 1982. In 2001, the study collected health and exposure histories and measured serum concentrations of 17 PCDD and PCDF congeners in 47 potentially exposed people, selected nonsystematically from among former workers, their families, and residents. Logistic regression was used to predict the prevalence of health outcomes from TEQs with adjustment for age, race, sex, BMI, tobacco and alcohol use, and worker status.

Viel et al. (2000) reported on an investigation of apparent clusters of cases of STS and NHL in the vicinity of a municipal solid-waste incinerator in Doubs, France. The presumptive source of TCDD in the region is a municipal solid-waste incinerator (MSWI) in the Besançon electoral ward in western Doubs. Dioxin emissions from the incinerator were measured in international TEQ units at 16.3 ng/m^3, far in excess of the European Union (EU) standard of 0.1 ng/m^3. TCDD concentrations in cow's milk measured at three farms near the incinerator were well below the EU guideline of 6 ng/kg of fat, but the concentrations were highest on the farm closest to the incinerator. Floret et al. (2003) examined the same population and investigated the rates of NHL in Besançon, France. Cases were identified from a cancer registry of people who had a diagnosis of NHL in 1980–1995. Viel et al. (2008a) examined the same population and reported a case–control study conducted with 434 women who had breast cancer compared with 2,170 community controls selected according to the proximity of their residence to emissions from the waste incinerator.

Viel et al. (2008b) expanded the previous work and studied the association between NHL and dioxin exposure from MSWIs in four French administrative departments (Isère, Bas-Rhin, Haut-Rhin, and Tarn), which were covered by a population-based cancer registry. (The study did not include the study area of previous studies, Doubs, which is a separate administrative department.) The study was conducted with geostatistical analysis at the level of block groups and compared exposures and outcomes in the 2,270 block groups in the study area. The block groups had an average surface area of 9.45 km^2. The cases considered for this study were in people 15 years old and older who had received a diagnosis of NHL during the period 1990–1999 and were living in the study area at the time of their diagnosis. Anonymous data were extracted from cancer registries on date of birth, sex, date of diagnosis, address at the time of diagnosis, and cancer

category. The block group for each case was geocoded by using the residential address.

A second-generation Gaussian atmospheric-dispersion model (ADMS 3) was used to derive "immission" estimates (defined by the researchers as "the amount of pollutant reaching a particular location as a result of—and in contrast to—the emission coming out the chimney") for dioxins, metals, and dusts in the area near each of 13 MSWIs operating in the study area. That involved a receptor grid of 200 m that was based on emission estimates for the MSWI, plant characteristics (chimney height and diameter, emission temperature, particle size, and density), topography indicators (roughness and relief), local meteorologic conditions, and so on. For each of the 2,270 block groups, the median of all immission estimates for receptors in the block group was used as the immission for the block group. For block groups under the plumes of multiple MSWIs, the sum of the immission estimates was used. A cumulative ground-level dioxin concentration estimate was derived for each block group by using the immission estimates transformed to account for the number of years that the plant had operated and the degradation rate in the soil. Poisson regression was applied at the block-group level to assess the association between observed number of NHL cases in each block group and the dioxin concentration (with a square-root transformation) estimated for the block group and adjusted for population density, urbanization, socioeconomic level, airborne traffic pollution, and industrial pollution.

Cordier et al. (2004, 2010) studied the risk of birth defects attributable to environmental dioxins released from MSWIs in the Rhône-Alpes region (Lyon and surrounding areas) in southern France. The studies partially overlapped the study areas in Viel et al. (2008b): all three studies included the administrative department of Isère.

Cordier et al. (2004) conducted a geostatistical analysis at the level of communities (official municipalities), studying 2,872 communities that had fewer than 50,000 residents. Birth defects during the study period, 1988–1997, were identified from a population-based birth-defects registry (the French Central-East Registry). There were 70 MSWIs that operated in the study region for at least a year during the study period. Immission scores were derived by using a Gaussian plume model (POLAIR) for dioxin concentrations in kilometer grids within 10 km of the plants and using plant emission estimates, chimney heights, and local meteorologic data. For each community, the immission score at the geographic point with the highest population density was used as the contemporaneous exposure index for the community. (That is a bit different from the usual practice of using the population centroid for the community.) In addition, a cumulative exposure index was derived by multiplying the contemporaneous exposure index by the number of years that the plant was in operation. A total of 194 communities were classified as exposed, and the remaining 2,678 communities as unexposed. In the exposed communities, only births after the start of the MSWI were considered in the analysis. Poisson regression was used to derive the rela-

tive risk of congenital malformations with adjustment for year of birth, maternal age, department of birth, population density, average family income, and (when available) local road traffic.

Cordier et al. (2010) examined the same population with a case–control study in 2001–2003, comparing 304 infants who had urinary tract birth defects with a random sample of 226 population controls that were frequency matched for infant sex and year and district of birth. Of 353 cases identified in the birth-defects registry, 304 were located, and 187 were interviewed. The modest response rate (53% of all cases, although the authors claimed a higher response rate of 62%, excluding 49 cases not located) may compromise the validity of the study findings. The controls were recruited through a computer-assisted telephone interview that attempted to reach 3,000 telephone numbers in the region presumed to belong to families with children, and this resulted in 226 control participants after 1,989 ineligible candidates were excluded. Exposure estimates for dioxins, furans, and metals in areas near each MSWI (in 100-m grids) were derived by using Gaussian modeling software (ADMS 3) that took into account emissions, plant characteristics (chimney height and diameter, emission temperature and speed, and distribution between gaseous and particulate phases), and local meteorologic conditions. Participants were classified as exposed or unexposed; those exposed were further classified into above median or below. Multiple logistic regression was used to estimate the association between dioxin exposure and urinary tract birth defects with adjustment for stratification variables (child's sex and year and district of birth). Potential confounders were selected by using backward selection, including community characteristics (population density, deprivation score, and industrial dioxin sources besides MSWIs), maternal age, parental geographic origin, educational level, employment status during pregnancy, treatment for chronic disease during the first trimester, folic acid supplementation, history of urinary tract birth defects in first-degree relatives, parity, obesity, tobacco and alcohol use during pregnancy, and environmental tobacco-smoke exposure.

From 2002 to 2006, Ueruma et al. (2008a,b) assembled a stratified sample of 1,374 Japanese 15–73 years old (627 men and 747 women) who represented urban, farming, and fishing areas of the entire country. The participants completed questionnaires on occupational, medical, smoking, and residential histories and height and weight. They also provided blood samples that were analyzed with isotope dilution high-resolution gas chromatography–mass spectrometry for PCDDs, PCDFs, and dioxin-like PCBs. Ueruma et al. (2008a) investigated the relationship of those compounds with the prevalence of diabetes, defined as self-reported physician-diagnosed diabetes or occurrence of plasma HbA1c greater than 6.1% as a predictor of fasting plasma glucose above 126 mg/dL. Ueruma et al. (2008b) presented summary statistics on the serum concentrations of the individual compounds in the blood of the study participants and on their distributions with respect to various demographic characteristics; they also provided the results of log-transformed correlation analyses of all PCDDs and PCDFs

combined, of all dioxin-like PCBs, and of total TEQ with total cholesterol, high-density lipoprotein, and triglycerides.

Uemura et al. (2009) conducted further studies of the same cohort and examined the association of body burdens of dioxins and related compounds with the prevalence of metabolic syndromes, assessed by using a modification of the National Cholesterol Education Program Adult Treatment Panel III definition (NCEP, 2002) to accommodate differences between Asian and Caucasian populations (Ko et al., 2005; Tan et al., 2004). In particular, participants were classified as having metabolic syndrome if they satisfied three or more of the following five criteria: BMI of at least 25 kg/m2 (rather than abdominal waist circumference); serum triglycerides of at least 150 mg/dL; serum HDL under 40 mg/dL in men or under 50 mg/dL in women; systolic blood pressure of at least 130 mmHg or diastolic blood pressure of at least 85 mmHg or self-reported history of physician-diagnosed hypertension; and HbA1c of at least 5.6% (rather than fasting serum glucose) or self-reported history of physician-diagnosed diabetes. Logistic regression was used to assess the associations between exposures (TEQs for PCDDs, PCDFs, dioxin-like-PCBs, and total TEQs) and the prevalence of metabolic syndrome, both adjusted and not adjusted for age, sex, smoking and drinking habits, regional block, residential area, and survey year. The analysis was conducted both with and without prevalent diabetes cases. Further analyses were conducted for the adjusted associations of the TEQs with the five components of the metabolic syndrome and the adjusted associations of the concentrations of the 16 selected congeners of which more than 75% of the subjects had detectable concentrations with the prevalence of the metabolic syndrome.

Halldorsson et al. (2009) studied the association between consumption of fatty fish, as a source of environmental exposure to dioxins and dioxin-like compounds, and birthweight and development among 100 healthy pregnant women 25–35 years old selected from the Danish National Birth Cohort (which includes 101,046 women; Olsen et al., 2001). The 9,815 eligible women were stratified according to the frequency of fatty-fish intake (low, zero meals/month; medium, one to three; and high, more than three); 34, 33, and 33 were randomly sampled in each stratum, respectively. Four standardized computer-assisted telephone interviews (at gestation weeks 12 and 30 and at 6 and 18 months postpartum) were used to collect information on parental lifestyle and health. Participants received a food-frequency questionnaire in week 25 of gestation, and two maternal blood samples were collected during routine visits to the general practitioner. The blood samples were analyzed for CALUX-TEQs in picograms per gram of lipid. Birth outcomes (weight, length, and head circumference) based on measures performed by the midwives who attended the births were extracted from the Danish National Birth Registry. Developmental milestones (such as sitting without support and crawling) were obtained from the telephone interviews conducted when the children were 5.7–7 months old. A total developmental scale was derived by summing the indicators across the 13 milestones. Linear mixed models (with the

multiple plasma samples specified as an individual-level random effect) were used to estimate the association between CALUX-TEQ and birth weight with adjustment for gestational age, infant sex, and maternal smoking. Logistic regression was used for the association between CALUX-TEQ (dichotomized into high and low relative to the sample median) and infant development milestones with adjustment for gestational age, duration of breastfeeding, infant age at interview, and maternal fish intake. Spearman rank correlation was used for the association between CALUX-TEQ and the total developmental scale.

Turunen et al. (2008) studied mortality in 6,410 fishermen and their 4,260 wives in Finland, in comparison with the national mortality figures (standardized by sex, age, and period), assuming that the difference in mortality reflects the high consumption of contaminated fish by fishermen and their wives. A small subsample (88 fishermen and 94 wives) participated in a substudy of fish consumption and life habit and provided blood samples that were analyzed for nutrients and environmental contaminants, including dioxins and PCBs. The substudy found higher fish consumption and higher serum dioxins and PCBs in fishermen and their wives than in the general population studied in the 2000 health survey. However, the validity of the findings of the mortality study is limited by various types of confoundings including possible health benefits of fish consumption by fishermen and their wives and a possible healthy-worker effect in the cases of fishermen.

CASE–CONTROL STUDIES

Numerous case–control studies have been reviewed in previous updates. In 1977, case-series reports in Sweden (Hardell, 1977, 1979) of a potential connection between exposure to phenoxyacetic acids and STS prompted several case–control investigations (Eriksson et al., 1979, 1981, 1990; Hardell, 1981; Hardell and Eriksson, 1988; Hardell and Sandstrom, 1979; Wingren et al., 1990). After the initial STS reports (Hardell, 1977, 1979), case–control studies of other cancer outcomes were conducted in Sweden: of HL and NHL (Hardell and Bengtsson, 1983; Hardell et al., 1980, 1981; Persson et al., 1989, 1993), of NHL (Hardell and Eriksson, 1999; Olsson and Brandt, 1988), of nasal and nasopharyngeal carcinomas (Hardell et al., 1982), of gastric cancer (Ekström et al., 1999), and of primary or unspecified liver cancer (Hardell et al., 1984). To address criticism regarding potential observer bias in some of the case–control series, Hardell (1981) conducted another case–control study of colon cancer. Hardell et al. (1994) also examined the relationship between occupational exposure to phenoxyacetic acids and chlorophenols and various characteristics related to NHL—including histopathologic measures, stage, and anatomic location—on the basis of the NHL cases in a previous study (Hardell et al., 1981).

Prompted by the Swedish studies (Hardell, 1977, 1979), Smith and Pearce (1986) and Smith et al. (1983, 1984) conducted a set of case–control studies to

evaluate the association between phenoxy herbicide and chlorophenol exposure and STS incidence and mortality in New Zealand. An expanded case series was collected, and additional case–control studies of exposure to phenoxy herbicides or chlorophenols and the risks of malignant lymphoma, NHL, and multiple myeloma were conducted (Pearce et al., 1985, 1986a,b, 1987).

Geographic patterns of increased leukemia mortality in white men in the central part of the United States prompted a study of leukemia mortality in Nebraska farmers (Blair and Thomas, 1979). Additional case–control studies of leukemia were later conducted in Nebraska (Blair and White, 1985), in Iowa (Burmeister et al., 1982) on the basis of the cohort study of Burmeister (1981), and in Iowa and Minnesota (Brown et al., 1990). Another study investigated leukemia in association with NHL and 2,4-D in eastern Nebraska (Zahm et al., 1990).

Case–control studies have been conducted in various US populations for associations of herbicides with other cancers, including NHL (Cantor, 1982; Cantor et al., 1992; Hartge et al., 2005; Tatham et al., 1997; Zahm et al., 1993); multiple myeloma (Boffetta et al., 1989; Brown et al., 1993; Morris et al., 1986); gastric cancer, prostate cancer, NHL, and multiple myeloma (Burmeister et al., 1983); STS, HL, and NHL (Hoar et al., 1986); NHL and HL (Dubrow et al., 1988); and STS and NHL (Woods and Polissar, 1989; Woods et al., 1987). In a subset of participants in the Hartge et al. (2005) study, De Roos et al. (2005b) studied associations between overall TEQs of PCBs, furans, and dioxins but not dioxin alone.

Other studies outside the United States have examined STS and other cancers in the 15 regional cancer registries that constitute the National Cancer Register in England in connection with the chemicals of interest (Balarajan and Acheson, 1984); ovarian cancer in the Piedmont region of Italy (Donna et al., 1984); STS in rice weeders in northern Italy (Vineis et al., 1986); mortality from esophageal cancer, pancreatic cancer, cutaneous melanoma, renal cancer, and brain cancer in three English counties (Magnani et al., 1987); brain gliomas in two hospitals in Milan, Italy (Musicco et al., 1988); lymphoid cancer in Milan, Italy (LaVecchia et al., 1989); primary lung cancer in pesticide users in Saskatchewan (McDuffie et al., 1990); STS and malignant lymphomas in the Victorian Cancer Registry of Australia (Smith and Christophers, 1992); and renal-cell carcinoma in the Denmark Cancer Registry (Mellemgaard et al., 1994). Nanni et al. (1996) conducted a population-based case–control study, based on the work of Amadori et al. (1995), of occupational and chemical risk factors for lymphocytic leukemia and NHL in northeastern Italy.

Noncancer health outcomes also have been investigated in case–control studies: spontaneous abortion (Carmelli et al., 1981); congenital malformations (García et al., 1998); immunosuppression and later decreased host resistance to infection in AIDS patients who had Kaposi sarcoma (Hardell et al., 1987); mortality in US Department of Agriculture extension agents (Alavanja et al., 1988, 1989); PD associated with occupational risk factors (Semchuk et al., 1993); birth defects in offspring of agricultural workers (Nurminen et al., 1994); mor-

tality from neurodegenerative diseases associated with occupational risk factors (Schulte et al., 1996); PD associated with various rural factors, including exposure to herbicides and wood preservatives (Seidler et al., 1996); spina bifida in offspring associated with paternal occupation (Blatter et al., 1997); PD associated with occupational and environmental risk factors (Liou et al., 1997); and mortality from neurodegenerative diseases, including Alzheimer disease and presenile dementia, PD, and motor neuron disease associated with occupational factors (Park et al., 2005). Those studies are discussed in detail in previous updates.

Several relevant new case–control studies have been published since *Update 2008*. They are reviewed below prior to discussion of case–control study populations that have been the basis of several publications considered in the VAO series.

Since *Update 2008*, Orsi et al. (2009) have studied the association between occupational exposures to pesticides and lymphoid neoplasms by using a hospital-based case–control study in the main hospitals of six French cities (Brest, Caen, Nantes, Lille, Toulouse, and Bordeaux) from September 2000 to December 2004. Cases were eligible if male, 20–75 years old, residing in the hospital's catchment area (the administrative department where the hospital is or a neighboring department), without a history of immunosuppression or taking immunosuppressant drugs, and had recently received a diagnosis of any lymphoid neoplasm except acute lymphoid leukaemia. The diagnoses were classified by using the World Health Organization (WHO) third edition of the *International Classification of Diseases for Oncology* codes (ICD-O-3) and confirmed cytologically or histologically by a panel of pathologists and hematologists. Among 513 eligible incident cases, 491 (96%) participated: 87 Hodgkin lymphoma (HLs), 244 NHL, 56 multiple myelomas (MMs), and 104 lymphoproliferative syndromes (LPS). The controls were male patients from the same hospitals with no prior history of lymphoid neoplasm (LN), residing in the hospital's catchment area, and not admitted to the hospital for conditions directly related to occupation, smoking, or alcohol abuse. The controls were individually matched with the cases by hospital and age (± 3 years). Among 501 eligible controls, 456 (91%) participated. Participants were given a self-administered questionnaire, had a face-to-face interview, and had a reinterview by an occupational hygienist and an agronomist when needed to collect socioeconomic and lifestyle information, personal and family medical history, residential and occupational histories, and detailed information on occupational and non-occupational exposure to herbicides and pesticides. Dichotomous exposure measures (ever or never exposed) were constructed for each category (insecticides, fungicides, and herbicides) and for each chemical family (such as organochlorines and phenoxy herbicides). Unconditional logistic regression was used to estimate the odds ratios and confidence intervals for each outcome (all LN, NHL, HL, LPS, and MM) and chemical exposure with adjustment for age, hospital, and socioeconomic category (white collar or blue collar). Logistic regression was used for NHL subtypes (diffuse large B-cell lymphoma,

follicular lymphoma, and other NHL) and LPS (chronic lymphocytic leukemia and hairy-cell leukemia).

Spinelli et al. (2007) conducted a population-based case–control study of histologically confirmed NHL in men and women 20–79 years old who lived in the greater metropolitan areas of Vancouver and Victoria, British Columbia, during 2000–2004. Population controls, frequency-matched to cases by 5-year age groups and area, were identified from the client registry of the provincial healthcare system. A random subset of controls was included in the analyses. The analyses were based on concentrations of organochlorines and related chemicals in serum obtained from controls at the time of interview and from cases before chemotherapy. NHL patients who lost weight rapidly were excluded. Ng et al. (2010) examined the single-nucleotide polymorphisms (SNPs) in the AHR gene that were genotyped for the same study cohorts (422 NHL cases and 459 controls) to measure the association between individual SNPs, haplotypes, and risk of NHL. Gene–environment interaction analyses were conducted for organochlorines and AHR SNPs by using logistic regression.

Hartge et al. (2005) conducted a case–control study that used four NCI Surveillance, Epidemiology and End Results (SEER) registries (Iowa, Los Angeles County, Detroit, and Seattle) for associations of herbicides with NHL. In a subset of participants in the Hartge et al. study, De Roos et al. (2005b) studied associations between NHL and overall TEQs of PCBs, furans, and dioxins but not dioxin alone. Colt et al. (2009) studied whether the relationship between organochlorine exposure and NHL is modified by immune-gene variation in the SEER study participants (1,172 cases and 513 controls). The study genotyped 61 polymorphisms in 36 immune genes and examined three exposures measured in plasma and dust: PCB180, TEQ for OC pesticides, and α-chlordane. Unconditional logistic regresson was used to estimate the exposure–outcome association, with stratification by genotype and adjustment for sex, age, race, education, and study region.

Firestone et al. (2005) reported on a population-based case–control study of incident PD cases in Washington state (250 cases and 388 controls). PD cases were identified in 1992–2002 at the Group Health Cooperative (GHC, a large managed-care organization) or the University of Washington. Control participants were sampled randomly from GHC enrollees who had no history of PD or other progressive neurologic disorder and were frequency-matched to cases by age, sex, GHC clinic location, and year of GHC enrollment. Participants were interviewed to obtain information on demographics, medical and occupational history, occupational and home-based pesticide use, drinking-water source, residential history, and smoking history. Both occupational exposures and residential exposures were reported. No specific chemicals of interest were reported beyond the broad category "herbicide." Unconditional logistic regression was used to estimate the association between PD and exposure with adjustment for age, sex, and smoking.

Firestone et al. (2010) provided an expanded update (404 cases and 526

controls) that extended the same recruitment protocol through 2006. The participation rates were good among eligible cases (70%) and modest among eligible controls (60%) this left some room for selection bias due to nonresponse. Only occupational exposure was reported. Exposures to specific compounds were reported, including 2,4-D (9 exposed among cases and 12 among controls).

Cross-Canada Study of Pesticides and Health

In a nationwide case–control study of men who were 19 years old or older in 1991–1994 and lived in six Canadian provinces, Pahwa et al. (2006) investigated whether exposure to phenoxy herbicides and other pesticides was associated with the incidence of HL, multiple myeloma, or STS.

McDuffie et al. (2001, 2005) followed an analogous protocol in conducting a case–control study of male NHL cases and controls. McDuffie et al. (2005) and Pahwa et al. (2006) considered the possible interaction of exposure to insect repellents, particularly *N,N*-diethyl-*m*-toluamide (DEET) and phenoxy herbicides, in the genesis of the malignancies in question.

Since *Update 2008*, McDuffie et al. (2009) have examined family histories of cancer in first-degree relatives of the study participants (1,528 cases and 1,506 controls) to assess the interacton between family history and pesticide exposure, using conditional logistic regression adjusted for the matching variables (age and province) used to select controls.

Children's Oncology Group

In two related case–control studies, Chen Z et al. (2005, 2006) reported on exposure to pesticides (including herbicides) and the risk of childhood germ-cell tumors. One focused on parental occupational exposures (Chen Z et al., 2005) and the other on parental exposures to residential pesticides and chemicals (Chen Z et al., 2006), but they are based on the same overall case–control study.

No reports from the Children's Oncology Group have been published since *Update 2008*.

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[1]Throughout the report the same alphabetic indicator following year of publication is used consistently for the same article when there were multiple citations by the same first author in a given year. The convention of assigning the alphabetic indicator in order of citation in a given chapter is not followed.

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6

Immune-System Disorders

For the first time in the Veterans and Agent Orange series, immune-system disorders are being addressed in a separate chapter preceding those on other types of adverse health outcomes. In previous Veterans and Agent Orange reports—*Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*, hereafter referred to as *VAO* (IOM, 1994), *Veterans and Agent Orange: Update 1996* (IOM, 1996), *Update 1998* (IOM, 1999), *Update 2000* (IOM, 2001), *Update 2002* (IOM, 2003), *Update 2004* (IOM, 2005), *Update 2006* (IOM, 2007), and *Update 2008* (IOM, 2009)—possible adverse health outcomes arising from disruptions of the immune system were included in the Other Health Outcomes chapter. The current committee elected to comprehensively revisit the limited epidemiologic evidence concerning association of immune disease with herbicide exposure in light of the substantial volume of toxicologic evidence of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin's (TCDD's) impairment of the immune systems of laboratory animals. The chapter opens with an overview of the various types of health problems that can arise from malfunctioning of the human immune system. The standard VAO sections leading to the committee's assignment of a health outcome to a category of association follow and include a new tabulation of all the immune-related epidemiologic information that has been considered in this series, plus a synopsis of the information new to this update. The next section discusses a series of factors that may contribute to the immune responses of animals exposed to the chemicals of interest being considerably more pronounced than any observed to date in humans. The chapter closes with the committee's thoughts for research on the possibility that immune perturbations in humans may function as a mechanistic step in the development of disease processes in other organ systems.

The immune system plays three important roles in the body:

- It defends the body against infection by viruses, bacteria, and other disease-producing microorganisms, known as pathogens.
- It defends against cancer by destroying mutated cells that might otherwise develop into tumors and by providing immunity against tumors.
- It provides resident immune cells that are specially adapted for different tissues and organs (such as microglia in the central nervous system and Kupffer cells in the liver) that help to regulate the functional activity and integrity of those tissues.

To recognize the wide array of pathogens in the environment, the immune system relies on many cell types that operate together to generate immune responses. Those cells arise from stem cells in the bone marrow, they are found in lymphoid tissues throughout the body, and they circulate in the blood as white blood cells (WBCs). The main types of WBCs are granulocytes, monocytes, and lymphocytes. Each category has many specialized cell populations that are responsible for specific functions connected to the production of specific immune hormones (generically known as cytokines). Imbalances in these specialized populations or in their level of functional activity can result in inadequate or improper immune responses that may lead to pathologic outcomes. Diseases arising from immune dysfunction may be apparent immediately or observed only after an organism encounters an environmental challenge that causes immune cells to respond (such as an infection). Immune dysfunctions are in four major categories that need not be mutually exclusive: immune suppression, allergy, autoimmunity, and inflammatory dysfunction (inappropriate and/or misdirected inflammation). Although immune suppression usually is seen as an increased incidence of infections or an increased risk of cancer, allergic, autoimmune, and inflammatory disorders can be manifested as diseases affecting virtually any tissue. It is often difficult to diagnose such diseases, so they may or may not be medically categorized as immune disorders.

Immune Suppression

Suppression of immune responses can reduce resistance to infectious disease and increase the risk of cancer. Infection with the human immunodeficiency virus (HIV) is a well-recognized example of an acquired immune deficiency in which a specific type of lymphocyte (CD4+ T cells) is the target of the virus. The decline in the number of CD4+ T cells after HIV infection correlates with an increased incidence of infectious diseases, including fatal opportunistic infections, and with an increased incidence of several types of cancer. Treatment of cancer patients with toxic chemotherapeutic drugs suppresses the immune system by inhibiting the generation of new WBCs by the bone marrow and by blocking proliferation

of lymphocytes during an immune response. Both those examples represent severe immune suppression in which the adverse outcome is easily detected with clinical measurements.

Immune suppression can also result from exposure to chemicals in the workplace or in the environment and be manifested as recurrent infections, opportunistic infections, a higher incidence of a specific category of infections, or a higher incidence of cancer. However, unless the immune suppression is severe, it is often difficult to obtain clinical evidence that directly links chemically induced changes in immune function to increased infectious disease or cancer, because many confounding factors can influence a person's ability to combat infection. Such confounders include age, vaccination status, the virulence of the pathogen, the presence of other diseases (such as diabetes), stress, smoking, and the use of drugs or alcohol. Therefore, immunotoxicology studies are often conducted in laboratory animals to understand the scope and mechanism of chemical-induced immune suppression. Results of such studies can be used to develop biomarkers to assess effects in human populations. Infectious-disease models in animals can also be used to determine whether the pattern of disease changes with chemical exposure.

Allergic Diseases

The immune system sometimes responds to a foreign substance that is not pathogenic. Such immunogenic substances are called allergens. Like most immune-based diseases, allergic diseases have both environmental and genetic risk factors. Their prevalence has increased in many countries in recent decades (CDC, 2004; Linneberg et al., 2000; Simpson et al., 2008; Sly, 1999). Major forms of allergic diseases are asthma, allergic rhinitis, atopic dermatitis, and food allergy. The response to some allergens, such as pollen and bee venom, results in the production of immunoglobulin E (IgE) antibodies. Once produced, IgE antibodies bind to mast cells, specialized cells that occur in tissues throughout the body, including lung airways, the intestinal wall, and blood-vessel walls. When a person is exposed to the allergen again, it binds to the antibodies on the mast cells and caused them to release histamine and leukotrienes, which produce the symptoms associated with an allergic response. Other allergens, such as poison ivy and nickel, activate allergen-specific lymphocytes at the site of contact (usually the skin) that release substances that cause inflammation and tissue damage. Some allergic responses, such as those to food allergens, may involve a combination of allergen-specific lymphocyte–driven and IgE–driven inflammation. Allergic responses may be manifested in specific tissues (such as skin, eye, airways, and gastrointestinal tract) or result in a system-wide response called anaphylaxis.

Autoimmune Diseases

At least 60 recognized diseases and conditions affecting the cardiovascular, respiratory, nervous, endocrine, dermal, gastrointestinal, hepatic, and excretory systems are classified as autoimmune diseases (WHO, 2006). They affect both men and women. Most of the autoimmune diseases affect more women than men (Fairweather et al., 2008). Genetic predisposition, age, hormone status, and environmental factors, such as infectious diseases and stress, are known to affect the risk of developing autoimmune diseases. The existence of some autoimmune diseases is also a risk factor for the development of other immune-related diseases, such as some types of cancer (Landgren et al., 2010).

Autoimmune disease is an example of the immune system's causing rather than preventing disease: the immune system attacks the body's own cells and tissues as though they are foreign. Inappropriate immune responses that result in autoimmune disease can be promoted by different components of the immune system (such as antibodies and lymphocytes) and can be directed against a wide variety of tissues or organs. For example, the autoimmune reaction in multiple sclerosis is directed against the myelin sheath of the nervous system; in Crohn disease, the intestine is the target of attack; in type 1 diabetes mellitus, the insulin-producing cells of the pancreas are destroyed by the immune response; rheumatoid arthritis arises from immune attack on the joints.

More generalized forms of autoimmune diseases also occur. Systemic lupus erythematosus (SLE) is an autoimmune disease that has no specific target organ of immune attack. Instead, patients have a variety of symptoms that often occur in other diseases, and this makes diagnosis difficult. A characteristic rash across the cheeks and nose and sensitivity to sunlight are common symptoms; oral ulcers, arthritis, pleurisy, proteinuria, and neurologic disorders may be present. Almost all people who have SLE test positive for antinuclear antibodies in the absence of drugs known to induce them. The causes of SLE are unknown, but environmental and genetic factors have been implicated. Some of the environmental factors that may trigger it are infections, antibiotics (especially those in the sulfa and penicillin groups) and some other drugs, ultraviolet radiation, extreme stress, and hormones. Occupational exposures to such chemicals as crystalline silica, solvents, and pesticides have also been associated with SLE (Cooper and Parks, 2004; Parks and Cooper, 2005).

Inflammatory Diseases

Inflammatory diseases make up a more recently identified category of immune-related disorders characterized by dysfunctional inflammatory responses (usually involving immune cells) that are exaggerated, excessively prolonged, or misdirected. Tissue disease can result from this inappropriate inflammation,

which can affect virtually any organ. Examples of diseases and other conditions that are most often included in other disease categories but are also considered to be inflammatory diseases are coronary arterial disease, asthma, eczema, chronic sinusitis, hepatic steatosis, psoriasis, celiac disease, and prostatitis. Inflammatory diseases often occur with one another, and this has resulted in the categorizing of different but linked inflammatory diseases together as a single chronic inflammatory disorder (Borensztajn et al., 2011); among these are atherosclerosis and chronic pulmonary obstructive disease. Inappropriate inflammation also appears to play a role in promoting the growth of cancer (Bornschein et al., 2010; Hillegass et al., 2010; Landgren et al., 2010; Porta et al., 2010; Winans et al., 2010). Examples of this can be seen in the higher prevalence of specific cancers in patients who have such inflammatory diseases as inflammatory bowel disease (Lucas et al., 2010; Viennot et al., 2009; Westbrook et al., 2010), prostatitis (Sandhu, 2008; Wang et al., 2009) and psoriasis (Ji et al., 2009).

Ordinarily, inflammation can be advantageous in fighting infectious diseases. It is one component of the normal host response to infection and is mediated by innate immune cells. Inflammatory responses have evolved to speed the trafficking of macrophages, granulocytes, and some lymphocytes to the area of infection, where they produce toxic metabolites that kill pathogens. Interactions among innate immune cells and epithelial and endothelial cells are important in regulating the level of inflammation. However, improperly regulated inflammation can contribute to diseases that arise in nonlymphoid tissues such as the lungs, skin, nervous system, endocrine system, and reproductive system.

CONCLUSIONS FROM *VAO* AND PREVIOUS UPDATES

The following comments are restricted to findings on the immune system after adult human exposure. For a discussion of potential effects on the immune system arising from early-life (such as perinatal) exposures (which would not be directly applicable to the Vietnam veterans who are the target of this report), see Chapters 4 and 8. Studies that served as the basis of prior updates of *VAO* and one 2009 study are shown in Table 6-1.

Vietnam Veterans

A handful of the direct studies of veterans listed in Table 6-1 reported a statistical difference in a single immune measure (Kim et al., 2003; Michalek et al., 1999a). But invariably the same effect was not found in other studies of Vietnam veterans, nor was support found in epidemiologic studies of other populations. Thus, there were no consistent findings indicative of immunosuppression, increased risk of autoimmunity (usually as measured with autoantibodies), or biomarkers of atopy or allergy (such as increased IgE concentrations). Much of

TABLE 6-1 Selected Epidemiologic Studies—Immune Effects in Adult Humans

Reference	Study Population	Exposure/Results
VIETNAM VETERANS		
US Air Force Health Study (AFHS)—Ranch Hand veterans vs SEA veterans		**All COIs**
AFHS, 2000	Participants in 1987 examination cycle, Ranch Hands vs comparisons—mortality	A small dose-related increase in T-cell counts and a high-dose increase in NK markers, neither considered by authors to be biologically important; no dose–response relationship for TCCD exposure associated with T-cell activation markers (CD25), serum Ig, or autoantibodies
Michalek et al., 1999a	Participants in 1997 examination cycle, Ranch Hands vs comparisons—incidence	No change in surface markers for B and T cells, no change in serum Ig, no change in autoantibodies (antinuclear antibody, smooth muscle autoantibody, parietal cell autoantibody, rheumatoid factor, and monoclonal immunoglobulins) and no dose-related change in DTH response
Wolfe et al., 1990	Participants in 1987 examination cycle, Ranch Hands vs comparisons—morbidity	No change in surface markers for B and T cells
Wolfe et al., 1985	Participants in 1985 examination cycle, Ranch Hands vs comparisons—morbidity and mortality	No change in surface markers for B and T cells
US CDC Vietnam Experience Study (VES)		**All COIs**
Boehmer et al., 2004	Mortality (1965–2000)	No increase in infectious or parasitic diseases
CDC, 1988b	Deployed vs nondeployed—morbidity	No differences in infections, no changes in B and T cell-surface markers, WBC counts, or circulating serum Ig
US VA Cohort of Monozygotic Twins		**All COIs**
Eisen et al., 1991	Physical health—morbidity	Increase in skin conditions of unknown etiology, no increase in blood disorders
American Legion Cohort		**All COIs**
Stellman et al., 1988	Physical health and reproductive outcomes	Increase in skin conditions and arthritis

continued

TABLE 6-1 Continued

Reference	Study Population	Exposure/Results
State Studies of US Vietnam Veterans		**All COIs**
Visintainer et al., 1995	Michigan Vietnam Veterans (deployed vs nondeployed)	Increased mortality from infectious (including parasitic) diseases
Kahn et al., 1992	New Jersey Agent Orange Commission	Depressed response to tetanus in DTH tests, decrease in CD4 and SmIg+ B cells
Newell, 1984	Agent Orange Advisory Committee of Texas	Increase in percentage of active T rosette-forming cells
Australian Vietnam Veterans		**All COIs**
O'Toole et al., 2009	Australian Vietnam Veterans—longitudinal cohort study of 67 conditions in randomly selected Vietnam veterans vs general population	Increase in hay fever, increases in infectious and parasitic diseases, increase in arthritis
CDVA, 1997b	National Service Vietnam Veterans—mortality	No change in mortality from infectious (including parasitic) diseases
Korean Vietnam Veterans		**All COIs**
Kim et al., 2003	Immunotoxicologic study	Increase in IgE and IL-4, decrease in IgG1 and IFN-gamma, no change in lymphocyte counts
Vietnamese Vietnam Veterans		**All COIs**
Chinh et al., 1996	Antinuclear and sperm autoantibodies	No change in autoantibodies to sperm, antinuclear bodies
OCCUPATIONAL STUDIES		
Chemical or Industrial Workers		
Baranska et al., 2008	A prospective multicenter cohort study of 238 pesticide-exposed workers vs 138 unexposed workers	**Pesticide factories** (not specifically TCDD): Reduced antibody responses to hepatitis B vaccination among exposed workers carrying a specific IL-1 allele
Neubert et al., 2000	Updated and expanded evaluation of 158 workers in a German chemical plant with differing exposure studied in two trials	**TCDD** (or "TCDD toxic equivalents" from PCDD/PCDF): No differences in serum Ig or cytokine (IL1, IL6, TNF-alpha)

TABLE 6-1 Continued

Reference	Study Population	Exposure/Results
Ernst et al., 1998	19 highly exposed chemical workers vs 28 unexposed controls in two chemical plants in Hamburg, Germany	**TCDD** (in chemical plant): In subset of leukocytes, increase in CD8+ memory T cells and decrease in naïve T cells (CD45RA+) after TCDD exposure, as was stimulated IFN-gamma production from whole blood cultures associated with TCDD exposure
Halperin et al., 1998	Cross-sectional study of 259 TCDD-exposed 2,4,5-trichlorophenate (and its derivatives) workers (mean serum TCDD, 223 ppt) and 243 unexposed residential controls (mean serum TCDD, 6 ppt)	**TCDD** (exposure in a chemical plant): No significant changes in serum Ig or major leukocyte categories; TCDD associated with decreased circulating CD26 cells (activated T cells)
Jung et al., 1998	192 workers in a German pesticide plant, including 29 highly exposed and 28 controls compared for immune functional tests	**TCDD** (or TEQs from PCDD/PCDF exposure): No significant changes in TCDD and lymphocyte subsets, antibody responses to vaccination, lymphocyte proliferation, or autoantibody production; decrease in chromate resistance of PHA-stimulated lymphocytes in highest exposure group
Sweeney et al., 1997/1998	1987 cross-sectional study of 281 chemical-plant workers in NJ and MO at least 15 years after exposure vs 260 unexposed controls	**TCDD** (as a contaminant in chemical production): Increase in TCDD associated with a decrease in CD3/Ta1 (helper lymphocytes) cells
Tonn et al., 1996	Comparison of 11 2,4,5-trichlorophenol production workers 20 years after exposure vs 10 unexposed age-matched workers in the same company	**TCDD:** No differences in any lymphoid subset or in mitogen-induced proliferation; TCDD exposure was associated with decreases in MLR response and in stimulation with IL-2 in vitro
Jansing and Korff, 1994	Examination of eight trichlorophenol production workers who developed chloracne and were re-examined 15–25 years after initial exposure	**TCDD:** Reduced gamma globulins in the most-exposed workers; no significant effects on T4, T8 ratios

continued

TABLE 6-1 Continued

Reference	Study Population	Exposure/Results
Benner et al., 1994	Cross-sectional study of 153 male workers in six chemical plants in Germany	**TCDD** (during production of TCP): DTH responses not correlated with dioxin concentration; slight decrease in IgM was reported with increasing dioxin exposure; overall lymphoid counts not different
Ott et al., 1994	138 surviving workers from a larger cohort of 254 exposed workers after an accident in a BASF TCP production facility	**TCDD:** Among 14 immune measures; regression analysis of TCDD concentration suggested marginal positive associations with IgG, IgA, C3, and C4; marginal reductions in some lymphocyte population were also reported
Neubert et al., 1993, 1994	89 volunteers involved in decontamination work at a chemical plant in Hamburg, German; no control population	**TCDD** (or equivalents via PCDD/PCDF exposure): Potentially complicated by age differences among the compared groups; only subtle, clinically nonsignificant changes were seen among immune-cell surface markers in a comparison of higher exposed vs low-exposed to moderately exposed workers
Jennings et al., 1988	18 chemical workers in a 2,4,5-T factory exposed as a result of an industrial accident 17 years before study vs 15 matched controls	**TCDD:** No changes in serum Ig classes, increases in antinuclear antibodies and immune complexes, and increase in circulating NK cells (Leu7+) in exposed workers
Waste Incinerator Workers		
Oh et al., 2005	Comparison of immune measures in 31 waste-incineration workers vs 84 controls	**TCDD** (via waste incineration): Lymphoid subsets, IFN-gamma, and Ig not statistically different; decrease in IL-4 and increase in T-cell activation (measured as combined CD3 and CD69 markers) associated with TCDD exposure
Agricultural Health Study (AHS)		**Various categories of agricultural pesticides**
Beseler et al., 2008	Comparison from the AHS of 534 cases of self-reported physician-diagnosed depression vs 17,051 controls	Both high-level acute pesticide exposure (OR = 2.57, 95% CI 1.74–3.79) and cumulative pesticide exposure (OR = 1.54, 95% CI 1.16–2.04) were positively associated with increase in depression
Beseler et al., 2006	29,074 female spouses of pesticide applicators in the AHS	Depression was significantly associated with pesticide poisoning (OR = 3.26, 95% CI 1.72–6.19) but not with lower cumulative exposure

TABLE 6-1 Continued

Reference	Study Population	Exposure/Results
De Roos et al., 2005b	Nested case–control study of rheumatoid arthritis in agricultural families (57,000 pesticide applicators and their spouses).	No strong risk factors were identified for pesticide mixing or application or for any specific class of pesticides in the AHS of rheumatoid arthritis.
Other Agricultural Studies		
Faustini et al., 1996	Longitudinal study of 10 farmers during 1994 within 7 days before and 1–12 days and 50–70 days after exposure	**2,4-D and MCPA formulations:** Decreases in percentages of CD4, CD8, CTL, CD8-DR, and NK cells and in NK activity and mitogen-stimulated lymphoproliferation; CD4:CD8 ratio was unaltered; CD3 and CD8 percentages had recovered by the second assessment period; no significant correlations between immune changes and amount of pesticides applied
ENVIRONMENTAL STUDIES		
Seveso Cleanup Workers		**TCDD**
Ghezzi et al., 1982	Prospective study using analysis of samples from 36 cleanup workers (divided into three groups based on time spent in the contamination area); pre-employment samples and samples after 9 months were analyzed for comparison with samples from 31 nonexposed workers	No differences in WBC counts and platelet counts
Seveso Residential Population		**TCDD**
Baccarelli et al., 2005b	Study of 101 chloracne cases vs 211 controls 20 years after the accident; relatively low statistical power was available because the study examined the occurrence of individual diseases	Persistent increase in TCDD in chloracne cases; younger people seemed to be more susceptible; no major trends in disease occurrence
Baccarelli et al., 2002	Study of 62 people from a highly exposed zone and 53 from noncontaminated areas 20 years after the accident	Plasma concentration of TCDD was determined; multivariate regression analysis showed significant decrease in plasma IgG with increasing TCDD concentration and no changes in IgM, IgA, or C3

continued

TABLE 6-1 Continued

Reference	Study Population	Exposure/Results
Pocchiari et al., 1979	45 children (3–7 yrs of age) living in exposed areas vs 45 nonexposed children as controls	No differences in serum IG, mitogen responses of lymphocytes (PHA and pokeweed), or percentage of rosette-forming lymphocytes
Times Beach (MO) Cohort		**TCDD**
Webb et al., 1987	82 people in more highly contaminated areas vs 40 in low-risk exposure areas as controls	No differences in DTH response or T-cell subsets (T4/T8)
Stehr et al., 1986	80 people in highly contaminated areas vs 40 controls in lower-risk areas	No differences in DTH induration or T-cell subset analysis (T4/T8)
Knutsen, 1984	Pilot study of small numbers of people; for comparisons, people were assigned to two environmental-exposure groups: those in high-risk areas (27 men, 23 women, and 15 children) and those in low-risk areas (12 men, 10 women, and 8 children)	Multitest DTH evaluation to seven recall antigens was performed, no statistical differences were reported, and only trends were noted; no statistical differences were reported for T-cell markers (T3, T4, and T8) or mitogen-induced lymphocyte proliferation (PHA, Con A, and pokeweed mitogen), and only trends were noted
Quail Run Mobile Home Park (MO) Cohort		**TCDD**
Evans et al., 1988	A subset of the previously anergic persons in the Stehr-Green et al. (1987) study were re-evaluated in the DTH test with a higher DTH test dose and highly trained, blinded readers	Retesting of DTH failed to produce the differences observed initially
Knutsen et al., 1987	Small (ill-defined) samples were used; comparisons of residents of the Quail Run Mobile Home Park with residents of St. Louis–area trailer parks as controls	DTH suppression in the exposed group was reported, but data from two of four readers were discarded; no differences in T-cell mitogen stimulation; decreases in percentages of T3, T4, and T11 cells in the exposed group
Stehr-Green et al., 1987	154 people in highly contaminated area vs 155 in three low–environmental-contamination areas as controls	Increase in anergy and decrease in induration for DTH in exposed group; data from some readers were excluded; decrease in percentages of T3, T4, and T11 cells, but no difference in cell number of T4/T8 ratio.

TABLE 6-1 Continued

Reference	Study Population	Exposure/Results
Andrews et al., 1986	80 people in a high–exposure risk group vs 40 controls	Decreases in DTH indurations, number of positive reactors, and percentages of T3, T4, and T11 cells in the exposed group
Hoffman et al., 1986	154 people in the exposed area vs 155 non-exposed people in an uncontaminated area	Recall antigen multitest for DTH, increase in percentage of anergy and decrease in induration in exposed group; data from two of four readers were excluded
Missouri Residential Population		**TCDD**
Webb et al., 1989	Regression analysis used for comparisons among 41 exposed people for adipose-tissue TCDD vs immune measures; three exposed groups defined by tissue dioxin	No TCDD–DTH response relationships were reported; no change in mitogen responsiveness; some serum markers (A/G ratio and serum IgG) were affected
Other Environmental Studies		
Lee et al., 2007a	NHANES—1,721 adults were assessed for serum dioxin-like PCBs and self-reported arthritis	**Dioxin-like PCBs:** Association between serum dioxin-like PCBs and prevalence of arthritis particularly among women
Van den Heuvel et al., 2002	200 people 17–18 yrs of age in three areas of Flanders (Belgium); TEQ values were calculated from serum dioxin-like PCB concentrations and relationships with immune measures were examined	**Dioxins and PCBs:** Decreases in eosinophil and NK-cell counts with increasing TEQ; IgE concentrations; history of upper airway allergy, and odds of a positive RAST test correlated negatively with serum TEQ; IgA concentrations correlated positively with TEQ
Lovik et al., 1996	Blood samples from 24 Norwegian hobby fishermen were compared with those of 10 male referents as controls	**PCDD**, exposure from food: The study generally lacks experimental details; no differences in an NK cell marker or in NK activity were seen; apparently, some effects on lymphoid markers were observed but specific details are lacking
Wolf and Karmaus, 1995	Cross-sectional study of 221 teachers who worked in German day-care centers treated with wood preservatives vs 189 teachers who worked in untreated facilities	**Dioxin in wood preservatives**, exposure primarily via inhalation: No effects of inhaled dioxin were seen on T4 or T8 cell numbers or on the ratio; some evidence of a dose–response relationship was seen for risk of anergy (or hypoergy) in the DTH assay

continued

TABLE 6-1 Continued

Reference	Study Population	Exposure/Results
Svensson et al., 1994	23 high consumers of fatty fish from the Baltic Sea (containing low concentrations of PCDD) vs 20 low consumers or nonconsumers of fish as controls	**PCDD**, exposure from food: Blood PCDDs were significantly different between the groups; mercury concentrations also differed; NK cells correlated negatively with blood concentrations of persistent organic chemicals; no other differences were found in lymphocyte populations or in mitogen stimulation of lymphocytes
Hardell et al., 1987	Telephone interviews concerning environmental and occupational chemical exposures were conducted with 50 AIDS patients (with Kaposi sarcoma) and 50 homosexual men as controls	**Chemical exposures, including pesticides, and Agent Orange:** No significant differences were reported in a small study that generally lacked focus

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; AFHS, Air Force Health Study; AHS, Agricultural Health Study; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; Con A, concanavalin A; DTH, delayed-type hypersensitivity; IFN-gamma, interferon-gamma; Ig, immunoglobulin; IL, interleukin; MCPA, methyl-4-chlorophenoxyacetic acid; MLR, mixed lymphocyte response; NHANES, National Health and Nutrition Examination Survey; NK, natural killer; OR, odds ratio; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCDF, polychlorinated dibenzofurans; PHA, polyhydroxyalkanoates; RAST, radioallergosorbent; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; TEQ, total toxic equivalent; TNF, tumor necrosis factor; VA, Department of Veterans Affairs; VES, Vietnam Experience Study; WBC, white blood cell.

the focus of the studies was on measuring T4/T8 ratios. The T4/T8 ratio is an effective biomarker of the progression of HIV-induced AIDS, but, on the basis of the TCDD-exposure animal data, it is not an immunologic index that is expected to be altered.

Occupational Exposures

Occupational-exposure studies shown in Table 6-1 evaluated concentrations of lymphoid populations in circulation, such as CD4, CD8 (and their ratio), and natural killer (NK) cells; cell-mediated immunity (the delayed-hypersensitivity response); serum concentrations of immunoglobulins, such as IgM, IgG, and IgA; concentrations of complement, such as C3 and C4; and concentrations of cytokines, such as IL-1, IL-2, interferon-gamma, IL-4, IL-6, and tumor necrosis factor-alpha. A few studies also included disease or condition end points, such as

rheumatoid arthritis, SLE, and depression. Ex vivo analyses included measures of NK activity, lymphoid mitogen-induced proliferation, and the mixed lymphocyte response (MLR) against allogeneic cells. Some studies identified one or more dioxin-related shifts in immune measures, but many reported no significant differences in the same measures. That is particularly true of the study by Neubert et al. (2000), which measured toxicity equivalents (TEQs) for dioxin but found no immunoglobulin or cytokine alterations. In general, the spectrum of occupational-exposure findings does not provide a consistent or clear picture of alterations in immune measures that could be extrapolated to an increased risk of a single disease or even a broader category of diseases. The exception may be observations of pesticide-associated autoimmunity and depression. Immune depression was rather consistently associated with very high pesticide exposures or pesticide poisonings. However, because the studies generally concerned broad categories of pesticide exposure, their relevance to herbicide exposures in Vietnam is not clear.

Environmental Exposures

Several environmental-exposure studies reported alterations, but findings were inconsistent among the studies (Table 6-1). Some studies reported alterations in immune measures associated with TEQs for dioxin. For example, Van den Heuvel et al. (2002) reported that IgE, positive radioallergosorbent (RAST) tests in response to specific allergens, eosinophils counts, and NK cell counts correlated negatively with dioxin TEQs, but that IgA increased; these alterations, however, were not seen consistently in other studies. Baccarelli et al. (2002) found no changes in IgA but saw changes in IgG in the Seveso population. Svennson et al. (1994) found that NK cell numbers were reduced with increasing concentrations of persistent organic chemicals, but Lovik et al. (1996) found no difference in NK numbers or activity. Similarly, the occupational-exposure studies (Table 6-1) that examined NK concentrations reported the full spectrum of results: no alterations (Halperin et al., 1998), a decrease (Faustini et al., 1996), and even an increase in NK numbers (Jennings et al., 1988) in dioxin-exposed people.

As seen Table 6-1, some early studies of the Quail Run Mobile Home Park population exposures reported that dioxin exposure was associated with a reduced cell-mediated immune response, the delayed-type hypersensitivity (DTH) response (Andrews et al., 1986; Hoffman et al., 1986; Knutsen et al., 1987; Stehr-Green et al., 1987). But some of those studies had technical problems in assessment and in followup analyses. Dioxin-associated changes were not confirmed (Evans et al., 1988; Webb et al., 1989). In addition, several studies of the Times Beach population did not find any alteration of the DTH response in dioxin-exposed populations (Knutsen, 1984; Stehr et al., 1986; Webb et al., 1987).

Analysis of National Health and Nutrition Examination Survey (NHANES) data found that exposure to dioxin-like PCBs was associated with an increase in

self-reported arthritis (Lee et al., 2007a), but De Roos et al. (2005b) had found no such association in their study.

Prior VAO updates concluded that human data were either insufficient or inconsistent with respect to an increased risk of immunosuppression, allergic disease, or autoimmune disease.

UPDATE OF THE EPIDEMIOLOGIC LITERATURE AND HUMAN STUDIES

For this update, the committee revisited the entire literature of herbicide–human immune findings from studies of Vietnam veterans, occupationally exposed people, and environmentally exposed people (Table 6-1), including studies reviewed in prior VAO updates and one study published since *Update 2008*.

Among the previously considered human studies, only two stand out for special consideration on the basis of their analysis of actual immune-based disease or clinically relevant human immune responses. Zober et al. (1994) studied three categories of occupationally exposed workers based on chloracne status (chloracne not evident, moderate, or severe) and nonexposed workers. They found that the frequencies of episodes of parasitic diseases, respiratory infections, and skin diseases were elevated with respect to the nonexposed workers ($p = 0.067$, $p = 0.003$, and $p = 0.001$, respectively), and each of these outcomes showed increasing trends over the three chloracne categories (an indicator of higher dioxin exposure). Baccarelli et al. (2002) reported that higher TCDD exposure was associated with lower serum IgG in the exposed Seveso populations.

Only one new epidemiologic study addressed exposure to the chemicals of interest and outcomes in which immune function may play a prominent role. Infectious and parasitic diseases, respiratory disorders, and skin disorders were among the many conditions that O'Toole et al. (2009) found to be significantly more prevalent in Australian Vietnam veterans, on the basis of self-reports, than in the general population. The confidence that can be placed in this new study is substantially hampered by a poor response rate, its reliance on self-reported diagnoses, the questionable suitability of the general population as a control group, and the fact that the veterans and the controls were interviewed under quite different circumstances. Reporting bias and a "healthy-warrior" effect might be expected to bias the findings in opposite directions, but the near uniformity of significant findings on these self-reported health problems in the deployed veterans suggests that problems associated with reporting bias may have been dominant.

In combination, the studies raise the question of whether high TCDD exposure may contribute to a reduced ability to fend off or to clear some types of infections.

BIOLOGIC PLAUSIBILITY

There is an extensive body of evidence from experimental studies in animal-model systems that TCDD, other dioxins, and several dioxin-like chemicals (DLCs) are immunotoxic (Kerkvliet, 2009). Immunotoxicity is due primarily to changes in adaptive immune responses that result in suppression of both antibody and cell-mediated immunity and a reduction in the ability to clear pathogenic infections and prevent tumor growth. Studies in laboratory mice have shown that the immunotoxicity of TCDD and DLCs depends on activation of the arylhydrocarbon receptor (AHR). Most of the cell types involved in the immune system express the AHR, so there are many potential pathways to immunotoxicity. TCDD has also been shown to alter macrophages and neutrophils in a manner that exacerbates some forms of inflammation during infections and may contribute to the development of chronic inflammatory lung disease (Teske et al., 2005; Wong et al., 2010).

TCDD is a potent immunosuppressive chemical in laboratory animals. The relative potencies of given DLCs based on induction hepatic enzymes (their toxicity equivalency factors [TEFs]) appear to predict the degree of immunosuppression induced (Smialowicz et al., 2008). Exposure of animals to dioxin not only suppresses some adaptive immune responses but also has been shown to increase the incidence and severity of various infectious diseases and to increase the development of cancer (Choi et al., 2003; Head and Lawrence, 2009; Jin et al., 2010). It is consistent with its immunosuppressive effects that TCDD exposure suppresses the allergic immune response of rodents, and this in turn results in decreased allergen-associated pathologic lung conditions and has recently been shown to suppress the development of experimental autoimmune disease (Quintana et al., 2008). Thus, depending on the disease, TCDD exposure could result in exacerbation or amelioration of symptoms.

Recent attention has focused on the ability of the AHR to induce regulatory T cells (Marshall and Kerkvliet, 2010). These so-called Tregs have potent suppressive activity in the immune system, and their inappropriate induction by TCDD could account for much of the immune suppression. AHR activation in dendritic cells has also been shown to promote the development of Tregs by inducing tryptophan metabolism. AHR activation in B cells can directly disrupt the production of antibodies (Sulentic and Kaminski, 2011). The recent demonstration that AHR activation by TCDD leads to the development of regulatory T cells helps to explain the diversity of effects seen after exposure to TCDD (Funatake et al., 2008; Marshall et al., 2008; Quintana et al., 2008).

SYNTHESIS

Immune Suppression

One would expect exposure to substantial doses of TCDD to result in immune suppression in Vietnam veterans. However, several studies of various measures of human immune function failed to reveal consistent correlations with TCDD exposure, probably because the exposures were inadequate to produce immune suppression or the characteristics measured were not among those most relevant with respect to biological plausibility. No clear pattern of an increase in infectious disease has been documented in the studies of veterans exposed to TCDD or to the herbicides used in Vietnam. However, one occupational-exposure study and one environmental-exposure study do support the possibility that sufficiently high exposure to TCDD may result in an increased frequency of infections. It was also supported by the self-reporting study by O'Toole et al. (2009). As a result, frequency and duration of specific types of infections should be a focus of future studies. Suppression of the immune response by TCDD might increase the risk of some kinds of cancer in Vietnam veterans, but there is no evidence to support that connection.

Allergic and Autoimmune Diseases

Epidemiologic studies have been inconsistent with regard to TCDD's influence on IgE production in humans. No human studies have specifically addressed the influence of TCDD on autoimmune disease, but several animal studies have shown that TCDD suppresses the development of autoimmune diseases. In studying postservice mortality, Boehmer et al. (2004) found no increase in deaths of Vietnam veterans that could be attributed to immune-system disorders. The present committee's review included a study that found a significant association between concentrations of dioxin-like PCBs and the prevalence of arthritis in women but not in men (Lee et al., 2007a). There is no experimental evidence to support that finding, but increased inflammatory responses could be involved. Future studies are needed to determine a potential mechanism of TCDD-induced rheumatoid arthritis.

Few effects of phenoxy herbicide or cacodylic acid exposure on the immune system have been reported in animals or humans, and no clear association between such exposure and autoimmune or allergic disease has been found. Exposure of laboratory animals to phenoxy herbicides or cacodylic acid has not been associated with immunotoxicity.

Inflammatory Diseases

There are no human data on the potential for dioxin or the herbicides of interest to induce dysregulation of inflammation that could contribute to an increased risk of inflammation-associated diseases.

Possible associations involving infectious or inflammation-related diseases should be a focus for the future. Examples of studies that would add support for these potential adverse outcomes are Baccarelli et al. (2002), Baranska et al. (2008), Beseler et al. (2008), Oh et al. (2005), O'Toole et al. (2009), Tonn et al. (1996), and Visintainer et al. (1995).

Conclusions

On the basis of the evidence reviewed here and in previous VAO reports, the present committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and specific infectious, allergic, or autoimmune diseases.

TRANSLATION BETWEEN ANIMAL AND HUMAN STUDIES

Animal studies and in vitro studies with human cells and cell lines are important ways of trying to understand underlying biologic mechanisms associated with immunotoxic and other responses to xenobiotics, which are "foreign" substances that do not normally occur in biologic systems. However, as discussed above, despite the vast array of data supporting the immunotoxicity of TCDD in laboratory animals, there is little evidence from studies of Vietnam veterans or other human populations that suggests that TCDD or the herbicides of concern produce immune alterations. Many factors must be considered in examining the relevance of animal and in vitro studies to human disease and disease progression, and they are discussed Chapter 4. Here, we present the factors that are probably most important in considering differences between the results of laboratory studies and the findings of observational epidemiologic studies.

Magnitude and Timing of Exposure

In general, the TCDD exposures used in animal studies have been orders of magnitude higher than Vietnam veterans are likely to have received during military service. It is well known that the immune system is highly susceptible to xenobiotic exposure during critical stages of development, such as gestation. It is also well known that primary immune responses are easier to alter than secondary immune responses. In vivo studies show that exposure to antigens may be important, so the timing of antigen exposure relative to TCDD exposure may be an important variable.

Genetic Susceptibilities

Human immune diseases are likely to have complex etiologies and to be under the influence of numerous genes and gene-by-environment interactions (Dietert et al., 2010). Differences in AHR affinity between species may be a factor in animal-to-human extrapolation. For example, many strains of mice (AHR^b) are known to exhibit greater susceptibility of CYP1A1 induction and immune suppression than other strains (AHR^d). In contrast, a simple single-haplotype difference in susceptibility to TCDD has not been observed in humans. Rats appear to be more similar to the resistant AHR^d phenotype of mice in their sensitivity to TCDD. Indeed, it is difficult to produce immune suppression in rats with TCDD because of that, and there probably are other genetic reasons as well.

Sex Differences

There are well-known differences in the susceptibility to xenobiotic exposures between male and female animals. There are probably multiple reasons for the differences, some of which may pertain to immunomodulation by sex steroids. Similarly, evidence suggests that specific immune-based health risks in humans have important sex differences. For example, women generally are much more susceptible to the development of several autoimmune diseases than men; such differences in humans may result from a combination of genetic factors and environmental exposures. That has ramifications for future studies. In considering the potential impact of Agent Orange on the immune system and the risk of disease, sex-based differences in chemically induced adverse immune outcomes need to be investigated. Future studies should ensure that, whether in animal models or in direct human studies, gene- or sex-specific immune effects are able to be evaluated with sufficient statistical power to support distinctions.

Stress

Stress produced is a well known modifier of human immune responses. It is an ever-present variable that is difficult to assess or control for in epidemiologic studies.

SUBJECTS FOR FUTURE RESEARCH

Immune biomarkers (such as cytokines, antibodies, antitumor activity, populations of specialized cells, and inflammatory metabolites) can be used to examine the risks of such specific health problems as heightened allergic responses, deficiency in cell-mediated immunity, and susceptibility to autoimmune responses. In addition, there may be more generalized biomarkers; for example, a recent human study reported that the concentrations of a specific cytokine produced by macro-

phages (macrophage inhibitory cytokine-1) was a useful biomarker for predicting all-causes mortality (in subjects who already had particular chronic diseases) over a span of 14 years (Wiklund et al., 2010). In the absence of clearly defined immune diseases, combinations of immune measures may be used as biomarkers of altered immune responses associated with risks of specific diseases. As a result, antibody concentrations, recall antigen tests, lymphoid subpopulation sizes, and cytokine, receptor, and metabolite concentrations are often used in combination for the prediction of immune-associated health risks. Immune biomarkers, when appropriately selected, could provide useful information regarding potential immune-associated health risk connected with TCDD. However, it is critical that the biomarkers used in such studies be those most predictive for risk of disease, and not just those most readily measured.

On the basis of extensive animal studies involving TCDD, the most plausible immune alterations expected in dioxin-exposed human adults are suppression of selected adaptive immune responses and misregulated inflammation. Several human studies (Baccarelli et al., 2002; Halperin et al., 1998; Jung et al., 1998; Michalek et al., 1999a) have examined measures that could reflect functional immune suppression (for example the DTH recall antigen test and concentrations of various antibodies). However, most studies have failed to show a significant effect of dioxin exposure on those measures. Regulation of inflammation is best assessed under the conditions of vaccination or infectious challenge rather than in a resting state. Biomarkers of inflammation would normally include the cytokines TNF-a, TGF-b, IL-6, IL-8, IL-10; receptors for TNF-a and IL-6, VCAM-1, ICAM-1, PGE2 and thromboxane; and C-reactive protein–reactive oxygen species production and nitric oxide production. Although a handful of studies included resting (unchallenged) measures for one or two of those biomarkers, no comprehensive testing or challenge-associated analysis has been performed. That constitutes a data gap. Finally, additional studies should focus on novel immune subpopulations, such as Fox p3+ T regulatory cells, Th17 cells, and dendritic cells, on which dioxin has reportedly exerted effects in laboratory animals (Chmill et al., 2010; Jin et al., 2010; Marshall and Kerkvliet, 2010).

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[1]Throughout the report the same alphabetic indicator following year of publication is used consistently for the same article when there were multiple citations by the same first author in a given year. The convention of assigning the alphabetic indicator in order of citation in a given chapter is not followed.

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7

Cancer

Cancer is the second-leading cause of death in the United States. Among men 50–64 years old, the group that includes most Vietnam veterans (see Table 7-1), however, the risk of dying from cancer exceeds the risk of dying from heart disease, the leading cause of death in the United States, and does not fall to second place until after the age of 75 years (Heron et al., 2009). About 570,000 Americans of all ages were expected to die from cancer in 2010—more than 1,500 per day. In the United States, one-fourth of all deaths are from cancer (Jemal et al., 2010).

This chapter summarizes and presents conclusions about the strength of the evidence from epidemiologic studies regarding associations between exposure to

TABLE 7-1 Age Distribution of Vietnam-Era and Vietnam-Theater Male Veterans, 2009–2010 (numbers in thousands)

	Vietnam Era		Vietnam Theater	
Age Group (Years)	n	(%)	n	(%)
All ages	7,805		3,816	
≤ 54	133	(1.8)	32	(0.9)
55–59	1,109	(15.1)	369	(10.4)
60–64	3,031	(41.3)	1,676	(47.0)
65–69	2,301	(31.3)	1,090	(30.6)
70–74	675	(9.2)	280	(7.9)
75–84	511	(6.9)	322	(9.0)
≥ 85	178	(2.4)	83	(2.4)

SOURCE: IOM, 1994, Table 3-3, updated by 20 years.

the chemicals of interest—2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), picloram, and cacodylic acid—and various types of cancer. The committee also considers studies of exposure to polychlorinated biphenyls (PCBs) and other dioxin-like chemicals (DLCs) informative if their results were reported in terms of TCDD toxic equivalents (TEQs) or concentrations of specific congeners of DLCs. If a new study reported on only a single type of cancer and did not revisit a previously studied population, its design information is summarized here with its results; design information on all other new studies can be found in Chapter 5.

The objective of this chapter is assessment of whether the occurrence of various cancers in Vietnam veterans themselves may be associated with exposure they may have received during military service. Therefore, studies of childhood cancers in relation to parental exposure to the chemicals of interest are discussed in Chapter 8, which addresses possible adverse effects in the veterans' offspring. Studies that consider only childhood exposure are not considered relevant to the committee's charge.

In an evaluation of a possible connection between herbicide exposure and risk of cancer, the approach used to assess the exposure of study subjects is of critical importance in determining the overall relevance and usefulness of findings. As noted in Chapters 3 and 5, there is great variety in detail and accuracy of exposure assessment among studies. A few studies used biologic markers of exposure, such as the presence of a chemical in serum or tissues; some developed an index of exposure from employment or activity records; and some used other surrogate measures of exposure, such as presence in a locale when herbicides were used. As noted in Chapter 2, inaccurate assessment of exposure can obscure the relationship between exposure and disease.

Each section on a type of cancer opens with background information, including data on its incidence in the general US population and known or suspected risk factors. Cancer-incidence data on the general US population are included in the background material to provide a context for consideration of cancer risk in Vietnam veterans; the figures presented are estimates of incidence in the entire US population, not predictions for the Vietnam-veteran cohort. The data reported are for 2004–2008 and are from the most recent dataset available (NCI, 2010). Incidence data are given for all races combined and separately for blacks and whites. The age range of 55–69 years now includes about 80% of Vietnam-era veterans, and incidences are presented for three 5-year age groups: 55–59 years, 60–64 years, and 65–69 years. The data were collected for the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute and are categorized by sex, age, and race, all of which can have profound effects on risk. For example, the incidence of prostate cancer is about 2.6 times as high in men who are 65–69 years old as in men 55–59 years old and almost twice as high in blacks 55–64 years old as in whites in the same age group (NCI, 2010).

Many other factors can influence cancer incidence, including screening methods, tobacco and alcohol use, diet, genetic predisposition, and medical history. Those factors can make someone more or less likely than the average to contract a given kind of cancer; they also need to be taken into account in epidemiologic studies of the possible contributions of the chemicals of interest.

Each section of this chapter pertaining to a specific type of cancer includes a summary of the findings described in the previous Agent Orange reports: *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*, hereafter referred to as *VAO* (IOM, 1994); *Veterans and Agent Orange: Update 1996*, referred to as *Update 1996* (IOM, 1996); *Update 1998* (IOM, 1999); *Update 2000* (IOM, 2001); *Update 2002* (IOM, 2003); *Update 2004* (IOM, 2005); *Update 2006* (IOM, 2007); and *Update 2008* (IOM, 2009). That is followed by a discussion of the most recent scientific literature, a discussion of biologic plausibility, and a synthesis of the material reviewed. When it is appropriate, the literature is discussed by exposure type (service in Vietnam, occupational exposure, or environmental exposure). Each section ends with the committee's conclusion regarding the strength of the evidence from epidemiologic studies. The categories of association and the committee's approach to categorizing the health outcomes are discussed in Chapters 1 and 2.

Biologic plausibility corresponds to the third element of the committee's congressionally mandated statement of task. In fact, the degree of biologic plausibility itself influences whether the committee perceives positive findings to be indicative of an association or the product of statistical fluctuations (chance) or bias.

Information on biologic mechanisms by which exposure to TCDD could contribute to the generic (rather than tissue-specific or organ-specific) carcinogenic potential of the chemicals of interest is summarized in Chapter 4. It distills toxicologic information concerning the mechanisms by which TCDD affects the basic process of carcinogenesis; such information, of course, applies to all the cancer sites discussed individually in this chapter. When biologic plausibility is discussed in this chapter's sections on particular cancer types, the generic information is implicit, and only experimental data peculiar to carcinogenesis at the site in question are presented. It is of note that in this update we have explicitly included an examination of the contribution of epigenetic mechanisms in assessing the carcinogenicity of TCDD. A large literature indicates that carcinogenesis is a process that involves not only genetic changes but also epigenetic changes (Johnstone and Baylin, 2010). There is emerging evidence that TCDD and the chemicals of interest may disturb epigenetic processes (see Chapter 4), and reference to this evidence, as it applies to cancers is included where it exists, by cancer site.

Considerable uncertainty remains about the magnitude of risk posed by exposure to the chemicals of interest. Many of the veteran, occupational, and environmental studies reviewed by the committee did not control fully for important

confounders. There is not enough information about the exposure experience of individual Vietnam veterans to permit combining exposure estimates for them with any potency estimates that might be derived from scientific research studies to quantify risk. The committee therefore cannot accurately estimate the risk to Vietnam veterans that is attributable to exposure to the chemicals of interest. The (at least currently) insurmountable problems in deriving useful quantitative estimates of the risks of various health outcomes in Vietnam veterans are explained in Chapter 1 and the summary of this report, but the point is not reiterated for every health outcome addressed.

ORGANIZATION OF CANCER GROUPS

For *Update 2006*, a system for addressing cancer types was described to clarify how specific cancer diagnoses were grouped for evaluation by the committee and to ensure that the full array of cancer types would be considered. The organization of cancer groups follows major and minor categories of cause of death related to cancer sites established by the National Institute for Occupational Safety and Health (NIOSH). The NIOSH groups map the full range of *International Classification of Diseases, Revision 9* (ICD-9) codes for malignant neoplasms (140–208). The ICD system is used by physicians and researchers to group related diseases and procedures in a standard form for statistical evaluation. Revision 10 (ICD-10) came into use in 1999 and constitutes a marked change from the previous four revisions that evolved into the ninth ICD-9. ICD-9 was in effect from 1979 to 1998; because ICD-9 is the version most prominent in the research reviewed in this series, it has been used when codes are given for a specific health outcome. Appendix B describes the correspondence between the NIOSH cause-of-death groupings and ICD-9 codes (Table B-1); the groupings for mortality are largely congruent with those of the SEER program for cancer incidence (see Table B-2, which presents equivalences between the ICD-9 and ICD-10 systems). For the present update, the committee gave more attention to the World Health Organization's classification for lymphohematopoietic neoplasms (WHO, 2008), which stresses partitioning of these disorders first according to the lymphoid or myeloid lineage of the transformed cells rather than into lymphomas and leukemias.

The system of organization used by the committee simplifies the process for locating a particular cancer for readers and facilitated the committee's identification of ICD codes for malignancies that had not been explicitly addressed in previous updates. *VAO* reports' default category for any health outcome on which no epidemiologic research findings have been recovered has always been "inadequate evidence" of association, which in principle is applicable to specific cancers. Failure to review a specific cancer or other condition separately reflects the paucity of information, so there is indeed inadequate or insufficient information to categorize such a disease outcome.

BIOLOGIC PLAUSIBILITY

The studies considered with respect to the biologic plausibility of associations between exposure to the chemicals of interest and human cancers have been performed primarily in laboratory animals (rats, mice, hamsters, and monkeys) or cultured cells. Collectively, the evidence obtained from studies of TCDD indicates that a connection between human exposure to this chemical and cancers is biologically plausible, as will be discussed more fully in a generic sense below and more specifically in the biologic-plausibility sections on individual cancers. Recent reviews have affirmed the now well-established mechanistic roles of the aryl hydrocarbon receptor (AHR) in cancer (Androutsopoulos et al., 2009; Barouki and Coumoul, 2010; Dietrich and Kaina, 2010; Ray and Swanson, 2009), and the data have firmly established the biologic plausibility of an association between TCDD exposure and cancer.

With respect to 2,4-D, 2,4,5-T, and picloram, several studies have been performed in laboratory animals. In general, the results were negative although some would not meet current standards for cancer bioassays; for instance, there is some question of whether the highest doses (generally 30–50 mg/kg) in some of these studies reached a maximum tolerated dose (MTD). It is not possible to have absolute confidence that these chemicals have no carcinogenic potential. Further evidence of a lack of carcinogenic potential is provided, however, by negative findings on genotoxic effects in assays conducted primarily in vitro. The evidence indicates that 2,4-D is genotoxic only at very high concentrations. Although 2,4,5-T was shown to increase the formation of DNA adducts by cytochrome P450–derived metabolites of benzo[*a*]pyrene, most available evidence indicates that 2,4,5-T is genotoxic only at high concentrations. Recently, Hernández et al. (2009) have reviewed the mechanisms of action of nongenotoxic carcinogens, including TCDD in this category

There is some evidence that cacodylic acid is carcinogenic. Studies performed in laboratory animals have shown that it can induce neoplasms of the kidney (Yamamoto et al., 1995) and bladder (Arnold et al., 2006; Wei et al., 2002). In the lung, treatment with cacodylic acid induced formation of neoplasms when administered to mouse strains that are genetically susceptible to them (Hayashi et al., 1998). Other studies have used the two-stage model of carcinogenesis in which animals are exposed first to a known genotoxic agent and then to a suspected tumor-promoting agent. With that model, cacodylic acid has been shown to act as a tumor-promoter with respect to lung cancer (Yamanaka et al., 1996).

Studies in laboratory animals in which only TCDD has been administered have reported that it can increase the incidence of a number of neoplasms, most notably of the liver, lungs, thyroid, and oral mucosa (Kociba et al., 1978; NTP, 2006). Some studies have used the two-stage model of carcinogenesis and shown that TCDD can act as a tumor-promoter and increase the incidence of ovarian cancer (Davis et al., 2000), liver cancer (Beebe et al., 1995), and skin cancers

(Wyde et al., 2004). As to the mechanisms by which TCDD exerts its carcinogenic effects, it is thought to act primarily as a tumor-promoter. In many of the animal studies reviewed, treatment with TCDD has resulted in hyperplasia or metaplasia of epithelial tissues. In addition, in both laboratory animals and cultured cells, TCDD has been shown to exhibit a wide array of effects on growth regulation, hormone systems, and other factors associated with the regulation of cellular processes that involve growth, maturation, and differentiation. Thus, it may be that TCDD increases the incidence or progression of human cancers through an interplay between multiple cellular factors. Tissue-specific protective cellular mechanisms may also affect the response to TCDD and complicate our understanding of its site-specific carcinogenic effects.

As shown with long-term bioassays in both sexes of several strains of rats, mice, hamsters, and fish, there is adequate evidence that TCDD is a carcinogen in laboratory animals, increasing the incidence of tumors at sites distant from the site of treatment at doses well below the maximum tolerated. On the basis of animal studies, TCDD has been characterized as a nongenotoxic carcinogen because it does not have obvious DNA-damaging potential, but it is a potent "promoter" and a weak initiator in two-stage initiation–promotion models for liver, skin, and lung. Early studies demonstrated that TCDD is 2 orders of magnitude more potent than the "classic" promoter tetradecanoyl phorbol acetate and that TCDD skin-tumor promotion depends on the AHR. For many years, it has been known that TCDD is a potent tumor-promoter. Recent evidence has shown that AHR activation by TCDD in human breast and endocervical cell lines induces sustained high concentrations of the interleukin-6 (IL-6) cytokine, which has tumor-promoting effects in numerous tissues—including breast, prostate, ovary, and malignant cholangiocytes—and opens up the possibility that TCDD would promote carcinogenesis in these and possibly other tissues (Hollingshead et al., 2008). TCDD has been shown to downregulate reduced folate carrier (Rfc1) mRNA and protein in rat liver, which is essential in maintaining folate homeostasis (Halwachs et al., 2010). Reduced Rfc1 activity and a functional folate deficiency may contribute to the risk of carcinogenesis posed by TCDD exposure.

Mechanisms by which TCDD induces G1 arrest in hepatic cells (Mitchell et al., 2006; Weiss et al., 2008) and decreases viability of endometrial endothelial cells (Bredhult et al., 2007), insulin-secreting beta cells (Piaggi et al., 2007), peripheral T cells (Singh et al., 2008), and neuronal cells (Bredhult et al., 2007) have recently been identified, and these results suggest possible carcinogenic mechanisms. TCDD may contribute to tumor progression by inhibiting p53 regulation (phosphorylation and acetylation) triggered by genotoxicants via the increased expression of the metastasis marker AGR2 (Ambolet-Camoit et al., 2010) and through a functional interaction between the AHR and FHL2 ("four and a half LIM protein 2," where the LIM domain is a highly conserved protein structure) (Kollara and Brown, 2009). Borlak and Jenke (2008) demonstrated that the AHR is a major regulator of c-raf and proposed that there is cross-talk

between the AHR and the mitogen-activated protein kinase signaling pathway in chemically induced hepatocarcinogenesis. TCDD inhibits ultraviolet-C (UV-C) radiation-induced apoptosis in primary rat hepatocytes and Huh-7 human hepatoma cells, and this supports the hypothesis that TCDD acts as a tumor-promoter by preventing initiated cells from undergoing apoptosis (Chopra et al., 2009). Additional in vitro work with mouse hepatoma cells has shown that activation of the AHR results in increased concentrations of 8-hydroxy-2′-deoxyguanosine (8-OHdG), a product of DNA-base oxidation and later excision repair and a marker of DNA damage. Induction of cytochrome P4501A1 (CYP1A1) by TCDD or indolo(3,2-b)carbazole is associated with oxidative DNA damage (Park et al., 1996). In vivo experiments in mice corroborated those findings by showing that TCDD caused a sustained oxidative stress, as determined by measurements of urinary 8-hydroxydeoxyguanosine (Shertzer et al., 2002), involving AHR-dependent uncoupling of mitochondrial respiration (Senft et al., 2002). Mitochondrial reactive-oxygen production depends on the AHR.

Electronics-dismantling workers, experiencing complex exposures including polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs), had elevated levels of urinary 8-OHdG indicative of oxidative stress and genotoxicity; this cannot, however, be ascribed directly to the dioxin-like chemicals (DLCs) (Wen et al., 2008). In a study of New Zealand Vietnam War veterans (Rowland et al., 2007), clastogenic genetic disturbances arising as a consequence of confirmed exposure to Agent Orange were determined by analyzing sister-chromatid exchanges (SCEs) in lymphocytes from a group of 24 New Zealand Vietnam War veterans and 23 control volunteers. The results showed a highly significant difference ($p < 0.001$) in mean SCE frequency between the experimental group and the control group. The Vietnam War veterans also had a much higher proportion of cells with SCE frequencies above the 95th percentile than the controls (11.0 and 0.07%, respectively).

The weight of evidence that TCDD and dioxin-like PCBs make up a group of chemicals with carcinogenic potential includes unequivocal animal carcinogenesis and biologic plausibility based on mode-of-action data. Although the specific mechanisms by which dioxin causes cancer remain to be established, the intracellular factors and mechanistic pathways involved in dioxin's cancer-promotion mode of action all have parallels in animals and humans. No qualitative differences have been reported to indicate that humans should be considered as fundamentally different from the multiple animal species in which bioassays have demonstrated dioxin-induced neoplasia.

Thus, the toxicologic evidence indicates that a connection of TCDD and perhaps cacodylic acid with cancer in humans is, in general, biologically plausible, but (as discussed below) it must be determined case by case whether such potential is realized in a given tissue. Experiments with 2,4-D, 2,4,5-T, and picloram in animals and cells have not provided a strong biologic basis of the presence or absence of carcinogenic effects.

THE COMMITTEE'S VIEW OF "GENERAL" HUMAN CARCINOGENS

To address its charge, the committee weighed the scientific evidence linking the chemicals of interest to specific individual cancer sites. That was appropriate given the different susceptibilities of various tissues and organs to cancer and the various genetic and environmental factors that can influence the occurrence of a particular type of cancer. Before considering each site in turn, however, it is important to address the concept that cancers share some characteristics among organ sites and to clarify the committee's view regarding the implications of a chemical's being a "general" human carcinogen. All cancers share phenotypic characteristics: uncontrolled cell proliferation, increased cell survival, invasion outside normal tissue boundaries, and eventually metastasis. The current understanding of cancer development holds that a cell or group of cells must acquire a series of sufficient genetic mutations to progress and that particular epigenetic events (events that affect gene function but do not involve a change in gene coding sequence) must occur to accelerate the mutational process and provide growth advantages for the more aggressive clones of cells. That means that a carcinogen can stimulate the process of cancer development by either genetic (mutational) or epigenetic (nonmutational) activities.

In classic experiments based on the induction of cancer in mouse skin that were conducted over 40 years ago, carcinogens were categorized as initiators, those capable of causing an initial genetic insult to the target tissue, and promoters, those capable of promoting the growth of initiated tumor cells, generally through nonmutational events. Some carcinogens, such as those found in tobacco smoke, were considered "whole carcinogens;" that is, they were capable of both initiation and promotion. Today, cancer researchers recognize that the acquisition of important mutations is a continuing process in tumors and that promoters, or epigenetic processes that favor cancer growth, enhance the accumulation of genotoxic damage, which traditionally would be regarded as initiating activity.

As discussed above and in Chapter 4, 2,4-D, 2,4,5-T, and picloram have shown little evidence of genotoxicity in laboratory studies, except at very high doses, and little ability to facilitate cancer growth in laboratory animals. However, cacodylic acid and TCDD have shown the capacity to increase cancer development in animal experiments, particularly as promoters rather than as pure genotoxic agents. Extrapolating organ-specific results from animal experiments to humans is problematic because of important differences between species in overall susceptibility of various organs to cancer development and in organ-specific responses to particular putative carcinogens. Therefore, judgments about the "general" carcinogenicity of a compound in humans are based heavily on the results of epidemiologic studies, particularly on the question of whether there is evidence of excess cancer risk at multiple organ sites. As the evaluations of particular types of cancer in the remainder of this chapter indicate, the committee finds that TCDD in particular appears to be

a multisite carcinogen. That finding is in agreement with the International Agency for Research on Cancer (IARC), which has determined that TCDD is a category 1 "known human carcinogen," and with the US Environmental Protection Agency (EPA), which has concluded that TCDD is "likely to be carcinogenic to humans." It is important to emphasize that the goals and methods of IARC and EPA in making their determinations were different from those of the present committee; the missions of those organizations focus on evaluating risk to minimize future exposure, whereas this committee focuses on risk after exposure. Furthermore, recognition that TCDD and cacodylic acid are multisite carcinogens does not imply that they cause human cancer at every organ site.

The distinction between ***general carcinogen*** and ***site-specific carcinogen*** is more difficult to grasp in light of the common practice of beginning analyses of epidemiologic cohorts with a category of "all malignant neoplasms," which is a routine first screen for any unusual cancer activity in the study population rather than a test of a biologically based hypothesis. When the distribution of cancers among anatomic sites is lacking in the report of a cohort study, a statistical test for an increase in all cancers is not meaningless, but it is usually less scientifically supportable than analyses based on specific sites, for which more substantial biologically based hypotheses can be developed. The size of a cohort and the length of the observation period often constrain the number of cases of cancer types observed and the extent to which specific types can be analyzed. For instance, the present update includes an analysis of cumulative results on diabetes and cancer from a report of the prospective Air Force Health Study (Michalek and Pavuk, 2008). For the fairly common condition of diabetes, that publication presents important information summarizing previous findings, but the cancer analysis does not go beyond "all cancers." The committee does not accept those findings as an indication that exposure to Agent Orange increases the risk of every variety of cancer. It acknowledges that the highly stratified analyses conducted suggest that some increase in the incidence of some cancers did occur in the Ranch Hand subjects, but it views the "all cancers" results as a conglomeration of information on specific cancers—most important, melanoma and prostate cancer, on which provocative results have been published (Akhtar et al., 2004; Pavuk et al., 2006) and which merit individual longitudinal analysis to resolve outstanding questions.

The remainder of this chapter deals with the committee's review of the evidence on each individual cancer site in accordance with its charge to evaluate the statistical association between exposure and cancer occurrence, the biologic plausibility and potential causal nature of the association, and the relevance to US veterans of the Vietnam War.

ORAL, NASAL, AND PHARYNGEAL CANCER

Oral, nasal, and pharyngeal cancers are found in many anatomic sites, including the structures of the mouth (inside lining of the lips, cheeks, gums, tongue,

and hard and soft palate) (ICD-9 140–145), oropharynx (ICD-9 146), nasopharynx (ICD-9 147), hypopharynx (ICD-9 148), other buccal cavity and pharynx (ICD-9 149), and nasal cavity and paranasal sinuses (ICD-9 160). Until recently, cancers that occur in the oral cavity and pharynx have been thought to be similar in descriptive epidemiology and risk factors, whereas cancer of the nasopharynx is known to have a different epidemiologic profile. However, we now recognize that human papilloma virus (HPV) is an important risk factor for squamous-cell carcinoma of the head and neck, with the risk estimates being highest for the base of the tongue and tonsils (Marur et al., 2010).

The American Cancer Society (ACS) estimated that about 36,540 men and women would receive diagnoses of oral, nasal, or pharyngeal cancer in the United States in 2010 and that 7,880 men and women would die from these diseases (Jemal et al., 2010). Almost 91% of those cancers originate in the oral cavity or oropharynx. Most oral, nasal, and pharyngeal cancers are squamous-cell carcinomas. Nasopharyngeal carcinoma (NPC) is the most common malignant epithelial tumor of the nasopharynx although it is relatively rare in the United States. There are three types of NPC: keratinizing squamous-cell carcinoma, nonkeratinizing carcinoma, and undifferentiated carcinoma.

The average annual incidences reported in Table 7-2 show that men are at greater risk than women for those cancers and that the incidences increase with age—although there are few cases, and care should be exercised in interpreting the numbers. Tobacco and alcohol use are established risk factors for oral and pharyngeal cancers. Reported risk factors for nasal cancer include occupational exposure to nickel and chromium compounds (d'Errico et al., 2009; Feron et al., 2001; Grimsrud and Peto, 2000), wood dust (d'Errico et al., 2009), leather dust (Bonneterre et al., 2007), and high doses of formaldehyde (Nielsen and Wolkoff, 2010).

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the chemicals of interest and oral, nasal, and pharyngeal cancers. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008* did not change that conclusion.

In *Update 2006* at the request of the the Department of Veterans Affairs (VA), the committee attempted to evaluate tonsil-cancer cases separately, but it was able to identify only three cohort studies that provided the number of tonsil-cancer cases in their study populations and concluded that these studies did not provide sufficient evidence to determine whether an association existed between exposure to the chemicals of interest and tonsil cancer. Since then, no studies have offered any important additional insight into this question. The committee

TABLE 7-2 Average Annual Incidence (per 100,000) of Nasal, Nasopharyngeal, Oral-Cavity and Pharyngeal, and Oropharyngeal Cancers in United States[a]

	55–59 Years Old			60–64 Years Old			65–69 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Nose, Nasal Cavity, and Middle Ear:									
Men	1.4	1.3	2.4	2.2	1.8	4.0	2.7	2.4	3.5
Women	1.2	1.1	0.9	1.0	1.0	1.6	2.0	2.3	1.3
Nasopharynx:									
Men	2.5	1.4	2.6	1.9	1.3	0.8	3.2	1.8	2.3
Women	1.1	0.6	0.4	0.8	0.7	0.3	1.1	1.0	0.4
Oral Cavity and Pharynx:									
Men	42.1	42.7	44.9	50.2	52.1	46.8	55.9	55.9	64.5
Women	12.7	12.8	11.9	15.1	15.8	14.2	20.7	21.8	18.2
Oropharynx:									
Men	1.9	1.7	4.2	1.9	1.8	4.0	2.4	2.2	3.5
Women	0.3	0.3	0.2	0.6	0.6	1.0	0.4	0.5	0.0

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2004–2008 (NCI, 2010).

responsible for *Update 2006* recommended that VA evaluate the possibility of studying health outcomes, including tonsil cancer, in Vietnam-era veterans by using existing administrative and health-services databases. Anecdotal evidence provided to that committee suggested a potential association between the exposures in Vietnam and tonsil cancer. The new evidence indicating that cancer of the tonsils can have a viral (HPV) etiology underscores a reasonable mechanistic hypothesis for an excess of cancers in Vietnam-era veterans exposed to Agent Orange; as a result of immune alterations associated with exposure, veterans may be susceptible to HPV infection in the oral cavity and tonsils. The present committee strongly reiterates the 2006 and 2008 recommendation that VA develop a strategy that uses existing databases to evaluate tonsil cancer in Vietnam-era veterans.

Studies evaluated previously and in the present report are summarized in Table 7-3.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

Cypel and Kang (2010) updated the study of Vietnam-era Army Chemical Corps (ACC) veterans, comparing mortality through 2005 among ACC veterans by Vietnam service. They reported six cases of oral-cavity and pharyngeal cancer in the deployed cohort compared with two cases in the nondeployed cohort for an

TABLE 7-3 Selected Epidemiologic Studies—Oral, Nasal, and Pharyngeal Cancer

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
United States			
Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)			**All COIs**
Akhtar et al., 2004	White AFHS subjects vs national rates (buccal cavity)		
	Ranch Hand veterans		
	Incidence	6	0.9 (0.4–1.9)
	With tours in 1966–1970	6	1.1 (0.5–2.3)
	Mortality	0	0.0 (nr)
	Comparison veterans		
	Incidence	5	0.6 (0.2–1.2)
	With tours in 1966–1970	4	0.6 (0.2–1.4)
	Mortality	1	0.5 (nr)
AFHS, 2000	Participants in 1997 examination cycle, Ranch Hands vs comparisons (oral cavity, pharynx, and larynx), incidence	4	0.6 (0.2–2.4)
US Cohort of Army Chemical Corp			**All COIs**
Cypel and Kang et al., 2010	ACC—deployed vs nondeployed and vs US men (Vietnam-service status through 2005)		
	Oral cavity and pharyngeal cancer		
	Deployed vs nondeployed	6 vs 2	1.7 (0.3–8.7)
	ACC vs US men		
	Vietnam cohort	6	1.5 (0.6–3.3)
	Non-Vietnam cohort	2	0.8 (0.1–2.8)
US CDC Vietnam Experience Study			**All COIs**
Boehmer et al., 2004	Follow-up of CDC VES cohort (ICD-9 140–149)	6	nr
US Centers for Disease Control and Prevention			**All COIs**
CDC, 1990a	Case–control study of US males born 1929–1953		
	89 nasopharyngeal carcinomas		
	Vietnam service	3	0.5 (0.2–1.8)
	62 nasal carcinomas		
	Vietnam service	2	0.7 (0.2–2.9)
State Studies of US Vietnam Veterans			**All COIs**
Visintainer et al., 1995	PM study of deaths (1974–1989) of Michigan Vietnam-era veterans—deployed vs nondeployed		
	Lip, oral cavity, and pharynx	12	1.0 (0.5–1.8)
Australian Vietnam Veterans vs Australian Population			**All COIs**
ADVA, 2005a	Follow-up 1982–2000—incidence		
	Head and neck	247	1.5 (1.3–1.6)
	Navy	56	1.6 (1.1–2.0)
	Army	174	1.6 (1.3–1.8)
	Air Force	17	0.9 (0.5–1.5)

TABLE 7-3 Oral, Nasal, and Pharyngeal Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
ADVA, 2005b	Follow-up through 2001		
	Head and neck	101	1.4 (1.2–1.7)
	Navy	22	1.5 (0.9–2.1)
	Army	69	1.5 (1.1–1.8)
	Air Force	9	1.1 (0.5–2.0)
	Nasal	3	0.8 (0.2–2.2)
CDVA, 1997a	Follow-up 1980–1994		
	Lip (ICD-9 140)	0	nr
	Nasopharyngeal cancer (ICD-9 147)	2	0.5 (0.1–1.7)
	Nasal cavities (ICD-9 160)	2	1.2 (0.1–4.1)
Australian Conscripted Army National Service Vietnam-Era Veterans (deployed vs nondeployed)			**All COIs**
ADVA, 2005c	Follow-up		
	Head and neck		
	Incidence (1982–2000)	44	2.0 (1.2–3.4)
	Mortality (1966–2001)	16	1.8 (0.8–4.3)
	Nasal		
	Mortality (1966–2001)	0	0.0 (0.0–48.2)
CDVA, 1997b	Follow-up (1980–1994)		
	Nasopharyngeal cancer (ICD-9 147)	1	1.3 (0.0– > 10)
	Nasal cavities (ICD-9 160)	0	0.0 (0.0– > 10)
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			**Dioxin, Phenoxy Herbicides**
Kogevinas et al., 1997	IARC cohort, male and female workers exposed to any phenoxy herbicide or chlorophenol—update to 1992		
	Oral cavity, pharynx cancer (ICD-9 140–149)	26	1.1 (0.7–1.6)
	Exposed to highly chlorinated PCDDs	22	1.3 (0.8–2.0)
	Not exposed to highly chlorinated PCDDs	3	0.5 (0.1–1.3)
	Nose, nasal sinus cancer (ICD-9 160)	3	1.6 (0.3–4.7)
	Exposed to highly chlorinated PCDDs	0	0.0 (0.0–3.5)
	Not exposed to highly chlorinated PCDDs	3	3.8 (0.8–11.1)
Saracci et al., 1991	IARC cohort—exposed subcohort (males, females)—updated to 1987		
	Buccal cavity, pharynx (ICD-8 140–149)	11	1.2 (0.6–2.1)
	Nose, nasal cavities (ICD-8 160)	3	2.9 (0.6–8.5)
BASF Production Workers (included in IARC cohort)			**Dioxin, Phenoxy Herbicides**
Zober et al., 1990	BASF Aktiengesellschaft accident cohort—33 cancers in 247 workers at 34-yr follow-up		
	Squamous-cell carcinoma of tonsil	1	nr

continued

TABLE 7-3 Oral, Nasal, and Pharyngeal Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Dutch Production Workers (included in IARC cohort)			**Dioxin, Phenoxy Herbicides**
Hooiveld et al., 1998	Dutch chemical production workers (lip, oral cavity, pharynx)		
	All working any time in 1955–1985	1	2.3 (0.1–12.4)
	Cleaned up 1963 explosion	1	7.1 (0.2–39.6)
German Production Workers (included in IARC cohort)			**Dioxin, Phenoxy Herbicides**
Becher et al., 1996	German phenoxy herbicide or chlorophenol production workers		
	Buccal cavity, pharynx (ICD-9 140–149)	9	3.0 (1.4–5.6)
	Tongue	3	nr
	Floor of mouth	2	nr
	Tonsil	2	nr
	Pharynx	2	nr
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)			**Dioxin, Phenoxy Herbicides**
McBride et al., 2009a	1,599 production workers (male and female) vs national rates—mortality 1969 through 2004		
	Buccal cavity and pharynx		
	Ever-exposed workers	3	2.6 (0.5–7.6)
't Mannetje et al., 2005	New Zealand phenoxy herbicide producers (men and women) (ICD-9 140–149)	2	2.8 (0.3–9.9)
	Lip (ICD-9 140)	0	nr
	Mouth (ICD-9 141–145)	2	5.4 (0.7–20)
	Oropharynx (ICD-9 146)	0	nr
	Nasopharynx (ICD-9 147)	0	0.0 (0.0–42)
	Hypopharynx, other (ICD-9 148–149)	0	nr
	Phenoxy herbicide sprayers (> 99% men) (ICD-9 140–149)	1	1.0 (0.0–5.7)
	Lip (ICD-9 140)	0	nr
	Mouth (ICD-9 141–145)	0	0.0 (0.0–7.5)
	Oropharynx (ICD-9 146)	0	nr
	Nasopharynx (ICD-9 147)	1	8.3 (0.2–46)
	Hypopharynx, other (ICD-9 148–149)	0	nr
United Kingdom Production Workers (included in IARC cohort)			**Dioxin, Phenoxy Herbicides**
Coggon et al., 1986	British MCPA production workers		
	Lip (ICD-9 140)	0	nr
	Tongue (ICD-9 141)	1	1.1 (0.0–6.2)
	Pharynx (ICD-9 146–149)	1	0.5 (0.0–3.0)
	Nose (ICD-9 160)	3	4.9 (1.0–14.4)

TABLE 7-3 Oral, Nasal, and Pharyngeal Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Agricultural Health Study			**Herbicides**
Alavanja et al., 2005	US AHS—incidence (buccal cavity)		
	Private applicators (men and women)	66	0.7 (0.5–0.8)
	Lip	25	1.4 (0.9-2.1)
	Spouses of private applicators (> 99% women)	14	0.7 (0.4–1.2)
	Lip	2	1.4 (0.2–5.1)
	Commercial applicators (men and women)	5	0.9 (0.3–2.2)
	Lip	3	2.7 (0.6–8.0)
Blair et al., 2005a	US AHS (buccal cavity and pharynx)		
	Private applicators (men and women)	5	0.3 (0.1–0.7)
	Spouses of private applicators (> 99% women)	0	0.0 (0.0–25.4)
Other Agricultural Workers			**Herbicides**
Hansen et al., 2007	Danish gardeners—incidence (buccal cavity and pharynx, ICD-7 140–148)		
	10-year follow-up (1975–1984) reported in Hansen et al. (1992)	6	1.1 (0.4–2.5)
	25-year follow-up (1975–2001)		
	Born before 1915 (high exposure)	3	0.7 (0.2–2.3)
	Born 1915–1934 (medium exposure)	6	0.7 (0.3–1.4)
	Born after 1934 (low exposure)	0	0.0 (0.0–1.0)
Nordby et al., 2004	Norwegian farmers born 1925–1971—incidence, lip		
	Reported pesticide use	nr	0.7 (0.4–1.0)
Blair et al., 1993	White male farmers in 23 states—deaths 1984–1988		
	Lip	21	2.3 (1.4–3.5)
Ronco et al., 1992	Italian farmers (lip, tongue, salivary glands, mouth, pharynx)—mortality		
	Self-employed	13	0.9 (nr)
	Employees	4	0.5 (nr)
	Danish self-employed farmers—incidence		
	Lip	182	1.8 ($p < 0.05$)
	Tongue	9	0.6 (nr)
	Salivary glands	13	0.9 (nr)
	Mouth	14	0.5 ($p < 0.05$)
	Pharynx	13	0.3 ($p < 0.05$)
	Nasal cavities, sinuses	11	0.6 (nr)
	Danish farming employees—incidence		
	Lip	43	2.1 ($p < 0.05$)
	Tongue	2	0.6 (nr)
	Salivary glands	0	0.0 (nr)
	Mouth	0	0.0 ($p < 0.05$)
	Pharynx	9	1.1 (nr)
	Nasal cavities and sinuses	5	1.3 (nr)

continued

TABLE 7-3 Oral, Nasal, and Pharyngeal Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Wiklund, 1983	Swedish male and female agricultural workers—incidence		*99% CI*
	Lip	508	1.8 (1.6–2.1)
	Tongue	32	0.4 (0.2–0.6)
	Salivary glands	68	1.0 (0.7–1.4)
	Mouth	70	0.6 (0.5–0.8)
	Throat	84	0.5 (0.4–0.7)
	Nose, nasal sinuses	64	0.8 (0.6–1.2)
Burmeister, 1981	Iowa farmers—deaths in 1971–1978		
	Lip	20	2.1 ($p < 0.01$)
Forestry Workers			**Herbicides**
Reif et al., 1989	New Zealand forestry workers—incidence		
	Buccal cavity	3	0.7 (0.2–2.2)
	Nasopharynx	2	5.6 (1.6–19.5)
Other Herbicide and Pesticide Applicators			**Herbicides**
Swaen et al., 2004	Dutch licensed herbicide applicators		
	Nose	0	—
	Mouth, pharynx	0	—
Caplan et al., 2000	Case–control study of US males born 1929–1953, all 70 nasal cancers (carcinomas, 11 lymphomas, 5 sarcomas) in CDC (1990a) study population		
	Selected landscaping, forestry occupations	26	1.8 (1.1–3.1)
	Living, working on farm	23	0.5 (0.3–0.8)
	Herbicides, pesticides	19	0.7 (0.4–1.3)
	Phenoxy herbicides	5	1.2 (0.4–3.3)
Asp et al., 1994	Finnish herbicide applicators		
	Buccal, pharynx (ICD-8 140–149)		
	Incidence	5	1.0 (0.3–2.3)
	Mortality	0	0.0 (0.0–3.0)
	"Other respiratory" (ICD-8 160, 161, 163)—nose, larynx, pleura		
	Incidence	4	1.1 (0.3–2.7)
	Mortality	1	0.5 (0.0–2.9)
Torchio et al., 1994	Italian licensed pesticide users		
	Buccal cavity, pharynx	18	0.3 (0.2–0.5)
Wiklund et al., 1989a	Licensed Swedish pesticide applicators—incidence		
	Lip	14	1.8 (1.0–2.9)

TABLE 7-3 Oral, Nasal, and Pharyngeal Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Paper and Pulp Workers			**Dioxin**
McLean et al., 2006 (Includes cohort studied in Rix et al., 1998)	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds (oral cavity, and pharynx)		
	Never	33	0.9 (0.6–1.3)
	Ever	15	0.5 (0.3–0.9)
Rix et al., 1998	Danish male, female paper-mill workers		
	Buccal cavity (ICD-7 140–144)		
	Men	24	1.0 (0.7–1.5)
	Women	4	1.5 (0.4–3.8)
	Pharynx (ICD-7 145–149)		
	Men	15	2.0 (1.1–3.3)
	Women	2	2.1 (0.2–7.6)
	Tonsil cancers among pharyngeal cancers	11	nr
Robinson et al., 1986	Northwestern US paper and pulp workers		*90% CI*
	Buccal cavity, pharynx (ICD-7 140–148)	1	0.1 (0.0–0.7)
	Nasal (ICD-7 160)	0	nr
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Bertazzi et al., 1993	Seveso residents—10-yr follow-up—incidence		
	Buccal cavity (ICD-9 140–149)		
	Zone B—Men	6	1.7 (0.8–3.9)
	Women	0	nr
	Zone R—Men	28	1.2 (0.8–1.7)
	Women	0	nr
	Nose, nasal cavities (ICD-9 160)		
	Zone R—Men	0	nr
	Women	2	2.6 (0.5–13.3)
Other Environmental Studies			
Hardell et al., 1982	Residents of northern Sweden (44 nasal, 27 nasopharyngeal cancers)		**Phenoxy acid, chlorophenols**
	Phenoxy acid exposure	8	2.1 (0.9–4.7)
	Chlorophenol exposure	9	6.7 (2.8–16.2)

ABBREVIATIONS: ACC, Army Chemical Corps; AFHS, Air Force Health Study; AHS, Agricultural Health Study; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; MCPA, 2 methyl-4-chlorophenoxyacetic acid; nr, not reported; NZ, New Zealand; PCDD, polychlorinated dibenzo-*p*-dioxins (highly chlorinated, if four or more chlorines); PM, proportionate mortality; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; VES, Vietnam Experience Study.

[a]Subjects are male, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

increased but nonsignificant adjusted relative risk (RR) of 1.68 (95% confidence interval [CI] 0.33–8.73). In the prior report on mortality through 1991 (Dalager and Kang, 1997), they had observed three cases in the Vietnam cohort and no cases in the non-Vietnam cohort.

Occupational Studies

McBride et al. (2009a,b) reported on the mortality experience through 2004 of the New Zealand cohort of 1,599 workers who had been employed in manufacturing phenoxy herbicides from trichlorophenol (TCP); picloram was also produced in the plant. In their analysis (McBride et al., 2009a), there were three deaths from buccal cavity and pharyngeal cancer in the ever-exposed group and no deaths in the smaller never-exposed group, for a nonsignificant excess standardized mortality ratio (SMR) of 2.6 (95% CI 0.5–7.6). No deaths from nasopharyngeal cancer were observed in either group. The small numbers of cases limit interpretation of the data. The results in McBride et al. (2009b) have not been included, because they were diluted by inclusion of a set of workers who had no possible opportunity for TCDD exposure and no observed deaths.

Environmental Studies

There have been no environmental studies of oral, nasal, or pharyngeal cancers and exposure to the chemicals of interest since *Update 2008*.

Biologic Plausibility

As noted above, there is now accepted evidence that HPV contributes causally to cancers of the head and neck (Marur et al., 2010; Szentirmay et al., 2005) and to tonsil cancers in particular (Gillison and Shah, 2001). It is unknown whether Agent Orange exposure contributes to a susceptibility to viral infection or action, but it warrants further exploration. The sparseness of data on the specific tumor site and a general lack of information on smoking, drinking, and viral exposure status in the few available epidemiologic studies preclude exploration of this hypothesis in the literature today.

Long-term animal studies have examined the effect of exposure to the chemicals of interest on tumor incidences (Charles et al., 1996; Stott et al., 1990; Walker et al., 2006; Wanibuchi et al., 2004). The National Toxicology Program study (Yoshizawa et al., 2005a) has also reported an increase in the incidence of gingival squamous-cell carcinoma in female rats treated orally (by gavage) with TCDD at 100 ng/kg 5 days/week for 104 weeks. The incidences of gingival squamous-cell hyperplasia was significantly increased in all groups treated at 3–46 ng/kg. In addition, squamous-cell carcinoma of the oral mucosa of the palate was increased. Increased neoplasms of the oral mucosa were previously

observed and described as carcinomas of the hard palate and nasal turbinates (Kociba et al., 1978). Kociba et al. (1978) also reported a small increase in the incidence of tongue squamous-cell carcinoma. A similar 2-year study performed in female rats failed to reveal a pathologic effect of TCDD on nasal tissues (Nyska et al., 2005).

The biologic plausibility of the carcinogenicity of the chemicals of interest is discussed in general at the beginning of this chapter.

Synthesis

The new studies of oral, nasal, and pharyngeal cancers reported small, non-significant excesses in mortality from oral and pharyngeal cancers with very small numbers of cases. These data are not sufficient, taken in combination with the previously reviewed literature, to suggest an association with the herbicides sprayed in Vietnam.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and oral, nasal, or pharyngeal cancers.

CANCERS OF THE DIGESTIVE ORGANS

Until *Update 2006*, VAO committees had reviewed "gastrointestinal tract tumors" as a group consisting of stomach, colorectal, and pancreatic cancers, with esophageal cancer being formally factored in only since *Update 2002*. With more evidence from occupational studies available, VAO updates now address cancers of the digestive organs individually. Findings on cancers of the digestive organs as a group (ICD-9 150–159) are too broad for useful etiologic analysis and will no longer be considered.

Esophageal cancer (ICD-9 150), stomach cancer (ICD-9 151), colon cancer (ICD-9 153), rectal cancer (ICD-9 154), and pancreatic cancer (ICD-9 157) are among the most common cancers. ACS estimated that about 223,350 people would receive diagnoses of those cancers in the United States in 2010 and that 113,240 people would die from them (Jemal et al., 2010). When other digestive cancers (for example, small intestine, anal, and hepatobiliary cancers) were included, the 2010 estimates for the United States were about 274,330 new diagnoses and 139,580 deaths (Jemal et al., 2010). Collectively, tumors of the digestive organs were expected to account for 19% of new cancer diagnoses and 24% of cancer deaths in 2010. The average annual incidences of gastrointestinal cancers are presented in Table 7-4.

TABLE 7-4 Average Annual Incidence (per 100,000) of Selected Gastrointestinal Cancers in United States[a]

	55–59 Years Old			60–64 Years Old			65–69 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Stomach:									
Men	15.3	13.7	22.4	23.3	21.2	38.5	37.9	32.6	72.7
Women	7.1	5.5	11.7	8.9	7.1	14.5	15.5	12.8	23.1
Esophagus:									
Men	16.5	16.5	21.4	24.6	25.0	31.0	34.3	36.1	36.0
Women	3.0	2.7	6.4	3.8	3.7	7.0	8.3	7.5	14.6
Colon (excluding rectum):									
Men	53.5	50.2	85.1	81.7	77.9	128.6	129.6	126.0	181.3
Women	41.5	37.6	66.4	61.7	57.8	95.1	104.2	101.6	140.1
Rectum and rectosigmoid junction:									
Men	32.1	30.2	34.7	42.7	41.4	41.3	62.0	59.7	67.4
Women	19.3	18.2	22.1	23.5	23.1	28.4	31.8	29.9	39.9
Liver and intrahepatic bile duct:									
Men	32.6	25.2	78.8	31.6	24.8	67.1	34.5	26.3	48.8
Women	8.1	6.4	14.5	8.1	6.0	13.6	12.7	10.3	13.6
Pancreas:									
Men	22.6	21.7	33.9	36.5	35.2	58.4	53.6	52.7	79.6
Women	15.6	15.1	21.7	25.0	23.8	40.1	36.7	34.7	56.3
Small intestine:									
Men	5.3	5.4	6.8	6.6	6.6	9.9	9.2	8.8	14.5
Women	3.6	3.4	7.0	4.2	3.9	8.5	6.1	6.1	11.1
Anus, anal canal, and anorectum:									
Men	3.3	3.4	4.7	3.2	3.5	2.8	4.0	4.4	4.1
Women	4.5	4.8	4.9	4.6	5.0	3.5	5.4	5.8	6.2
Other digestive organs:									
Men	1.1	0.8	3.4	1.3	1.4	1.6	2.2	2.4	1.2
Women	0.6	0.5	0.9	1.4	1.4	1.3	1.4	1.2	3.1
Gallbladder:									
Men	1.0	0.8	1.6	1.4	1.3	2.0	2.9	2.4	3.5
Women	2.2	1.8	4.9	2.5	2.3	3.5	4.9	4.6	6.2
Other biliary:									
Men	2.5	2.1	5.0	5.4	5.1	5.2	7.0	6.8	4.7
Women	1.8	1.8	0.9	2.7	2.5	4.1	5.1	4.8	4.9

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2004–2008 (NCI, 2010).

The incidences of stomach, colon, rectal, and pancreatic cancers increase with age. In general, the incidences are higher in men than in women and higher in blacks than in whites. Other risk factors for the cancers vary but always include family history of the same form of cancer, some diseases of the affected organ, and diet. Tobacco use is a risk factor for pancreatic cancer and possibly stomach cancer (Miller et al., 1996). Infection with the bacterium *Helicobacter*

pylori increases the risk of stomach cancer. Type 2 diabetes is associated with an increased risk of cancers of the colon and pancreas (ACS, 2006).

It is noteworthy that there has been one report of Vietnam veterans that included all gastrointestinal cancers collectively. Cypel and Kang (2010) published an update on the disease-related mortality experience of ACC veterans who handled or sprayed herbicides in Vietnam in comparison with their non-Vietnam veteran peers or US men. Vital status was determined through December 31, 2005. In the analyses, the site-specific rates for digestive cancers were not examined. No statistically significant excess mortality from all cancers of the digestive tract was found in ACC Vietnam veterans compared with non-Vietnam veterans (adjusted RR = 1.01, 95% CI 0.56–1.83).

Esophageal Cancer

Epithelial tumors of the esophagus (squamous-cell carcinomas and adenocarcinomas) are responsible for more than 95% of all esophageal cancers (ICD-9 150); 16,640 newly diagnosed cases and 14,500 deaths were estimated for 2010 (Jemal et al., 2010). The considerable geographic variation in the incidence of esophageal tumors suggests a multifactorial etiology. Rates of esophageal cancer have been increasing in the last 2 decades. Adenocarcinoma of the esophagus has slowly replaced squamous-cell carcinoma as the most common type of esophageal malignancy in the United States and western Europe (Blot and McLaughlin, 1999). Squamous-cell esophageal carcinoma rates are higher in blacks than in whites and higher in men than in women. Smoking and alcohol ingestion are associated with the development of squamous-cell carcinoma; these risk factors have been less thoroughly studied for esophageal adenocarcinoma, but they appear to be associated. The rapid increase in obesity in the United States has been linked to increasing rates of gastroesophageal reflux disease (GERD), and the resulting rise in chronic inflammation has been hypothesized as explaining the link between GERD and esophageal adenocarcinoma. The average annual incidence of esophageal cancers is shown in Table 7-4.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* explicitly excluded esophageal cancer from the group of gastrointestinal tract tumors, for which it was concluded that there was limited or suggestive evidence of *no* association with exposure to the herbicides used by the US military in Vietnam. Esophageal cancers were not separately evaluated and were not categorized with this group until *Update 2004*. The committee responsible for *Update 2006* concluded that there was not enough evidence on each of the chemicals of interest to sustain that negative conclusion for any of the cancers in the gastrointestinal group and that, because these various types of cancer are generally regarded as separate disease entities, the evidence

on each should be evaluated separately. Esophageal cancer was thus reclassified into the default category of inadequate or insufficient evidence to determine whether there is an association. No additional studies reporting on esophageal cancer were reviewed in *Update 2008*. Table 7-5 summarizes the results of the relevant studies concerning esophageal cancer.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies There have been no published studies of esophageal cancer in Vietnam veterans since the last VAO update in 2008.

Occupational Studies Four occupational cohort studies have been published since the last VAO update in 2008. Collins et al. (2008, 2009a,b) published a series of papers examining the mortality experience of TCP and pentachlorophenol (PCP) workers employed in a Dow Chemical Company in Midland, Michigan, from 1937 to 1980. The TCP workers constitute the Dow cohort in the NIOSH cohort. Serum dioxin evaluation to estimate exposures to five dioxins was used in a subgroup of 98 workers (Collins et al., 2008). Although the serum dioxin, furan, and PCB concentrations were measured many years after exposure, distinct patterns of dioxin congeners among workers with different chlorophenol exposures were found.

The mortality experience of Dow chemical TCP workers in Midland potentially exposed to TCDD was reported by Collins et al. (2009a). Their study followed 1,615 workers who worked at least 1 day in a department with potential TCDD exposure. Follow-up ended on December 31, 2003, and the mean duration of follow-up was 36.4 years. Cause of death was determined by death certificates and SMRs were calculated by using national mortality figures. Some 17% of the sample (280) had serum TCDD evaluations that indicated higher concentrations than those of unexposed workers (Collins et al., 2007). Five esophageal-cancer deaths were observed, for an SMR of 1.0 (95% CI 0.3–2.2). None of the five people had had concurrent PCP exposure.

The second report on the Dow Midland cohort (Collins et al., 2009b) described the mortality experience of 773 PCP workers who were exposed to chlorinated dioxins not including TCDD. Of the cohort, 75% had been followed for more than 27 years. SMRs were calculated by comparing the PCP workers with the general US population and with that of Michigan. There were two observed deaths from esophageal cancer (SMR = 0.8, 95% CI 0.1–2.9).

McBride et al. (2009a,b) published two reports on a mortality follow-up of the workers in the Dow AgroSciences plant in New Plymouth, New Zealand, who were potentially exposed to TCDD. In McBride et al. (2009a), the SMR of ever-exposed workers was compared with that of never-exposed workers. The SMR for esophageal-cancer deaths in exposed workers was 2.5 (95% CI 0.7–6.4) compared with an SMR of 2.1 (95% CI 0.1–12.2) in the never-exposed group. The

TABLE 7-5 Selected Epidemiologic Studies—Esophageal Cancer

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US Centers for Disease Control and Prevention			**All COIs**
Boehmer et al., 2004	Follow-up of CDC VES cohort (ICD-9 140–149)	6	1.2 (0.4–4.0)
State Studies of US Vietnam Veterans			**All COIs**
Visintainer et al., 1995	PM study of deaths (1974–1989) of Michigan Vietnam-era veterans—deployed vs nondeployed	9	0.9 (0.4–1.6)
Australian Vietnam Veterans vs Australian Population			**All COIs**
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence	70	1.2 (0.9–1.5)
	Navy	19	1.6 (0.9–2.4)
	Army	40	1.1 (0.7–1.4)
	Air Force	11	1.5 (0.8–2.8)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—mortality	67	1.1 (0.8–1.3)
	Navy	13	1.0 (0.5–1.7)
	Army	42	1.0 (0.7–1.3)
	Air Force	12	1.5 (0.8–2.6)
CDVA, 1997a	Australian military Vietnam veterans	23	1.2 (0.7–1.7)
Australian Conscripted Army National Service Vietnam-Era Veterans (deployed vs nondeployed)			**All COIs**
ADVA, 2005c	Australian male conscripted Army National Service Vietnam-era veterans: deployed vs nondeployed		
	Incidence	9	1.9 (0.6–6.6)
	Mortality	10	1.3 (0.5–3.6)
CDVA, 1997b	Australian National Service Vietnam veterans	1	1.3 (0.0– > 10)
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			**Dioxin, Phenoxy Herbicides**
Kogevinas et al., 1997	IARC cohort, male and female workers exposed to any phenoxy herbicide or chlorophenol	28	1.0 (0.7–1.4)
	Exposed to highly chlorinated PCDDs	20	1.3 (0.8–1.9)
	Not exposed to highly chlorinated PCDDs	6	0.5 (0.2–1.1)
Saracci et al., 1991	IARC cohort—exposed subcohort (men and women)	8	0.6 (0.3–1.2)
Dow Chemical Company—Midland, MI (included in IARC and NIOSH cohorts)			**Dioxin, Phenoxy Herbicides**
Collins et al., 2009a,b	Trichlorophenol workers	5	1.0 (0.3-2.2)
	Pentachlorophenol workers	2	0.8 (0.1-2.9)

continued

TABLE 7-5 Esophageal Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)			**Dioxin, Phenoxy Herbicides**
McBride et al., 2009a	1,599 production workers (male and female) vs national rates—mortality 1969 through 2004		
	Ever exposed	4	2.5 (0.7–6.4)
	Never exposed	1	2.1 (0.1–12.2)
't Mannetje et al., 2005	New Zealand phenoxy herbicide producers (men and women)	2	2.0 (0.2–7.0)
	Phenoxy herbicide sprayers (> 99% men)	1	0.7 (0.0–4.0)
United Kingdom Production Workers (included in IARC cohort)			**Dioxin, Phenoxy Herbicides**
Coggon et al., 1986	British MCPA production workers	8	0.9 (0.4–1.9)
Agricultural Health Study			**Herbicides**
Blair et al., 2005a	US AHS		
	Private applicators (men and women)	16	0.5 (0.3–0.9)
	Spouses of private applicators (> 99% women)	1	0.3 (0.1–1.9)
Other Agricultural Workers			**Herbicides**
Lee et al., 2004a	Population-based case–control—agricultural pesticide use and adenocarcinoma of the esophagus	137	
	Insecticides		0.7 (0.4–1.1)
	Herbicides		0.7 (0.4–1.2)
Ronco et al., 1992	Danish farm workers—incidence		
	Male—Self-employed	32	0.4 ($p < 0.05$)
	Employee	13	0.9 (nr)
	Female—Self-employed	1	1.4 (nr)
	Family worker	2	0.4 (nr)
Wiklund, 1983	Swedish male and female agricultural workers—incidence	169	*99% CI* 0.6 (0.5–0.7)
Other Studies of Herbicide and Pesticide Applicators			**Herbicides**
Magnani et al., 1987	UK case–control		
	Herbicides	nr	1.6 (0.7–3.6)
	Chlorophenols	nr	1.2 (0.7–2.2)
Asp et al., 1994	Finnish herbicide applicators—incidence	3	1.6 (0.3–4.6)
	Finnish herbicide applicators—mortality	2	1.3 (0.2–4.7)
Forestry Workers			
Reif et al., 1989	New Zealand forestry workers—nested case–control (incidence) correspondence	4	1.8 (0.7–4.8)
Paper and Pulp Workers			**Dioxins**
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Never	27	0.7 (0.4–1.0)
	Ever	26	0.8 (0.5–1.2)

TABLE 7-5 Esophageal Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Pesatori et al., 2009	Seveso—20-yr follow-up to 1996—incidence (men and women, combined)		
	Zone A	0	
	Zone B	1	0.3 (0.0–1.9)
	Zone R	35	1.3 (0.9–1.9)

ABBREVIATIONS: AHS, Agricultural Health Study; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MI, Michigan; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; NZ, New Zealand; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PM, proportionate mortality; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; VES, Vietnam Experience Study.

[a]Subjects are male, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

SMR for esophageal cancer according to estimated effective cumulative exposure to TCDD was not calculated. The results in McBride et al. (2009b) have not been included, because they were diluted by inclusion of a set of workers who had no opportunity for TCDD exposure and no observed deaths.

Environmental Studies Esophageal-cancer cases were reported in the cancer-incidence study of the population (males and females combined) exposed to dioxin after the Seveso accident in 1976 (Pesatori et al., 2009). No esophageal cancers were observed in Zone A (high exposure). Only one esophageal-cancer case was found in residents of Zone B (medium exposure area) (RR = 0.26, 95% CI 0.04–1.91). Some 35 esophageal-cancer cases were reported in Zone R (low exposure) (RR = 1.33, 95% CI 0.92–1.92).

Biologic Plausibility

Long-term animal studies have examined the effect of exposure to the chemicals of interest on tumor incidence (Charles et al., 1996; Stott et al., 1990; Walker et al., 2006; Wanibuchi et al., 2004), and no increase in the incidence of esophageal cancer has been reported in laboratory animals after exposure to them. A recent biomarker study analyzed esophageal-cell samples from patients who had been exposed to indoor air pollution of different magnitudes and did or did not have high-grade squamous–cell dysplasia or a family history of upper gas-

trointestinal tract (UGI) cancer (Roth et al., 2009). AHR expression was higher in patients with a family history of UGI cancer, whereas indoor air pollution, esophageal squamous-cell dysplasia category, age, sex, and smoking were not associated with AHR expression. The results suggest that enhanced expression of the AHR in patients who had a family history of UGI cancer may contribute to UGI-cancer risk associated with AHR ligands, such as polycyclic aromatic hydrocarbons, which are found in cigarette smoke, and with TCDD.

The biologic plausibility of the carcinogenicity of the chemicals of interest is discussed in general at the beginning of this chapter.

Synthesis

The studies reviewed previously did not provide sufficient evidence to determine whether there is an association between exposure to the chemicals of interest and esophageal cancer, and no new additional information that would alter this judgment was found by the present committee. No toxicologic studies provide evidence of the biologic plausibility of an association between the chemicals of interest and tumors of the esophagus.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and esophageal cancer.

Stomach Cancer

The incidence of stomach cancer (ICD-9 151) increases in people 50–64 years old. ACS estimated that 12,730 men and 8,270 women would receive diagnoses of stomach cancer in the United States in 2010 and that 6,350 men and 4,220 women would die from it (Jemal et al., 2010). In general, the incidence is higher in men than in women and higher in blacks than in whites. Other risk factors include family history of this cancer, some diseases of the stomach, and diet. Infection with the bacterium *Helicobacter pylori* increases the risk of stomach cancer. Tobacco use and consumption of nitrite- and salt-preserved food may also increase the risk of stomach cancer (Brenner et al., 2009; Key et al., 2004; Miller et al., 1996). The average annual incidence of stomach cancer is shown in Table 7-4.

Conclusions from *VAO* and Previous Updates

Update 2006 considered stomach cancer independently for the first time. Prior updates developed a table of results for stomach cancer, but conclusions about the adequacy of the evidence of its association with herbicide exposure

had been reached in the context of gastrointestinal tract cancers. The committee responsible for *VAO* concluded that there was limited or suggestive evidence of *no* association between exposure to the herbicides used by the US military in Vietnam and gastrointestinal tract tumors, including stomach cancer. The committee responsible for *Update 2006* concluded that there was not enough evidence on each of the chemicals of interest to sustain this negative conclusion for any of the cancers in the gastrointestinal group and that, because these various types of cancer are generally regarded as separate disease entities, the evidence on each should be evaluated separately. Stomach cancer was thus reclassified into the default category of inadequate or insufficient evidence to determine whether there was an association.

Positive findings of an association with phenoxy herbicide exposure from a well-conducted nested case–control study of stomach cancer in the United Farm Workers of America cohort (Mills and Yang, 2007) led the committee responsible for *Update 2008* to reconsider the results of several earlier studies. Reif et al. (1989) reported a significant relationship between stomach cancer and the nonspecific exposure of being a forestry worker. Cocco et al. (1999) had found an association with herbicide exposure but had not analyzed specific chemicals, and Ekström et al. (1999) found significant associations between the occurrence of stomach cancer and exposure to phenoxy herbicides in general and to several specific phenoxy herbicide products. In updated mortality findings from Seveso concerning TCDD exposure, Consonni et al. (2008) found no increases in deaths from stomach cancer. In the absence of supportive findings from studies of Vietnam-veteran cohorts or IARC cohorts or from the US Agricultural Health Study (AHS), that committee retained stomach cancer in the inadequate or insufficient category.

Table 7-6 summarizes the results of the relevant studies concerning stomach cancer.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies No studies of exposure to the chemicals of interest and stomach cancer in Vietnam veterans have been published since *Update 2008*.

Occupational Studies Three occupational-cohort studies have been published since *Update 2008*. Collins et al. (2008, 2009a,b) published a series of papers examining the mortality experience of workers employed by the Dow Chemical Company in Midland, Michigan, from 1937 to 1980. Serum dioxin was evaluated to estimate exposures to five dioxins in a group of 98 workers (Collins et al., 2008). Although serum dioxin, furan, and PCB concentrations were measured many years after exposure, distinct patterns of dioxin congeners in workers who had different chlorophenol exposures were found. Collins et al. (2009a) described the mortality experience of 1,615 workers who had been exposed to TCP production. The mean duration of follow-up was 36.4 years. Eight cases of stomach

TABLE 7-6 Selected Epidemiologic Studies—Stomach Cancer

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US Air Force Health Study—Ranch Hands veterans vs SEA veterans (unless otherwise noted)			**All COIs**
Pavuk et al., 2005	Comparison subjects only from AFHS (digestive system)—incidence		
	Serum TCDD (pg/g) based on model with exposure variable $\log_e$(TCDD)		
	Per unit increase of -$\log_e$(TCDD) (pg/g)	24	1.8 (0.8–3.9)
	Quartiles (pg/g)		
	0.4–2.6	4	nr
	2.6–3.8	3	1.0 (0.2–4.8)
	3.8–5.2	7	2.0 (0.5–8.2)
	> 5.2	10	3.3 (0.9–12.5)
	Number of years served in SEA		
	Per year of service	24	1.2 (1.0–1.4)
	Quartiles (years in SEA)		
	0.8–1.3	4	nr
	1.3–2.1	4	1.0 (0.2–3.8)
	2.1–3.7	5	1.1 (0.3–4.2)
	3.7–16.4	11	2.1 (0.6–7.3)
Akhtar et al., 2004	White AFHS subjects vs national rates (digestive system)		
	Ranch Hand veterans		
	Incidence	16	0.6 (0.4–1.0)
	Tours 1966–1970	14	0.6 (0.4–1.1)
	Mortality	6	0.4 (0.2–0.9)
	Comparison veterans		
	Incidence	31	0.9 (0.6–1.2)
	Tours 1966–1970	24	0.9 (0.6–1.3)
	Mortality	14	0.7 (0.4–1.1)
US CDC Vietnam Experience Study			**All COIs**
Boehmer et al., 2004	Follow-up of CDC VES (stomach)	5	nr
US VA Mortality Study of Army and Navy Veterans—Ground Troops Serving July 4, 1965–March 1, 1973			**All COIs**
Breslin et al., 1988	Army Vietnam veterans	88	1.1 (0.9–1.5)
	Marine Vietnam veterans	17	0.8 (0.4–1.6)
State Studies of US Vietnam Veterans			**All COIs**
Anderson et al., 1986	Wisconsin Vietnam veterans	1	nr
Australian Vietnam Veterans vs Australian Population			**All COIs**
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence	104	0.9 (0.7–1.1)
	Navy	28	1.1 (0.7–1.6)
	Army	66	0.9 (0.7–1.1)
	Air Force	10	0.7 (0.3–1.3)

TABLE 7-6 Stomach Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—mortality	76	0.9 (0.7–1.2)
	Navy	22	1.3 (0.8–1.8)
	Army	50	0.9 (0.7–1.2)
	Air Force	4	0.4 (0.1–1.0)
CDVA, 1997a	Australian military Vietnam veterans	32	1.1 (0.7–1.4)
Australian Conscripted Army National Service Vietnam-Era Veterans (deployed vs nondeployed)			**All COIs**
ADVA, 2005c	Australian male conscripted Army National Service Vietnam-era veterans: deployed vs nondeployed		
	Incidence	11	0.6 (0.2–1.2)
	Mortality	7	0.7 (0.2–2.0)
CDVA, 1997b	Australian National Service Vietnam veterans	4	1.7 (0.3– > 10)
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			**Dioxin, phenoxy herbicides**
Kogevinas et al., 1997	IARC cohort, male and female workers exposed to any phenoxy herbicide or chlorophenol	72	0.9 (0.7–1.1)
	Exposed to highly chlorinated PCDDs	42	0.9 (0.7–1.2)
	Not exposed to highly chlorinated PCDDs	30	0.9 (0.6–1.3)
Kogevinas et al., 1993	IARC cohort—women	1	1.4 (nr)
Saracci et al., 1991	IARC cohort—exposed subcohort (men and women)	40	0.9 (0.6–1.2)
NIOSH Mortality Cohort (12 US plants, production 1942–1984) (included in IARC cohort)			**Dioxin, Phenoxy Herbicides**
Steenland et al., 1999	US chemical production workers	13	1.0 (0.6–1.8)
Fingerhut et al., 1991	NIOSH—entire cohort	10	1.0 (0.5–1.9)
	≥ 1-year exposure, ≥ 20-year latency	4	1.4 (0.4–3.5)
Monsanto Plant in Nitro, WV (included in IARC and NIOSH cohorts)			**Dioxin, Phenoxy Herbicides**
Collins et al., 1993	Monsanto Company workers	0	0.0 (0.0–1.1)
Dow Chemical Company—Midland, MI (included in IARC and NIOSH cohorts)			**Dioxin, Phenoxy Herbicides**
Collins et al., 2009a	Trichlorophenol workers	8	1.4 (0.6–2.7)
Collins et al., 2009b	Pentachlorophenol workers	4	1.2 (0.3–3.1)
Bodner et al., 2003	Dow production workers	nr	1.5 (0.7–2.7)

continued

TABLE 7-6 Stomach Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Burns et al., 2001	Dow 2,4-D production worker		
	Digestive organs, peritoneum	16	0.7 (0.4–1.2)
Ramlow et al., 1996	Dow pentachlorophenol production workers		
	0-yr latency	4	1.7 (0.5–4.3)
	15-yr latency	3	1.8 (0.4–5.2)
Bond et al., 1988	Dow 2,4-D production workers	0	nr (0.0–3.7)
BASF Cohort (included in IARC cohort)			**Dioxin, Phenoxy Herbicides**
Ott and Zober, 1996	BASF employees—incidence	3	1.0 (0.2–2.9)
	TCDD < 0.1 µg/kg of body weight	0	0.0 (0.0–3.4)
	TCDD 0.1–0.99 µg/kg of body weight	1	1.3 (0.0–7.0)
	TCDD ≥ 1 µg/kg of body weight	2	1.7 (0.2–6.2)
Zober et al., 1990	BASF employees—basic cohort		*90% CI*
		3	3.0 (0.8–7.7)
Danish Production Workers (included in IARC cohort)			**Dioxin, Phenoxy Herbicides**
Lynge, 1985	Danish production workers—incidence		
	Men	12	1.3 (nr)
	Women	1	0.7 (nr)
Dutch Production Workers (included in IARC cohort)			**Dioxin, Phenoxy Herbicides**
Boers et al., 2010	Dutch chlorophenoxy workers		
	Factory A	5	2.2 (0.4–13.2)
	Factory B	4	1.2 (0.3–4.7)
Hooiveld et al., 1998	Dutch chemical production workers	3	1.0 (0.2–2.9)
Bueno de Mesquita et al., 1993	Dutch phenoxy herbicide workers	2	0.7 (0.1–2.7)
German Production Workers (included in IARC cohort)			**Dioxin, Phenoxy Herbicides**
Becher et al., 1996	German production workers		
	Plant I	12	1.3 (0.7–2.2)
	Plant II	0	nr
	Plant III	0	nr
	Plant IV	2	0.6 (0.1–2.3)
Manz et al., 1991	German production workers—men, women		
	Men	12	1.2 (0.6–2.1)
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)			**Dioxin, Phenoxy Herbicides**
McBride et al., 2009a	1,599 production workers (male and female) vs national rates—mortality 1969 through 2004		
	Ever exposed	4	1.4 (0.4–3.6)
	Never exposed	2	2.3 (0.3–8.4)

TABLE 7-6 Stomach Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
't Mannetje et al., 2005	New Zealand phenoxy herbicide producers (men and women)	2	1.1 (0.1–4.0)
	Phenoxy herbicide sprayers (> 99% men)	3	1.4 (0.3–4.0)
United Kingdom Production Workers (included in IARC cohort)			**Dioxin, Phenoxy Herbicides**
Coggon et al., 1986	British MCPA production workers	26	0.9 (0.6–1.3)
Agricultural Health Study			**Herbicides**
Alavanja et al., 2005	AHS—incidence (all digestive cancers)		
	Private applicators (men and women)	462	0.8 (0.8–0.9)
	Spouses of private applicators (> 99% women)	161	0.9 (0.7–1.0)
	Commercial applicators (men and women)	24	1.0 (0.6–1.4)
Blair et al., 2005a	AHS (stomach cancers)		
	Private applicators (men and women)	10	0.5 (0.2–1.0)
	Spouses of private applicators (> 99% women)	4	1.1 (0.3–2.8)
Other Agricultural Workers			**Herbicides**
Mills and Yang, 2007	Nested case–control study of agricultural exposure and gastric cancer in UFW cohort		
	Ever worked in area where 2,4-D used	42	1.9 (1.1–3.3)
	Quartile of lifetime exposure to 2,4-D (lb)		
	0	58	1.0
	1–14	17	2.2 (1.0–4.6)
	15–85	14	1.6 (0.7–3.5)
	86–1,950	11	2.1 (0.9–5.1)
Lee et al., 2004a	Population-based case–control—agricultural pesticide use and adenocarcinoma of stomach	170	
	Insecticides		0.9 (0.6–1.4)
	Herbicides		0.9 (0.5–1.4)
Ekström et al., 1999	Case–control study of Swedish residents with gastric adenocarcinoma		
	All occupational herbicide exposure	75	1.6 (1.1–2.2)
	Phenoxyacetic acid exposure	62	1.8 (1.3–2.6)
	Hormoslyr (2,4-D and 2,4,5-T)	48	1.7 (1.2–2.6)
	2,4-D only	3	nr (vs 0 controls)
	MCPA	11	1.8 (0.8–4.1)
	Duration of exposure		
	Nonexposed to all herbicides	490	1.0
	< 1 month	11	1.6 (0.7–3.5)
	1–6 months	30	1.9 (1.1–3.2)
	7–12 months	7	1.7 (0.6–4.7)
	> 1 year	13	1.4 (0.6–3.0)
	Other herbicide exposure	13	1.0 (0.5–1.9)

continued

TABLE 7-6 Stomach Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Gambini et al., 1997	Italian rice growers	39	1.0 (0.7–1.3)
Blair et al., 1993	US farmers in 23 states		
	White men	657	1.0 (1.0–1.1)
	White women	12	1.2 (0.6–2.0)
Ronco et al., 1992	Danish farm workers—incidence		
	Men	286	0.9 (nr)
	Women	5	1.0 (nr)
Wigle et al., 1990	Canadian farmers	246	0.9 (0.8–1.0)
Alavanja et al., 1988	USDA agricultural extension agents	10	0.7 (0.4–1.4)
Burmeister et al., 1983	Iowa residents—farming exposures	1,812	1.3 ($p < 0.05$)
Wiklund, 1983	Swedish male and female agricultural workers—incidence	2,599	*99% CI* 1.1 (1.0–1.2)
Burmeister, 1981	Iowa farmers	338	1.1 ($p < 0.01$)
Other Studies of Herbicide and Pesticide Applicators			**Herbicides**
Torchio et al., 1994	Italian licensed pesticide users	126	0.7 (0.6–0.9)
Swaen et al., 2004	Dutch licensed herbicide applicators		
	Stomach and small intestine	3	0.4 (0.1–1.3)
Swaen et al., 1992	Dutch licensed herbicide applicators		
	Stomach and small intestine	1	0.5 (0.0–2.7)
Blair et al., 1983	Florida pesticide applicators		*Expected exposed cases*
		4	3.3
Forestry Workers			**Herbicides**
Alavanja et al., 1989	USDA forest, soil conservationists	9	0.7 (0.3–1.3)
Reif et al., 1989	New Zealand forestry workers—nested case–control (incidence)	13	2.2 (1.3–3.9)
Paper and Pulp Workers			**Dioxins**
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	146	0.9 (0.8–1.1)
	Ever	98	0.9 (0.7–1.1)
Rix et al., 1998	Danish paper-mill workers—incidence		
	Men	48	1.1 (0.8–1.4)
	Women	7	1.0 (0.4–2.1)
Henneberger et al., 1989	New Hampshire pulp and paper workers	5	1.2 (0.4–2.8)
Robinson et al., 1986	Northwestern US paper and pulp workers		*90% CI*
		17	1.2 (0.8–1.9)

TABLE 7-6 Stomach Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Solet et al., 1989	US paper and pulp workers	1	0.5 (0.1–3.0)
Other Environmental Studies			**Dioxin, 2,4,5-T/**
Thomas, 1987	US flavor and fragrance chemical plant workers		*Expected exposed cases*
		6	4.2
Axelson et al., 1980	Swedish railroad workers—total exposure to herbicides	3	**Phenoxy acids** 2.2 (nr)
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Consonni et al., 2008	Seveso residents—25-yr follow-up—men, women		
	Zone A	3	0.7 (0.2–2.0)
	Zone B	24	0.8 (0.5–1.2)
	Zone R	212	1.0 (0.8–1.1)
Pesatori et al., 2009	Seveso—20-yr follow-up to 1996—incidence (men and women, combined)		
	Zone A	3	0.9 (0.3–2.7)
	Zone B	19	0.9 (0.6–1.4)
	Zone R	131	0.8 (0.7–1.0)
Bertazzi et al., 2001	Seveso residents—20-yr follow-up		
	Zones A, B—men	16	0.9 (0.5–1.5)
	women	11	1.0 (0.6–1.9)
Bertazzi et al., 1997	Seveso residents—15-yr follow-up		
	Zone A—women	1	0.9 (0.0–5.3)
	Zone B—men	10	0.8 (0.4–1.5)
	women	7	1.0 (0.4–2.1)
	Zone R—men	76	0.9 (0.7–1.1)
	women	58	1.0 (0.8–1.3)
Bertazzi et al., 1993	Seveso residents—10-yr follow-up—incidence		
	Zone B—men	7	1.0 (0.5–2.1)
	women	2	0.6 (0.2–2.5)
	Zone R—men	45	0.9 (0.7–1.2)
	women	25	1.0 (0.6–1.5)
Pesatori et al., 1992	Seveso residents—incidence		
	Zones A, B—men	7	0.9 (0.4–1.8)
	women	3	0.8 (0.3–2.5)
Bertazzi et al., 1989a	Seveso residents—10-yr follow-up		
	Zones A, B, R—men	40	0.8 (0.6–1.2)
	women	22	1.0 (0.6–1.5)
Bertazzi et al., 1989b	Seveso residents—10-yr follow-up		
	Zone B—men	7	1.2 (0.6–2.6)

continued

TABLE 7-6 Stomach Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Chapaevsk, Russia Cohort			
Revich et al., 2001	Residents of Chapaevsk, Russia		
	Men	59	1.7 (1.3–2.2)
	Women	45	0.7 (0.5–0.9)
Other Environmental Studies			**Serum dioxin**
Turunen et al., 2008	Finnish fishermen and spouses		
	Fishermen	16	0.8 (0.5–1.3)
	Spouses	2	0.3 (0.0–1.1)
Fukuda et al., 2003	Residents of Japanese municipalities with and without waste-incineration plants		***Dioxin emissions/*** *Age-adjusted mortality (per 100,000)*
	Men		
	With		38.2 ± 7.8 vs
	Without		39.0 ± 8.8 (p = 0.29)
	Women		
	With		20.7 ± 5.0 vs
	Without		20.7 ± 5.8 (p = 0.92)
Svensson et al., 1995	Swedish fishermen—mortality (men and women)		**Organochlorine compounds**
	East coast	17	1.4 (0.8–2.2)
	West coast	63	0.9 (0.7–1.2)
	Swedish fishermen—incidence (men and women)		
	East coast	24	1.6 (1.0–2.4)
	West coast	71	0.9 (0.7–1.2)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; AFHS, Air Force Health Study; AHS, Agricultural Health Study; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MI, Michigan; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; NZ, New Zealand; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; UFW, United Farm Workers of America; USDA, US Department of Agriculture; VA, US Department of Veterans Affairs; VES, Vietnam Experience Study; WV, West Virginia.

[a]Subjects are male, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

cancer were observed (SMR = 1.4, 95% CI 0.6–2.7). The later Collins et al. report (2009b) described the mortality experience of 773 workers who were exposed to chlorinated dioxins in the production of PCP. SMRs were calculated to compare the PCP workers with the general US population and with that of Michigan. There were four observed deaths from stomach cancer (SMR = 1.2, 95% CI 0.3–3.1).

McBride et al. (2009a,b) published two reports on a mortality follow-up of the workers in the Dow AgroSciences plant in New Plymouth, New Zealand, who were potentially exposed to TCDD. The first report (2009a) compared the SMR for stomach cancer in ever-exposed workers with that in never-exposed workers. The SMR for stomach-cancer deaths was 1.4 (95% CI 0.4–3.6) in exposed workers and 2.3 (95% CI 0.3–8.4) in the never-exposed group. The results in the second report (2009b) have not been included here, because they were diluted by inclusion of a set of workers who had no opportunity for TCDD exposure and no observed deaths.

Boers et al. (2010) published the third follow-up results of a retrospective cohort study of two Dutch chlorophenoxy herbicide manufacturing factories that produced mainly 2,4,5-T (factory A) and 2-methyl-4-chlorophenoxyacetic acid (MCPA), 2-methyl-4-chlorophenoxy propanoic acid (MCPP), and 2,4-D (factory B). The cohort consisted of all persons who worked in the factories during 1955–1985 (factory A) or 1965–1986 (factory B). No increases in stomach-cancer deaths were observed. The SMR was 2.23 (95% CI 0.38–13.2) in factory A and 1.21 (95% CI 0.31–4.65) in factory B.

Environmental Studies Stomach-cancer cases were reported in the cancer-incidence study of the population (males and females combined) exposed to dioxin after the Seveso accident in 1976 (Pesatori et al., 2009). Three stomach cancers were observed in Zone A (high exposure) (RR = 0.86, 95% CI 0.28–2.69); 19 in residents of Zone B (medium exposure) (RR = 0.87, 95% CI 0.55–1.37), and 131 in Zone R (the low exposure) (RR = 0.84, 95% CI 0.70–1.01).

A second environmental study was published by Turunen et al. (2008), who assessed the mortality experience of fishermen (registered since 1980) and fishermen's wives in Finland, presuming that their mortality would reflect their high consumption of contaminated fish. SMRs for the 6,410 fishermen and 4,260 wives were calculated on the basis of national mortality figures. The investigators had previously compared fish consumption and serum dioxin in fishermen and wives with those in control populations and found that consumption of fish and serum dioxin concentrations were higher in the fishermen and their wives. The fishermen and their wives were also more likely to be obese. Mortality rates from stomach cancer were found to be elevated in the study cohort (SMR = 0.82, 95% CI 0.47–1.33 in fishermen and SMR = 0.30, 95% CI 0.04–1.08 in their wives).

Biologic Plausibility

Long-term animal studies have examined the effect of exposure to the chemicals of interest (2,4-D and TCDD) on tumor incidence (Charles et al., 1996; Stott et al., 1990; Walker et al., 2006; Wanibuchi et al., 2004). No increase in the incidence of gastrointestinal cancer has been reported in laboratory animals. However, studies performed in laboratory animals have observed dose-dependent

increases in the incidence of squamous-cell hyperplasia of the forestomach or fundus of the stomach after administration of TCDD (Hebert et al., 1990; Walker et al., 2006). Similarly, in a long-term TCDD-treatment study in monkeys, hypertrophy, hyperplasia, and metaplasia were observed in the gastric epithelium (Allen et al., 1977). A transgenic mouse bearing a constitutively active form of the AHR has been shown to develop stomach tumors (Andersson et al., 2002a); the tumors are neither dysplastic nor metaplastic but are indicative of both squamous-cell and intestinal-cell metaplasia (Andersson et al., 2005). The validity of the transgenic-animal model is indicated by the similarities in the phenotype of the transgenic animal (increased relative weight of the liver and heart, decreased weight of the thymus, and increased expression of the AHR target gene CYP1A1) and animals treated with TCDD (Brunnberg et al., 2006).

In a biomarker study of cancer patients, AHR expression and nuclear translocation were significantly higher in gastric-cancer tissue than in precancerous tissue (Peng et al., 2009a). The results suggest that the AHR plays an important role in gastric carcinogenesis. AHR activation in a gastric-cancer cell line (AGS) has also been shown to enhance gastric-cancer cell invasiveness potentially through a c-Jun-dependent induction of matrix metalloproteinase-9 (Peng et al., 2009b).

The biologic plausibility of the carcinogenicity of the chemicals of interest is discussed in general at the beginning of this chapter.

Synthesis

The committee responsible for *Update 2008* noted several studies reporting evidence of association of stomach cancer with herbicides and with phenoxy herbicides in particular: two well-done occupational studies (Ekström et al., 1999; Mills and Yang, 2007) and a case–control study (Cocco et al., 1999) that indicated a relationship with herbicide exposure but was not specific as to type of herbicide. There was no suggestion of an association between TCDD and mortality from stomach cancer in the 25-year update of the Seveso population (Consonni et al., 2008). That committee noted that there had been no suggestion of an association between the chemicals of interest and stomach cancer in the studies of Vietnam-veteran cohorts, the IARC cohort studies, or the AHS. The several additional studies reviewed for the current update provided no new evidence of an association between the chemicals of interest and stomach cancer.

There is some evidence of biologic plausibility in animal models, but overall the epidemiologic studies do not support an association between exposure to the chemicals of interest and stomach cancer.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to

determine whether there is an association between exposure to the chemicals of interest and stomach cancer.

Colorectal Cancer

Colorectal cancers include malignancies of the colon (ICD-9 153) and of the rectum and anus (ICD-9 154); less prevalent tumors of the small intestine (ICD-9 152) are often included. Findings on cancers of the retroperitoneum and other unspecified digestive organs (ICD-9 159) are considered in this category. Colorectal cancers account for about 55% of digestive tumors; ACS estimated that 154,790 people would receive diagnoses of colorectal cancer in the United States in 2010 and that 53,190 would die from it (Jemal et al., 2010). Excluding basal-cell and squamous-cell skin cancers, colorectal cancer is the third-most common form of cancer both in men and in women. The average annual incidence of colorectal cancers is shown in Table 7-4.

The incidence of colorectal cancer increases with age; it is higher in men than in women and higher in blacks than in whites. Because it is recommended that all persons over 50 years old receive colon-cancer screening, screening can affect the incidence. Other risk factors include family history of this form of cancer, some diseases of the intestines, and diet. Type 2 diabetes is associated with an increased risk of cancer of the colon (ACS, 2007a).

Conclusions from *VAO* and Previous Updates

Update 2006 considered colorectal cancer independently for the first time. Prior updates developed tables of results on colon and rectal cancer, but conclusions about the adequacy of the evidence of their association with herbicide exposure had been reached only in the context of gastrointestinal tract cancers. The committee responsible for *VAO* concluded that there was limited or suggestive evidence of *no* association between exposure to the herbicides used by the US military in Vietnam and gastrointestinal tract tumors, including colorectal cancer. The committee responsible for *Update 2006* concluded that there was not enough evidence on each of the chemicals of interest to sustain that negative conclusion for any of the cancers in the gastrointestinal group and that, because these various types of cancer are generally regarded as separate disease entities, the evidence on each should be evaluated separately. Colorectal cancer was thus reclassified into the default category of inadequate or insufficient evidence to determine whether there is an association. The information considered in *Update 2008* did not provide evidence to support moving colorectal cancers out of the category of inadequate or insufficient evidence.

Table 7-7 summarizes the results of the relevant studies concerning colon and rectal cancers.

TABLE 7-7 Selected Epidemiologic Studies—Colon and Rectal Cancer

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US Air Force Health Study			**All COIs**
AFHS, 2000	Ranch Hand veterans from AFHS—mortality		
	Colon, rectum combined	7	1.5 (0.4–5.5)
US CDC Vietnam Experience Study			**All COIs**
Boehmer et al., 2004	Follow-up of CDC Vietnam Experience Cohort—mortality (1965–2000)		
	Colon, rectum, and anus	9	1.0 (0.4–2.6)
US VA Mortality Study of Army and Marine Veterans—Ground troops serving July 4, 1965–March 1, 1973			**All COIs**
Breslin et al., 1988	Army and Marine Vietnam veterans—mortality		
	Army Vietnam veterans		
	Colon, other gastrointestinal (ICD-8 152–154, 158, 159)	209	1.0 (0.7–1.3)
	Marine Vietnam veterans		
	Colon, other gastrointestinal (ICD-8 152–154, 158, 159)	33	1.3 (0.7–2.2)
US VA Cohort of Female Vietnam Veterans			**All COIs**
Cypel and Kang, 2008	US female Vietnam Veterans—mortality through 2004		
	US Vietnam veterans	11	0.5 (0.2–1.0)
	Vietnam-veteran nurses	9	0.6 (0.2–1.4)
Dalager et al., 1995	US female Vietnam Veterans—mortality through 1991		
	US Vietnam veterans		
	Colon	4	0.4 (0.1–1.2)
	Vietnam-veteran nurses		
	Colon	4	0.5 (0.2–1.7)
State Studies of US Vietnam Veterans			**All COIs**
Anderson et al., 1986	Wisconsin Vietnam veterans—mortality		
	Colon	6	1.0 (0.4–2.2)
	Rectum	1	nr
Australian Vietnam Veterans vs Australian Population			**All COIs**
ADVA, 2005a	Australian male Vietnam veterans vs Australian population		
	Colon—incidence	376	1.1 (1.0–1.2)
	Navy	91	1.3 (1.0–1.5)
	Army	239	1.1 (0.9–1.2)
	Air Force	47	1.1 (0.8–1.5)
	Rectum—incidence		
	Navy	54	1.1 (0.8–1.4)
	Army	152	1.0 (0.8–1.1)
	Air Force	28	1.0 (0.6–1.4)

TABLE 7-7 Colon and Rectal Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
ADVA, 2005b	Australian male Vietnam veterans vs Australian population		
	Colon—mortality	176	1.0 (0.8–1.1)
	Navy	49	1.3 (0.9–1.6)
	Army	107	0.9 (0.7–1.0)
	Air Force	21	0.9 (0.5–1.3)
	Rectum—mortality		
	Navy	13	0.8 (0.4–1.4)
	Army	44	0.9 (0.6–1.1)
	Air Force	12	1.3 (0.6–2.2)
AIHW, 1999	Australian Vietnam veterans (men)—incidence (validation study)		*Expected number of exposed cases (95% CI)*
	Colorectal cancer	188	221 (191–251)
CDVA, 1998a	Australian Vietnam veterans (men)—incidence		
	Self-reported colon cancer	405	117 (96–138)
CDVA, 1998b	Australian Vietnam veterans (women)—incidence		
	Self-reported colon cancer	1	1 (0–5)
CDVA, 1997a	Australian military Vietnam veterans—mortality		
	Colon	78	1.2 (0.9–1.5)
	Rectum	16	0.6 (0.4–1.0)
Australian Conscripted Army National Service (deployed vs nondeployed)			**All COIs**
ADVA, 2005c	Australian male conscripted Army National Service Vietnam-era veterans: deployed vs nondeployed		
	Colon		
	Incidence	54	0.9 (0.7–1.4)
	Mortality	29	0.8 (0.5–1.3)
	Rectum		
	Incidence	46	1.4 (0.9–2.2)
	Mortality	10	1.8 (0.6–5.6)
CDVA, 1997b	Australian National Service Vietnam veterans—mortality		
	Colon	6	0.6 (0.2–1.5)
	Rectum	3	0.7 (0.2–9.5)

continued

TABLE 7-7 Colon and Rectal Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			**Dioxin, phenoxy herbicides**
Kogevinas et al., 1997	IARC cohort, male and female workers exposed to any phenoxy herbicide or chlorophenol		
	Colon	86	1.1 (0.9–1.3)
	Rectum	44	1.1 (0.8–1.4)
	Exposed to highly chlorinated PCDDs		
	Colon	52	1.0 (0.8–1.3)
	Rectum	29	1.3 (0.9–1.9)
Saracci et al., 1991	IARC cohort—exposed subcohort (men and women)—mortality		
	Colon (except rectum)	41	1.1 (0.8–1.5)
	Rectum	24	1.1 (0.7–1.6)
NIOSH Mortality Cohort (12 US plants, production 1942–1984) (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Steenland et al., 1999	US chemical production workers		
	Small intestine and colon	34	1.2 (0.8–1.6)
	Rectum	6	0.9 (0.3–1.9)
Fingerhut et al., 1991	NIOSH cohort—mortality		
	Entire NIOSH cohort		
	Small intestine, colon	25	1.2 (0.8–1.8)
	Rectum	5	0.9 (0.3–2.1)
	≥ 1-yr exposure, ≥ 20-yr latency		
	Small intestine, colon	13	1.8 (1.0–3.0)
	Rectum	2	1.2 (0.1–4.2)
Monsanto Plant in Nitro, WV (included in IARC and NIOSH cohorts)			**Dioxin, phenoxy herbicides**
Collins et al., 1993	Monsanto Company workers—mortality		
	Colon	3	0.5 (0.1–1.3)
Dow Chemical Company—Midland, MI (included in IARC and NIOSH cohorts)			**Dioxin, phenoxy herbicides**
Collins et al., 2009a	Trichlorophenol workers		
	Large intestine	18	1.2 (0.7–1.8)
	Rectum	2	0.6 (0.1–2.1)
Collins et al., 2009b	Pentachlorophenol workers		
	Large intestine	10	1.2 (0.6–2.3)
	Rectum	1	0.5 (0.0–2.9)
Ramlow et al., 1996	Dow pentachlorophenol production workers—mortality		
	0-yr latency		
	Colon	4	0.8 (0.2–2.1)
	Rectum	0	nr
	15-yr latency		
	Colon	4	1.0 (0.3–2.6)
	Rectum	0	nr

TABLE 7-7 Colon and Rectal Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Bond et al., 1988	Dow 2,4-D production workers—mortality		
	Colon	4	2.1 (0.6–5.4)
	Rectum	1	1.7 (0.0–9.3)
BASF Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Ott and Zober, 1996	BASF employees—colorectal—incidence	5	1.0 (0.3–2.3)
	TCDD < 0.1 µg/kg of body weight	2	1.1 (0.1–3.9)
	TCDD 0.1–0.99 µg/kg of body weight	2	1.4 (0.2–5.1)
	TCDD ≥ 1 µg/kg of body weight	1	0.5 (0.0–3.0)
Zober et al., 1990	BASF employees—basic cohort—mortality		*90% CI*
	Colon, rectum	2	2.5 (0.4–7.8)
Thiess et al., 1982	BASF production workers—mortality		
	Colon	1	0.4 (nr)
Danish Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Lynge, 1985	Danish production workers—incidence		
	Men		
	Colon	10	1.0 (nr)
	Rectum	14	1.4 (nr)
	Women		
	Colon	1	0.3 (nr)
	Rectum	2	1.0 (nr)
Dutch Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Hooiveld et al., 1998	Dutch chemical production workers		
	Intestine (except rectum)	3	1.4 (0.3–4.0)
	Rectum	1	1.0 (0.0–5.6)
Bueno de Mesquita et al., 1993	Dutch phenoxy herbicide workers—mortality		
	Colon	3	1.8 (0.4–5.4)
	Rectum	0	nr
German Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Becher et al., 1996	German production workers—mortality		
	Plant I		
	Colon	2	0.4 (0.1–1.4)
	Rectum	6	1.9 (0.7–4.0)
	Plant II		
	Colon	0	nr
	Rectum	0	nr
	Plant III		
	Colon	1	2.2 (0.1–2.2)
	Rectum	0	nr
	Plant IV		
	Colon	0	nr
	Rectum	1	0.9 (0.0–4.9)

continued

TABLE 7-7 Colon and Rectal Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Manz et al., 1991	German production workers—mortality		
	Colon	8	0.9 (0.4–1.8)
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)			**Dioxin, phenoxy herbicides**
McBride et al., 2009a	1,599 production workers (male and female) vs national rates—mortality 1969 through 2004		
	Large intestine		
	Ever	3	0.6 (0.1–1.7)
	Never	0	0.0 (0.0–2.0)
	Rectum		
	Ever	6	2.0 (0.7–4.4)
	Never	2	2.1 (0.3–7.7)
't Mannetje et al., 2005	New Zealand phenoxy herbicide producers, sprayers—mortality		
	Phenoxy herbicide producers (men and women)		
	Colon	2	0.6 (0.0–2.3)
	Rectum, rectosigmoid junction, anus	5	2.5 (0.8–5.7)
	Phenoxy herbicide sprayers (> 99% men)		
	Colon	8	1.9 (0.8–3.8)
	Rectum, rectosigmoid junction, anus	4	1.5 (0.4–3.8)
United Kingdom Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Coggon et al., 1986	British MCPA production workers—mortality		
	Colon	19	1.0 (0.6–1.6)
	Rectum	8	0.6 (0.3–1.2)
Agricultural Health Study			**Herbicides**
Lee WJ et al., 2007	Pesticide applicators (men and women) in AHS—colorectal-cancer incidence (enrollment–2002) and any use before enrollment of:		
	2,4-D	204	0.7 (0.5–0.9)
	2,4,5-T	65	0.9 (0.7–1.2)
	2,4,5-TP	24	0.8 (0.5–1.2)
	Dicamba	110	0.9 (0.7–1.2)

TABLE 7-7 Colon and Rectal Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Samanic et al., 2006	Pesticide applicators in AHS—colon-cancer incidence (enrollment–2002)		
	Dicamba—days of use		
	None	76	1.0
	1– < 20	9	0.4 (0.2–0.9)
	20– < 56	20	0.9 (0.5–1.5)
	56– < 116	13	0.8 (0.4–1.5)
	≥ 116	17	1.4 (0.8–2.9)
			p-trend = 0.10
	Dicamba—intensity-weighted quartiles		
	None	76	1.0
	Lowest	16	0.6 (0.4–1.1)
	Second	17	0.7 (0.4–1.2)
	Third	6	0.5 (0.2–1.2)
	Highest	20	1.8 (1.0–3.1)
			p-trend = 0.02
Alavanja et al., 2005	US AHS—incidence		
	Colon		
	Private applicators (men and women)	208	0.9 (0.8–1.0)
	Spouses of private applicators (> 99% women)	87	0.9 (0.7–1.1)
	Commercial applicators (men and women)	12	1.2 (0.6–2.1)
	Rectum		
	Private applicators (men and women)	94	0.8 (0.7–1.0)
	Spouses of private applicators (> 99% women)	23	0.6 (0.4–0.9)
	Commercial applicators (men and women)	7	1.3 (0.5–2.6)
Blair et al., 2005a	US AHS—mortality		
	Colon		
	Private applicators (men and women)	56	0.7 (0.6–1.0)
	Spouses of private applicators (> 99% women)	31	1.2 (0.8–1.6)
	Rectum		
	Private applicators (men and women)	nr	nr
	Spouses of private applicators (> 99% women)	nr	nr

continued

TABLE 7-7 Colon and Rectal Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Other Agricultural Workers			**Herbicides**
Gambini et al., 1997	Italian rice growers—mortality		
	Intestines	27	1.1 (0.7–1.6)
Blair et al., 1993	US farmers in 23 states—mortality		
	White men		
	Colon	2,291	1.0 (0.9–1.0)
	Rectum	367	1.0 (0.9–1.1)
	White women		
	Colon	59	1.0 (0.8–1.3)
	Rectum	4	0.5 (0.1–1.3)
Ronco et al., 1992	Danish workers—incidence		
	Men—self-employed		
	Colon	277	0.7 ($p < 0.05$)
	Rectum	309	0.8 ($p < 0.05$)
	Men—employees		
	Colon	45	0.6 ($p < 0.05$)
	Rectum	55	0.8 (nr)
	Women—self-employed		
	Colon	14	0.9 (nr)
	Rectum	5	0.6 (nr)
	Women—employees		
	Colon	112	0.9 (nr)
	Rectum	55	0.8 (nr)
	Women—family worker		
	Colon	2	0.2 ($p < 0.05$)
	Rectum	2	0.4 (nr)
Alavanja et al., 1988	USDA agricultural extension agents—mortality		
	Colon	41	1.0 (0.7–1.5)
	Rectum	5	nr
Wiklund, 1983	Swedish male and female agricultural workers—incidence		
	Colon	1,332	
			99% CI
	Rectum	1,083	0.8 (0.7–0.8)
Burmeister, 1981	Iowa farmers—mortality		
	Colon	1,064	0.9 (0.9–1.0)
Other Studies of Herbicide and Pesticide Applicators			**Herbicides**
Swaen et al., 2004	Dutch licensed herbicide applicators—mortality		
	Colon	7	1.0 (0.4–2.1)
	Rectum	5	2.1 (0.7–4.8)
Torchio et al., 1994	Italian licensed pesticide users—mortality		
	Colon	84	0.6 (0.5–0.7)
	Rectum	nr	nr
Swaen et al., 1992	Dutch licensed herbicide applicators—mortality		
	Colon	4	2.6 (0.7–6.5)

TABLE 7-7 Colon and Rectal Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Blair et al., 1983	Florida pesticide applicators—mortality		
	Colon	5	0.8 (nr)
	Rectum	2	nr
Forestry Workers			**Herbicides**
Alavanja et al., 1989	USDA forest or soil conservationists—mortality		
	Colon	44	1.5(1.1–2.0)
	Rectum	9	1.0 (0.5–1.9)
Reif et al., 1989	New Zealand forestry workers—nested case–control (incidence)		
	Colon	7	0.5 (0.2–1.1)
	Small intestine	2	5.2 (1.4–18.9)
	Rectum	10	1.2 (0.6–2.3)
Paper and Pulp Workers			**Dioxins**
McLean et al., 2006	IARC cohort of pulp and paper workers—mortality		
	Ever exposed to nonvolatile organochlorine compounds		
	Colon	62	0.7 (0.6–1.0)
	Rectum	60	0.9 (0.7–1.1)
Rix et al., 1998	Danish paper-mill workers—incidence		
	Men		
	Colon	58	1.0 (0.7–1.2)
	Rectum	43	0.9 (0.6–1.2)
	Women		
	Colon	23	1.1 (0.7–1.7)
	Rectum	15	1.5 (0.8–2.4)
Henneberger et al., 1989	New Hampshire pulp and paper workers—mortality		
	Colon	9	1.0 (0.5–2.0)
	Rectum	1	0.4 (0.0–2.1)
Solet et al., 1989	US pulp and paper workers—mortality		
	Colon	7	1.5 (0.6–3.0)
Robinson et al., 1986	Northwestern US pulp and paper workers		
	Intestines (ICD-7 152, 153)	7	0.4 (0.2–0.7)
Other Occupational Studies			**Herbicides**
Lo et al., 2010	Egyptian case–control study		
	Colorectal cancer	nr	5.5 (2.4–12.3)
Thomas, 1987	US flavor and fragrance chemical plant workers exposed to 2,4,5-T, TCDD		**Dioxin, 2,4,5-T**
	Colon	4	0.6 (nr)
	Rectum	6	2.5 (nr)

continued

TABLE 7-7 Colon and Rectal Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Hardell, 1981	Swedish residents—incidence		**Phenoxy acid and chlorophenils**
	Colon		
	Exposed to phenoxy acids	11	1.3 (0.6–2.8)
	Exposed to chlorophenols	6	1.8 (0.6–5.3)
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Consonni et al., 2008	Seveso residents—25-yr follow-up—men, women		
	Zone A		
	Colon	3	1.0 (0.3–3.0)
	Rectum	1	0.9 (0.1–6.4)
	Zone B		
	Colon	12	0.6 (0.3–1.1)
	Rectum	11	1.5 (0.8–2.8)
	Zone R		
	Colon	137	0.9 (0.7–1.3)
	Rectum	50	0.9 (0.7–1.3)
Pesatori et al., 2009	Seveso—20-yr follow-up to 1996—incidence (men and women, combined)		
	Zone A		
	Colon	2	0.7 (0.2–2.7)
	Rectum	0	
	Zone B		
	Colon	19	1.0 (0.7–1.6)
	Rectum	17	1.8 (1.1–2.9)
	Zone R		
	Colon	137	1.0 (0.9–1.3)
	Rectum	71	1.1 (0.8–1.4)
Bertazzi et al., 2001	Seveso residents—20-yr follow-up—mortality		
	Zones A, B—men		
	Colon	10	1.0 (0.5–1.9)
	Rectum	9	2.4 (1.2–4.6)
	Zones A, B—men		
	Colon	5	0.6 (0.2–1.4)
	Rectum	3	1.1 (0.4–3.5)

TABLE 7-7 Colon and Rectal Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Bertazzi et al., 1997	Seveso residents—15-yr follow-up—mortality		
	Zone A—women		
	Colon	2	2.6 (0.3–9.4)
	Zone B—men		
	Colon	5	0.8 (0.3–2.0)
	Rectum	7	2.9 (1.2–5.9)
	Zone B—women		
	Colon	3	0.6 (0.1–1.8)
	Rectum	2	1.3 (0.1–4.5)
	Zone R—men		
	Colon	34	0.8 (0.6–1.1)
	Rectum	19	1.1 (0.7–1.8)
	Zone R—women		
	Colon	33	0.8 (0.6–1.1)
	Rectum	12	0.9 (0.5–1.6)
Bertazzi et al., 1993	Seveso residents—10-yr follow-up—morbidity		
	Zone B—men		
	Colon	2	0.5 (0.1–2.0)
	Rectum	3	1.4 (.04–4.4)
	Zone B—women		
	Colon	2	0.6 (0.1–2.3)
	Rectum	2	1.3 (0.3–5.4)
	Zone R—men		
	Colon	32	1.1 (0.8–1.6)
	Rectum	17	1.1 (0.7–1.9)
	Zone R—women		
	Colon	23	0.8 (0.5–1.3)
	Rectum	7	0.6 (.03–1.3)
Pesatori et al., 1992	Seveso residents—incidence		
	Zones A, B—men		
	Colon	3	0.6 (0.2–1.9)
	Rectum	3	1.2 (0.4–3.8)
	Zones A, B—women		
	Colon	3	0.7 (0.2–2.2)
	Rectum	2	1.2 (0.3–4.7)
Bertazzi et al., 1989a	Seveso residents—10-yr follow-up—mortality		
	Zones A, B, R—men		
	Colon	20	1.0 (0.6–1.5)
	Rectum	10	1.0 (0.5–2.7)
	Zones A, B, R—women		
	Colon	12	0.7 (0.4–1.2)
	Rectum	7	1.2 (0.5–2.7)
Bertazzi et al., 1989b	Seveso residents—10-yr follow-up—mortality		
	Zone B—men		
	Rectum	2	1.7 (0.4–7.0)

continued

TABLE 7-7 Colon and Rectal Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Chapaevsk, Russia Cohort			
Revich et al., 2001	Residents of Chapaevsk, Russia—mortality		
	Men		
	Colon	17	1.3 (0.8–2.2)
	Rectum	21	1.5 (1.0–2.4)
	Women		
	Colon	24	1.0 (0.7–1.5)
	Rectum	24	0.9 (0.6–1.4)
Other Environmental Studies			
Turunen et al., 2008	Finnish fishermen and spouses		**Serum dioxin**
	Fishermen		*SMRs*
	Colon	8	0.5 (0.2–1.0)
	Rectum and anus	8	0.8 (0.4–1.6)
	Spouses		
	Colon	10	1.3 (0.6–2.4)
	Rectum and anus	8	2.1 (0.9–4.2
Svensson et al., 1995	Swedish fishermen—mortality (men and women)		**Organochlorine compounds**
	East coast		
	Colon	1	0.1 (0.0–0.7)
	Rectum	4	0.7 (0.2–1.9)
	West coast		
	Colon	58	1.0 (0.8–1.3)
	Rectum	31	1.0 (0.7–1.5)
	Swedish fishermen—incidence (men and women)		
	East coast		
	Colon	5	0.4 (0.1–0.9)
	Rectum	9	0.9 (0.4–1.6)
	West coast		
	Colon	82	1.0 (0.8–1.2)
	Rectum	59	1.1 (0.8–1.4)
Lampi et al., 1992	Finnish community exposed to chlorophenol contamination—incidence		**Chlorophenols**
	Colon—men, women	9	1.1 (0.7–1.8)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TP, 2-(2,4,5-trichlorophenoxy) propionic acid; AFHS, Air Force Health Study; AHS, Agricultural Health Study; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; MCPA, methyl-4-chlorophenoxyacetic acid; MI, Michigan; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; NZ, New Zealand; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; USDA, US Department of Agriculture; VA, US Department of Veterans Affairs; WV, West Virginia.

[a]Subjects are male, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies No studies of exposure to the chemicals of interest and colorectal cancer in Vietnam veterans have been published since *Update 2008*.

Occupational Studies Two occupational-cohort studies have been updated since *Update 2008*. Collins et al. (2008, 2009a,b) published a series of papers examining the mortality experience of workers employed in a Dow Chemical Company in Midland, Michigan, from 1937 to 1980. Serum dioxin was evaluated to estimate exposures to five dioxins in a group of 98 workers (Collins et al., 2008). Although the serum dioxin, furan, and PCB concentrations were measured many years after exposure, distinct patterns of dioxin congeners were found in workers who had different chlorophenol exposures. Collins et al. (2009a) examined 1,615 workers who had been exposed to TCP production. The mean duration of follow-up was 36.4 years. Some 18 cases of cancer of the large intestine were observed, for an SMR of 1.2 (95% CI 0.7–1.8); two cases of rectal cancer were observed, for an SMR of 0.6 (95% CI 0.1–2.1). Collins et al. (2009b) also described the mortality experience of 773 workers who were exposed to chlorinated dioxins in the production of PCP. SMRs were calculated to compare the PCP workers with the general US population and with that of Michigan. There were 10 observed deaths from cancer of the large intestine (SMR = 1.2, 95% CI 0.6–2.3) and 1 death from cancer of the rectum (SMR = 0.5; 95% CI 0.0–2.9).

The second occupational-cohort follow-up study was that of workers in the Dow AgroSciences plant in New Plymouth, New Zealand, who were potentially exposed to TCDD (McBride et al., 2009a,b). Workers employed during the period from January 1969 to November 1988 (when 2,4,5-T was no longer produced at the work sites) were followed to the end of 2004, and SMRs were calculated by using national mortality figures. In McBride et al. (2009a), the SMR for large intestine–cancer deaths was 0.6 (95% CI 0.1–1.7) in workers exposed to TCDD and 0.0 (95% CI 0.0–2.0) in the never-exposed group. The SMR for rectal-cancer deaths was 2.0 (95% CI 0.7–4.4) in exposed workers and 2.1 (95% CI 0.3–7.7) in nonexposed workers. The SMRs for large intestine and rectal cancer according to estimated effective cumulative exposure to TCDD were not calculated; however, no trend was observed for all cancers of the digestive organs and peritoneum. The results in McBride et al. (2009b) have not been included, because they were diluted by inclusion of a set of workers who had no opportunity for TCDD exposure and no observed deaths.

Lo et al. (2010) published a case–control study of 421 Egyptian cases of colorectal carcinoma and 439 hospital-matched controls. Histories of lifestyle, occupational, and reproductive factors were obtained with questionnaires. A history of pesticide exposure was significantly associated with a higher risk of

colorectal carcinoma (odds ratio [OR] = 2.6, 95% CI 1.1–5.9). Among 73 subjects who reported farming as their longest lifetime occupation, self-reported exposure to herbicides was associated with increased risk of colorectal cancer (adjusted OR = 5.5, 95% CI 2.4–12.3). Information on specific types of herbicides was not obtained.

Environmental Studies Colon-cancer cases were reported in the cancer-incidence study of the population (males and females combined) exposed to dioxin after the Seveso accident in 1976 (Pesatori et al., 2009). Two colon cancers were observed in Zone A (high exposure) (RR = 0.68, 95% CI 0.17–2.72); 19 in Zone B (medium exposure) (RR = 1.04, 95% CI 0.66–1.64), and 137 in Zone R (low exposure) (RR = 1.04, 95% CI 0.87–1.26). Rectal-cancer cases were reported separately. No rectal-cancer cases were observed in Zone A, 17 in Zone B (RR = 1.78, 95% CI 1.09–2.88), and 71 in Zone R (RR = 1.05, 95% CI 0.82–1.35).

A second environmental study was published by Turumen et al. (2008), who assessed the mortality experience of fishermen (registered since 1980) and fishermen's wives in Finland, presuming that their mortality reflected their high consumption of contaminated fish. SMRs for the 6,410 fishermen and 4,260 wives were calculated on the basis of national mortality figures. The investigators had previously compared fish consumption and serum dioxin level in fishermen and their wives with those in control populations and found that consumption of fish and serum dioxin were higher in the fishermen and their wives. The fishermen and their wives were also more likely to be obese. Mortality from colon cancer was not increased in the study cohort (SMR = 0.52, 95% CI 0.23–1.03 in fishermen; SMR = 1.30, 95% CI 0.62–2.39 in fishermen's wives). Mortality from rectal and anal cancers also was not increased (SMR = 0.82, 95% CI 0.35–1.60 in fishermen; SMR = 2.13, 95% CI 0.92–4.19 in fishermen's wives).

Biologic Plausibility

Long-term animal studies have examined the effect of exposure to the chemicals of interest on tumor incidences (Charles et al., 1996; Stott et al., 1990; Walker et al., 2006; Wanibuchi et al., 2004). No increase in the incidence of colorectal cancer in laboratory animals exposed to the chemicals of interest has been reported.

The biologic plausibility of the carcinogenicity of the chemicals of interest is discussed in general at the beginning of this chapter.

Synthesis

The epidemiologic studies reviewed yielded no evidence that suggested an association between the chemicals of interest and colorectal cancer. There is no evidence of biologic plausibility of an association between exposure to any of the

chemicals of interest and tumors of the colon or rectum. Overall, the available evidence does not support an association between the chemicals of interest and colorectal cancer.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and colorectal cancer.

Hepatobiliary Cancers

Hepatobiliary cancers include cancers of the liver (ICD-9 155.0, 155.2) and the intrahepatic bile duct (ICD-9 155.1). ACS estimated that 17,430 men and 6,690 women would receive diagnoses of liver cancer or intrahepatic bile duct cancer in the United States in 2010 and that 12,720 men and 6,190 women would die from these cancers (Jemal et al., 2010). Gallbladder cancer and extrahepatic bile duct cancer (ICD-9 156) are fairly uncommon and are often grouped with liver cancers when they are addressed.

In the United States, liver cancers account for about 1.5% of new cancer cases and 3.3% of cancer deaths. Misclassification of metastatic cancers as primary liver cancer can lead to overestimation of the number of deaths attributable to liver cancer (Percy et al., 1990). In developing countries, especially those in sub-Saharan Africa and Southeast Asia, liver cancers are common and are among the leading causes of death. Known risk factors for liver cancer include chronic infection with hepatitis B or hepatitis C virus and exposure to the carcinogens aflatoxin and vinyl chloride. Alcohol cirrhosis and obesity-associated metabolic syndrome may also contribute to the risk of liver cancer. In the general population, the incidence of liver and intrahepatic bile duct cancer increases slightly with age; at the ages of 50–64 years, it is greater in men than in women and greater in blacks than in whites. The average annual incidence of hepatobiliary cancers is shown in Table 7-4.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the chemicals of interest and hepatobiliary cancers. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008* did not change that conclusion.

Table 7-8 summarizes the results of the relevant studies.

TABLE 7-8 Selected Epidemiologic Studies—Hepatobiliary Cancer

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans			**All COIs**
AFHS, 2000	Air Force Ranch Hand veterans—incidence	2	1.6 (0.2–11.4)
US CDC Vietnam Experience Study			
Boehmer et al., 2004	Follow-up of CDC Vietnam Experience Cohort (liver, intrahepatic bile ducts [ICD-9 155])	5	nr
CDC, 1990a	US men born 1921–1953—incidence	8	1.2 (0.5–2.7)
US VA Mortality Study of Army and Marine Veterans			**All COIs**
Breslin et al., 1988	Army Vietnam veterans (liver, bile duct)	34	1.0 (0.8–1.4)
	Marine Vietnam veterans (liver, bile duct)	6	1.2 (0.5–2.8)
State Studies of US Vietnam Veterans			**All COIs**
Anderson et al., 1986	Wisconsin Vietnam veterans	0	nr
Australian Vietnam Veterans vs Australian Population			
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence	27	
	Navy	8	1.0 (0.4–1.9)
	Army	18	0.7 (0.4–1.1)
	Air Force	1	0.2 (0.0–1.2)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—mortality (liver, gallbladder)	48	0.9 (0.6–1.1)
	Navy	11	1.0 (0.5–1.7)
	Army	33	0.9 (0.6–1.2)
	Air Force	4	0.6 (0.2–1.5)
CDVA, 1997a	Australian military Vietnam veterans		
	Liver (ICD-9 155)	8	0.6 (0.2–1.1)
	Gallbladder (ICD-9 156)	5	1.3 (0.4–2.8)
Australian Conscripted Army National Service (deployed vs nondeployed)			**All COIs**
ADVA, 2005c	Australian male conscripted Army National Service Vietnam-era veterans: deployed vs nondeployed		
	Incidence	2	2.5 (0.1–147.2)
	Mortality (liver, gallbladder)	4	2.5 (0.4–27.1)
CDVA, 1997b	Australian National Service Vietnam veterans	1	nr
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			**Dioxin, phenoxy herbicides**
Kogevinas et al., 1997	IARC cohort, male and female workers exposed to any phenoxy herbicide or chlorophenol	15	0.7 (0.4–1.2)
	Exposed to highly chlorinated PCDDs	12	0.9 (0.5–1.5)
	Not exposed to highly chlorinated PCDDs	3	0.4 (0.1–1.2)

TABLE 7-8 Hepatobiliary Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
Saracci et al., 1991	IARC cohort—exposed subcohort (men and women)		
	Liver, gallbladder, bileduct (ICD-8 155–156)	4	0.4 (0.1–1.1)
NIOSH Mortality Cohort (12 US plants, production 1942–1984) (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Steenland et al., 1999	US chemical production workers		
	Liver, biliary tract (ICD-9 155–156)	7	0.9 (0.4–1.6)
Fingerhut et al., 1991	NIOSH—entire cohort (liver, biliary tract)—	6	1.2 (0.4–2.5)
	≥ 1-yr exposure, ≥ 20-yr latency	1	0.6 (0.0–3.3)
BASF Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Ott and Zober, 1996	BASF employees—incidence	2	2.1 (0.3–7.5)
	Liver, gallbladder, and bile duct		
	TCDD < 0.1 µg/kg of body weight	1	2.8 (0.1–15.5)
	TCDD 0.1–0.99 µg/kg of body weight	0	0.0 (0.0–15.4)
	TCDD ≥ 1 µg/kg of body weight	1	2.8 (0.1–15.5)
Dow Chemical Company—Midland, MI (included in IARC and NIOSH cohorts)			**Dioxin, phenoxy herbicides**
Collins et al., 2009a	Trichlorophenol workers	2	0.5 (0.1–1.6)
Collins et al., 2009b	Pentachlorophenol workers	0	0.0 (0.0–1.7)
Ramlow et al., 1996	Dow pentachlorophenol production workers		
	Liver, primary (ICDA-8 155–156)		
	0-yr latency	0	nr
	15-yr latency	0	nr
Bond et al., 1988	Dow 2,4-D production workers		
	Liver, biliary tract (ICDA-8 155–156)	0	1.2 (nr)
Monsanto Plant in Nitro, WV (included in IARC and NIOSH cohorts)			**Dioxin, phenoxy herbicides**
Collins et al., 1993	Monsanto Company 2,4-D production workers		
	Liver, biliary tract	2	1.4 (0.2–5.2)
Zack and Suskind, 1980	Monsanto Company production workers	0	nr
Danish Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Lynge, 1985	Danish production workers—incidence		
	Men	3	1.0 (nr)
	Women	0	nr
German Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Becher et al., 1996	German production workers		
	Liver and biliary tract	1	1.2 (0.0–6.9)

continued

TABLE 7-8 Hepatobiliary Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)			**Dioxin, phenoxy herbicides**
McBride et al., 2009a	1,599 production workers (male and female) vs national rates—mortality 1969 through 2004		
	Ever	2	1.4 (0.2–5.1)
	Never	0	0.0 (0.0–8.2)
't Mannetje et al., 2005	New Zealand phenoxy herbicide workers (ICD-9 155)		
	Producers (men and women)	1	1.6 (0.0–8.8)
	Sprayers (> 99% men)	0	0.0 (0.0–4.2)
Agricultural Health Study			**Herbicides**
Alavanja et al., 2005	US AHS—incidence		
	Liver		
	Private applicators (men and women)	35	1.0 (0.7–1.4)
	Spouses of private applicators (> 99% women)	3	0.9 (0.2–2.5)
	Commercial applicators (men and women)	nr	0.0 (0.0–4.2)
	Gallbladder		
	Private applicators (men and women)	8	2.3 (1.0–4.5)
	Spouses of private applicators (> 99% women)	3	0.9 (0.2–2.5)
	Commercial applicators (men and women)	nr	0.0 (0.0–35.8)
Blair et al., 2005a	US AHS		
	Liver		
	Private applicators (men and women)	8	0.6 (0.2–1.1)
	Spouses of private applicators (> 99% women)	4	1.7 (0.4–4.3)
	Gallbladder		
	Private applicators (men and women)	3	2.0 (0.4–5.7)
	Spouses of private applicators (> 99% women)	2	1.3 (0.1–4.6)
Other Agricultural Workers			**Herbicides**
Gambini et al., 1997	Italian rice growers	7	1.3 (0.5–2.6)
Blair et al., 1993	US farmers in 23 states		
	White men	326	1.0 (0.9–1.1)
	White women	6	0.7 (0.3–1.6)
Wiklund, 1983	Swedish male and female agricultural workers—incidence		*99% CI*
	Liver (primary)	103	0.3 (0.3–0.4)
	Biliary tract	169	0.6 (0.5–0.7)
	Liver (unspecified)	67	0.9 (0.7–1.3)
Other Studies of Herbicide and Pesticide Applicators			**Herbicides**
Torchio et al., 1994	Italian licensed pesticide users		
	Liver	15	0.6 (0.3–0.9)

TABLE 7-8 Hepatobiliary Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Swaen et al., 2004	Dutch licensed herbicide applicators	0	nr
Asp et al., 1994	Finnish herbicide applicators—liver, biliary tract		
	Incidence	3	0.9 (0.2–2.6)
	Mortality	2	0.6 (0.1–2.2)
Ronco et al., 1992	Danish farm workers—incidence		
	Liver		
	Men—self-employed	23	0.4 ($p < 0.05$)
	employees	9	0.8 (nr)
	Women—family workers	5	0.5 (nr)
	Gallbladder		
	Men—self-employed	35	0.8 (nr)
	employees	7	0.8 (nr)
	Women—self-employed	7	2.7 ($p < 0.05$)
	employees	1	0.7 (nr)
	family workers	17	1.0 (nr)
Forestry Workers			**Herbicides**
Reif et al., 1989	New Zealand forestry workers—nested case–control—incidence		
	Liver	1	0.8 (0.1–5.8)
	Gallbladder	3	4.1 (1.4–12.0)
Paper and Pulp Workers			**Dioxins**
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	27	0.9 (0.6–1.3)
	Ever	16	0.7 (0.4–1.1)
Rix et al., 1998	Danish paper-mill workers—incidence		
	Liver—men	10	1.1 (0.5–2.0)
	women	1	0.6 (0.0–3.2)
	Gallbladder—men	9	1.6 (0.7–3.0)
	women	4	1.4 (0.4–3.7)
Solet et al., 1989	US pulp and paper workers (ICD-8 155–156)	2	2.0 (0.2–7.3)
Other Occupational Studies			**Phenoxy acids, chlorophenols**
Hardell et al., 1984	Swedish residents—incidence, mortality combined	102	1.8 (0.9–4.0)

continued

TABLE 7-8 Hepatobiliary Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Consonni et al., 2008	Seveso residents—25-yr follow-up—men, women		
	Liver (ICD-9 155)		
	Zone A	3	1.0 (0.3–3.2)
	Zone B	16	0.9 (0.5–1.4)
	Zone R	107	0.8 (0.7–1.0)
	Biliary tract (ICD-9 156)		
	Zone A	0	0.0 (nr)
	Zone B	2	0.6 (0.1–2.3)
	Zone R	31	1.2 (0.8–1.7)
Pesatori et al., 2009	Seveso—20-yr follow-up to 1996—incidence (men and women, combined)		
	Zone A		
	Liver	0	
	Biliary tract	0	
	Zone B		
	Liver	14	1.3 (0.8–2.2)
	Biliary tract	6	2.3 (1.0–5.2)
	Zone R		
	Liver	56	0.7 (0.6–1.0)
	Biliary tract	16	0.8 (0.5–1.4)
Bertazzi et al., 2001	Seveso residents—20-yr follow-up		
	Zone A, B—men (liver, gallbladder)	6	0.5 (0.2–1.0)
	(liver)	6	0.5 (0.2–1.1)
	women (liver, gallbladder)	7	1.0 (0.5–2.2)
	(liver)	6	1.3 (0.6–2.9)
Bertazzi et al., 1997	Seveso residents—15-yr follow-up		
	Zone B—men (liver, gallbladder)	4	0.6 (0.2–1.4)
	(liver)	4	0.6 (0.2–1.6)
	women (liver, gallbladder)	4	1.1 (0.3–2.9)
	(liver)	3	1.3 (0.3–3.8)
	Zone R—men (liver, gallbladder)	35	0.7 (0.5–1.0)
	(liver)	31	0.7 (0.5–1.0)
	women (liver, gallbladder)	25	0.8 (0.5–1.3)
	(liver)	12	0.6 (0.3–1.1)
Bertazzi et al., 1993	Seveso residents—10-yr follow-up—incidence		
	Zone B—men (liver)	4	2.1 (0.8–5.8)
	(gallbladder—ICD-9 156)	1	2.3 (0.3–17.6)
	women (gallbladder—ICD-9 156)	4	4.9 (1.8–13.6)
	Zone R—men (liver)	3	0.2 (0.1–0.7)
	(gallbladder—ICD-9 156)	3	1.0 (0.3–3.4)
	women (liver)	2	0.5 (0.1–2.1)
	(gallbladder—ICD-9 156)	7	1.0 (0.5–2.3)

TABLE 7-8 Hepatobiliary Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Pesatori	Seveso residents—incidence		
et al., 1992	Zone A, B—men (liver)	4	1.5 (0.5–4.0)
	(gallbladder—ICD-9 156)	1	2.1 (0.3–15.6)
	women (liver)	1	1.2 (0.2–9.1)
	(gallbladder—ICD-9 156)	5	5.2 (2.1–13.2)
	Zone R—men (liver)	8	0.5 (0.2–0.9)
	(gallbladder—ICD-9 156)	3	1.0 (0.3–3.4)
	women (liver)	5	0.8 (0.3–2.1)
	(gallbladder—ICD-9 156)	7	1.0 (0.5–2.3)
Bertazzi	Seveso residents—10-yr follow-up		
et al., 1989b	Zone A—women (gallbladder—ICD-9 156)	1	12.1 (1.6–88.7)
	Zone B—men (liver)	3	1.2 (0.4–3.8)
	women (gallbladder—ICD-9 156)	2	3.9 (0.9–16.2)
	Zone R—men (liver)	7	0.4 (0.2–0.8)
	women (liver)	3	0.4 (0.1–1.4)
	(gallbladder—ICD-9 156)	5	1.2 (0.5–3.1)
Quail Run Cohort			**TCDD**
Hoffman	Residents of Quail Run Mobile Home Park	0	nr
et al., 1986	(men and women)		
Other Environmental Studies			
Svensson	Swedish fishermen (men and		**Organochlorine**
et al., 1995	women)—mortality		**compounds**
	East coast	1	0.5 (0.0–2.7)
	West coast (liver, bile ducts)	9	0.9 (0.4–1.7)
	Swedish fishermen (men and women)—incidence		
	East coast	6	1.3 (0.5–2.9)
	West coast (liver, bile ducts)	24	1.0 (0.6–1.5)
Cordier	Risk factors for hepatocellular carcinoma in		**Herbicides**
et al., 1993	Hanoi, Vietnam		
	Military service in South Vietnam for ≥ 10 years after 1960	11	8.8 (1.9–41.0)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; AHS, Agricultural Health Study; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; ICDA, International Classification of Diseases, Adapted for Use in the United States; MI, Michigan; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; NZ, New Zealand; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; VA, US Department of Veterans Affairs; WV, West Virginia.

[a]Subjects are male, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies No studies of exposure to the chemicals of interest and hepatobiliary cancer in Vietnam veterans have been published since *Update 2008*.

Occupational Studies Two occupational-cohort follow-up studies have been published since *Update 2008*. Collins et al. (2008, 2009a,b) published a series of papers examining the mortality experience of workers employed in a Dow Chemical Company in Midland, Michigan, from 1937 to 1980. Collins et al. (2009b) described the mortality experience of 773 workers who were exposed to chlorinated dioxins in the production of PCP; 75% of the cohort have been followed for more than 27 years. SMRs were calculated to compare the PCP workers with the general US population and the population of the state of Michigan. There were no observed deaths from cancer of the hepatobiliary tract. In a companion paper, the authors examined 1,615 workers who had been exposed to TCP production (Collins et al., 2009a). The mean duration of follow-up was 36.4 years. Two cases of cancer of the hepatobiliary tract were observed, for an SMR of 0.5 (95% CI 0.1–1.6).

The second occupational mortality study was of workers in the Dow AgroSciences plant in New Plymouth, New Zealand, who were potentially exposed to TCDD (McBride et al., 2009a,b). Workers employed during the period from January 1969 to November 1988 (when 2,4,5-T was no longer produced at the work sites) were followed to the end of 2004, and SMRs were calculated by using national mortality figures. McBride et al. (2009a) found that the SMR for hepatobiliary cancer deaths was 1.4 (95% CI 0.2–5.1) in exposed workers and 0.0 (95% CI 0.0–8.2) in the never-exposed group. The results of McBride et al. (2009b) have not been included, because they were diluted by inclusion of a set of workers who had no opportunity for TCDD exposure and no observed deaths.

Environmental Studies Hepatobiliary cancer was reported in the cancer-incidence study of the population (males and females combined) exposed to dioxin after the Seveso accident in 1976 (Pesatori et al., 2009). No liver-cancer cases were observed in Zone A (high exposure), 14 cases in Zone B (medium exposure) (RR = 1.29, 95% CI 0.76–2.20), and 56 in Zone R (low exposure) (RR = 0.74, 95% CI 0.56–0.97). Bilary-cancer cases were reported separately. No biliary cases were observed in Zone A, 6 in Zone B (RR = 2.28, 95% CI 1.00–5.17), and 16 in Zone R (RR = 0.82, 95% CI 0.49–1.39).

Biologic Plausibility

Long-term animal studies have examined the effect of exposure to the chemicals of interest on tumor incidences (Charles et al., 1996; Stott et al., 1990; Walker

et al., 2006; Wanibuchi et al., 2004). Studies performed in laboratory animals have consistently demonstrated that long-term exposure to TCDD results in the formation of liver adenomas and carcinomas (Knerr and Schrenk, 2006; Walker et al., 2006). Furthermore, TCDD increases the growth of hepatic tumors that are initiated by treatment with a complete carcinogen, and pathologic liver changes have been observed after exposure to TCDD, including nodular hyperplasia and massive inflammatory cell infiltration (Kociba et al., 1978; NTP, 2006; Walker et al., 2006; Yoshizawa et al., 2007). Inflammation and cancer are strongly intertwined in the development and progression of many cancers, including liver cancers (Mantovani et al., 2008). Similarly, in monkeys treated with TCDD, hyperplasia and an increase in cells that stain positive for alpha-smooth muscle actin have been observed (Korenaga et al., 2007). Postive staining for alpha-smooth muscle actin is thought to be indicative of a process (epithelial–mesenchymal transition) that is associated with the progression of malignant tumors (Weinberg, 2008).

With respect to cancers of the bile duct, bile duct hyperplasia (but not tumors) has been reported (Knerr and Schrenk, 2006; Walker et al., 2006; Yoshizawa et al., 2007). Similarly, monkeys treated with TCDD developed metaplasia, hyperplasia, and hypertrophy of the bile duct (Allen et al., 1977). Hollingshead et al. (2008) showed that TCDD-activated AHR in human breast and endocervical cell lines induces sustained high concentrations of the IL-6 cytokine, which has tumor-promoting effects in numerous tissues, including cholangiocytes. Thus TCDD might promote carcinogenesis in biliary tissue.

TCDD may contribute to tumor progression by inhibiting p53 regulation (phosphorylation and acetylation) triggered by genotoxicants via the increased expression of the metastasis marker AGR2 (Ambolet-Camoit et al., 2010) and through a functional interaction between the AHR and FHL2 (Kollara and Brown, 2009). The AHR was also shown to be a regulator of c-raf and propose cross-talk between the AHR and the mitogen-activated protein kinase signaling pathway in chemically induced hepatocarcinogenesis (Borlak and Jenke, 2008). TCDD inhibits UV-C radiation-induced apoptosis in primary rat hepatocytes and Huh-7 human hepatoma cells, and this supports the hypothesis that TCDD acts as a tumor-promoter by preventing initiated cells from undergoing apoptosis (Chopra et al., 2009).

In rodents, TCDD may promote hepatocarcinogenesis by cytotoxicity, chronic inflammation, and liver regeneration and by hyperplastic and hypertrophic growth due to sustained activation of the AHR (Köhle et al., 2008). Species differences associated with AHR activation are supported by the divergence in the transcriptomic responses to TCDD in mouse, rat, and human liver (Boutros et al., 2008, 2009; Carlson et al., 2009; Kim et al., 2009), but it should be noted that these in vitro human hepatocyte studies may not reflect the in vivo response of human liver to TCDD. In vitro studies with transformed cell-line and primary hepatocytes cannot replicate the complexity of a tissue response that is important in eliciting the toxic responses observed in vivo (Dere et al., 2006).

The biologic plausibility of the carcinogenicity of the chemicals of interest is discussed in general at the beginning of this chapter.

Synthesis

The isolated finding of a barely significant increase in mortality from biliary cancer in the intermediate-exposure zone at Seveso does not establish a consistent pattern of increased risk for biliary cancer. Despite the evidence of TCDD's activity as a hepatocarcinogen in animals, the evidence from epidemiologic studies remains inadequate to link the chemicals of interest with hepatobiliary cancer, which has a relatively low incidence in Western populations.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and hepatobiliary cancer.

Pancreatic Cancer

The incidence of pancreatic cancer (ICD-9 157) increases with age. ACS estimated that 21,370 men and 21,770 women would receive a diagnosis of pancreatic cancer in the United States in 2010 and that 18,770 men and 18,030 women would die from it (Jemal et al., 2010). The incidence is higher in men than in women and higher in blacks than in whites. Other risk factors include family history, diet, and tobacco use; the incidence is about twice as high in smokers as in nonsmokers (Miller et al., 1996). Chronic pancreatitis, obesity, and type 2 diabetes are also associated with an increased risk of pancreatic cancer (ACS, 2006). The average annual incidence of pancreatic cancers is shown in Table 7-4.

Conclusions from *VAO* and Previous Updates

Update 2006 considered pancreatic cancer independently for the first time. Prior updates developed tables of results for pancreatic cancer but reached conclusions about the adequacy of the evidence of its association with herbicide exposure in the context of gastrointestinal tract cancers. The committee responsible for *VAO* concluded that there was limited or suggestive evidence of *no* association between exposure to the herbicides used by the US military in Vietnam and gastrointestinal tract tumors, including pancreatic cancer. The committee responsible for *Update 2006* concluded that there was not enough evidence on each of the chemicals of interest to sustain that negative conclusion for any of the cancers in the gastrointestinal group and that, because these various types of cancer are generally regarded as separate disease entities, the evidence on each

should be evaluated separately. Pancreatic cancer was thus reclassified into the default category of inadequate or insufficient evidence of an association. The *Update 2006* committee reviewed the increased rates of pancreatic cancer in Australian National Service Vietnam veterans but concluded that the increased rates could be attributed to the rates of smoking in the cohort (ADVA, 2005c). The committee also noted the report of increased rates of pancreatic cancer in US female Vietnam nurse veterans (Dalager et al., 1995). That increase persisted in the follow-up study of the American female veterans (Cypel and Kang, 2008) considered in *Update 2008*, but the update on mortality in the Seveso population (Consonni et al., 2008) did not support an association with pancreatic cancer.

Table 7-9 summarizes the results of the relevant studies concerning pancreatic cancer.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies No studies of exposure to the chemicals of interest and pancreatic cancer in Vietnam veterans have been published since *Update 2008*.

Occupational Studies Collins et al. (2008, 2009a,b) published a series of papers on the mortality experience of workers employed in a Dow Chemical Company in Midland, Michigan, from 1937 to 1980. Serum dioxin was evaluated to estimate exposures to five dioxins in a group of 98 workers (Collins et al., 2008). Although the serum dioxin, furan, and PCB concentrations were measured many years after exposure, distinct patterns of dioxin congeners were found in workers who had different chlorophenol exposures. Collins et al. (2009b) described the mortality experience of 773 workers who were exposed to chlorinated dioxins in the production of PCP. Some 75% of the cohort have been followed for more than 27 years. SMRs were calculated to compare the PCP workers with the general US population and the population of the state of Michigan. There were five observed deaths from pancreatic cancer (SMR 1.1, 95% CI 0.3–2.5). In a companion paper, the authors examined 1,615 workers who had been exposed to TCP production (Collins et al., 2009a). The mean duration of follow-up was 36.4 years. Six deaths from pancreatic cancer were observed, for an SMR of 0.7 (95% CI 0.2–1.4).

McBride et al. (2009a,b) conducted an occupational mortality study of workers in the Dow AgroSciences plant in New Plymouth, New Zealand, who were potentially exposed to TCDD. Workers employed during the period from January 1969 to November 1988 (when 2,4,5-T was no longer produced at the work sites) were followed to the end of 2004, and SMRs were calculated by using national mortality figures. McBride et al. (2009a) found the SMR for pancreatic-cancer deaths was 0.3 (95% CI 0.13–3.39) in exposed workers and 0.0 (95% CI 0.0–4.9) in the never-exposed group. The results in McBride et al. (2009b) have not been included, because they were diluted by inclusion of a set of workers who had no opportunity for TCDD exposure and no observed deaths.

TABLE 7-9 Selected Epidemiologic Studies—Pancreatic Cancer

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US CDC Vietnam Experience Study			
Boehmer et al., 2004	Mortality (1965–2000) Follow-up of CDC Vietnam Experience Cohort	5	1.0 (0.3–3.5)
US VA Mortality Study of Army and Marine Veterans—Ground troops serving July 4, 1965–March 1, 1973			**All COIs**
Breslin et al., 1988	Army Vietnam veterans	82	0.9 (0.6–1.2)
	Marine Vietnam veterans	18	1.6 (0.5–5.8)
US VA Cohort of Female Vietnam Veterans			**All COIs**
Cypel and Kang, 2008	Mortality through 2004 US Vietnam veterans—women	17	2.1 (1.0–4.5)
	Vietnam-veteran nurses	14	2.5 (1.0–6.0)
Dalager et al., 1995	Mortality through 1991 US Vietnam veterans—women	7	2.8 (0.8–10.2)
	Vietnam-veteran nurses	7	5.7 (1.2–27.0)
Thomas et al., 1991	Mortality through 1987 US Vietnam veterans—women	5	2.7 (0.9–6.2)
State Studies of US Vietnam Veterans			**All COIs**
Visintainer et al., 1995	PM study of deaths (1974–1989) of Michigan Vietnam-era veterans—deployed vs nondeployed	14	1.0 (0.6–1.7)
	Non-black	9	0.7 (0.3–1.3)
	Black	5	9.1 (2.9–21.2)
Anderson et al., 1986	Wisconsin Vietnam veterans	4	nr
Australian Vietnam Veterans vs Australian Population			**All COIs**
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence	86	1.2 (0.9–1.4)
	Navy	14	0.9 (0.5–1.5)
	Army	60	1.2 (0.9–1.5)
	Air Force	12	1.3 (0.7–2.3)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—mortality	101	1.2 (1.0–1.5)
	Navy	18	1.0 (0.6–1.6)
	Army	71	1.3 (1.0–1.6)
	Air Force	11	1.1 (0.5–1.8)
CDVA, 1997a	Australian military Vietnam veterans	38	1.4 (0.9–1.8)
Australian Conscripted Army National Service (deployed vs nondeployed)			**All COIs**
ADVA, 2005c	Australian male conscripted Army National Service Vietnam-era veterans: deployed vs nondeployed		
	Incidence	17	2.5 (1.0–6.3)
	Mortality	19	3.1 (1.3–8.3)

TABLE 7-9 Pancreatic Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
CDVA, 1997b	Australian National Service Vietnam veterans	6	1.5 (nr)
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			**Dioxin, phenoxy herbicides**
Kogevinas et al., 1997	IARC cohort, male and female workers exposed to any phenoxy herbicide or chlorophenol	47	0.9 (0.7–1.3)
	Exposed to highly chlorinated PCDDs	30	1.0 (0.7–1.4)
	Not exposed to highly chlorinated PCDDs	16	0.9 (0.5–1.4)
Saracci et al., 1991	IARC cohort—exposed subcohort (males, females)	26	1.1 (0.7–1.6)
NIOSH Mortality Cohort (12 US plants, production 1942–1984) (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Steenland et al., 1999	US chemical production workers	16	1.0 (0.6–1.6)
Fingerhut et al., 1991	NIOSH—entire cohort	10	0.8 (0.4–1.6)
	≥ 1-yr exposure, ≥ 20-yr latency	4	1.0 (0.3–2.5)
Dow Chemical Company—Midland, MI (included in IARC and NIOSH cohorts)			**Dioxin, phenoxy herbicides**
Collins et al., 2009a	Trichlorophenol workers	6	0.7 (0.2–1.4)
Collins et al., 2009b	Pentachlorophenol workers	5	1.1 (0.3–2.5)
Ramlow et al., 1996	Dow pentachlorophenol production workers		
	0-yr latency	2	0.7 (0.1–2.7)
	15-yr latency	2	0.9 (0.1–3.3)
Danish Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Lynge, 1985	Danish production workers—incidence		
	Men	3	0.6 (nr)
	Women	0	nr
Dutch Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Boers et al., 2010	Dutch chlorophenoxy workers		
	Factory A	4	0.9 (0.2–4.2)
	Factory B	1	nr
Hooiveld et al., 1998	Dutch chemical production workers	4	2.5 (0.7–6.3)
Bueno de Mesquita et al., 1993	Dutch phenoxy herbicide workers	3	2.2 (0.5–6.3)

continued

TABLE 7-9 Pancreatic Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
German Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Becher et al., 1996	German production workers		
	Plant I	2	0.6 (0.1–2.3)
	Plant II	0	nr
	Plant III	0	nr
	Plant IV	2	1.7 (0.2–6.1)
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)			**Dioxin, phenoxy herbicides**
McBride et al., 2009a	1,599 production workers (male and female) vs national rates—mortality 1969 through 2004		
	Ever	3	1.3 (0.3–3.9)
	Never	0	0 (0.0–4.9)
't Mannetje et al., 2005	Phenoxy herbicide producers (men and women)	3	2.1 (0.4–6.1)
	Phenoxy herbicide sprayers (> 99% men)	0	0.0 (0.0–2.1)
United Kingdom Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Coggon et al., 1986	British MCPA production workers	9	0.7 (0.3–1.4)
Agricultural Health Study			**Herbicides**
Andreotti et al., 2009	AHS nested case–control (applicators and spouses combined)		
	2,4-D	48	0.9 (0.5–1.5)
	Dicamba	23	0.9 (0.6–1.6)
Alavanja et al., 2005	US AHS—incidence		
	Private applicators (men and women)	46	0.7 (0.5–1.0)
	Spouses of private applicators (> 99% women)	20	0.9 (0.6–1.4)
	Commercial applicators (men and women)	3	1.1 (0.2–3.2)
Blair et al., 2005a	US AHS		
	Private applicators (men and women)	29	0.6 (0.4–0.9)
	Spouses of private applicators (> 99% women)	10	0.7 (0.3–1.2)
Other Agricultural Workers			**Herbicides**
Gambini et al., 1997	Italian rice growers	7	0.9 (0.4–1.9)
Blair et al., 1993	US farmers in 23 states		
	White men	1,133	1.1 (1.1–1.2)
	White women	23	1.0 (0.6–1.5)
Ronco et al., 1992	Danish farm workers—incidence		
	Men—self-employed	137	0.6 ($p < 0.05$)
	employees	23	0.6 ($p < 0.05$)
	Women—self-employed	7	1.2 (nr)
	employees	4	1.3 (nr)
	family workers	27	0.7 ($p < 0.05$)

TABLE 7-9 Pancreatic Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Alavanja et al., 1988	USDA agricultural extension agents	21	1.3 (0.8–1.9)
Wiklund, 1983	Swedish male and female agricultural workers—incidence	777	*99% CI* 0.8 (0.8–0.9)
Burmeister, 1981	Iowa farmers	416	1.1 (nr)
Other Studies of Herbicide and Pesticide Applicators			**Herbicides**
Swaen et al., 2004	Dutch licensed herbicide applicators	5	1.2 (0.4–2.7)
Torchio et al., 1994	Italian licensed pesticide users	32	0.7 (0.5–1.0)
Swaen et al., 1992	Dutch licensed herbicide applicators	3	2.2 (0.4–6.4)
Blair et al., 1983	Florida pesticide applicators		*Expected exposed cases*
		4	4.0
Forestry Workers			**Herbicides**
Alavanja et al., 1989	USDA forest, soil conservationists	22	1.5 (0.9–2.3)
Reif et al., 1989	New Zealand forestry workers—nested case–control—incidence	6	1.8 (0.8–4.1)
Paper and Pulp Workers			**Dioxins**
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	67	0.8 (0.7–1.1)
	Ever	69	1.1 (0.9–1.4)
Rix et al., 1998	Danish paper-mill workers—incidence		
	Men	30	1.2 (0.8–1.7)
	Women	2	0.3 (0.0–1.1)
Henneberger et al., 1989	New Hampshire paper and pulp workers	9	1.9 (0.9–3.6)
Solet et al., 1989	US pulp and paper workers	1	0.4 (0.0–2.1)
Robinson et al., 1986	Northwestern US paper and pulp workers		*90% CI*
		4	0.3 (0.1–0.8)
Other Occupational Studies			
Magnani et al., 1987	UK case–control		**Herbicides and chlorophenols**
	Herbicides	nr	0.7 (0.3–1.5)
	Chlorophenols	nr	0.8 (0.5–1.4)
Thomas, 1987	US flavor and fragrance chemical plant workers	6	**Dioxin, 2,4,5-T** 1.4 (nr)

continued

TABLE 7-9 Pancreatic Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Consonni et al., 2008	Seveso residents (men and women)—25-yr follow-up		
	Zone A	2	1.2 (0.3–4.7)
	Zone B	5	0.5 (0.2–1.1)
	Zone R	76	1.0 (0.7–1.7)
Pesatori et al., 2009	Seveso—20-yr follow-up to 1995—incidence		
	Zone A	1	1.2 (0.2–8.2)
	Zone B	3	0.6 (0.2–1.7)
	Zone R	38	1.0 (0.7–1.4)
Bertazzi et al., 2001	Seveso residents—20-yr follow-up		
	Zones A, B—men	4	0.7 (0.3–1.9)
	women	1	0.3 (0.0–2.0)
Bertazzi et al., 1997	Seveso residents—15-yr follow-up		
	Zone A—men	1	1.9 (0.0–10.5)
	Zone B—men	2	0.6 (0.1–2.0)
	women	1	0.5 (0.0–3.1)
	Zone R—men	20	0.8 (0.5–1.2)
	women	11	0.7 (0.4–1.3)
Pesatori et al., 1992	Seveso residents—incidence		
	Zones A, B—men	2	1.0 (0.3–4.2)
	women	1	1.6 (0.2–12.0)
Bertazzi et al., 1989a	Seveso residents—10-yr follow-up		
	Zones A, B, R—men	9	0.6 (0.3–1.2)
	women	4	1.0 (0.3–2.7)
Bertazzi et al., 1989b	Seveso residents—10-yr follow-up		
	Zone B—men	2	1.1 (0.3–4.5)
Other Environmental Studies			
Svensson et al., 1995	Swedish fishermen (men and women)—mortality		**Organochlorine compounds**
	East coast	5	0.7 (0.2–1.6)
	West coast	33	0.8 (0.6–1.2)
	Swedish fishermen (men and women)—incidence		
	East coast	4	0.6 (0.2–1.6)
	West coast	37	1.0 (0.7–1.4)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; AHS, Agricultural Health Study; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; MCPA, methyl-4-chlorophenoxyacetic acid; MI, Michigan; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; NZ, New Zealand; PCDD, polychlorinated dibenzo-p-dioxin (highly chlorinated, if four or more chlorines); PM, proportionate mortality; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; UK United Kingdom; USDA, US Department of Agriculture; VA, Department of Veterans Affairs.

[a]Subjects are male, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

Andreotti et al. (2009) published a nested case–control study of pancreatic cancer in the AHS cohort. The analysis included 93 incident pancreatic-cancer cases—64 applicators (two female) and 29 spouses (all female)—and more than 82,000 controls. Applicators and their spouses had similar risks of pancreatic cancer, so risk estimates were shown for both combined. Exposure to 13 pesticides was examined, including two chemicals of interest: 2,4-D and dicamba. There were 48 cases of pancreatic cancer in the group exposed to 2,4-D (OR = 0.9, 95% CI 0.5–1.5) and 23 cases in the group exposed to dicamba (OR = 0.9, 95% CI 0.6–1.6); age, diabetes, and smoking were adjusted for. Results were also shown for intensity-weighted lifetime days of pesticide use and pancreatic-cancer risk. No statistically significant associations were seen for the two chemicals of interest.

Boers et al. (2010) published the third set of follow-up results of a retrospective cohort study of two Dutch chlorophenoxy herbicide manufacturing factories, producing mainly 2,4,5-T (factory A) and MCPA, MCPP, and 2,4-D (factory B). The cohort consisted of all persons who worked in either of the two factories during 1955–1985 (factory A) or 1965–1986 (factory B). No increases in pancreatic-cancer deaths were observed. The hazard ratio (HR) in factory A was 0.86 (95% CI 0.18–4.19). One case of pancreatic cancer was observed in factory B in exposed workers and none in controls.

Environmental Studies Pancreatic-cancer cases were reported in the cancer-incidence study of the population (males and females combined) exposed to dioxin after the Seveso accident in 1976 (Pesatori et al., 2009). One pancreatic-cancer case was observed in Zone A (high exposure) (RR = 1.15, 95% CI 0.16–8.19), 3 in Zone B (medium exposure) (RR = 0.56, 95% CI 0.18–1.74), and 38 in Zone R (low exposure) (RR = 0.99, 95% CI 0.70–1.40).

Biologic Plausibility

Long-term animal studies have examined the effect of exposure to the chemicals of interest on tumor incidence (Charles et al., 1996; Stott et al., 1990; Walker et al., 2006; Wanibuchi et al., 2004). No increase in the incidence of pancreatic cancer in laboratory animals after the administration of cacodylic acid, 2,4-D, or picloram has been reported. A 2-year study of female rats has reported increased incidences of pancreatic adenomas and carcinomas after treatment at the highest dose of TCDD (100 ng/kg per day) (Nyska et al., 2004). Other studies have observed chronic active inflammation, acinar-cell vacuolation, and an increase in proliferation of the acinar cells surrounding the vacuolated cells (Yoshizawa et al., 2005b). As previously discussed, both chronic inflammation and hyperproliferation are closely linked to the formation and progression of cancers, including that of the pancreas (Hahn and Weinberg, 2002; Mantovani et al., 2008). Metaplastic changes in the pancreatic ducts were also observed in female monkeys treated with TCDD (Allen et al., 1977).

The biologic plausibility of the carcinogenicity of the chemicals of interest is discussed in general at the beginning of this chapter.

Synthesis

The large excess of pancreatic cancers in female Vietnam veterans vs their nondeployed counterparts observed by Thomas et al. (1991) and Dalager et al. (1995) prevailed in a study by Cypel and Kang (2008), who found a significant increase in all female Vietnam veterans and in the nurse subset. The committee responsible for *Update 2006* reported a higher incidence of and mortality from pancreatic cancer in deployed Australian National Service veterans than in nondeployed veterans (ADVA, 2005c). A limitation of all the veteran studies considered has been the lack of control for the effect of smoking. For the 31 female and 62 male cases in the AHS case–control study considered in the present update (Andreotti et al., 2009), however, the risk of pancreatic cancer was not associated with 2,4-D exposure. No increase in risk has been reported in US male Vietnam veterans or in IARC follow-up studies.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and pancreatic cancer.

LARYNGEAL CANCER

ACS estimated that 10,110 men and 2,610 women would receive diagnoses of cancer of the larynx (ICD-9 161) in the United States in 2010 and that 2,870 men and 730 women would die from it (Jemal et al., 2010). Those numbers constitute a little more than 0.9% of new cancer diagnoses and 0.7% of cancer deaths. The incidence of cancer of the larynx increases with age, and it is more common in men than in women, with a sex ratio in the United States of about 4:1 in people 50–64 years old. The average annual incidence of laryngeal cancer is shown in Table 7-10.

Established risk factors for laryngeal cancer are tobacco use and alcohol use, which are independent and act synergistically. Occupational exposures—long and intense exposures to wood dust, paint fumes, and some chemicals used in the metalworking, petroleum, plastics, and textile industries—also could increase risk (ACS, 2007b). An Institute of Medicine committee concluded that asbestos is a causal factor in laryngeal cancer (IOM, 2006); infection with human papilloma virus is also thought to raise the risk of laryngeal cancer (Baumann et al., 2009; Hobbs and Birchall, 2004).

TABLE 7-10 Average Annual Incidence (per 100,000) of Laryngeal Cancer in United States[a]

	55–59 Years Old			60–64 Years Old			65–69 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Men	13.0	12.0	27.1	18.9	17.8	40.1	26.8	26.4	51.2
Women	3.0	2.9	6.2	4.0	4.1	6.3	6.2	6.1	12.4

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2004–2008 (NCI, 2010).

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was limited or suggestive evidence of an association between exposure to at least one of the chemicals of interest and laryngeal cancer on the basis of the evidence discussed below in the section "Synthesis." Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008* did not change that conclusion.

Table 7-11 summarizes the results of the relevant studies.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

No Vietnam-veteran studies addressing exposure to the chemicals of interest and laryngeal cancer have been published since *Update 2008*.

Occupational Studies

Collins et al. (2009a) reported on the mortality experience through 2003 of a group of workers in the Midland, Michigan, Dow Chemical plant previously included in analyses of the NIOSH mortality cohort, as reported by Fingerhut et al. (1991) and added to the expanded IARC phenoxy herbicide cohort (Kogevinas et al., 1997). In the updated analysis completed by Dow-employed epidemiologists, three laryngeal-cancer deaths were reported, and this led to estimated nonsignificant SMRs of 1.3 (95% CI 0.3–3.9) in all TCP workers and 1.5 (95% CI 0.3–4.4) when 196 workers who had some PCP exposure were excluded. As pointed out in follow-up correspondence (Collins et al., 2010; Villeneuve and Steenland, 2010), different latency models, different dose–response models, and in-depth analysis of serum exposure concentrations could alter some of the results reported in the analysis, but there were only three deaths from laryngeal cancer, so these issues are unlikely to affect the laryngeal-cancer risk estimates appreciably.

TABLE 7-11 Selected Epidemiologic Studies—Laryngeal Cancer

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans			**All COIs**
AFHS, 2000	AFHS veterans—incidence		
	Oral cavity, pharynx, larynx	4	0.6 (0.2–2.4)
US CDC Vietnam Experience Study			**All COIs**
Boehmer et al., 2004	CDC Vietnam Experience Cohort	0	0.0 (nr)
US VA Mortality Study of Army and Marine Veterans (ground troops serving July 4, 1965–March 1, 1973)			**All COIs**
Watanabe and Kang, 1996	Army Vietnam veterans compared with US men (follow-up through 1988)	50	1.3 (nr)
	Marine Vietnam veterans	4	0.7 (nr)
	Army Vietnam veterans	50	1.4 ($p < 0.05$)
Australian Vietnam Veterans vs Australian Population			**All COIs**
ADVA, 2005a	Australian Vietnam veterans vs Australian population—incidence	97	1.5 (1.2–1.8)
	Navy	21	1.5 (0.9–2.1)
	Army	69	1.6 (1.2–1.9)
	Air Force	7	0.8 (0.3–1.7)
ADVA, 2005b	Australian Vietnam veterans vs Australian population—mortality	28	1.1 (0.7–1.5)
	Navy	6	1.1 (0.4–2.4)
	Army	19	1.1 (0.7–1.7)
	Air Force	3	0.9 (0.2–2.5)
CDVA, 1997a	Australian military Vietnam veterans	12	1.3 (0.7–2.2)
Australian Conscripted Army National Service (deployed vs nondeployed)			**All COIs**
ADVA, 2005c	Australian men conscripted Army National Service Vietnam-era veterans: deployed vs nondeployed		
	Incidence	8	0.7 (0.2–1.6)
	Mortality	2	0.4 (0.0–2.4)
CDVA, 1997b	Australian National Service Vietnam veterans	0	0 (0– > 10)
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			**Dioxin, phenoxy herbicides**
Kogevinas et al., 1997	IARC cohort, male and female workers exposed to any phenoxy herbicide or chlorophenol	21	1.6 (1.0–2.5)
	Exposed to highly chlorinated PCDDs	15	1.7 (1.0–2.8)
	Not exposed to highly chlorinated PCDDs	5	1.2 (0.4–2.9)
Saracci et al., 1991	IARC cohort (men and women)—exposed subcohort	8	1.5 (0.6–2.9)

TABLE 7-11 Laryngeal Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
NIOSH Mortality Cohort (12 US plants, production 1942–1984) (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Fingerhut et al., 1991	NIOSH—entire cohort	7	2.1 (0.8–4.3)
	≥ 1-yr exposure, ≥ 20-yr latency	3	2.7 (0.6–7.8)
Dow Chemical Company—Midland, MI (included in IARC and NIOSH cohorts)			**Dioxin, phenoxy herbicides**
Collins et al., 2009a	Trichlorophenol workers	3	1.3 (0.3–3.9)
Collins et al., 2009b	Pentachlorophenol workers	2	1.7 (0.2–6.2)
Ramlow et al., 1996	Dow pentachlorophenol production workers	2	2.9 (0.3–10.3)
	0-yr latency	2	2.9 (0.4–10.3)
	15-yr latency	1	nr
Bond et al., 1988	Dow 2,4-D production workers	1	3.0 (0.0–16.8)
German Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Manz et al., 1991	German production workers—men, women	2	2.0 (0.2–7.1)
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)			**Dioxin, phenoxy herbicides**
McBride et al., 2009a	1,599 production workers (male and female) vs national rates—mortality 1969 through 2004	1	2.5 (0.1–14.0)
't Mannetje et al., 2005	New Zealand phenoxy herbicide producers, sprayers—mortality		
	Phenoxy herbicide producers (men and women)	0	nr
	Phenoxy herbicide sprayers (> 99% men)	0	nr
United Kingdom Production Workers (included in IARC cohort)			
Coggon et al., 1986	British MCPA production workers	4	1.7 (0.5–4.5)
Herbicide and Pesticide Applicators			**Herbicides**
Swaen et al., 2004	Dutch licensed herbicide applicators	1	1.0 (0.0–5.1)
Torchio et al., 1994	Italian farmers licensed to use pesticides	25	0.5 (0.3–0.7)
Agricultural Workers			**Herbicides**
Gambini et al., 1997	Italian rice growers	7	0.9 (0.4–1.9)
Blair et al., 1993	US farmers in 23 states		
	White men	162	0.7 (0.6–0.8)
	White women	0	nr (0.0–3.3)

continued

TABLE 7-11 Laryngeal Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
Forestry Workers			**Herbicides**
Thörn et al., 2000	Swedish lumberjacks exposed to phenoxyacetic herbicides		
	Foremen—incidence	0	nr
Reif et al., 1989	New Zealand forestry workers—nested case–control—incidence	2	1.1 (0.3–4.7)
Paper and Pulp Workers			**Dioxins**
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine chemicals		
	Never	18	0.9 (0.5–1.5)
	Ever	20	1.2 (0.8–1.9)
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Consonni et al., 2008	Seveso residents (men and women)—25-yr follow-up—all respiratory cancers (ICD-9 160–165) excluding reported lung cancers (ICD-9 162)		
	Zone A	0	nr
	Zone B	≤ 8	nr
	Zone R	≤ 49	nr
Bertazzi et al., 2001	Seveso residents (men and women)—20-yr follow-up—all respiratory cancers (ICD-9 160–165) excluding reported lung cancers (ICD-9 162)		
	Zone A	0	nr
	Zone B	8	nr
Bertazzi et al., 1998	Seveso residents—15-yr follow-up—all respiratory cancers (ICD-9 160–165) excluding reported lung cancers (ICD-9 162)		
	Zone B—men	6	nr
	women	0	nr
	Zone R—males	32	nr
	women	6	nr
Chapaevsk, Russia			**Dioxin**
Revich et al., 2001	Residents of Chapaevsk, Russia		
	Men	13	2.3 (1.2–3.8)
	Women	1	0.1 (0.0–0.6)

ABBREVIATIONS: AFHS, Air Force Health Study; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; MCPA, methyl-4-chlorophenoxyacetic acid; MI, Michigan; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; NZ, New Zealand; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; VA, US Department of Veterans Affairs.

[a]Subjects are male, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

Collins et al. (2009b) also reported on mortality in 773 Dow employees in Midland who were exposed to dioxins in the manufacture of PCP. They reported an estimated nonsignificant excess of laryngeal cancer with an SMR of 1.7 (95% CI 0.2–6.2) or, when they excluded 196 workers who had TCP exposure, 2.2 (95% CI 0.3–8.1). Again, those estimates were based on only two deaths from laryngeal cancer, so the study did not have sufficient power to support a strong inference on causality.

McBride et al. (2009a,b) studied mortality through 2004 in 1,599 Dow employees of an agricultural manufacturing plant in New Zealand that produced phenoxy herbicides and picloram. The cohort also was included in the original IARC Cohort of Phenoxy Herbicide Workers (Saracci et al., 1991). There were crude exposure estimates in this study and only one death from laryngeal cancer. When mortality from laryngeal cancer in ever-exposed workers was compared with New Zealand national death rates, the SMR was a nonsignificant 2.5 (0.1–14.0). The study was too small to be useful for establishing an etiologic role of the chemicals of interest. The results in McBride et al. (2009b) have not been included, because they were diluted by inclusion of a set of workers who had no opportunity for TCDD exposure and no observed deaths.

Environmental Studies

Turunen et al. (2008) studied fishermen's health in Finland, including in their assessment of mortality exposure to dioxins and PCBs by using assessment of serum and adipose tissue from a set of the study participants. They reported a deficit of laryngeal, tracheal, and lung cancers. It is difficult to interpret those results given the small numbers and the unknown effects of the diet high in fish that was probably consumed by the subjects.

Biologic Plausibility

Long-term animal studies have examined the effect of exposure to the chemicals of interest on tumor incidence (Charles et al., 1996; Stott et al., 1990; Walker et al., 2006; Wanibuchi et al., 2004). No increase in the incidence of laryngeal cancer in laboratory animals after the administration of any of the chemicals of interest has been reported.

The biologic plausibility of the carcinogenicity of the chemicals of interest is discussed in general at the beginning of this chapter.

Synthesis

The original *VAO* committee reviewed five studies that presented data separately for laryngeal cancer (Bond et al., 1988; Coggon et al., 1986; Fingerhut et al., 1991; Manz et al., 1991; Sarracci et al., 1991). That committee concluded

that "although the numbers are too small to draw strong conclusions, the consistency of a mild elevation in relative risk is suggestive of an association for laryngeal cancer." The original *VAO* committee also noted that the studies reviewed for laryngeal cancer did not control for potential confounders, such as smoking and alcohol consumption (IOM, 1994).

Since then, a combined analysis of many of the separate cohorts has been conducted (the IARC Cohort of Phenoxy Herbicide Workers analyzed by Kogevinas et al., 1997) and has shown significant effects in workers exposed to any phenoxyacetic acid herbicide or chlorophenol (RR = 1.6, 95% CI 1.0–2.5; 21 deaths), especially workers exposed to TCDD (or higher-chlorinated dioxins) (RR = 1.7, 95% CI 1.0–2.8; 15 deaths). Those RRs are remarkably close to the pooled estimate computed by the committee responsible for *VAO*. The study by Kogevinas et al. was a high-quality study that used an excellent method for assessing exposure, and its results were unlikely to have been affected by confounding, because the distribution of smoking in working cohorts is not likely to differ with degree of exposure (Siemiatycki et al., 1988). Another IARC cohort that was used in studying pulp and paper workers also showed an increase in risk (RR = 1.2, 95% CI 0.8–1.9; 20 deaths; McLean et al., 2006).

With regard to veteran studies, a positive association was found in the study of veterans in Australia that compared mortality from laryngeal cancer with that in the general population (ADVA, 2005a) but not in the study that compared Australian veterans of the Vietnam conflict with nondeployed soldiers (ADVA, 2005c). In contrast, Watanabe and Kang (1996) found a significant 40% excess of mortality from laryngeal cancer in Army personnel deployed to the Vietnam theater. The Ranch Hand study is not large enough to have sufficient power to detect an association if one exists.

An environmental study (Revich et al., 2001) of residents of Chapaevsk, Russia, which was heavily contaminated by many industrial pollutants, including dioxin, showed an association with laryngeal cancer in men (RR = 2.3, 95% CI 1.2–3.8).

The committee for *Update 2008* extensively reviewed and discussed the literature as part of its reassessment of all health outcomes. The additional data reviewed for the present update (the updated mortality study of Dow chemical workers) are largely consistent with the prior work, reporting a nonsignificant excess of laryngeal cancer. Although some 10% of laryngeal cancers now being diagnosed are associated with HPV, the small fraction is unlikely to have a substantial effect on studies over time.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is limited or suggestive evidence of an association between exposure to at least one chemical of interest and laryngeal cancer.

LUNG CANCER

Lung cancer (carcinoma of the lung or bronchus, ICD-9 162.2–162.9) is the leading cause of cancer death in the United States. ACS estimated that 116,750 men and 105,770 women would receive diagnoses of lung cancer in the United States in 2010 and that about 86,220 men and 71,080 women would die from it (Jemal et al., 2010). Those numbers represent roughly 15% of new cancer diagnoses and 28% of cancer deaths in 2010. The principal types of lung neoplasms are identified collectively as bronchogenic carcinoma and carcinoma of the lung. Cancer of the trachea (ICD-9 162) is often grouped with cancer of the lung and bronchus under ICD-9 162. The lung is also a common site of metastatic tumors.

In men and women, the incidence of lung cancer increases greatly beginning at about the age of 40 years. The incidence in people 50–54 years old is double that in people 45–49 years old, and it doubles again in those 55–59 years old. The incidence is consistently higher in black men than in women or white men. The average annual incidence of lung cancer in the United States is shown in Table 7-12.

ACS estimates that 87% of lung-cancer deaths are attributable to cigarette-smoking (ACS, 2011a). Smoking increases the risk of all histologic types of lung cancer, but the associations with squamous-cell and small-cell carcinomas are strongest. Other risk factors include exposure to asbestos, uranium, vinyl chloride, nickel chromates, coal products, mustard gas, chloromethyl ethers, gasoline, diesel exhaust, and inorganic arsenic. The latter statement does not imply that cacodylic acid, which is a metabolite of inorganic arsenic, can be assumed to be a risk factor. Important environmental risk factors include exposure to tobacco smoke and radon (ACS, 2007c).

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was limited or suggestive evidence of an association between exposure to at least one chemical of interest and lung cancer on the basis of the evidence discussed below in the section "Synthesis." Additional information available to the committees responsible

TABLE 7-12 Average Annual Incidence (per 100,000) of Lung and Bronchial Cancer in United States[a]

	55–59 Years Old			60–64 Years Old			65–69 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Men	101.8	95.1	179.8	182.0	175.1	299.8	308.5	301.4	475.4
Women	75.2	75.5	98.1	144.8	150.6	163.3	230.3	242.1	248.3

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2004–2008 (NCI, 2010).

for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008* did not change that conclusion.

Table 7-13 summarizes the results of the relevant studies.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

The mortality experience of the ACC veterans, who were responsible for handling and spraying herbicides around the perimeters of military base camps in Vietnam, was updated through 2005 by Cypel and Kang (2010). Vital status (through 1991) had last been reported in 1997 (Dalager and Kang, 1997). The new analysis abstracted records from some 18,000 Army personnel with chemical operations experience to create cohorts that had Vietnam experience (2,872) and did not have Vietnam experience (2,737). There were 593 deaths in the Vietnam cohort and 355 in the non-Vietnam cohort. It classified lung cancer with all cancers of the "respiratory system." There were 60 observed respiratory-cancer deaths in the Vietnam group and 26 in the non-Vietnam group, for a crude rate ratio of 2.22 and an adjusted relative risk of 1.29 (95% CI 0.79–2.10) for respiratory cancer. Compared with those in the US male population, the SMRs for respiratory cancers were significantly higher at 1.35 (95% CI 1.03–1.73) in the Vietnam cohort and 1.01 (95% CI 0.66–1.48) in the non-Vietnam veterans. The study did not have data on tobacco use, but questionnaire responses collected in 1999–2000 from a subset of ACC veterans who had documented exposure to herbicides used in theater showed that adjustment for the patterns of cigarette use did not affect their higher risk estimates for respiratory disease. The follow-up is long enough to allow for extended latency and to account for selection of healthy soldiers to apply these agents.

Occupational Studies

In an updated analysis of the mortality experience of a group of workers in the Midland, Michigan, Dow chemical plant previously studied by NIOSH as part of data reported in 1991 (Fingerhut et al., 1991), Collins et al. (2009a) found no excess lung cancer in 1,615 workers exposed to dioxin in TCP production. There were 46 deaths attributable to bronchial, lung, and tracheal cancers (SMR = 0.7, 95% CI 0.5–0.9) in all TCP workers and 41 deaths (SMR = 0.7, 95% CI 0.5–1.0) when 196 workers who had some PCP exposure were excluded. As pointed out in follow-up correspondence (Collins et al., 2010; Villeneuve and Steenland, 2010), different latency models, different dose–response models, and in-depth analysis of the serum exposure concentrations might alter some of the results reported.

Collins et al. (2009b) also reported on mortality in 773 Dow employees in Midland, Michigan, who were exposed to dioxins in the manufacture of PCP.

TABLE 7-13 Selected Epidemiologic Studies—Lung and Bronchus Cancer

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans			**All COIs**
Pavuk et al., 2005	Comparison subjects only from AFHS (respiratory system)—incidence		
	Serum TCDD (pg/g) based on model with exposure variable $\log_e$(TCDD)		
	Per unit increase of -$\log_e$(TCDD) (pg/g)	36	1.7 (0.9–3.2)
	Quartiles (pg/g)		
	0.4–2.6	6	1.0 (nr)
	2.6–3.8	8	1.1 (0.3–3.4)
	3.8–5.2	9	1.2 (0.4–3.5)
	> 5.2	13	1.9 (0.7–5.5)
	Number of years served in SEA		
	Per year of service	36	1.1 (0.9–1.2)
	Quartiles (years in SEA)		
	0.8–1.3	8	1.0 (nr)
	1.3–2.1	4	0.5 (0.2–1.8)
	2.1–3.7	11	0.7 (0.3–2.0)
	3.7–16.4	13	0.7 (0.3–2.0)
Akhtar et al., 2004	White AFHS subjects vs national rates (respiratory system)		
	Ranch Hand veterans		
	Incidence	33	1.1 (0.8–1.6)
	With tours between 1966–1970	26	1.1 (0.7–1.6)
	Mortality	21	0.9 (0.6–1.3)
	Comparison veterans		
	Incidence	48	1.2 (0.9–1.6)
	With tours 1966–1970	37	1.2 (0.9–1.6)
	Mortality	38	1.1 (0.8–1.5)
AFHS, 2000	Ranch Hand veterans from AFHS (lung and bronchus)—incidence	10	3.7(0.8–17.1)
US VA Cohort of Army Chemical Corps			**All COIs**
Cypel and Kang, 2010	ACC—deployed vs nondeployed and vs US men (Vietnam-service status through 2005)		
	Respiratory system		
	Deployed vs nondeployed	60 vs 26	1.3 (0.8–2.1)
	ACC vs US men		
	ACC Vietnam Cohort	60	1.4 (1.0–1.7)
	Non-Vietnam Cohort (no service in SEA)	26	1.0 (0.7–1.5)
Dalager and Kang, 1997	ACC veterans (respiratory system)—mortality	11	1.4 (0.4–5.4)
US CDC Vietnam Experience Study			**All COIs**
Boehmer et al., 2004	Follow-up of CDC Vietnam Experience Cohort (trachea, bronchus, and lung)	41	1.0 (0.6–1.5)
	Low pay grade at time of discharge	nr	1.6 (0.9–3.0)

continued

TABLE 7-13 Lung and Bronchus Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
US VA Marine Post Service Mortality Study (all Marines active 1967–1969)			**All COIs**
Watanabe and Kang, 1995	Marine Vietnam service vs non-Vietnam (lung)	42	1.3 (0.8–2.1)
US VA Mortality Study of Army and Marine Veterans (Ground troops serving July 4, 1965–March 1, 1973)			**All COIs**
Watanabe and Kang, 1996	US Army and Marine Corps Vietnam veterans (lung)—mortality		
	Army Vietnam service	1,139	1.1 (nr) ($p < 0.05$)
	Non-Vietnam	1,141	1.1 (nr) ($p < 0.05$)
	Marine Vietnam service	215	1.2 (1.0–1.3)
	Non-Vietnam	77	0.9 (nr)
US VA Cohort of Female Vietnam Veterans			**All COIs**
Cypel and Kang, 2008	US Vietnam veterans—women (lung)	50	1.0 (0.7–1.4)
	Vietnam veteran nurses	35	0.8 (0.5–1.2)
Australian Vietnam Veterans vs Australian General Population			**All COIs**
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence	576	1.2 (1.1–1.3)
	Branch of service		
	Navy	141	1.4 (1.2–1.7)
	Army	372	1.2 (1.1–1.3)
	Air Force	63	1.0 (0.7–1.2)
	Histologic type—all service branches combined		
	Adenocarcinoma	188	1.5 (1.2–1.7)
	Squamous	152	1.2 (1.0–1.4)
	Small-cell	87	1.2 (0.97–1.5)
	Large-cell	79	1.1 (0.8–1.3)
	Other	70	1.1 (0.8–1.3)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—mortality	544	1.2 (1.1–1.3)
	Branch of service		
	Navy	135	1.4 (1.2–1.6)
	Army	339	1.1 (1.0–1.3)
	Air Force	71	1.1 (0.9–1.4)
AIHW, 1999	Australian Vietnam veterans—(lung cancer)—incidence (validation study)		*Expected number of exposed cases (95% CI)*
		46	65 (49–81)
CDVA, 1998a	Australian Vietnam veterans (lung)—incidence	120	65 (49–89)
CDVA, 1997a	Australian Vietnam veterans		
	Lung (ICD-9 162)	212	1.3 (1.1–1.4)
	Respiratory systems (ICD-9 163–165)	13	1.8 (1.0–3.0)

TABLE 7-13 Lung and Bronchus Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
Australian Conscripted Army National Service (deployed vs unemployed)			**All COIs**
ADVA, 2005c	Australian male conscripted Army National Service Vietnam-era veterans: deployed vs nondeployed		
	Incidence (1982–2000)	78	1.2 (1.0–1.5)
	Histologic type		
	Adenocarcinoma	27	1.4 (0.8–1.9)
	Squamous	19	1.5 (0.9–2.3)
	Small-cell	14	1.4 (0.8–2.4)
	Large-cell	8	0.7 (0.3–1.3)
	Other	10	1.2 (0.6–2.2)
	Mortality (1966–2001)	67	1.8 (1.2–2.7)
CDVA, 1997b	Australian National Service Vietnam veterans (lung)—mortality	27	2.2 (1.1–4.3)
State Studies of US Vietnam Veterans			**All COIs**
Mahan et al., 1997	Case–control of Vietnam-era Vietnam veterans (lung)—incidence	134	1.4 (1.0–1.9)
Visintainer et al., 1995	PM study of deaths (1974–1989) of Michigan Vietnam-era veterans—deployed vs nondeployed (lung)	80	0.9 (0.7–1.1)
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			**Dioxin, phenoxy herbicides**
Kogevinas et al., 1997	IARC cohort, male and female workers exposed to any phenoxy herbicide or chlorophenol		
	Lung (ICD-9 162)	380	1.1 (1.0–1.2)
	Other respiratory organs (ICD-9 163–165)	12	2.3 (1.2–3.9)
	Exposed to highly chlorinated PCDDs		
	Lung (ICD-9 162)	225	1.1 (1.0–1.3)
	Other respiratory organs (ICD-9 163–165)	9	3.2 (1.5–6.1)
	Not exposed to highly chlorinated PCDDs		
	Lung (ICD-9 162)	148	1.0 (0.9–1.2)
	Other respiratory organs (ICD-9 163–165)	3	1.2 (0.3–3.6)
Saracci et al., 1991	IARC cohort, men, women—mortality		
	Trachea, bronchus, lung	173	1.0 (0.9–1.2)
NIOSH Mortality Cohort (12 US plants, production 1942–1984) (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Steenland et al., 1999	US chemical production workers—mortality		
	Lung	125	1.1 (0.9–1.3)

continued

TABLE 7-13 Lung and Bronchus Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Fingerhut et al., 1991	NIOSH workers exposed to TCDD—mortality		
	Entire cohort		
	Trachea, bronchus, lung (ICD-9 162)	89	1.1 (0.9–1.4)
	Respiratory system (ICD-9 160–165)	96	1.1 (0.9–1.4)
	≥ 1-yr exposure, ≥ 20-yr latency		
	Trachea, bronchus, lung (ICD-9 162)	40	1.4 (1.0–1.9)
	Respiratory system (ICD-9 160–165)	43	1.4 (1.0–1.9)
Dow Production Workers—Midland, MI (included in IARC and NIOSH cohorts)			**Dioxin, phenoxy herbicides**
Collins et al., 2009a	Trichlorophenol workers		
	Cancers of the bronchus, trachea, and lung	46	0.7 (0.5–0.9)
Collins et al., 2009b	Pentachlorophenol workers		
	Cancers of the bronchus, trachea, and lung	30	1.0 (0.6–1.4)
Bodner et al., 2003	Dow chemical production workers—mortality		
	Lung	54	0.8 (0.6–1.1)
Burns et al., 2001	Dow 2,4-D production workers—mortality		
	Respiratory system (ICD-8 160–163)	31	0.9 (0.6–1.3)
Ramlow et al., 1996	Dow pentachlorophenol production workers—mortality		
	0-yr latency		
	Respiratory system (ICD-8 160–163)	18	1.0 (0.6–1.5)
	Lung (ICD-8 162)	16	0.9 (0.5–1.5)
	15-yr latency		
	Respiratory system (ICD-8 160–163)	17	1.1 (0.6–1.8)
	Lung (ICD-8 162)	16	1.1 (0.6–1.8)
Bloemen et al., 1993	Dow 2,4-D production workers		
	Respiratory system (ICD-8 162–163)	9	0.8 (0.4–1.5)
Bond et al., 1988	Dow 2,4-D production workers—mortality		
	Lung (ICD-8 162–163)	8	1.0 (0.5–2.0)
	Respiratory (ICD-8 160–163) (exposure lagged 15 yrs)		
	Low cumulative exposure	1	0.7 (nr)
	Medium cumulative exposure	2	1.0 (nr)
	High cumulative exposure	5	1.7 (nr)
BASF Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Ott and Zober, 1996	BASF employees—incidence		
	Respiratory system	13	1.2 (0.6–2.0)
	TCDD 0.1–0.99 µg/kg of body weight	2	0.7 (0.1–2.5)
	TCDD ≥ 1 µg/kg of body weight	8	2.0 (0.9–3.9)
	Lung, bronchus	11	1.1 (0.6–2.0)
	TCDD 0.1–0.99 µg/kg of body weight	2	0.8 (0.1–2.8)
	TCDD ≥ 1 µg/kg of body weight	8	2.2 (1.0–4.3)
Zober et al., 1990	BASF employees—incidence		*90% CI*
	Trachea, bronchus, lung	4	2.0 (0.7–4.6)

TABLE 7-13 Lung and Bronchus Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Danish Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Lynge, 1993	Danish production workers—incidence (2 of original 4 plant)		
	Lung	13	1.6 (0.9–2.8)
Lynge, 1985	Danish production workers—incidence (all 4 plants)		
	Lung		
	Men	38	1.2 (nr)
	Women	6	2.2 (nr)
Dutch Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Boers et al., 2010	Dutch chlorophenoxy workers		
	Factory A		
	Respiratory cancer	21	1.1 (0.5–2.5)
	Trachea, lung, bronchus cancers	20	1.2 (0.5–2.8)
	Factory B		
	Respiratory cancer	12	1.2 (0.6–2.7)
	Trachea, lung, bronchus cancers	12	1.2 (0.6–2.7)
Bueno de Mesquita et al., 1993	Dutch phenoxy herbicide workers—mortality		
	Trachea, bronchus, lung (ICD-8 162)	9	0.8 (0.4–1.5)
	Respiratory system (ICD-8 160–163)	9	1.7 (0.5–6.3)
German Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Becher et al., 1996	German production workers—lung	47	1.4 (1.1–1.9)
Manz et al., 1991	German production workers—mortality		
	Lung	26	1.7 (1.1–2.4)
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)			**Dioxin, phenoxy herbicides**
McBride et al., 2009a	1,599 production workers (male and female) vs national rates—mortality 1969 through 2004		
	Respiratory cancer	13	0.9 (0.5–1.6)
	Trachea, bronchus, and lung	11	0.8 (0.4–1.5)
't Mannetje et al., 2005	New Zealand phenoxy herbicide workers—mortality		
	Producers (men and women)		
	Trachea, bronchus, lung (ICD-9 162)	12	1.4 (0.7–2.4)
	Other respiratory system sites (ICD-9 163–165)	1	3.9 (0.1–21.5)
	Sprayers (> 99% men)		
	Trachea, bronchus, lung (ICD-9 162)	5	0.5 (0.2–1.1)
	Other respiratory system sites (ICD-9 163–165)	1	2.5 (0.1–13.7)

continued

TABLE 7-13 Lung and Bronchus Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
United Kingdom Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Coggon et al., 1991	British phenoxy herbicide workers—mortality		
	Lung	19	1.3 (0.8–2.1)
	Workers with exposure above background	14	1.2 (0.7–2.1)
Coggon et al., 1986	British MCPA production workers—mortality		
	Lung, pleura, mediastinum (ICD-8 162–164)	117	1.2 (1.0–1.4)
	Background exposure	39	1.0 (0.7–1.4)
	Low-grade exposure	35	1.1 (0.8–1.6)
	High-grade exposure	43	1.3 (1.0–1.8)
Agricultural Health Study			**Herbicides**
Samanic et al., 2006	Pesticide applicators in AHS—lung-cancer incidence from enrollment through 2002		
	Dicamba—lifetime days exposure		
	None	95	1.0
	1– < 20	14	0.8 (0.5–1.5)
	20– < 56	11	0.6 (0.3–1.3)
	56– < 116	12	1.0 (0.5–1.9)
	≥ 116	15	1.5 (0.8–2.7)
			p-trend = 0.13
Alavanja et al., 2005	US AHS—incidence		
	Private applicators (men and women)		
	Lung	266	0.5 (0.4–0.5)
	Respiratory system	294	0.5 (0.4–0.5)
	Spouses of private applicators (> 99% women)		
	Lung	68	0.4 (0.3–0.5)
	Respiratory system	71	0.4 (0.3–0.5)
	Commercial applicators (men and women)		
	Lung	12	0.6 (0.3–1.0)
	Respiratory system	14	0.6 (0.3–1.0)
Blair et al., 2005a	US AHS (lung)—mortality		
	Private applicators (men and women)	129	0.4 (0.3–0.4)
	Years handled pesticides		
	≤ 10 years	25	0.4 (nr) ($p < 0.05$)
	> 10 years	80	0.3 (nr) ($p < 0.05$)
	Spouses of private applicators (> 99% women)	29	0.3 (0.2–0.5)
Other Agricultural Workers			**Herbicides**
Hansen et al., 2007	Danish gardeners (nasal, laryngeal, lung, and bronchus, ICD-7 160–165)—incidence		
	10-yr follow-up (1975–1984) reported in Hansen et al. (1992)	41	1.0 (0.7–1.3)
	25-yr follow-up (1975–2001)		
	Born before 1915 (high exposure)	34	0.9 (0.6–1.3)
	Born 1915–1934 (medium exposure)	72	1.0 (0.8–1.2)
	Born after 1934 (low exposure)	8	0.8 (0.4–1.7)

TABLE 7-13 Lung and Bronchus Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Gambini	Italian rice growers—mortality		
et al., 1997	Lung	45	0.8 (0.6–1.1)
	Pleura	2	2.2 (0.2–7.9)
Torchio et al.,	Italian licensed pesticide users—mortality		
1994	Lung	155	0.5 (0.4–0.5)
Blair et al.,	US farmers in 23 states (lung)—mortality		
1993	White men	6,473	0.9 (0.9–0.9)
	White women	57	0.8 (0.6–1.1)
Dutch Licensed Herbicide Applicators			**Herbicides**
Swaen et al.,	Dutch licensed herbicide applicators (trachea,	27	0.7 (0.5–1.0)
2004	and lung)—mortality		
Swaen et al.,	Dutch herbicide applicators—mortality		
1992	Trachea and lung	12	1.1 (0.6–1.9)
Other Studies of Herbicide and Pesticide Applicators			**Herbicides**
Asp et al.,	Finnish herbicide applicators, 1972–1989		
1994	Incidence		
	Trachea, bronchus, lung (ICD-8 162)	39	0.9 (0.7–1.3)
	Other respiratory (ICD-8 160, 161, 163)	4	1.1 (0.7–1.3)
	Mortality		
	Trachea, bronchus, lung (ICD-8 162)	37	1.0 (0.7–1.4)
	Other respiratory (ICD-8 160, 161, 163)	1	0.5 (0.0–2.9)
Green, 1991	Herbicide sprayers in Ontario (lung)—mortality	5	nr
McDuffie	Saskatchewan farmers applying herbicides—		
et al., 1990	incidence		
	Lung	103	0.6 (nr)
Bender et al.,	Herbicide sprayers in Minnesota—mortality		
1989	Trachea, bronchus, lung (ICD-9 162.0–162.8)	54	0.7 (0.5–0.9)
	All respiratory (ICD-9 160.0–165.9)	57	0.7 (0.5–0.9)
Wiklund	Swedish pesticide applicators—incidence		
et al., 1989a	Trachea, bronchus, lung	38	0.5 (0.4–0.7)
Blair et al.,	Licensed pesticide applicators in Florida, lawn,		
1983	ornamental pest category only—mortality		
	Lung (ICD-8 162–163)	7	0.9 (nr)
Axelson	Swedish herbicide sprayers (lung)—mortality	3	1.4 (nr)
et al., 1980			
Forestry Workers			**Herbicides**
Thörn et al.,	Swedish lumberjacks exposed to phenoxy		
2000	herbicides		
	Foremen (bronchus and lung)—incidence	1	4.2 (0.0–23.2)
Reif et al.,	New Zealand forestry workers—incidence		
1989	(nested case–control)		
	Lung	30	1.3 (0.8–1.9)

continued

TABLE 7-13 Lung and Bronchus Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
Paper and Pulp Workers			**Dioxins**
McLean et al., 2006	IARC cohort of pulp and paper workers—exposure to nonvolatile organochlorine compounds		
	Lung (ICD-9 162)		
	Never	356	1.0 (0.9–1.1)
	Ever	314	1.0 (0.9–1.2)
	Pleura (ICD-9 163)		
	Never	17	2.8 (1.6–4.5)
	Ever	4	0.8 (0.2–2.0)
	Other respiratory (ICD-9 164–165)		
	Never	8	2.1 (0.9–4.2)
	Ever	2	0.7 (0.1–2.4)
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Consonni et al., 2008	Seveso residents—25-yr follow-up—men, women (lung ICD-9 162)		
	Zone A	11	1.1 (0.6–2.0)
	Zone B	62	1.1 (0.9–1.4)
	Zone R	383	1.0 (0.8–1.1)
Pesatori et al., 2009	Seveso residents—20-yr follow-up to 1996—incidence (lung ICD-9 162)		
	Zone A	7	1.1 (0.5–2.4
	Zone B	37	0.96 (0.7–1.3)
	Zone R	280	1.0 (0.9–1.2)
Bertazzi et al., 2001	Seveso residents—20-yr follow-up (lung)—incidence		
	Zones A, B—men	57	1.3 (1.0–1.7)
	women	4	0.6 (0.2–1.7)
Bertazzi et al., 1998	Seveso residents—15-yr follow-up (lung)—incidence		
	Zone A—men	4	1.0 (0.4–2.6)
	women	0	nr
	Zone B—men	34	1.2 (0.9–1.7)
	women	2	0.6 (0.1–2.3)
	Zone R—men	176	0.9 (0.8–1.1)
	women	29	1.0 (0.7–1.6)
Bertazzi et al., 1997	Seveso residents—15-yr follow-up (lung)—incidence		
	Zone A—men	4	1.0 (0.3–2.5)
	Zone B—men	34	1.2 (0.9–1.7)
	women	2	0.6 (0.1–2.1)
	Zone R—men	176	0.9 (0.8–1.0)
	women	29	1.0 (0.7–1.5)

TABLE 7-13 Lung and Bronchus Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Bertazzi et al., 1993	Seveso residents—10-yr follow-up (trachea, bronchus, lung)—incidence		
	Zone A—men	2	0.8 (0.2–3.4)
	Zone B—men	18	1.1 (0.7–1.8)
	Zone R—men	96	0.8 (0.7–1.0)
	women	16	1.5 (0.8–2.5)
Chapaevsk, Russia			**Dioxin**
Revich et al., 2001	Residents of Chapaevsk, Russia (lung)		
	Men	168	3.1 (2.6–3.5)
	Women	40	0.4 (0.3–0.6)
Other Environmental Studies			
Turunen et al., 2008	Finnish fishermen and spouses		
	Larynx, trachea, and lung combined		
	Fishermen	72	0.8 (0.6–1.0)
	Spouses	8	0.7 (0.3–1.4)
Fukuda et al., 2003	Residents of Japanese municipalities with and without waste-incineration plants		*Age-adjusted mortality (per 100,000)*
	Men		
	With		39.0 ± 6.7 vs
	Without		41.6 ± 9.1 (p = 0.001)
	Women		
	With		13.7 ± 3.8 vs
	Without		14.3 ± 4.6 (p = 0.11)
Svensson et al., 1995	Swedish fishermen		
	East coast (lung, larynx)	16	0.8 (0.5–1.3)
	West coast (lung, larynx)	77	0.9 (0.7–1.1)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; ACC, Army Chemical Corps; AFHS, Air Force Health Study; AHS, Agricultural Health Study; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; MCPA, methyl-4-chlorophenoxyacetic acid; MI, Michigan; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PM, proportionate mortality; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; VA, US Department of Veterans Affairs.

[a]Subjects are male, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

In that report, there were 30 lung-, tracheal-, or bronchial-cancer deaths, for an estimated SMR of 1.0 (95% CI 0.6–1.4) or 1.1 (95% CI 0.7–1.6) when 196 workers who had TCP exposure were excluded. An accompanying estimated dose–response relationship did not support an increase in risk associated with an estimated increase in exposure.

McBride et al. (2009a,b) studied 1,599 Dow employees who manufactured 2,4,5-TCP in New Zealand. McBride et al. (2009a) reported crude exposure estimates and 13 deaths from respiratory cancer (11 of the bronchus, trachea, or lung). The SMR for lung cancer was not increased (0.9 for respiratory cancer and 0.8 for cancer of the trachea, bronchus, or lung). The highest SMR for lung cancer was observed in the highest exposure category created in an effort to perform exposure–response analysis, but the other risk estimates were not increased for other exposure categories. A crude effort was made to control for smoking, but its overall effect is difficult to assess. The proportional-hazards model also showed that the highest RR estimate occurred in the most heavily exposed workers, but again this was not reported to be significantly increased or to represent a trend. The results in McBride et al. (2009b) have not been included, because they were diluted by inclusion of a set of workers who had no opportunity for TCDD exposure and no observed deaths.

Finally, Boers et al. (2010) reported on the mortality experience of workers in two chlorophenoxy herbicide plants in the Netherlands. The previously significant increases in respiratory cancer were attenuated in this follow-up. Increased risk remained significant for all cancers. Factory A had 1,167 workers from 1955 to 1985. Factory B included 1,143 who had worked from 1965 to 1986. Crude exposure estimates were based on job. Respiratory-cancer risks were not significantly increased, with HRs of 1.11 (95% CI 0.49–2.52) for factory A (21 deaths in the exposed) and 1.22 (95% CI 0.56–2.66) for factory B (12 deaths in the exposed). Similar estimates of risk were evident for tracheal, lung, and bronchial cancers (factory A, HR = 1.15, 95% CI 0.48–2.77; factory B, HR = 1.22, 95% CI 0.56–2.66). HRs, calculated by factory did not show significant increases although the data were unstable when broken down into finer exposure categories (exposed in 1963 accident for factory A, main production worker exposed, and occasionally exposed for both factories). Although the previously reported significant increases in risks of respiratory cancer were not replicated in this analysis with 15 years of additional follow-up, the magnitude of the risks estimated in the Dutch workers was quite similar to that of the significant risks estimated by the ACC follow-up.

Environmental Studies

Pesatori et al. (2009) reported on cancer incidence in a 20-year follow-up of people exposed in the industrial accident in Seveso. Cancer of the lung occurred with an RR estimated by zone, drawn from residents in three exposure zones—very high (Zone A), high (Zone B), and low (Zone R). The RRs for lung-cancer incidence in the exposure groups were 1.12 (95% CI 0.53–2.36) in Zone A, 0.96 (95% CI 0.69–1.33) in Zone B, and 1.04 (95% CI 0.92–1.19) in Zone R. There were 7, 37, and 280 lung-cancer cases during the follow-up period in Zones A,

B, and R, respectively. The highest lung-cancer risk estimates were found in the longest-latency group in each exposure zone, although there was no clear evidence of an exposure–response relationship based on the small numbers of cases.

Turunen et al. (2008) conducted a study of dioxin-exposed and PCB-exposed fisherman in Finland that included assessment of mortality and estimates of exposure to dioxins and PCBs derived by using serum and adipose tissue from a set of the study participants. They reported a deficit (SMR = 0.80, 95% CI 0.63–1.01) of laryngeal, tracheal, and lung cancers—72 cases—and the SMR in their wives was even lower (0.70, 95% CI 0.30–1.38) with eight cases. The exposed fishermen were at slightly higher RR than their wives, but this excess was not significant and there was a deficit of these cancers compared with those in the general population.

Biologic Plausibility

Long-term animal studies have examined the effects of exposure to the chemicals of interest on tumor incidence (Charles et al., 1996; Stott et al., 1990; Walker et al., 2006; Wanibuchi et al., 2004). As noted in previous VAO reports, there is evidence of increased incidence of squamous-cell carcinoma of the lung in male and female rats exposed to TCDD at high concentrations (Kociba et al., 1978; Van Miller et al., 1977). A significant increase in neoplastic and nonneoplastic lung lesions was found in female rats exposed to TCDD for 2 years (Kociba et al., 1978; NTP, 1982a,b, 2006; Walker et al., 2006, 2007). The most common nonneoplastic lesions were bronchiolar metaplasia and squamous metaplasia of the alveolar epithelium. Cystic keratinizing epithelioma was the most commonly observed neoplasm. The lung was also identified as a target organ in a tumor-promotion study after 60 weeks of exposure to TCDD in ovariectomized female Sprague Dawley rats initiated with a single dose of diethyl-*N*-nitrosamine (Beebe et al., 1995; Tritscher et al., 2000). Those studies ended with increased incidences of alveolar epithelial hyperplasia and alveolar–bronchiolar metaplasia; this result was similar to what was observed in the National Toxicology Program (NTP) studies (Tritscher et al., 2000).

A 2-year study of F344 rats exposed to cacodylic acid at 0–100 ppm and B6C3F1 mice exposed at 0–500 ppm failed to detect lung neoplasms at any dose (Arnold et al., 2006); this finding is consistent with those of previous studies. However, exposure to cacodylic acid had previously been shown to increase tumor multiplicity in mouse strains that were susceptible to developing lung tumors (for example, A/J strain; Hayashi et al., 1998) or in mice pretreated with an intitiating agent (4-nitroquinoline 1-oxide; Yamanaka et al., 1996). The data indicate that cacodylic acid may act as a tumor-promoter in the lung.

The biologic plausibility of the carcinogenicity of the chemicals of interest is discussed in general at the beginning of this chapter.

Synthesis

The evidence remains limited but suggestive of an association between exposure to at least one chemical of interest and the risk of developing or dying from lung cancer. In the present update, there are compelling new data from the follow-up of the heavily exposed ACC (Cypel and Kang, 2010) that show significantly increased lung-cancer risks in ACC veterans who used herbicides in Vietnam; the magnitude of the estimated risk is consistent with those in many similar investigations. Additional updates of occupational data are unchanged, showing no increase in respiratory-cancer risk (Collins et al., 2009a,b). The latest update of the Netherlands occupationally exposed cohort is somewhat changed, showing still increased but now nonsignificant lung-cancer risk (Boers et al., 2010). Those estimates are not significant, but they remain increased and, in magnitude, again very similar to the ACC estimates and other published data.

In the past, the most compelling evidence has come from studies of heavily exposed occupational cohorts, including British MCPA production workers (Coggon et al., 1986), German production workers (Becher et al., 1996; Manz et al., 1991), a BASF cohort (Ott and Zober, 1996), a NIOSH cohort (Fingerhut et al., 1991; Steenland et al., 1999), and Danish production workers (Lynge, 1993). The latest findings from the Ranch Hand study (Pavuk et al., 2005) suggest an increase in risk with serum TCDD concentration even in subjects who made up the comparison group, whose TCDD exposure was considerably lower (but not zero) than that of the Ranch Hand cohort. The American and Australian cohort studies of Vietnam veterans (ADVA, 2005a,b,c; Dalager and Kang, 1997), which presumably cover a large proportion of exposed soldiers, showed higher than expected incidence of and mortality from lung cancer. The main limitations of those studies are that there was no assessment of exposure—as there was in, for example, the Ranch Hand study—and that some potential confounding variables, notably smoking, could not be accounted for. The committee believes that it is unlikely that the distribution of smoking differed greatly between the two cohorts of veterans, so confounding by smoking is probably minimal. The studies therefore lend support to the findings of the Ranch Hand study. The methodologically sound AHS did not show any increased risk of lung cancer, but, although there was substantial 2,4-D exposure in this cohort (Blair et al., 2005b), dioxin exposure of the contemporary farmers was probably negligible.

Results of the environmental studies were mostly consistent with *no* association, although in the cancer-incidence update from Seveso the highest risks occurred in the most exposed.

Also supportive of an association, however, are the numerous lines of mechanistic evidence, discussed in the section on biologic plausibility, which provide further support for the conclusion that the evidence of an association is limited or suggestive.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is limited or suggestive evidence of an association between exposure to at least one chemical of interest and carcinomas of the lung, bronchus, and trachea.

BONE AND JOINT CANCER

ACS estimated that about 1,530 men and 1,120 women would receive diagnoses of bone or joint cancer (ICD-9 170) in the United States in 2010 and that 830 men and 630 women would die from these cancers (Jemal et al., 2010). Primary bone cancers are among the least common malignancies, but the bones are frequent sites of tumors secondary to cancers that have metastasized. Only primary bone cancer is considered here. The average annual incidence of bone and joint cancer is shown in Table 7-14.

Bone cancer is more common in teenagers than in adults. It is rare among people in the age groups of most Vietnam veterans (50–64 years). Among the risk factors for bone or joint cancer in adults are exposure to ionizing radiation in treatment for other cancers and a history of some noncancer bone diseases, including Paget disease.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the chemicals of interest and bone and joint cancer. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008* did not change that conclusion. Table 7-15 summarizes the results of the relevant studies.

TABLE 7-14 Average Annual Incidence (per 100,000) of Bone and Joint Cancer in United States[a]

	55–59 Years Old			60–64 Years Old			65–69 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Men	1.1	1.3	0.3	1.1	1.0	1.2	1.6	1.6	2.9
Women	0.8	0.9	0.6	1.6	1.7	2.2	0.9	1.0	0.4

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2004–2008 (NCI, 2010).

TABLE 7-15 Selected Epidemiologic Studies—Bone and Joint Cancer

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans			**All COIs**
AFHS, 1996	Air Force Ranch Hand veterans	0	nr
US VA Mortality Study of Army and Marine Veterans (ground troops serving July 4, 1965–March 1, 1973)			**All COIs**
Breslin et al., 1988	Army Vietnam veterans	27	0.8 (0.4–1.7)
	Marine Vietnam veterans	11	1.4 (0.1–21.5)
State Studies of Vietnam Veterans			**All COIs**
Clapp, 1997	Massachusetts Vietnam veterans	4	0.9 (0.1–11.3)
Anderson et al., 1986	Wisconsin Vietnam veterans	1	nr
Lawrence et al., 1985	New York Vietnam veterans	8	1.0 (0.3–3.0)
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			**Dioxin, phenoxy herbicides**
Kogevinas et al., 1997	IARC cohort, male and female workers exposed to any phenoxy herbicide or chlorophenol	5	1.2 (0.4–2.8)
	Exposed to highly chlorinated PCDDs	3	1.1 (0.2–3.1)
	Not exposed to highly chlorinated PCDDs	2	1.4 (0.2–5.2)
NIOSH Mortality Cohort (12 US plants, production 1942–1984) (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Fingerhut et al., 1991	NIOSH—entire cohort	2	2.3 (0.3–8.2)
	≥ 1-yr exposure, ≥ 20-yr latency	1	5.5 (0.1–29.0)
Dow Production Workers—Midland, MI (included in IARC and NIOSH cohorts)			**Dioxin, phenoxy herbicides**
Ramlow et al., 1996	Dow pentachlorophenol production workers	0	nr
	0-yr latency	0	nr
	15-yr latency	0	nr
Bond et al., 1988	Dow 2,4-D production workers	0	nr (0.0–31.1)
BASF Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Zober et al., 1990	BASF employees—basic cohort	0	*90% CI* 0 (0.0–65.5)
Monsanto Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Collins et al., 1993	Monsanto Company workers	2	5.0 (0.6–18.1)
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)			**Dioxin, phenoxy herbicides**
McBride et al., 2009a	1,599 production workers (male and female) vs national rates—mortality 1969 through 2004	0	0 (0.0–21.8)

TABLE 7-15 Bone and Joint Cancer

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
't Mannetje et al., 2005	Phenoxy herbicide producers and sprayers (men and women)	0	nr
United Kingdom Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Coggon et al., 1986	British MCPA production workers	1	0.9 (0.0–5.0)
Studies of Agricultural Workers			**Herbicides**
Gambini et al., 1997	Italian rice growers	1	0.5 (0.0–2.6)
Blair et al., 1993	US farmers in 23 states		
	White men	49	1.3 (1.0–1.8)
	White women	1	1.2 (0.0–6.6)
Ronco et al., 1992	Danish, Italian farm workers		
	Male Danish farmers	9	0.9 (nr)
	Female Danish farmers	0	nr
Wiklund, 1983	Swedish male and female agricultural workers—incidence	44	*99% CI* 1.0 (0.6–1.4)
Burmeister, 1981	Iowa farmers	56	1.1 (nr)
Other Studies of Herbicide and Pesticide Applicators			**Herbicides**
Swaen et al., 2004	Dutch licensed herbicide applicators	0	nr
Torchio et al., 1994	Italian licensed pesticide users	10	0.8 (0.4–1.4)
Forestry Workers			**Herbicides**
Hertzman et al., 1997	British Columbia sawmill workers		
	Mortality	5	1.3 (0.5–2.7)
	Incidence	4	1.1 (0.4–2.4)
	Not exposed to highly chlorinated PCDDs	2	1.4 (0.2–5.2)
Reif et al., 1989	New Zealand forestry workers—nested case–control—incidence	1	1.7 (0.2–13.3)
Paper and Pulp Workers			**Dioxins**
Rix et al., 1998	Danish paper-mill workers—incidence		
	Men	1	0.5 (0.0–2.7)
	Women	0	nr
Other Occupational Studies			
Herbicides			
Merletti et al., 2006	Association between occupational exposure and risk of bone sarcoma	18	2.6 (1.5–4.6)
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			
Bertazzi et al., 1998	Seveso residents—15-yr follow-up		
	Zone B women	1	2.6 (0.3–19.4)
	Zone R men	2	0.5 (0.1–2.0)
	Zone R women	7	2.4 (1.0–5.7)

continued

TABLE 7-15 Bone and Joint Cancer

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Bertazzi et al., 1997	Seveso residents—15-yr follow-up		
	Zone B women	1	2.6 (0.0–14.4)
	Zone R men	2	0.5 (0.1–1.7)
	Zone R women	7	2.4 (1.0–4.9)
Chapaevsk, Russia			
Revich et al., 2001	Residents of Chapaevsk, Russia Mortality standardized to Samara region (bone, soft-tissue cancer)		
	Men	7	2.1 (0.9–4.4)
	Women	7	1.4 (0.6–3.0)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; MCPA, methyl-4-chlorophenoxyacetic acid; MI, Michigan; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; NZ, New Zealand; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); SEA, Southeast Asia; VA, US Department of Veterans Affairs.

[a]Subjects are male, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

Update of the Epidemiologic Literature

Vietnam-Veteran and Occupational Studies

No Vietnam-veteran studies or occupational studies concerning exposure to the chemicals of interest and bone and joint cancer have been published since *Update 2008*.

Environmental Studies

McBride et al. (2009a,b) examined mortality in an occupational cohort of TCP workers employed in a Dow Agrosciences site in New Zealand during the period 1969–1988. This set of the IARC occupational cohort (see Chapter 5) includes 1,599 workers. No bone-cancer deaths were identified in the study. The results in McBride et al. (2009b) have not been included, because they were diluted by inclusion of a set of workers who had no opportunity for TCDD exposure and no observed deaths.

Biologic Plausibility

No animal studies have reported an increased incidence of bone and joint cancers after exposure to the chemicals of interest. The biologic plausibility of

the carcinogenicity of the chemicals of interest is discussed in general at the beginning of this chapter.

Synthesis

The new study of Dow production workers in New Zealand found no cases of bone and joint cancer, and the previous body of results summarized in Table 7-15 does not indicate an association between exposure to the chemicals of interest and bone cancer.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and bone and joint cancers.

SOFT-TISSUE SARCOMA

Soft-tissue sarcoma (STS) (ICD-9 164.1, 171) arises in soft somatic tissues in and between organs. Three of the most common types of STS—liposarcoma, fibrosarcoma, and rhabdomyosarcoma—occur in similar numbers in men and women. Because of the diverse characteristics of STS, accurate diagnosis and classification can be difficult. ACS estimated that about 5,680 men and 4,840 women would receive diagnoses of STS in the United States in 2010 and that about 2,020 men and 1,900 women would die from it (Jemal et al., 2010). The average annual incidence of STS is shown in Table 7-16.

Among the risk factors for STS are exposure to ionizing radiation during treatment for other cancers and some inherited conditions, including Gardner syndrome, Li-Fraumeni syndrome, and neurofibromatosis. Several chemical exposures have been identified as possible risk factors (Zahm and Fraumeni, 1997).

TABLE 7-16 Average Annual Incidence (per 100,000) of Soft-Tissue Sarcoma (Including Malignant Neoplasms of the Heart) in United States[a]

	55–59 Years Old			60–64 Years Old			65–69 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Men	5.3	5.4	5.2	6.7	7.1	5.2	8.6	8.9	6.4
Women	4.5	4.4	6.2	5.3	5.2	7.3	6.7	6.9	4.0

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2004–2008 (NCI, 2010).

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* judged that the strong findings in the IARC and NIOSH cohorts and the extensive Scandinavian case–control studies, complemented by consistency in preliminary reports on the Seveso population and one statistically significant finding in a state study of Vietnam veterans, constituted sufficient information to determine that there is an association between exposure to at least one of the chemicals of interest and STS. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, and *Update 2006* did not change that conclusion. A case–control study conducted in Italy (Zambon et al., 2007) and an update on Danish gardeners (Hansen et al., 1992) considered in *Update 2008* reinforced the evidence of an association, but the TCDD-exposed Seveso population has shown no evidence of an association (Consonni et al., 2008). Table 7-17 summarizes the relevant studies.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

No Vietnam-veteran studies concerning exposure to the chemicals of interest and STS have been published since *Update 2008*.

Occupational Studies

Collins et al. (2009a,b) reported on the mortality experience of the occupational cohort in the Midland, Michigan, Dow Chemical plant previously included in analyses of the NIOSH Mortality Cohort, as reported by Fingerhut et al. (1991) and added to the expanded IARC Cohort of Phenoxy Herbicide Workers (Kogevinas et al., 1997). TCP was produced at the plant from 1942 to 1979, and PCP was produced from 1937 to 1980. Job histories of the workers were used to determine duration of time spent in the TCP or PCP units. Mortality in the workers and SMRs were calculated by using the US population as the referent. In the PCP analysis (Collins et al., 2009b), one death from STS of a worker who was exposed to both PCP and TCP was identified, for a PCP SMR for STS of 2.2 (95% CI 0.0–12.1). In a separate analysis of the 1,615 TCP workers (Collins et al., 2009a), four deaths from STS were identified, for a TCP SMR of 4.1 (95% CI 1.1–10.5). One of the deaths occurred in a worker who was exposed to both TCP and PCP; when this death was removed from the analysis, the SMR was reduced to 3.5 (95% CI 0.7–10.2). As pointed out in follow-up correspondence (Collins et al., 2010; Villeneuve and Steenland, 2010) and discussed in detail in Chapter 5, different latency models, different dose–response models, and in-depth analysis of the serum concentrations could alter some of the results reported in

TABLE 7-17 Selected Epidemiologic Studies—Soft-Tissue Sarcoma

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US Air Force Health Study			**All COIs**
AFHS, 2000	AFHS veterans	1	0.8 (0.1–12.8)
AFHS, 1996	Ranch Hand veterans	0	nr
Michalek et al., 1990	Ranch Hand veterans	1	nr
	Comparisons	1	nr
US VA Marine Post-service Mortality Study (all Marines active 1967–1969)			**All COIs**
Watanabe and Kang, 1995	US Marines in Vietnam	0	nr
US VA Mortality Study of Army and Marine Veterans (ground troops serving July 4, 1965–March 1, 1973)			**All COIs**
Watanabe et al., 1991	Army Vietnam veterans	43	1.1
	Marine Vietnam veterans	11	0.7
Bullman et al., 1990	Army I Corps Vietnam veterans	10	0.9 (0.4–1.6)
Breslin et al., 1988	Army Vietnam veterans	30	1.0 (0.8–1.2)
	Marine Vietnam veterans	8	0.7 (0.4–1.3)
Breslin et al., 1986	US Vietnam veterans		
	Army	30	1.0 (nr)
	Marines	8	0.7 (nr)
Australian Vietnam Veterans vs Australian General Population			**All COIs**
ADVA, 2005a	Australian Vietnam veterans vs Australian population—incidence	35	(0.7–1.3)
	Navy	6	0.8 (0.3–1.7)
	Army	29	1.2 (0.8–1.6)
	Air Force	0	0.0 (0.0–1.1)
ADVA, 2005b	Australian Vietnam veterans vs Australian population—mortality	12	0.8 (0.4–1.3)
	Navy	3	0.9 (0.2–2.4)
	Army	9	0.8 (0.4–1.5)
	Air Force	0	0.0 (0.0–2.3)
AIHW, 1999	Male Australian Vietnam veterans—incidence (validation study)		*Expected number of exposed cases (95% CI)*
		14	27 (17–37)
CDVA, 1998a	Male Australian Vietnam veterans—self-reported incidence	398	27 (17–37)
CDVA, 1998b	Female Australian Vietnam veterans—self-reported incidence	2	0 (0–4)
CDVA, 1997a	Australian military Vietnam veterans	9	1.0 (0.4–1.8)

continued

TABLE 7-17 Soft-Tissue Sarcoma, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
Australian Conscripted Army National Service (deployed vs nondeployed)			**All COIs**
ADVA, 2005c	Australian men conscripted Army National Service Vietnam era veterans—deployed vs nondeployed		
	Incidence	10	1.0 (0.4–2.4)
	Mortality	3	0.5 (0.1–2.0)
CDVA, 1997b	Australian National Service Vietnam veterans	2	0.7 (0.6–4.5)
Fett et al., 1987	Australian Vietnam veterans	1	1.3 (0.1–20.0)
VA Case–control Studies			**All COIs**
Kang et al., 1986	Vietnam veterans vs Vietnam-era veterans	86	0.8 (0.6–1.1)
Vietnam Veterans of Massachusetts			**All COIs**
Clapp, 1997	Massachusetts Vietnam veterans	18	1.6 (0.5–5.4)
Kogan and Clapp, 1988	Massachusetts Vietnam veterans	9	5.2 (2.4–11.1)
State Studies of US Vietnam Veterans			**All COIs**
Visintainer et al., 1995	PM study of deaths (1974–1989) of Michigan Vietnam-era veterans—deployed vs nondeployed	8	1.1 (0.5–2.2)
Anderson et al., 1986	Wisconsin Vietnam veterans	4	nr
Lawrence et al., 1985	New York State Vietnam veterans	2	1.1 (0.2–6.7)
Greenwald et al., 1984	New York State Vietnam veterans	10	0.5 (0.2–1.3)
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			**Dioxin, phenoxy herbicides**
Kogevinas et al., 1997	IARC cohort, male and female workers exposed to any phenoxy herbicide or chlorophenol	9	2.0 (0.9–3.8)
	Exposed to highly chlorinated PCDDs	6	2.0 (0.8–4.4)
	Not exposed to highly chlorinated PCDDs	2	1.4 (0.2–4.9)
Kogevinas et al., 1995	IARC cohort (men and women)—incidence	11	nr
Kogevinas et al., 1992	IARC cohort (men and women)		
	10–19 years since first exposure	4	6.1 (1.7–15.5)
Saracci et al., 1991	IARC cohort—exposed subcohort (men and women)	4	2.0 (0.6–5.2)
NIOSH Mortality Cohort (12 US plants, production 1942–1984) (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Steenland et al., 1999	US chemical production workers	0	nr

TABLE 7-17 Soft-Tissue Sarcoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Fingerhut	NIOSH cohort—entire cohort	4	3.4 (0.9–8.7)
et al., 1991	≥ 1-yr exposure, ≥ 20-yr latency	3	9.2 (1.9–27.0)
BASF Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Ott and Zober, 1996	BASF employees—incidence		*Expected number of exposed cases*
		0	0.2
Zober et al., 1990	BASF employees—basic cohort	0	nr
Dow Production Workers—Midland, MI (included in IARC and NIOSH cohorts)			**Dioxin, phenoxy herbicides**
Collins et al., 2009a	Trichlorophenol workers	4	4.1 (1.1–10.5)
Collins et al., 2009b	Pentachlorophenol workers	1	2.2 (0.0–12.1)
Bodner et al., 2003	Dow chemical production workers	2	2.4 (0.3–8.6)
Ramlow et al., 1996	Dow pentachlorophenol production workers	0	*Expected number of exposed cases* 0.2
Bond et al., 1988	Dow 2,4-D production workers	0	nr
Danish Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Lynge, 1993	Danish production workers—updated incidence for men, women	5	2.0 (0.7–4.8)
Lynge, 1985	Danish production workers—incidence		
	Men	5	2.7 (0.9–6.3)
	Women	0	nr
Dutch Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Hooiveld et al., 1998	Dutch chemical production workers	0	nr
Bueno de Mesquita et al., 1993	Dutch phenoxy herbicide workers	0	0.0 (0.0–23.1)
German Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Manz et al., 1991	German production workers—men, women	0	nr
United Kingdom Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Coggon et al., 1986	British MCPA chemical workers	1	1.1 (0.03–5.9)

continued

TABLE 7-17 Soft-Tissue Sarcoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)			**Dioxin, phenoxy herbicides**
McBride et al., 2009a	1,599 production workers (male and female) vs national rates—mortality 1969 through 2004		
	Ever exposed workers	1	3.4 (0.1–19.5)
't Mannetje et al., 2005	Phenoxy herbicide producers (men and women)	0	0.0 (0.0–19.3)
	Phenoxy herbicide sprayers (> 99% men)	1	4.3 (0.1–23.8)
Agricultural Health Study			**Herbicides**
Alavanja et al., 2005	US AHS—incidence		
	Private applicators (men and women)	10	0.7 (0.3–1.2)
	Spouses of private applicators (> 99% women)	3	0.5 (0.1–1.4)
	Commercial applicators (men and women)	nr	0.0 (0.0–3.8)
Blair et al., 2005a	US AHS		
	Private applicators (men and women)	4	0.7 (0.2–1.8)
	Spouses of private applicators (> 99% women)	3	1.4 (0.3–4.1)
Other Agricultural Workers			**Herbicides**
Hansen et al., 2007	Danish gardeners (ICD-7 197)—incidence		
	10-yr follow-up (1975–1984) reported in Hansen et al. (1992)	3	5.3 (1.1–15.4)
	25-yr follow-up (1975–2001)		
	Born before 1915 (high exposure)	3	5.9 (1.9–18.2)
	Born 1915–1934 (medium exposure)	0	0.0 (0.0–3.8)
	Born after 1934 (low exposure)	1	1.8 (0.3–12.9)
Blair et al., 1993	US farmers in 23 states	98	0.9 (0.8–1.1)
Hansen et al., 1992	Danish gardeners—incidence	3	5.3 (1.1–15.4)
Wiklund et al., 1988, 1989b	Swedish agricultural workers (men and women)	7	*99% CI* 0.9 (0.4–1.9)
Hoar et al., 1986	Kansas residents—incidence		
	All farmers	95	1.0 (0.7–1.6)
	Farm use of herbicides	22	0.9 (0.5–1.6)
Vineis et al., 1986	Italian rice growers		
	Among all living females	5	2.4 (0.4–16.1)
Balarajan and Acheson, 1984	Agricultural workers in England		
	Overall	42	1.7 (1.0–2.9)
	Under 75 yrs of age	33	1.4 (0.8–2.6)
New Zealand Pesticide Workers			**Herbicides**
Smith and Pearce, 1986	Reanalysis of New Zealand workers	133	*90% CI* 1.1 (0.7–1.8)
Smith et al., 1984	Update of New Zealand workers	17	*90% CI* 1.6 (0.7–3.8)

TABLE 7-17 Soft-Tissue Sarcoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Smith et al., 1983	New Zealand workers exposed to herbicides	17	*90% CI* 1.6 (0.8–3.2)
Other Studies of Herbicide and Pesticide Applicators			**Herbicides**
Torchio et al., 1994	Italian licensed pesticide users	2	1.0 (0.1–3.5)
Blair et al., 1983	Florida pesticide applicators	0	nr
Forestry Workers			**Herbicides**
Hertzman et al., 1997	Canadian sawmill workers	11	1.0 (0.6–1.7)
Alavanja et al., 1989	USDA forest and soil conservationists	2	1.0 (0.1–3.6)
Reif et al., 1989	New Zealand forestry workers—nested case–control—incidence	4	3.2 (1.2–9.0)
Paper and Pulp Workers			**Dioxins**
McLean et al., 2006	IARC cohort of pulp and paper workers Exposure to nonvolatile organochlorine compounds		
	Never	8	1.2 (0.5–2.4)
	Ever	4	0.8 (0.2–2.0)
Rix et al., 1998	Danish paper-mill workers—incidence		
	Women employed in sorting and packing	8	4.0 (1.7–7.8)
	Men employed in sorting and packing	12	1.2 (0.6–2.0)
Other Occupational Studies			**Herbicides**
Mack, 1995	US cancer registry data (SEER program) review		
	Men	3,526	nr
	Women	2,886	nr
Smith and Christophers, 1992	Australia residents	30	1.0 (0.3–3.1)
Woods et al., 1987	Washington state residents—incidence		
	High phenoxy exposure	nr	0.9 (0.4–1.9)
	Self-reported chloracne	nr	3.3 (0.8–14.0)
Hardell, 1981	Swedish residents		
	Exposed to phenoxy acids	13	5.5 (2.2–13.8)
	Exposed to chlorophenols	6	5.4 (1.3–22.5)
Eriksson et al., 1979, 1981	Swedish workers	25	(2.5–10.4) 5:1 matched

continued

TABLE 7-17 Soft-Tissue Sarcoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
ENVIRONMENTAL			
Seveso, Italy Residential Population			**Dioxin**
Consonni et al., 2008	Seveso residents—25-yr follow-up—men, women		
	Zone A	0	nr
	Zone B	0	nr
	Zone R	4	0.8 (0.3–2.1)
Pesatori et al., 2009	Seveso—20-yr follow-up to 1996—incidence		
	Zone A	0	nr
	Zone B	0	nr
	Zone R	9	1.3 (0.6–2.7)
Bertazzi et al., 2001	Seveso—20-yr follow-up (men and women)	0	nr
Bertazzi et al., 1998	Seveso—15-yr follow-up (men and women)		
	Zone R men	4	2.1 (0.7–6.5)
Bertazzi et al. 1997	Seveso residents—15-yr follow-up (men and women)		
	Zone R men	4	2.1 (0.6–5.4)
Bertazzi et al., 1993	Seveso residents—10-yr follow-up—morbidity		
	Zone R men	6	2.8 (1.0–7.3)
	Zone R women	2	1.6 (0.3–7.4)
Bertazzi et al., 1989a	Seveso residents—10-yr follow-up		
	Zone A, B, R men	2	5.4 (0.8–38.6)
	Zone A, B, R women	1	2.0 (0.2–1.9)
Bertazzi et al., 1989b	Seveso residents—10-yr follow-up		
	Zone R men	2	6.3 (0.9–45.0)
	Zone B women	1	17.0 (1.8–163.6)
Other Environmental Studies			
Read et al., 2007	Residents of New Plymouth Territorial Authority, New Zealand near plant manufacturing 2,4,5-T in 1962–1987		**2,4,5-T**
	Incidence	56	1.0 (0.8–1.4)[c]
	1970–1974	7	1.0 (0.4–2.1)
	1975–1979	3	0.4 (0.1–2.1)
	1980–1984	10	1.3 (0.6–2.4)
	1985–1989	11	1.2 (0.6–2.2)
	1990–1994	9	0.9 (0.4–1.7)
	1995–1999	14	1.3 (0.7–2.2)
	2000–2001	2	0.8 (0.1–3.0)
	Mortality	27	1.2 (0.8–1.8)[c]
	1970–1974	5	1.8 (0.6–4.3)
	1975–1979	1	0.4 (0.0–2.0)
	1980–1984	4	1.1 (0.3–2.9)
	1985–1989	5	1.5 (0.5–3.6)
	1990–1994	5	1.3 (0.4–3.0)
	1995–1999	5	1.3 (0.4–3.0)
	2000–2001	2	0.9 (0.1–3.1)

TABLE 7-17 Soft-Tissue Sarcoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Zambon et al., 2007	Population-based Veneto Tumour Registry, Italy, average exposure based on duration and distance of residence from 33 industrial sources—incidence		**Dioxin**
	Sarcoma (ICD-9 158, 171, 173, visceral sites)		
	Men		
	< 4 TCDD (fg/m^3)	31	1.0
	4–6	39	1.1 (0.6–2.0)
	≥ 6	17	1.9 (0.9–4.0)
			p-trend = 0.15
	Women		
	< 4 TCDD (fg/m^3)	24	1.0
	4–6	44	1.5 (0.8–2.7)
	≥ 6	17	2.4 (1.0–5.6)
			p-trend = 0.04
	Men, women combined		
	Connective, other soft tissue (ICD-9 171)		
	< 4 TCDD (fg/m^3)	25	1.0
	4–6	39	1.4 (0.7–2.5)
	≥ 6	17	3.3 (1.4–7.9)
			p-trend = 0.01
	Skin (ICD-9 173)		
	< 4 TCDD (fg/m^3)	5	1.0
	4–6	10	0.0 (0.3–4.7)[d]
	≥ 6	2	0.3 (0.0–3.4)
			p-trend = 0.48
	Retroperitoneum, peritoneum (ICD-9 158)		
	< 4 TCDD (fg/m^3)	6	1.0
	4–6	12	1.1 (0.3–3.4)
	≥ 6	3	0.8 (0.1–4.5)
			p-trend = 0.86
	Visceral sites		
	< 4 TCDD (fg/m^3)	19	1.0
	4–6	22	1.2 (0.6–2.6)
	≥ 6	12	2.5 (1.0–6.3)
			p-trend = 0.08
Pahwa et al., 2006	Canadian residents		**Phenoxyherbicides**
	Any phenoxyherbicide	46	1.1 (0.7–1.5)
	2,4-D	41	1.0 (0.6–1.5)
	Mecoprop	12	1.0 (0.5–1.9)
	MCPA	12	1.1 (0.5–2.2)
Comba et al., 2003	Residents near industrial-waste incinerator in Mantua, Italy—incidence		**Dioxin**
	Residence within 2 km of incinerator	5	31.4 (5.6–176.1)

continued

TABLE 7-17 Soft-Tissue Sarcoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Tuomisto et al., 2004	Finnish STS patients vs controls within quintiles based on TEQ in subcutaneous fat—incidence	110	**Dioxin**
	Quintile 1 (median, ~12 ng/kg TEQ)	nr	1.0
	Quintile 2 (median, ~20 ng/kg TEQ)	nr	0.4 (0.2–1.1)
	Quintile 3 (median, ~28 ng/kg TEQ)	nr	0.6 (0.2–1.7)
	Quintile 4 (median, ~40 ng/kg TEQ)	nr	0.5 (0.2–1.3)
	Quintile 5 (median, ~62 ng/kg TEQ)	nr	0.7 (0.2–2.0)
Costani et al., 2000	Residents near chemical plant in Mantua, Italy—incidence	20	**TCDD emissions** 2.3 (1.3–3.5)
Viel et al., 2000	Residents near French solid-waste incinerator—incidence		**Dioxin**
	Spatial cluster	45	1.4 (p = 0.004)
	1994–1995	12	3.4 (p = 0.008)
Gambini et al., 1997	Italian rice growers		**Chlophenoxy acids and chlorophenols**
		1	4.0 (0.1–22.3)
Svensson et al., 1995	Swedish fishermen—incidence (men and women)		**Organochlorine compounds and chlorophenol**
	West coast		
		3	0.5 (0.1–1.4)
Lampi et al., 1992	Finnish community exposed to chlorophenol contamination (men and women)	6	1.6 (0.7–3.5)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; AFHS, Air Force Health Study; AHS, Agricultural Health Study; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; MCPA, methyl-4-chlorophenoxyacetic acid; MI, Michigan; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; NZ, New Zealand; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PM, proportionate mortality; SEER, Surveillance, Epidemiology, and End Results; STS, soft-tissue sarcoma; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEQ, toxicity equivalent; USDA, US Department of Agriculture; VA, US Department of Veterans Affairs.

[a]Subjects are male, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

[c]Committee computed total SMR and standard incidence ratio by dividing sum of observed values by sum of expected values over all years; 95% CIs on these total ratios were computed with exact methods.

[d]There appears to be an error in this entry because lower 95% CL (0.3) is not smaller than odds ratio (0.0).

the analysis; given the small number of deaths from STS, however, those methodologic considerations are unlikely to alter the conclusions regarding STS.

McBride et al. (2009a,b) evaluated mortality from cancers in an occupational cohort of TCP workers in New Zealand, a set of the IARC cohort (see Chapter 5). Workers were employed at the plant from 1969 to 1988, and SMRs were calculated by using the New Zealand population as the comparison group. Exposure was classified as ever exposed or never exposed to TCDD. One case of STS was identified in the ever-exposed group and none in the never-exposed group. When compared with the expected number of deaths in the New Zealand population, an increased association was observed, with an SMR of 3.4 (95% CI 0.1–19.5) for the ever-exposed workers. Results in McBride et al. (2009b) have not been included, because they were diluted by inclusion of a set of workers who had no opportunity for TCDD exposure and no observed deaths.

Environmental Studies

Cancer incidence was re-evaluated in the Seveso cohort for the period 1977–1996 (Pesatori et al., 2009). The Seveso cohort, described in Chapter 5, includes all residents of Seveso at the time of the accident and those who migrated into or were born in the area in the 10-year period after the accident. A total of 218,761 residents are included in the analysis: 723 residents in the high-exposure zone (Zone A); 4,821 in the medium-exposure zone (Zone B); 31,643 in the low-exposure zone (Zone R); and the remainder who lived outside the zone of exposure. A total of nine STS cases were identified; all nine were in Zone R. Compared with the incidence in the reference zone, STS incidence in Zone R was higher, with an RR of 1.32 (95% CI 0.64–2.73).

Biologic Plausibility

In a 2-year study, dermal application of TCDD to Swiss-Webster mice led to an increase in fibrosarcomas in females but not in males (NTP, 1982b). There is some concern that the increase in fibrosarcomas may be associated with the treatment protocol rather than with TCDD. The NTP gavage study (NTP, 1982a) also found increased incidences of fibrosarcomas in male and female rats and in female mice.

The biologic plausibility of the carcinogenicity of the chemicals of interest is discussed in general at the beginning of this chapter.

Synthesis

Previous committees have concluded that the occupational, environmental, and Vietnam-veteran studies showed sufficient evidence to link herbicide exposure to STS. Although confidence intervals in the new studies were broad because

of the small samples, that conclusion is consistent with the findings of McBride et al. (2009a), Collins et al. (2009a,b), and Pesatori et al. (2009).

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is sufficient evidence of an association between exposure to at least one of the chemicals of interest and STS.

SKIN CANCER—MELANOMA

Skin cancers are generally divided into two broad categories: neoplasms that develop from melanocytes (malignant melanoma, or simply melanoma) and neoplasms that do not. Nonmelanoma skin cancers (primarily basal-cell and squamous-cell carcinomas) have a far higher incidence than melanoma but are considerably less aggressive and therefore more treatable. The average annual incidence of melanoma is shown in Table 7-18. The committee responsible for *Update 1998* first chose to address melanoma studies separately from those of nonmelanoma skin cancer. Some researchers report results by combining all types of skin cancer without specifying type. The present committee believes that combined information is not interpretable (although there is a supposition that mortality figures refer predominantly to melanoma and that sizable incidence figures refer to nonmelanoma skin cancer); therefore, it is interpreting data only when results specify melanoma or nonmelanoma skin cancer.

ACS estimated that about 38,870 men and 29,260 women would receive diagnoses of cutaneous melanoma (ICD-9 172) in the United States in 2008 and that about 5,670 men and 3,030 women would die from it (Jemal et al., 2010). More than a million cases of nonmelanoma skin cancer (ICD-9 173), primarily basal-cell and squamous-cell carcinomas, are diagnosed in the United States each year (ACS, 2006); it is not required to report them to registries, so the numbers of cases are not as precise as those of other cancers. ACS reports that although

TABLE 7-18 Average Annual Incidence (per 100,000) of Skin Cancers (Excluding Basal-Cell and Squamous-Cell Cancers) in United States[a]

	55–59 Years Old			60–64 Years Old			65–69 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Melanomas of the Skin:									
Men	49.0	58.8	1.8	68.7	81.4	2.0	86.7	103.0	5.2
Women	30.2	37.2	1.5	35.5	43.0	1.6	39.2	47.2	2.2

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2004–2008. SEER incidence data not available for nonmelanocytic skin cancer (NCI, 2010).

melanoma accounts for less than 5% of skin-cancer cases, it is responsible for about 73% of skin-cancer deaths (ACS, 2011a). It estimates that 2,000 people die each year from nonmelanoma skin cancer (ACS, 2011b).

Melanoma occurs more frequently in fair-skinned people than in dark-skinned people; the risk in whites is roughly 20 times that in dark-skinned blacks. The incidence increases with age, more strikingly in males than in females. Other risk factors include the presence of particular kinds of moles on the skin, suppression of the immune system, and excessive exposure to UV radiation, typically from the sun. A family history of the disease has been identified as a risk factor, but it is unclear whether that is attributable to genetic factors or to similarities in skin type and sun-exposure patterns.

Excessive exposure to UV radiation is the most important risk factor for nonmelanoma skin cancer; some skin diseases and chemical exposures have also been identified as potential risk factors. Exposure to inorganic arsenic is a risk factor for skin cancer; this does not imply that exposure to cacodylic acid, which is a metabolite of inorganic arsenic, can be assumed to be a risk factor.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the chemicals of interest and skin cancer. Additional information available to the committee responsible for *Update 1996* did not change that conclusion. The committee responsible for *Update 1998* considered the literature on melanoma separately from that of nonmelanoma skin cancer and found that there was inadequate or insufficient information to determine whether there is an association between the chemicals of interest and melanoma. The committees responsible for *Update 2000*, *Update 2002*, and *Update 2004* concurred with the findings of *Update 1998*. The committee responsible for *Update 2006* was unable to reach a consensus as to whether there was limited or suggestive evidence of an association between exposure to the chemicals of interest and melanoma or inadequate or insufficient evidence to determine whether there is an association, so melanoma was left in the lower category. The committee for *Update 2008* determined that evidence of an association between exposure to the chemicals of interest and melanoma remained inadequate or insufficient to determine whether an association exists. Table 7-19 summarizes the relevant melanoma studies.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

Cypel and Kang (2010) analyzed the mortality of ACC veterans who used herbicides in Vietnam (see Chapter 5). All-causes mortality and cause-specific

TABLE 7-19 Selected Epidemiologic Studies—Melanoma

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans			**All COIs**
Pavuk et al., 2005	White Air Force comparison subjects only—incidence		
	Serum TCDD (pg/g), based on model with exposure variable $\log_e$(TCDD)		
	Per unit increase of $-\log_e$(TCDD)	25	2.7 (1.1–6.3)
	Quartiles (pg/g)		
	0.4–2.6	3	1.0
	2.6–3.8	5	2.1 (0.4–11.0)
	3.8–5.2	8	3.2 (0.7–15.5)
	> 5.2	9	3.6 (0.7–17.2)
	Number years served SEA		
	Per year of service	25	1.1 (0.9–1.3)
	Quartiles (years in SEA)		
	0.8–1.3	3	1.0
	1.3–2.1	4	1.9 (0.3–10.3)
	2.1–3.7	8	3.2 (0.7–15.3)
	3.7–16.4	10	4.1 (0.9–19.7)
Akhtar et al., 2004	AFHS subjects vs national rates		
	White AFHS Ranch Hand veterans		
	Incidence	17	2.3 (1.4–3.7)
	With tours between 1966–1970	16	2.6 (1.5–4.1)
	Mortality	nr	
	White AFHS comparison veterans		
	Incidence	15	1.5 (0.9–2.4)
	With tours between 1966–1970	12	1.5 (0.8–2.6)
	Mortality	nr	
	White AFHS subjects—incidence		
	Who spent at most 2 yrs in SEA		
	Per unit increase of $-\log_e$(TCDD) (pg/g)	14	2.2 (1.3–3.9)
	Comparison group	3	1.0
	Ranch Hand—< 10 TCDD pg/g in 1987	4	3.0 (0.5–16.8)
	Ranch Hand—< 118.5 TCDD pg/g at end of service	4	7.4 (1.3–41.0)
	Ranch Hand—> 118.5 TCDD pg/g at end of service	3	7.5 (1.1–50.2)
	Only Ranch Hands with 100% service in Vietnam, comparisons with 0% service in Vietnam		
	Per unit increase of $-\log_e$(TCDD) in pg/g	14	1.7 (1.0–2.8)
	Comparison group	2	1.0
	Ranch Hand—< 10 TCDD pg/g in 1987	5	3.9 (0.4–35.3)

TABLE 7-19 Melanoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
	Ranch Hand—< 118.5 TCDD pg/g at end of service	4	7.2 (0.9–58.8)
	Ranch Hand—> 118.5 TCDD pg/g at end of service	3	5.5 (0.6–46.1)
AFHS, 2000	Air Force Ranch Hand veterans—incidence	16	1.8 (0.8–3.8)
Ketchum et al., 1999	Ranch Hand veterans, comparisons through June 1997—incidence		
	Comparisons	9	1.0
	Ranch Hand background exposure	4	1.1 (0.3–4.5)
	Ranch Hand low exposure	6	2.6 (0.7–9.1)
	Ranch Hand high exposure	2	0.9 (0.2–5.6)
Wolfe et al., 1990	Air Force Ranch Hand veterans—incidence	4	1.3 (0.3–5.2)
US VA Cohort of Army Chemical Corps			**All COIs**
Cypel and Kang et al., 2010	ACC—deployed vs nondeployed and vs US men (Vietnam-service status throught 2005)		
	Deployed vs nondeployed	5 vs 4	1.5 (0.4–6.2)
	ACC veterans vs US men		
	Vietnam cohort	5	1.3 (0.4–3.1)
	Non-Vietnam cohort	4	1.3 (0.4–3.4)
US CDC Vietnam Experience Study			**All COIs**
Boehmer et al., 2004	Follow-up of CDC Vietnam Experience Cohort	6	1.4 (0.4–4.9)
US VA Mortality Study of Army and Marine Veterans (ground troops serving July 4, 1965–March 1, 1973)			**All COIs**
Breslin et al., 1988	Army Vietnam veterans	145	1.0 (0.9–1.1)
	Marine Vietnam veterans	36	0.9 (0.6–1.5)
State Studies of US Vietnam Veterans			**All COIs**
Clapp, 1997	Massachusetts Vietnam veterans—incidence	21	1.4 (0.7–2.9)
Australian Vietnam Veterans vs Australian population			**All COIs**
O'Toole et al., 2009	Survey of Australian Vietnam Veterans compared to Australian general populations	nr	4.7 (1.3–8.2)
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence	756	1.3 (1.2–1.4)
	Navy	173	1.4 (1.2–1.6)
	Army	510	1.2 (1.2–1.4)
	Air Force	73	1.4 (1.1–1.7)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—mortality	111	1.1 (0.9–1.3)
	Navy	35	1.6 (1.0–2.1)
	Army	66	1.0 (0.7–1.2)
	Air Force	10	1.0 (0.5–1.8)

continued

TABLE 7-19 Melanoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
AIHW, 1999	Australian Vietnam veterans—incidence (validation study)		*Expected number of exposed cases (95% CI)*
		483	380 (342–418)
CDVA, 1998a	Australian Vietnam veterans (men)—self-reported incidence	2,689	380 (342–418)
CDVA, 1998b	Australian Vietnam veterans (women)—self-reported incidence	7	3 (1–8)
CDVA, 1997a	Australian Vietnam veterans (men)	51	1.3 (0.9–1.7)
Australian Conscripted Army National Service (deployed vs nondeployed)			**All COIs**
ADVA, 2005c	Australian male conscripted Army National Service Vietnam-era veterans—deployed vs nondeployed		
	Incidence	204	1.1 (0.9–1.4)
	Mortality	14	0.6 (0.3–1.1)
CDVA, 1997b	Australian National Service Vietnam veterans	16	0.5 (0.2–1.3)
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			**All COIs**
Kogevinas et al., 1997	IARC cohort, male and female workers exposed to any phenoxy herbicide or chlorophenol	9	0.6 (0.3–1.2)
	Exposed to highly chlorinated PCDDs	5	0.5 (0.2–3.2)
	Not exposed to highly chlorinated PCDDs	4	0.0 (0.3–2.4)
Dow Chemical Company—Midland, MI (included in IARC and NIOSH cohorts)			**All COIs**
Collins et al., 2009a	Trichlorophenol workers	2	0.6 (0.1–2.3)
Collins et al., 2009b	Pentachlorophenol workers	1	0.7 (0.0–4.0)
Danish Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Lynge, 1993	Danish production workers—updated incidence	4	4.3 (1.2–10.9)
Dutch Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Hooiveld et al., 1998	Dutch chemical production workers	1	2.9 (0.1–15.9)
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)			**Dioxin, phenoxy herbicides**
McBride et al., 2009a	1,599 production workers (male and female) vs national rates—mortality 1969 through 2004		
	Ever-exposed workers	2	1.0 (0.1–3.7)

TABLE 7-19 Melanoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Hansen et al., 2007	Danish gardeners—incidence (skin, ICD-7 190–191)		
	10-yr follow-up (1975–1984) reported in Hansen et al. (1992)	31	1.3 (0.9–1.8)
	25-yr follow-up (1975–2001)		
	Born before 1915 (high exposure)	28	0.9 (0.6–1.4)
	Born 1915–1934 (medium exposure)	36	0.6 (0.4–0.9)
	Born after 1934 (low exposure)	5	0.3 (0.1–0.7)
't Mannetje et al., 2005	New Zealand phenoxy herbicide producers, sprayers—mortality		
	Phenoxy herbicide producers (men and women)	0	0.0 (0.0–3.0)
	Phenoxy herbicide sprayers (> 99% men)	1	0.6 (0.0–3.4)
Agricultural Health Study			**Herbicides**
Dennis et al., 2010	AHS (licensed, male pesticide applicators)—150 cutaneous melanomas among 24,704 pesticide applicators		
	Ever-exposed to arsenic-based pesticides vs never-exposed		1.3 (0.7–2.4)
	Ever used lead arsenate insecticide		1.2 (0.6–2.3)
Samanic et al., 2006	Pesticide applicators in AHS—melanoma incidence from enrollment through 2002		
	Dicamba—lifetime days exposure		
	None	32	1.0
	1– < 20	10	1.0 (0.5–2.1)
	20– < 56	18	1.6 (0.8–3.0)
	56– < 116	6	0.7 (0.3–1.8)
	≥ 116	6	0.8 (0.3–2.1)
			p-trend = 0.51
Alavanja et al., 2005	US AHS—incidence		
	Private applicators (men and women)	100	1.0 (0.8–1.2)
	Spouses of private applicators (> 99%women)	67	1.6 (1.3–2.1)
	Commercial applicators (men and women)	7	1.1 (0.4–2.2)
Blair et al., 2005a	US AHS		
	Private applicators (men and women)	13	0.7 (0.4–1.3)
	Spouses of private applicators (> 99%women)	2	0.4 (0.1–1.6)
Other Agricultural Workers			**Herbicides**
Blair et al., 1993	US farmers in 23 states		
	White men	244	1.0 (0.8–1.1)
	White women	5	1.1 (0.4–2.7)
Ronco et al., 1992	Danish workers—incidence		
	Men	72	0.7 (p < 0.05)
	Women	5	1.2 (nr)

continued

TABLE 7-19 Melanoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Wigle et al., 1990	Canadian farmers	24	1.1 (0.7–1.6)
Wiklund, 1983	Swedish male and female agricultural workers—incidence	268	*99% CI* 0.8 (0.7–1.0)
Other Studies of Herbicide and Pesticide Applicators			**Herbicides**
Swaen et al., 2004	Dutch licensed herbicide applicators		
	Melanoma, squamous-cell carcinoma, unknown skin cancer (mortality presumably attributable to melanoma)	5	3.6 (1.2–8.3)
Torchio et al., 1994	Italian licensed pesticide users	9	1.2 (0.6–2.3)
Magnani et al., 1987	UK case–control		
	Herbicides	nr	1.2 (0.4–4.0)
	Chlorophenols	nr	0.9 (0.4–2.3)
Forestry Workers			**Herbicides**
Thörn et al., 2000	Swedish lumberjack workers exposed to phenoxyacetic herbicides—incidence		
	Women	1	3.5 (0.1–19.2)
	Men	0	nr
Hertzman et al., 1997	British Columbia sawmill workers		
	Incidence	38	1.0 (0.7–1.3)
	Mortality	17	1.4 (0.9–2.0)
Paper and Pulp Workers			**Dioxins**
McLean et al., 2006	IARC cohort of pulp and paper workers Exposure to nonvolatile organochlorine compounds		
	Never	20	0.8 (0.5–1.3)
	Ever	21	1.2 (0.7–1.8)
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Consonni et al., 2008	Seveso residents—25-yr follow-up—men, women		
	Zone A	1	3.1 (0.4–22.0)
	Zone B	2	1.0 (0.2–3.9)
	Zone R	12	0.8 (0.4–1.5)
Pesatori et al., 2009	Seveso—20-yr follow-up to 1996—incidence		
	Zone A	1	1.6 (0.2–11.6)
	Zone B	2	0.5 (0.1–2.0)
	Zone R	19	0.7 (0.4–1.1)
Bertazzi et al., 2001	Seveso residents—20-yr follow-up		
	Zones A, B—men	1	1.5 (0.2–12.5)
	women	2	1.8 (0.4–7.3)

TABLE 7-19 Melanoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Bertazzi et al., 1997	Seveso residents—15-yr follow-up		
	Zone A—women	1	9.4 (0.1–52.3)
	Zone R—men	3	1.1 (0.2–3.2)
	women	3	0.6 (0.1–1.8)
Bertazzi et al., 1989a	Seveso residents—10-yr follow-up		
	Zones A, B, R—men	3	3.3 (0.8–13.9)
	women	1	0.3 (0.1–2.5)
Other Environmental Studies			
Svensson et al., 1995	Swedish fishermen (men and women)		**Organochlorine compounds**
	East coast		
	Incidence	0	0.0 (0.0–0.7)
	Mortality	0	0.0 (0.0–1.7)
	West coast		
	Incidence	20	0.8 (0.5–1.2)
	Mortality	6	0.7 (0.3–1.5)

ABBREVIATIONS: ACC, Army Chemical Corps; AFHS, Air Force Health Study; AHS, Agricultural Health Study; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; MI, Michigan; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; NZ, New Zealand; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; VA, US Department of Veterans Affairs.

[a]Cohorts are male, and outcome mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

mortality were compared in people who served in Vietnam (2,872) and those who did not (2,737). In comparing the Vietnam cohort with the nondeployed cohort, a moderate but not statistically significant increase in risk of malignant skin cancer was observed (adjusted RR = 1.52, 95% CI 0.37–6.20). In comparing mortality with that in males in the US population, the risk of skin cancer was slightly increased in both veteran cohorts (SMR = 1.33, 95% CI 0.43–3.10 for Vietnam veterans; SMR = 1.31, 95% CI 0.36–3.36 for the nondeployed veterans). Analyses of examining those who reported spraying herbicides in Vietnam (compared with veterans who reported no spraying) did not measure risk of mortality from malignant skin cancer associated with herbicide exposure.

A cohort study of Australian Vietnam veterans (O'Toole et al., 2009) was conducted in 1990–1993 and re-examined in 2005–2006. In the original assessment, 641 Australian Vietnam veterans were randomly selected for participation from the list of Army veterans deemed eligible for previous studies of Agent Orange, and 450 are included in the more recent assessment. Interviewers ad-

ministered the Australian Bureau of Statistics National Health Survey that assessed physical health and associated risk factors, a 32-item combat index, an assessment for combat-related posttraumatic stress disorder and an assessment of general psychiatric status. The prevalence of a variety of self-reported health conditions was compared with that in the general population, and SMRs were calculated (standardized to the Australian male population in 5-year age groups). Compared with the general population, Vietnam veterans had a higher prevalence of melanoma (SMR = 4.73, 95% CI 1.25–8.21). Given the self-reported outcome, the possibility that nonmelanoma skin cancers were misclassified into the melanoma category cannot be ruled out.

Occupational Studies

McBride et al. (2009a,b) evaluated mortality from cancers in an occupational cohort of TCP workers in New Zealand, a set of the IARC cohort (see Chapter 5). Workers were employed during the period 1969–1988, and SMRs were calculated by using the New Zealand population as the comparison group. Exposure was classified as ever exposed or never exposed to TCDD. In McBride et al. (2009a), two cases of malignant melanoma were identified in the ever-exposed group and none in the never-exposed group. When those cases were compared with the expected number of deaths in the New Zealand population, no association was observed (SMR = 1.0, 95% CI 0.1–3.7) in the ever-exposed workers. Results in McBride et al. (2009b) have not been included, because they were diluted by inclusion of a set of workers who had no opportunity for TCDD exposure and no observed deaths.

Collins et al. (2009a,b) reported the mortality experience in the occupational cohort in the Midland, Michigan, Dow Chemical plant previously included in analyses of the NIOSH mortality cohort, as reported by Fingerhut et al. (1991) and added to the expanded IARC phenoxy herbicide cohort (Kogevinas et al., 1997). TCP was produced at the plant in 1942–1979 and PCP in 1937–1980. Job histories of the workers were used to determine the amount of time that they spent in the TCP or PCP units. Mortality in the workers and SMRs were calculated by using the US population as the referent. One death from malignant melanoma was identified in the PCP-only workers (SMR = 0.7, 95% CI 0.0–4.0) (Collins et al., 2009b). In a separate analysis of the TCP workers (Collins et al., 2009a), two deaths from malignant melanoma were identified (SMR = 0.6, 95% CI 0.1–2.3); one of the deaths occurred in a worker who was exposed to both TCDD and PCP, and when this death was removed from the analysis, the SMR was reduced to 0.4 (95% CI 0.0–2.0). As pointed out in follow-up correspondence (Collins et al., 2010; Villeneuve and Steenland, 2010) and discussed in detail in Chapter 5, different latency models, different dose–response models, and in-depth analysis of the serum concentrations could alter some of the results reported in this analysis; given the small number of deaths from malignant melanoma, such methodologic considerations are unlikely to alter the conclusions regarding melanoma.

A possible association between pesticide use and melanoma was also evaluated in the AHS (Dennis et al., 2010). The AHS is described in Chapter 5. Among the pesticides of interest, any history of exposure to arsenic-based pesticides was weakly associated with melanoma in comparison with applicators who reported never using these types of pesticides (adjusted OR = 1.3, 95% CI 0.7–2.4). A similar result was observed for applicators who reported ever using lead arsenate insecticides (OR = 1.2, 95% CI 0.6–2.3).

Environmental Studies

Cancer incidence was re-evaluated in the Seveso cohort for the period 1977–1996 (Pesatori et al., 2009). The Seveso cohort, described in Chapter 5, includes all residents of Seveso at the time of the accident and those who migrated into or were born in the area in the 10-year period after the accident. A total of 218,761 residents are included in the analysis: 723 in the high-exposure zone (Zone A), 4,821 in the medium-exposure zone (Zone B), 31,643 in the low-exposure zone (Zone R), and the remainder who lived in the noncontaminated zone. A total of 22 melanoma cases were identified: 1 in Zone A, 2 in Zone B, and 19 in Zone R. Compared with the incidence in the reference zone, melanoma incidence was higher, but imprecise, in Zone A (RR = 1.62, 95% CI 0.23–11.61) and lower in Zones B and R (RR = 0.50, 95% CI 0.12–2.03; RR = 0.71, 95% CI 0.44–1.14, respectively).

Biologic Plausibility

There have been no new studies of animal models of skin cancer. TCDD and related herbicides have not been found to cause melanoma in animal models. In general, rodents, which are used in most toxicology studies, are not a good model for studying melanoma. TCDD does produce nonmelanoma skin cancers in animal models (Wyde et al., 2004). As discussed elsewhere in this chapter, TCDD is a known tumor-promoter and could act as a promoter for skin-cancer initiators, such as UV radiation. Ikuta et al. (2009) examined the physiologic role of the AHR in human skin and theorized that overactivation can lead to skin cancers, but they provided no evidence that melanoma incidence is increased after TCDD exposure.

The biologic plausibility of the carcinogenicity of the chemicals of interest is discussed in general at the beginning of this chapter.

Synthesis

No association between the chemicals of interest and melanoma was observed in any of the three new occupational studies. Although the risk of melanoma was increased in those living in the highest-exposure zone in the Seveso

cohort, this finding was based on only one melanoma case. The new studies do not provide evidence to support moving melanoma to the category of limited or suggestive evidence. Of the two new Vietnam veteran studies, no association was observed in the ACC study, which was based on five cases of malignant skin cancer in the Vietnam cohort and four cases in the non-Vietnam cohort, as reflected in the similar RRs in the two cohorts when mortality was compared with that in the general population. An increased risk of melanoma was reported in the O'Toole study of Australian Vietnam veterans, but the prevalence of self-reported melanoma in the veteran population (1.6%) suggests that nonmelanoma skin cancer may have been misclassified as melanoma.

The committee responsible for *Update 2006* was unable to reach a consensus as to whether there was limited or suggestive evidence of an association between exposure to the chemicals of interest and melanoma or inadequate or insufficient evidence to determine whether there is an association. That committee recognized that the findings from the AFHS, including the evaluation of TCDD measurements and melanoma (Akhtar et al., 2004; Pavuk et al., 2005), were of prime interest. However, the data from the final AFHS examination cycle indicate that many more melanoma cases were diagnosed in the comparison veterans than in the Ranch Hand subjects, so the committee responsible for *Update 2006* recommended that the Akhtar et al. analyses be rerun on the final AFHS dataset. The final data on the Ranch Hand and comparison subjects still have not been analyzed in a satisfactory and uniform manner, so the present committee also strongly encourages such an analysis to provide documentation of the full melanoma experience revealed by the AFHS and to permit definitive evaluation of the possible association between the chemicals of interest and melanoma.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and melanoma.

SKIN CANCER—BASAL-CELL CANCER AND SQUAMOUS-CELL CANCER (NONMELANOMA SKIN CANCERS)

The preceding section on melanoma presented background information on nonmelanoma skin cancers (ICD-9 173).

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between

exposure to the chemicals of interest and skin cancer, and additional information available to the committee responsible for *Update 1996* did not change that conclusion. The committee responsible for *Update 1998* considered the literature on nonmelanocytic skin cancer separately from that on melanoma and concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the chemicals of interest and basal-cell or squamous-cell cancer. The committees responsible for *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008* did not change that conclusion. Table 7-20 summarizes the relevant studies.

Update of the Epidemiologic Literature

No Vietnam-veteran studies or occupational studies concerning exposure to the chemicals of interest and basal-cell or squamous-cell cancer have been published since *Update 2006*.

Environmental Studies

Cancer incidence was re-evaluated in the Seveso cohort for the period 1977–1996 (Pesatori et al., 2009). The Seveso cohort, described in Chapter 5, includes all residents of Seveso at the time of the accident and those who migrated into or were born in the area in the 10-year period after the accident. A total of 218,761 residents are included in the analysis: 723 in the high-exposure zone (Zone A), 4,821 in the medium-exposure zone (Zone B), 31,643 in the low-exposure zone (Zone R), and the remainder who lived outside the zone of exposure. A total of 96 skin-cancer cases were identified; 3 in Zone A, 5 in Zone B, and 88 in Zone R. Compared with the incidence in the reference zone, the incidence of skin cancer was increased, but imprecise, in Zone A (RR = 1.39, 95% CI 0.45–4.32) and decreased in Zones B and R (RR = 0.37, 95% CI 0.15–0.90; RR = 0.93, 95% CI 0.75–1.17, respectively).

Biologic Plausibility

There are no new studies on animal models of skin cancer to report. TCDD has been shown to produce nonmelanoma skin cancers in animal models (Wyde et al., 2004). As discussed elsewhere in this chapter, TCDD is a known tumor-promoter and could act as a promoter for skin-cancer initiators, such as UV radiation, but no experiments have been conducted specifically to support this potential mechanism.

The biologic plausibility of the carcinogenicity of the chemicals of interest is discussed in general at the beginning of this chapter.

TABLE 7-20 Selected Epidemiologic Studies—Other Nonmelanoma (Basal-Cell and Squamous-Cell) Skin Cancer

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans			**All COIs**
Pavuk et al., 2005	White Air Force comparison subjects only (basal cell and squamous cell)—incidence		
	Serum TCDD (pg/g), based on model with exposure variable $\log_e$(TCDD)		
	Per unit increase of –$\log_e$(TCDD)	253	1.2 (0.9–1.4)
	Quartiles (pg/g)		
	0.4–2.6	50	nr
	2.6–3.8	59	1.2 (0.8–1.8)
	3.8–5.2	71	1.5 (1.1–2.3)
	> 5.2	73	1.4 (0.9–2.0)
	Number of years served in SEA		
	Per year of service	253	1 (0.9 –1.1)
	Quartiles (years in SEA)		
	0.8–1.3	55	nr
	1.3–2.1	50	0.9 (0.6–1.4)
	2.1–3.7	73	1.1 (0.8–1.6)
	3.7–16.4	75	1.2 (0.8–1.7)
AFHS, 2000	Air Force Ranch Hand veterans—incidence		
	Basal-cell carcinoma	121	1.2 (0.9–1.6)
	Squamous-cell carcinoma	20	1.5 (0.8–2.8)
Wolfe et al., 1990	Air Force Ranch Hand veterans—incidence		
	Basal cell carcinoma	78	1.5 (1.0–2.1)
	Squamous cell carcinoma	6	1.6 (0.5–5.1)
Australian Vietnam Veterans vs Australian Population			**All COIs**
CDVA, 1998a	Australian Vietnam veterans (men)—self-reported incidence	6,936	nr
CDVA, 1998b	Australian Vietnam veterans (women)—self-reported incidence	37	nr
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			**Dioxin, phenoxy herbicides**
Kogevinas et al., 1997	IARC cohort, male and female workers exposed to any phenoxy herbicide or chlorophenol	4	0.9 (0.3–2.4)
	Exposed to highly chlorinated PCDDs	4	1.3 (0.3–3.2)
	Not exposed to highly chlorinated PCDDs	0	0.0 (0.0–3.4)
Dow Production Workers—Midland, MI (included in IARC and NIOSH cohorts)			**Dioxin, phenoxy herbicides**
Burns et al., 2001	Dow 2,4-D production workers		
	Nonmelanoma skin cancer	0	nr
United Kingdom Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Coggon et al., 1986	British MCPA production workers	3	3.1 (0.6–9.0)

TABLE 7-20 Other Nonmelanoma (Basal-Cell and Squamous-Cell) Skin Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Agricultural Workers			**Herbicides**
Hansen et al., 2007	Danish gardeners—incidence (skin, ICD-7 190–191)		
	10-yr follow-up (1975–1984) reported in Hansen et al. (1992)	31	1.3 (0.9–1.8)
	25-yr follow-up (1975–2001)		
	Born before 1915 (high exposure)	28	0.9 (0.6–1.4)
	Born 1915–1934 (medium exposure)	36	0.6 (0.4–0.9)
	Born after 1934 (low exposure)	5	0.3 (0.1–0.7)
Blair et al., 1993	US farmers in 23 states		
	Skin (including melanoma)		
	White men	425	1.1 (1.0–1.2)
	White women	6	1.0 (0.4–2.1)
Ronco et al., 1992	Danish workers—incidence		
	Men—self-employed	493	0.7 ($p < 0.05$)
	employee	98	0.7 ($p < 0.05$)
	Women—self-employed	5	0.3 ($p < 0.05$)
	employee	10	0.9 (nr)
	family worker	90	0.6 ($p < 0.05$)
Wiklund, 1983	Swedish male and female agricultural workers—incidence	708	*99% CI* 1.1 (1.0–1.2)
Studies of Herbicide and Pesticide Applicators			**Herbicides**
Swaen et al., 2004	Dutch licensed herbicide applicators		
	Melanoma, squamous-cell carcinoma, unknown skin cancer (mortality presumably attributable to melanoma)	5	3.6 (1.2–8.3)
Torchio et al., 1994	Italian licensed pesticide users	3	0.6 (0.1–1.8)
Zhong and Rafnsson, 1996	Icelandic pesticide users (men, women—incidence)		
	Men	5	2.8 (0.9–6.6)
Forestry Workers			**Herbicides**
Thörn et al., 2000	Swedish lumberjacks exposed to phenoxyacetic herbicides—incidence		
	Foremen	1	16.7 (0.2–92.7)
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Pesatori et al., 2009	Seveso—20-yr follow-up to 1996—incidence		
	Zone A	3	1.4 (0.5–4.3)
	Zone B	5	0.4 (0.2–0.9)
	Zone R	88	0.9 (0.8–1.2)

continued

TABLE 7-20 Other Nonmelanoma (Basal-Cell and Squamous-Cell) Skin Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Bertazzi	Seveso residents—10-yr follow-up—incidence		
et al., 1993	Zone A—men	1	2.4 (0.3–17.2)
	women	1	3.9 (0.5–28.1)
	Zone B—men	2	0.7 (0.2–2.9)
	women	2	1.3 (0.3–5.1)
	Zone R—men	20	1.0 (0.6–1.6)
	women	13	1.0 (0.6–1.9)
Pesatori	Seveso residents—incidence		
et al., 1992	Zones A, B—men	3	1.0 (0.3–3.0)
	women	3	1.5 (0.5–4.9)
	Zone R—men	20	1.0 (0.6–1.6)
	women	13	1.0 (0.5–1.7)
Other Environmental Studies			**Herbicides**
Gallagher	Alberta, Canada, residents—squamous-cell		
et al., 1996	carcinoma—incidence		
	All herbicide exposure	79	1.5 (1.0–2.3)
	Low herbicide exposure	33	1.9 (1.0–3.6)
	High herbicide exposure	46	3.9 (2.2–6.9)
	Alberta, Canada, residents—basal-cell carcinoma		
	All herbicide exposure	70	1.1 (0.8–1.7)
Svensson	Swedish fishermen		**Organochlorine**
et al., 1995	East coast		**compounds**
	Incidence	22	2.3 (1.5–3.5)
	Mortality	0	0.0 (0.0–15.4)
	West coast		
	Incidence	69	1.1 (0.9–1.4)
	Mortality	5	3.1 (1.0–7.1)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MI, Michigan; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

[a]Subjects are male, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

Synthesis

In accord with the results of reports previously assessed, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and basal-cell or squamous-cell cancer.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and basal-cell or squamous-cell cancer.

BREAST CANCER

Breast cancer (ICD-9 174 for females, ICD-9 175 for males) is the second-most common type of cancer (after nonmelanoma skin cancer) in women in the United States. ACS estimated that 207,090 women would receive diagnoses of breast cancer in the United States in 2010 and that 39,840 would die from it (Jemal et al., 2010). Overall, those numbers represent about 28% of the new cancers and 15% of cancer deaths in women. Incidence data on breast cancer are presented in Table 7-21.

Breast-cancer incidence generally increases with age. In the age groups of most Vietnam veterans, the incidence is higher in whites than in blacks. Established risk factors other than age include personal or family history of breast cancer and some characteristics of reproductive history—specifically, early menarche, late onset of menopause, and either no pregnancies or first full-term pregnancy after the age of 30 years. A pooled analysis of six large-scale prospective studies of invasive breast cancer showed that alcohol consumption over the range of consumption reported by most women was associated with a small linear increase in incidence in women (Smith-Warner et al., 1998). It is now generally accepted that breast-cancer risk is increased by prolonged use of hormone-replacement therapy, particularly preparations that combine estrogen and progestins (Chlebowski et al., 2003). The potential of other personal behavioral and environmental factors (including use of exogenous hormones) to affect breast-cancer incidence is being studied extensively.

Most of the roughly 10,000 female Vietnam veterans who were potentially exposed to herbicides in Vietnam are approaching or have recently reached meno-

TABLE 7-21 Average Annual Incidence (per 100,000) of Breast Cancer in United States[a]

	55–59 Years Old			60–64 Years Old			65–69 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Men	1.9	1.9	2.9	3.3	3.3	7.2	4.9	5.3	4.1
Women	283.2	289.4	273.6	357.1	369.8	339.6	412.1	430.9	376.9

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2004–2008 (NCI, 2010).

pause. Given the high incidence of breast cancer in older and postmenopausal women in general, it is expected on the basis of demographics alone that the breast-cancer burden in female Vietnam veterans will increase in the near future.

The vast majority of breast-cancer epidemiologic studies involve women, but the disease also occurs rarely in men, with 1,970 new cases expected in 2010 (Jemal et al., 2010). Reported instances of male breast cancer are noted, but the committee's conclusions are based on the studies in women.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the chemicals of interest and breast cancer. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion. After consideration of a new study with positive findings for association of breast cancer with 2,4-D exposure in female farm workers in California (Mills and Yang, 2005)—in conjunction with the earlier findings of Kang et al. (2000), Kogevinas et al. (1997), Revich et al. (2001), and Warner et al. (2002)—the committee responsible for *Update 2006* was unable to reach consensus as to whether there might be limited or suggestive evidence of an association between the chemicals of interest and breast cancer. After reviewing studies that had null findings on mortality from breast cancer in the important cohorts of female Vietnam-era veterans (Cypel and Kang, 2008) and Seveso residents (Consonni et al., 2008), all members of the committee for *Update 2008* concurred that breast cancer should remain in the category of inadequate or insufficient evidence of an association.

Table 7-22 summarizes the relevant research.

Update of the Epidemiologic Literature

No Vietnam-veteran studies concerning exposure to the chemicals of interest and breast cancer have been published since *Update 2008*.

Occupational Studies

McBride et al. (2009a,b) extended their earlier research by including additional exposed and unexposed workers, constructing exposure estimates based on serum dioxin (TCDD) concentrations in exposed and unexposed workers, and extending follow-up by 4 years. The authors reported on the mortality experience of 1,599 workers employed during 1969–1988 in a New Zealand site that manufactured TCP and a nearby field station where 2,4,5-T was occasionally used and tested (McBride et al., 2009a). Measurements of 346 blood samples confirmed higher exposure than New Zealand background. The study was limited

TABLE 7-22 Selected Epidemiologic Studies—Breast Cancer

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US CDC Vietnam Experience Study			
Boehmer et al., 2004	Follow-up of CDC VES	0	nr
US VA Cohort of Female Vietnam Veterans			**All COIs**
Cypel and Kang, 2008	US Vietnam veterans—women	57	1.0 (0.7–1.4)
	Vietnam-veteran nurses	44	0.9 (0.6–1.4)
Kang et al., 2000	Female US Vietnam veterans	170	1.2 (0.9–1.5)
Dalager et al., 1995	Female US Vietnam veterans	26	1.0 (0.6–1.8)
Thomas et al., 1991	Female US Vietnam veterans	17	1.2 (0.6–2.5)
Australian Vietnam Veterans vs Australian General Population			**All COIs**
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence	7	0.9 (0.4–1.9)
	Navy	1	0.6 (0.0–3.3)
	Army	5	1.0 (0.3–2.2)
	Air Force	1	1.1 (0.0–6.3)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—mortality	4	2.2 (0.6–5.4)
	Navy	1	2.5 (0.0–13.5)
	Army	3	2.5 (0.5–7.2)
	Air Force	0	0.0 (0.0–14.6)
			Expected number of exposed cases (95% CI)
CDVA, 1998b	Australian Vietnam veterans (women)—self-reported incidence	17	5 (2–11)
CDVA, 1997a	Australian military Vietnam veterans (men)	3	5.5 (1.0– > 10.0)
Australian Conscripted Army National Service (deployed vs nondeployed)			**All COIs**
ADVA, 2005c	Australian male conscripted Army National Service Vietnam era veterans—deployed vs nondeployed	0	nr
	Incidence	0	0.0 (0.0–2.4)
	Mortality	nr	
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			**Dioxin, phenoxy herbicides**
Kogevinas et al., 1993	IARC cohort—women	7	0.9 (0.4–1.9)

continued

TABLE 7-22 Breast Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Saracci et al., 1991	IARC cohort—exposed subcohort (men and women)		
	Men	2	3.5 (0.4–12.5)
	Women	1	0.3 (0.0–1.7)
Danish Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Lynge, 1985	Danish male and female production workers—incidence		
	Women	13	0.9 (nr)
German Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Manz et al., 1991	German production workers—men, women		
	Women	9	2.2 (1.0–4.1)
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)			**Dioxin, phenoxy herbicides**
McBride et al., 2009a	1,599 production workers (male and female) vs national rates—mortality 1969 through 2004		
	Ever-exposed female workers	2	1.4 (0.2–5.0)
't Mannetje et al., 2005	Phenoxy herbicide producers		
	Women	1	1.3 (0.0–7.2)
	Men	1	32 (0.8–175)
	Phenoxy herbicide sprayers (> 99% men)	0	0.0 (nr)
Agricultural Health Study			**Herbicides**
Alavanja et al., 2005	US AHS—incidence		
	Private applicators (men and women)	27	1.1 (0.7–1.6)
	Spouses of private applicators (> 99% women)	474	1.0 (0.9–1.1)
	Commercial applicators (men and women)	1	0.6 (0.1–3.5)
Engel et al., 2005	US AHS, wives of private applicators—incidence		
	Wives' own use of phenoxy herbicides	41	0.8 (0.6–1.1)
	2,4-D	41	0.8 (0.6–1.1)
	Husbands' use of phenoxy herbicides	110	1.1 (0.7–1.8)
	2,4-D	107	0.9 (0.6–1.4)
	2,4,5-T	44	1.3 (0.9–1.9)
	2,4,5-TP	19	2.0 (1.2–3.2)
Blair et al., 2005a	US AHS—mortality		
	Private applicators (men and women)	3	0.9 (0.2–2.7)
	Spouses of private applicators (> 99% women)	54	0.9 (0.7–1.1)
Paper and Pulp Workers			**Dioxin**
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	21	0.9 (0.6–1.4)
	Ever	32	0.9 (0.6–1.3)

TABLE 7-22 Breast Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Other Agricultural Workers			**Herbicides**
Mills and Yang, 2005	Hispanic agricultural farm workers (women)		
	Cancer diagnosis 1987–1994		
	Low 2,4-D use	12	0.6 (0.2–1.9)
	High 2,4-D use	8	0.6 (0.2–1.7)
	Cancer diagnosis 1995–2001		
	Low 2,4-D use	19	2.2 (1.0–4.9)
	High 2,4-D use	21	2.1 (1.1–4.3)
Duell et al., 2000	Female farm workers, residents in North Carolina		
	Used pesticides in garden	228	2.3 (1.7–3.1)
	Laundered clothes for pesticide user	119	4.1 (2.8–5.9)
Blair et al., 1993	US farmers in 23 states		
	Men—white	18	0.7 (0.4–1.2)
	nonwhite	4	1.7 (0.5–4.4)
	Women—white	71	1.0 (0.8–1.3)
	nonwhite	30	0.7 (0.5–1.0)
Ronco et al., 1992	Danish, Italian farm workers		
	Male farmers	5	0.5 (nr)
	Female farmers	41	0.9 (nr)
	Female family workers	429	0.8 ($p < 0.05$)
Wiklund, 1983	Swedish agricultural workers—incidence		*99% CI*
	Men and women	444	0.8 (0.7–0.9)
	Men only	nr	1.0 (nr)
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			
TCDD			
Consonni et al., 2008	Seveso residents (men and women)—25-yr follow-up		
	Zone A	2	0.6 (0.2–2.4)
	Zone B	13	0.6 (0.3–1.2)
	Zone R	133	0.9 (0.7–1.1)
Pesatori et al., 2009	Seveso—20-yr follow-up to 1996—incidence		
	Zone A	8	1.4 (0.7–2.9)
	Zone B	30	0.9 (0.6–1.2)
	Zone R	249	1.0 (0.9–1.2)
	Zone A only (15+ yrs after accident)	5	2.6 (1.1–6.2)
	Zone A only (10–14 yrs after accident)	2	1.4 (0.4–5.7)
	Zone A only (5–9 yrs after accident)	1	0.8 (0.1–5.7)
Bertazzi et al., 2001	Seveso residents—20-yr follow-up		
	Zone A, B—females	14	0.7 (0.4–1.3)
Bertazzi et al., 1997	Seveso residents—15-yr follow-up		
	Zone A—women	1	0.6 (0.0–3.1)
	Zone B—women	9	0.8 (0.4–1.5)
	Zone R—women	67	0.8 (0.6–1.0)

continued

TABLE 7-22 Breast Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Bertazzi et al., 1993	Seveso residents—10-yr follow-up—incidence		
	Zone A—women	1	0.5 (0.1–3.3)
	Zone B—women	10	0.7 (0.4–1.4)
	Zone R—women	106	1.1 (0.9–1.3)
	men	1	1.2 (0.1–10.2)
Bertazzi et al., 1989b	Seveso residents—10-yr follow-up		
	Zone A—women	1	1.1 (0.1–7.5)
	Zone B—women	5	0.9 (0.4–2.1)
	Zone R—women	28	0.6 (0.4–0.9)
Seveso Women's Health Study			**Dioxin**
Warner et al., 2002	SWHS—981 women who were infants to 40 yrs of age when exposed—incidence		
	With 10-fold increase in TCDD	15	2.1 (1.0–4.6)
Chapaevsk, Russia Residential Cohort			
Revich et al., 2001	Residents of Chapaevsk, Russia—women	58	2.1 (1.6–2.7)
Other Environmental Studies			
Turunen et al., 2008	Finnish fishermen and spouses		**Dioxin**
	Fishermen's wives	18	0.8 (0.5–1.3)
Viel et al., 2008	Case–control study in Besançon, France—incidence		**Dioxin**
	Residence in zones of dioxin exposure around solid-waste incinerator		
	Women, 20–59 yrs of age		
	Very low	41	1.0
	Low	81	1.1 (0.7–1.6)
	Intermediate	64	1.3 (0.8–1.9)
	High	11	0.9 (0.4–1.8)
	Women, at least 60 yrs of age		
	Very low	50	1.0
	Low	111	0.9 (0.6–1.3)
	Intermediate	72	1.0 (0.7–1.4)
	High	4	0.3 (0.1–0.9)
Teitelbaum et al., 2007	Case–control study in Long Island, New York—incidence		**Pesticides**
	Used lawn and garden pesticides		
	Never	240	1.0
	Ever	1,254	1.3 (1.1–1.6)
	Product for weeds	1,109	1.4 (1.2–1.8)

TABLE 7-22 Breast Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Reynolds et al., 2005	Women undergoing breast biopsies in San Francisco area hospitals—79 breast-cancer cases vs 52 controls with benign breast conditions—incidence		**PCDDs, PCDFs**
	Total TEQs (pg/g) in adipose breast tissue		
	≤ 14.0	24	1.0
	14.1–20.9	22	0.7 (0.3–1.9)
	≤ 21.0	33	0.3 (0.3–2.0)
			p-trend = 0.99
Reynolds et al., 2004	California Teachers Study cohort		**2,4-D, cacodylic acid**
	Residential proximity to use of "endocrine disruptors" (including 2,4-D, cacodylic acid)		
	Quartiles of use (lb/mi^2)		
	< 1	1,027	1.0
	1–21	274	1.0 (0.8–1.1)
	22–323	114	0.9 (0.7–1.1)
	≥ 324	137	1.0 (0.9–1.3)
Bagga et al., 2000	Women receiving medical care in Woodland Hills, California	73	**Organochlorines** nr
Demers et al., 2000	Women in Quebec City—newly diagnosed	314	**Organochlorines** nr
Holford et al., 2000	Patients at Yale–New Haven hospital with breast related surgery; dioxin-like congener 156	nr	**dl-PCBs** 0.9 (0.8–1.0)
Høyer et al., 2000	Female participants in Copenhagen City Heart Study	195	**Organochlorines** *Overall survival relative risk* 2.8 (1.4–5.6)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TP, 2 (2,4,5-trichlorophenoxy) propionic acid; AHS, Agricultural Health Study; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; nr, not reported; NZ, New Zealand; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCDF, polychlorinated dibenzofurans; SWHS, Seveso Women's Health Study; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEQ, toxicity equivalent quotient; VA, US Department of Veterans Affairs; VES, Vietnam Experience Study.

[a]Subjects are female, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

by a high loss of follow-up (21%). The SMR for ever-exposed female workers was 1.4 ((95% CI 0.2–5.0) on the basis of two observed death. It should be noted that the authors reported increased SMRs for other cancers previously found to be associated with dioxins. Results in McBride et al. (2009b) have not been included, because they were diluted by inclusion of a set of workers who had no opportunity for TCDD exposure and no observed deaths.

Environmental Studies

Pesatori et al. (2009) updated mortality and cancer-incidence results for the study conducted among residents of Seveso, Italy. Poisson regression models were used to calculate sex-, age-, and period-adjusted rate ratios. The use of exposure zones (A, B, and R) to define individual exposure introduces misclassification that is likely to be random and to attenuate associations. However, later serum measurements on a subset confirmed the utility of assigning zone of residence as a proxy for exposure to TCDD.

The rate ratio for Zone A was increased (1.43, 95% CI 0.71–2.87), whereas the RRs for Zones B and R were 0.85 (95% CI 0.59–1.22) and 1.00 (95% CI 0.88–1.15), respectively. Analyses accounting for time since acute high exposure to TCDD found a significantly increased incidence of breast cancer 15 or more years after the accident in Zone A (RR 2.57, 95% CI 1.07–6.20) on the basis of five cases. The RR 10–14 years after the accident was 1.42 (95% CI 0.35–5.68), and for 5–9 years after the accident it was 0.81 (95% CI 0.11–5.74) on the basis of two and one deaths, respectively.

Turunen et al. (2008) conducted a mortality study of Finnish fishermen and fishermen's wives. The cohort consisted of 6,410 Finnish professional fisherman and their wives (4,260). The cohort was linked with Statistics Finland's national cause-of-death data for 1980–2005. SMRs were calculated by using national mortality figures. The SMR for breast cancer in fishermen's wives was not increased (SMR = 0.80, 95% CI 0.47–1.25) on the basis of 18 observed deaths.

Dai and Oyana (2008) conducted an epidemiologic study with an ecologic study design to explore the spatial variation in breast-cancer incidence in Midland, Saginaw, and Bay Counties in Michigan. They used spatial modeling and soil concentrations to assign exposure on the basis of ZIP codes. The authors reported that there was a temporal increase in the number of breast-cancer cases from 1985 to 2002; that ZIP codes with the highest rates were clustered in or near contaminated areas, adjusted for age; and that living near or close to contaminated areas was spatially associated with increased breast-cancer incidence. The study has several limitations, the most important of which is that it did not collect information on individual exposure to dioxins. Therefore, the relevance of the study to the VAO report is low.

Biologic Plausibility

The experimental evidence indicates that 2,4-D, 2,4,5-T, and TCDD are weakly genotoxic at most. However, TCDD is a demonstrated carcinogen in animals and is recognized as having carcinogenic potential in humans because of the mechanisms discussed in Chapter 4.

With respect to breast cancer, studies performed in laboratory animals (Sprague-Dawley rats) indicate that the effect of TCDD may depend on the age

of the animal. For example, TCDD exposure was found to inhibit mammary-tumor growth in the adult rat (Holcombe and Safe, 1994) but to increase tumor growth in the neonatal rat (21 days old) (Desaulniers et al., 2001). Other studies have failed to demonstrate an effect of TCDD on mammary-tumor incidence or growth (Desaulniers et al., 2004).

Fenton (2009) recently reviewed the literature on TCDD and breast cancer and suggested that a mechanism may be related to endocrine disruption, which might indicate a close association between the development of mammary cancers and mammary gland differentiation. Agents capable of disrupting the ability of the normal mammary epithelial cell to enter or maintain its appropriate status (a proliferative, differentiated, apoptotic state), to maintain its appropriate architecture, or to conduct normal hormone (estrogen) signaling are likely to act as carcinogenic agents (Fenton, 2006; McGee et al., 2006). In that light, it is interesting that postnatal exposure of pregnant rats to TCDD has been found to alter proliferation and differentiation of the mammary gland (Birnbaum and Fenton, 2003; Vorderstrasse et al., 2004). Jenkins et al. (2007) used a carcinogen-induced rat mammary-cancer model to show that prenatal exposure to TCDD alters mammary gland differentiation and increases susceptibility to mammary cancer by altering the expression of estrogen-receptor genes and of genes involved in oxidative-stress defense. Thus, the effect of TCDD may depend on the timing of the exposure and on the magnitude of gene expression at the time of exposure; TCDD may influence mammary-tumor development only if exposure to it occurs during a specific window during breast development. The breast is the only human organ that does not fully differentiate until it becomes ready for use; nulliparous women have less-differentiated breast lobules, which are presumably more susceptible to carcinogenesis.

Activation of the AHR by dioxin or by the nondioxin ligand indole-3-carbinol is believed to protect against breast cancer by mechanisms that disrupt migration and metastasis (Bradlow, 2008; Hsu et al., 2007).

TCDD has been shown to modulate the induction of DNA chain breaks in human breast-cancer cells by regulating the activity of the enzymes responsible for estradiol catabolism and generating more reactive intermediates, which might contribute to TCDD-induced carcinogenesis by altering the ratio of 4-OH-estradiol to 2-OH-estradiol (Lin et al., 2007, 2008). A similar imbalance in metabolite ratios has been observed in pregnant Taiwanese women, in whom the ratio of 4-OH-estradiol to 2-OH-estradiol, a breast-cancer–risk marker, decreased with increasing exposure to TCDD (Wang et al., 2006). Expression of CYP1B1, the cytochrome P450 enzyme responsible for 2-OH-estradiol formation, but not CYP1A1, the one responsible for 4-OH estradiol formation, was found to be highly increased in premalignant and malignant rat mammary tissues in which the AHR was constitutively active in the absence of ligand (Yang et al., 2008). On the basis of recent mechanistic data, it has been proposed that the AHR contributes to mammary-tumor cell growth by inhibiting apoptosis while promoting

transition to an invasive, metastatic phenotype (Marlowe et al., 2008; Schlezinger et al., 2006).

Recent evidence has shown that AHR activation by TCDD in human breast and endocervical cell lines induces sustained high concentrations of the IL-6 cytokine, which has tumor-promoting effects in numerous tissues, including breast tissue, so TCDD might promote carcinogenesis in these tissues (DiNatali et al., 2010; Hollingshead et al., 2008). Degner et al. (2009) have shown that AHR ligands can upregulate the expression of COX-2, and this may lead to a proinflammatory environment that can support tumor development.

The biologic plausibility of the carcinogenicity of the chemicals of interest is discussed in general at the beginning of this chapter.

Synthesis

In the early 1990s, it was suggested that exposure to some environmental chemicals, such as organochlorine compounds, might play a role in the etiology of breast cancer through estrogen-related pathways. The relationship between organochlorines and breast-cancer risk has been studied extensively especially in the last decade; TCDD and dioxin-like compounds have been among the organochlorines so investigated. Today, there is no clear evidence of a causal role of most organochlorines in human breast cancer (Salehi et al., 2008).

Because of concerns raised by a combination of a new study that had good exposure assessment and positive findings (Mills and Yang, 2005) and several earlier studies (Kang et al., 2000; Kogevinas et al., 1997; Revich et al., 2001; Warner et al., 2002), some members of the committee responsible for *Update 2006* believed that there was suggestive evidence of an association, but that committee was unable to reach a consensus. After reviewing new studies that had null findings on mortality from breast cancer in the important cohorts of female Vietnam-era veterans (Cypel and Kang, 2008) and Seveso residents (Consonni et al., 2008), the committee for *Update 2008* readily reached consensus that breast cancer should remain in the category of inadequate or insufficient evidence of an association.

New evidence since the last VAO report includes the updated cancer-incidence results for residents of Seveso (Pesatori et al., 2009). The most compelling evidence from the recent study was the increased RR in Zone A for breast-cancer incidence after time since the accident was accounted for: 15 or more years and 10–14 years after the accident, the RR for breast cancer was RR 2.57 (95% CI 1.07–6.20), 1.42 (95% CI 0.35–5.68), respectively, whereas it was 0.81 (95% CI 0.11–5.74) 5–9 years after the accident. Accounting for latency between exposure and outcome led to stronger associations. However, despite evidence from the Seveso cohort, results from the occupational study by McBride et al. (2009a) did not support an increased risk of mortality from breast cancer.

Conclusion

Having considered the new evidence and the results of studies reviewed in previous updates, the present committee concludes that there is inadequate or insufficient evidence to determine whether there is an association (either positive or negative) between exposure to the chemicals of interest and breast cancer.

CANCERS OF THE FEMALE REPRODUCTIVE SYSTEM

This section addresses cancers of the cervix (ICD-9 180), endometrium (also referred to as the corpus uteri; ICD-9 182.0–182.1, 182.8), and ovary (ICD-9 183). Other cancers of the female reproductive system that are infrequently reported separately are unspecified cancers of the uterus (ICD-9 179), placenta (ICD-9 181), fallopian tube and other uterine adnexa (ICD-9 183.2–183.9), and other female genital organs (ICD-9 184); findings on these cancers are included in this section. It also presents statistics on other cancers of the female reproductive system. ACS estimates of the numbers of new female reproductive-system cancers in the United States in 2010 are presented in Table 7-23, with genital-system cancers representing roughly 10% of new cancer cases and 12% of cancer deaths in women (Jemal et al., 2010).

Cervical cancer occurs more often in blacks than in whites, whereas whites are more likely to develop endometrial and ovarian cancer. The incidence of endometrial and ovarian cancer is increased in older women and in those with positive family histories. Use of unopposed estrogen-hormone therapy and obesity, which increases endogenous concentrations of estrogen, both increase the risk of endometrial cancer. Human papilloma virus (HPV) infection, particularly infection with HPV types 16 and 18, is the most important risk factor for cervical cancer. Use of oral contraceptives is associated with a substantial reduction in the risk of ovarian cancer.

TABLE 7-23 Estimates of New Cases and Deaths from Selected Cancers of the Female Reproductive System in the United States in 2010

Site	New Cases	Deaths
Cervix	12,200	4,210
Endometrium	43,470	7,950
Ovary	21,880	13,850
Other female genital	2,300	7,810

SOURCE: Jemal et al., 2010.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the chemicals of interest and female reproductive cancers. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008* did not change that conclusion.

Tables 7-24, 7-25, and 7-26 summarize the results of the relevant studies.

Update of the Epidemiologic Literature

No Vietnam-veteran studies concerning exposure to the chemicals of interest and cancers of the female reproductive system have been published since *Update 2008*.

Occupational Studies

McBride et al. (2009a,b) published two reports of a mortality follow-up of the workers in the Dow AgroSciences plant in New Plymouth, New Zealand, who were potentially exposed to TCDD. No deaths were attributed to cancer of the corpus uteri (ICD-10 C54–C55) or ovary (ICD-10 C56). One death due to cancer of the cervix uteri (ICD-10 C53) was recorded in the group of never-exposed workers; no deaths from this cancer were recorded in the exposed workers. The results in McBride et al. (2009b) have not been included, because they were diluted by inclusion of a set of workers who had no opportunity for TCDD exposure and no observed deaths.

TABLE 7-24 Selected Epidemiologic Studies—Cervical Cancer

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US VA Cohort of Female Vietnam Veterans			**All COIs**
Kang et al., 2000	Female Vietnam veterans	57	1.1 (0.7–1.7)
Australian Vietnam Veterans vs Australian General Population			
All COIs			
CDVA, 1998b	Australian Vietnam veterans—self-reported incidence		*Expected number of exposed cases (95% CI)*
		8	1 (0–5)

TABLE 7-24 Cervical Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			**Dioxin, phenoxy herbicides**
Kogevinas et al., 1997	IARC cohort, female workers exposed to any phenoxy herbicide or chlorophenol	3	1.1 (0.2–3.3)
	Exposed to highly chlorinated PCDDs	0	0.0 (0.0–3.8)
	Not exposed to highly chlorinated PCDDs	3	1.8 (0.4–5.2)
Danish Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Lynge, 1993	Danish phenoxy herbicide workers	7	3.2 (1.3–6.6)
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)			**Dioxin, phenoxy herbicides**
McBride et al., 2009a	Dow trichlorophenol workers		
	Cervix uteri (ICD-10 C53)	0	0.0 (0.0–14.6)
Agricultural Workers			**Herbicides**
Blair et al., 1993	US farmers in 23 states		
	Whites	6	0.9 (0.3–2.0)
	Nonwhites	21	2.0 (1.3–3.1)
Ronco et al., 1992	Danish farmers—incidence		
	Self-employed farmers	7	0.5 ($p < 0.05$)
	Family workers	100	0.5 ($p < 0.05$)
	Employees	12	0.8 (nr)
Wiklund, 1983	Swedish female agricultural workers—incidence		*99% CI*
		82	0.6 (0.4–0.8)
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Pesatori et al., 2009	Seveso—20-yr follow-up to 1996—incidence		
	Zone A	2	2.7 (0.7–10.8)
	Zone B	7	1.5 (0.7–3.1)
	Zone R	28	0.8 (0.6–1.3)
Chapaevsk, Russia Residential Cohort			**Dioxin**
Revich et al., 2001	Residents of Chapaevsk, Russia	13	1.8 (1.0–3.1)

ABBREVIATIONS: CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; nr, not reported; NZ, New Zealand; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; VA, US Department of Veterans Affairs.

[a]Subjects are female, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

TABLE 7-25 Selected Epidemiologic Studies—Uterine Cancer

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US VA Cohort of Female Vietnam Veterans			**All COIs**
Cypel and Kang, 2008	US non-Vietnam veterans	5	0.8 (0.2–2.8)
	vs non-Vietnem nurses	5	1.3 (0.3–5.0)
Kang et al., 2000	US Vietnam veterans—incidence	41	1.0 (0.6–1.6)
Dalager et al., 1995	US Vietnam veterans	4	2.1 (0.6–5.4)
Australian Vietnam Veterans vs Australian Population			**All COIs**
CDVA, 1998b	Australian Vietnam veterans—self-reported incidence		*Expected number of exposed cases (95% CI)*
		4	1 (0–5)
OCCUPATIONAL			**All COIs**
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			**Dioxin, phenoxy herbicides**
Kogevinas et al., 1997	IARC cohort, female workers exposed to any phenoxy herbicide or chlorophenol (includes cancers of endometrium)	3	3.4 (0.7–10.0)
	Exposed to highly chlorinated PCDDs	1	1.2 (0.0–6.5)
	Not exposed to highly chlorinated PCDDs	4	2.3 (0.6–5.9)
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)			**Dioxin, phenoxy herbicides**
McBride et al., 2009a	1,599 production workers (male and female) vs national rates—mortality 1969 through 2004		
	Corpus uteri (ICD-10 C54–C55)	0	0.0 (0.0–30.6)
Agricultural Workers			**Herbicides**
Blair et al., 1993	US farmers in 23 states		
	Whites	15	1.2 (0.7–2.1)
	Nonwhites	17	1.4 (0.8–2.2)
Ronco et al., 1992	Danish farmers—incidence		
	Self-employed farmers	8	0.6 (nr)
	Family workers	103	0.8 ($p < 0.05$)
	Employees	9	0.9 (nr)
Wiklund, 1983	Swedish female agricultural workers—incidence	135	*99% CI* 0.9 (0.7–1.1)
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Consonni et al., 2008	Seveso residents—25-yr follow-up		
	Zone A	0	0
	Zone B	2	0.5 (0.1–1.9)
	Zone R	41	1.3 (0.9–1.8)

TABLE 7-25 Uterine Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Pesatori et al., 2009	Seveso—20-yr follow-up to 1996—incidence		
	Uterus (ICD-9 179–182)		
	Zone A	4	2.3 (0.9–6.3)
	Zone B	10	0.9 (0.5–1.7)
	Zone R	61	0.8 (0.6–1.0)
	Endometrium (ICD-9 182)		
	Zone A	1	1.2 (0.2–8.8)
	Zone B	3	0.6 (0.2–1.9)
	Zone R	27	0.7 (0.5–1.1)
Bertazzi et al., 2001	Seveso residents—20-yr follow-up		
	Zones A, B	2	0.5 (0.1–1.9)
Bertazzi et al., 1998	Seveso residents—15-yr follow-up		
	Zone B	1	0.3 (0.0–2.4)
Bertazzi et al., 1997	Seveso residents—15-yr follow-up		
	Zone B	1	0.3 (0.0–1.9)
	Zone R	27	1.1 (0.8–1.7)
Other Environmental Studies			
Weiderpass et al., 2000	Swedish women	154	1.0 (0.6–2.0)

ABBREVIATIONS: CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; nr, not reported; NZ, New Zealand; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; VA, US Department of Veterans Affairs.

[a]Subjects are female, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

Environmental Studies

Pesatori et al. (2009) updated cancer-incidence results for the study conducted among residents of Seveso, Italy. Poisson regression models were used to calculate sex-, age- and period-adjusted rate ratios. The use of exposure zones (A, B, and R) to define individual exposure introduces misclassification that is likely to be random and attenuate associations. However, later serum measurements of a subset confirmed the utility of assigning zone of residence as a proxy for exposure to TCDD.

The rate ratios for cancer of the uterus in Zones A, B, and R were 2.34 (95% CI 0.87–6.27), 0.93 (95% CI 0.49–1.73), and 0.79 (95% CI 0.60–1.03), respectively. The rate ratios for cancer of the cervix in Zones A, B, and R were 2.67 (95% CI 0.66–10.77), 1.47 (95% CI 0.69–3.12), and 0.84 (95% CI 0.57–1.25), respectively. Although cancer of the uterus and cancer of the cervix were higher in Zone A, the estimates were not statistically significant. For cancer of the en-

TABLE 7-26 Selected Epidemiologic Studies—Ovarian Cancer

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US VA Cohort of Female Vietnam Veterans			**All COIs**
Kang et al., 2000	Vietnam veterans—prevalence	16	1.8 (0.7–4.6)
Australian Vietnam Veterans vs Australian General Population			**All COIs**
CDVA, 1998b	Australian Vietnam veterans—self-reported incidence		*Expected number of exposed cases (95% CI)*
		1	0 (0–4)
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			**Dioxin, phenoxy herbicides**
Kogevinas et al., 1997	IARC cohort, female workers exposed to any phenoxy herbicide or chlorophenol	1	0.3 (0.0–1.5)
	Exposed to highly chlorinated PCDDs	0	0.0 (0.0–2.6)
	Not exposed to highly chlorinated PCDDs	1	0.5 (0.0–2.5)
Kogevinas et al., 1993	IARC cohort	1	0.7 (nr)
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)			**Dioxin, phenoxy herbicides**
McBride et al., 2009a	1,599 production workers (male and female) vs national rates—mortality 1969 through 2004		
	Ovarian cancer (ICD-10 C56)	0	0.0 (0.0–9.5)
Agricultural Health Study			**Herbicides**
Blair et al., 2005a	US AHS		
	Private applicators (men and women)	4	3.9 (1.1–10.1)
	Spouses of private applicators (> 99% women)	13	0.7 (0.4–1.2)
Alavanja et al., 2005	US AHS—incidence		
	Private applicators (men and women)	8	3.0 (1.3–5.9)
	Spouses of private applicators (> 99% women)	32	0.6 (0.4–0.8)
	Commercial applicators (men and women)	0	0.0 (0.0–16.0)
Other Agricultural Workers			**Herbicides**
Ronco et al., 1992	Danish farmers—incidence		
	Self-employed farmers	12	0.9 (nr)
	Family workers	104	0.8 ($p < 0.05$)
	Employees	5	0.5 (nr)
Other Occupational Studies			**Herbicides**
Donna et al., 1984	Female residents near Alessandria, Italy	18	4.4 (1.9–16.1)

TABLE 7-26 Ovarian Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Consonni et al., 2008	Seveso residents—25-yr follow-up		
	Zone A	1	1.2 (0.2–8.5)
	Zone B	2	0.4 (0.1–1.6)
	Zone R	37	1.0 (0.7–1.4)
Pesatori et al., 2009	Seveso—20-yr follow-up to 1996—incidence		
	Zone A	1	1.1 (0.2–7.9)
	Zone B	1	0.2 (0.0–1.3)
	Zone R	45	1.1 (0.8–1.5)
Bertazzi et al., 2001	Seveso residents—20-yr follow-up		
	Zones A, B	3	0.7 (0.2–2.0)
Bertazzi et al., 1998	Seveso residents—15-yr follow-up		
	Zone A	1	2.3 (0.3–16.5)
Bertazzi et al., 1997	Seveso residents—15-yr follow-up		
	Zone A—women	1	2.3 (0.0–12.8)
	Zone R—women	21	1.0 (0.6–1.6)

ABBREVIATIONS: AHS, Agricultural Health Study; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; nr, not reported; NZ, New Zealand; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); TCDD, 2,3,7,8-tetrachlorodibenxo-*p*-dioxin; VA, US Department of Veterans Affairs.

[a]Subjects are female, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

dometrium, the RRs in Zones A, B, and R were 1.24 (95% CI 0.17–8.82), 0.6 (95% CI 0.19–1.87), and 0.73 (95% CI 0.49–1.1), respectively. The RRs for ovarian cancer in Zones A, B, and R were 1.11 (95% CI 0.16–7.90), 0.18 (95% CI 0.02–1.25), and 1.12 (95% CI 0.82–1.54), respectively.

Biologic Plausibility

Yoshizawa et al. (2009) have shown that chronic administration of TCDD and other AHR ligands to female adult Harlan Sprague-Dawley rats results in chronic inflammation and increases in reproductive-tissue tumors, including cystic endometrial hyperplasia and uterine squamous-cell carcinoma. The mechanism of action might be related to endocrine disruption and chronic inflammation. Hollingshead et al. (2008) also showed that TCDD activation of the AHR in human breast and endocervical cell lines induces sustained high concentrations

of the IL-6 cytokine, which has tumor-promoting effects in numerous tissues, including ovarian; thus, TCDD might promote carcinogenesis in these tissues.

The biologic plausibility of the carcinogenicity of the chemicals of interest is discussed in general at the beginning of this chapter.

Synthesis

New information concerning female reproductive cancers since *Update 2008* was sparse and inconsistent. The results from the updated follow-up of residents of Seveso and the occupational study add little weight to the existing body of evidence.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and uterine, ovarian, or cervical cancer.

PROSTATE CANCER

ACS estimated that 217,730 new cases of prostate cancer (ICD-9 185) would be diagnosed in the United States in 2010 and that 32,050 men would die from it (Jemal et al., 2010). That makes prostate cancer the second-most common cancer in men (after nonmelanoma skin cancers); it is expected to account for about 28% of new cancer diagnoses and 11% of cancer deaths in men in 2010. The average annual incidence of prostate cancer is shown in Table 7-27.

The incidence of prostate cancer varies dramatically with age and race. The risk more than doubles from the ages of 50–54 years and 55–59 years, and it nearly doubles again from the ages of 55–59 years and 60–64 years. As a group, American black men have the highest recorded incidence of prostate cancer in the world (Miller et al., 1996); their risk is roughly twice that in whites in the

TABLE 7-27 Average Annual Incidence (per 100,000) of Prostate Cancer in United States[a]

55–59 Years Old			60–64 Years Old			65–69 Years Old		
All Races	White	Black	All Races	White	Black	All Races	White	Black
347.7	330.6	616.7	609.6	586.6	1,020.7	887.2	864.2	1,387.4

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2004–2008 (NCI, 2010).

United States, 5 times that in Alaska natives, and nearly 8.5 times that in Korean Americans. Little is known about the causes of prostate cancer. Other than race and age, risk factors include a family history of the disease and possibly some elements of the Western diet, such as high consumption of animal fats. The drug finasteride, which has been widely used to treat benign enlargement of the prostate, was found to decrease the prevalence of prostate cancer substantially in a major randomized trial (Thompson et al., 2003). Finasteride acts by decreasing the formation of potent androgen hormones in the prostate.

The study of the incidence of and mortality from prostate cancer is complicated by trends in screening for the disease. The widespread adoption of serum prostate-specific antigen (PSA) screening in the 1990s led to very large increases in prostate-cancer incidence in the United States, which have recently subsided as exposure to screening has become saturated. The long-term influence of better screening on incidence and mortality in any country or population is difficult to predict and will depend on the rapidity with which the screening tool is adopted, its differential use in men of various ages, and the aggressiveness of tumors detected early with this test (Gann, 1997). Because exposure to PSA testing is such a strong determinant of prostate-cancer incidence, epidemiologic studies must be careful to exclude differential PSA testing as an explanation of a difference in risk observed between two populations.

Prostate cancer tends not to be fatal, so mortality studies might miss an increased incidence of the disease. Findings that show an association between an exposure and prostate-cancer mortality should be examined closely to determine whether the exposed group might have had poorer access to treatment that would have increased the likelihood of survival.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was limited or suggestive evidence of an association between exposure to the chemicals of interest and prostate cancer. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008* did not change that conclusion.

Table 7-28 summarizes results of the relevant studies, including both morbidity and mortality studies. The type, quality, and specificity of each study must be considered in the interpretation and weighing of evidence. Because of study heterogeneity, simply examining all the estimated risks in the table together will not yield a good assessment of the risks.

TABLE 7-28 Selected Epidemiologic Studies—Prostate Cancer

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
Air Force Ranch Hands—Ranch Hand veterans vs SEA veterans			**All COIs**
Pavuk et al., 2006	AFHS subjects—incidence		
	20-year cumulative TCDD (ppt-year)		
	Comparison group	81	1.0
	Ranch Hand low (≤ 434 ppt-year)	31	1.0 (0.7–1.6)
	Ranch Hand high (> 434 ppt-year)	28	1.2 (0.8–1.9)
			p-trend = 0.42
	Last tour in SEA before 1969 (heavy spraying)		
	Yes		
	Comparison group	17	1.0
	Ranch Hand low (≤ 434 ppt-year)	9	1.0 (0.4–2.3)
	Ranch Hand high (> 434 ppt-year)	15	2.3 (1.1–4.7)
			p-trend = 0.04
	No		
	Comparison group	64	1.0
	Ranch Hand low (≤ 434 ppt-year)	22	1.1 (0.7–1.8)
	Ranch Hand high (> 434 ppt-year)	13	0.9 (0.5–1.6)
			p-trend = 0.75
	Less than 2 years served in SEA		
	Yes		
	Comparison group	16	1.0
	Ranch Hand low (≤ 434 ppt-year)	20	1.9 (1.0–3.7)
	Ranch Hand high (> 434 ppt-year)	14	2.2 (1.0–4.5)
			p-trend = 0.03
	No		
	Comparison group	65	1.0
	Ranch Hand low (≤ 434 ppt-year)	11	0.8 (0.4–1.5)
	Ranch Hand high (> 434 ppt-year)	14	1.1 (0.6–1.9)
			p-trend = 0.89
Pavuk et al., 2005	White Air Force comparison subjects only—incidence		
	Serum TCDD (pg/g) based on model with exposure variable $\log_e$(TCDD)		
	Per unit increase of –$\log_e$(TCDD)	83	1.1 (0.7–1.5)
	Quartiles (pg/g)		
	0.4–2.6	13	1.0
	2.6–3.8	24	1.7 (0.8–3.3)
	3.8–5.2	24	1.5 (0.7–2.9)
	> 5.2	22	1.2 (0.6–2.4)

TABLE 7-28 Prostate Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
	Number of years served in SEA		
	Per year of service	83	1.1 (1.0–1.2)
	Quartiles (years in SEA)		
	0.8–1.3	8	1.0
	1.3–2.1	11	1.3 (0.5–3.2)
	2.1–3.7	28	2.2 (1.0–4.9)
	3.7–16.4	36	2.4 (1.1–5.2)
Akhtar et al., 2004	AFHS subjects vs national rates		
	White AFHS Ranch Hand veterans		
	Incidence	36	1.5 (1.0–2.0)
	With tours in 1966–1970	34	1.7 (1.2–2.3)
	Mortality	2	0.7 (0.1–2.3)
	White AFHS comparison veterans		
	Incidence	54	1.6 (1.2–2.1)
	With tours between 1966–1970	42	1.6 (1.2–2.2)
	Mortality	3	0.8 (0.2–2.1)
	White AFHS subjects—incidence		
	Who spent at most 2 years in SEA		
	Per unit increase of $-\log_e$(TCDD)	28	1.5 (0.9–2.4)
	Comparison group	7	1.0
	Ranch Hand—< 10 TCDD pg/g in 1987	10	1.5 (0.5–4.4)
	Ranch Hand—< 118.5 TCDD pg/g at end of service	6	2.2 (0.7–6.9)
	Ranch Hand—> 118.5 TCDD pg/g at end of service	5	6.0 (1.4–24.6)
	Only Ranch Hands with 100% service in Vietnam and comparisons with no service in Vietnam		
	Per unit increase of $-\log_e$(TCDD)	20	1.1 (0.6–1.8)
	Comparison group	3	1.0
	Ranch Hand—< 10 TCDD pg/g in 1987	9	2.5 (0.4–16.1)
	Ranch Hand—< 118.5 TCDD pg/g at end of service	4	2.4 (0.4–16.0)
	Ranch Hand—> 118.5 TCDD pg/g at end of service	4	4.7 (0.8–29.1)
AFHS, 2000	Air Force Ranch Hand veterans	26	0.7 (0.4–1.3)
AFHS, 1996	Air Force Ranch Hand veterans	2	0.6 expected

continued

TABLE 7-28 Prostate Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
US VA Cohort of Army Chemical Corps			**All COIs**
Cypel and Kang, 2010	ACC—deployed vs nondeployed and vs US men (Vietnam-service status throught 2005)		
	Deployed vs nondeployed	5 vs 2	1.0 (0.2–5.6)
	ACC veterans vs US men		
	Vietnam cohort	5	1.1 (0.3–2.5)
	Non-Vietnam cohort	2	0.95 (0.1–3.4)
US CDC Vietnam Experience Study			**All COIs**
Boehmer et al., 2004	Follow-up of CDC VES cohort	1	0.4 (nr)
Department of Veterans Affairs			**All COIs**
Watanabe and Kang, 1996	US Army and Marine Corps Vietnam veterans		
	Army Vietnam Service	58	1.1 (nr)
	Non-Vietnam	1	1.2 (nr)[c]
	Marine Vietnam Service	9	1.2 (nr)
	Non-Vietnam	6	1.3 (nr)
Breslin et al., 1988	Army Vietnam veterans	30	0.9 (0.6–1.2)
	Marine Vietnam veterans	5	1.3 (0.2–10.3)
State Studies of US Vietnam Veterans			**All COIs**
Chamie et al., 2008	Vietnam-era veterans in northern California Veterans Affairs Health System—self-reported exposure to Agent Orange	239	2.9 (2.3–3.6)
Giri et al., 2004	Veterans using the VA Medical Center in Ann Arbor, Michigan		
	All cases	11	OR 2.1 (0.8–5.2)
	Cases in white veterans only	nr	OR 2.7 (0.9–8.2)
Clapp, 1997	Massachusetts Vietnam veterans—incidence	15	0.8 (0.4–1.6)
Visintainer et al., 1995	PM study of deaths (1974–1989) of Michigan Vietnam-era veterans—deployed vs nondeployed		
	Male genital system	19	1.1 (0.6–1.7)
Anderson et al., 1986	Wisconsin Vietnam veterans	0	nr
Other Studies of US Vietnam Veterans			**All COIs**
Shah et al., 2009	Veterans with radical prostatectomies examined in VA Healthcare facilities		
	AO-exposed veterans with biochemical progression	nr	1.5 (1.1–2.0)
Australian Vietnam Veterans vs Australian Population			**All COIs**
O'Toole et al., 2009	Survey of Australian Vietnam Veterans compared to the Australian general population	nr	1.3 (0.3–6.7)
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence	692	1.3 (1.2–1.3)
	Navy	137	1.2 (1.0–1.4)
	Army	451	1.8 (1.2–1.4)
	Air Force	104	1.3 (1.0–1.5)

TABLE 7-28 Prostate Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—mortality	107	1.2 (1.0–1.5)
	Navy	22	1.3 (0.8–1.8)
	Army	65	1.2 (0.9–1.5)
	Air Force	19	1.4 (0.8–2.1)
AIHW, 1999	Australian Vietnam veterans—incidence (validation study)		*Expected number of exposed cases (95% CI)*
		212	147 (123–171)
CDVA, 1998a	Australian Vietnam veterans—self-reported incidence	428	147 (123–171)
CDVA, 1997a	Australian military Vietnam veterans	36	1.5 (1.0–2.0)
Australian Conscripted Army National Service (deployed vs nondeployed)			**All COIs**
ADVA, 2005c	Australian male conscripted Army National Service Vietnam-era veterans		
	Incidence	65	1.2 (0.9–1.5)
	Mortality	0	0.0 (0.0–0.7)
Other Australian Vietnam Veterans			**All COIs**
Leavy et al., 2006	606 prostate cancer cases in Western Australia Vietnam service	25	2.1 (0.9–5.1)
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			**Dioxin, phenoxy herbicides**
Kogevinas et al., 1997	IARC cohort, workers exposed to any phenoxy herbicide or chlorophenol	68	1.1 (0.9–1.4)
	Exposed to highly chlorinated PCDDs	43	1.1 (0.8–1.5)
	Not exposed to highly chlorinated PCDDs	25	1.1 (0.7–1.6)
Saracci et al., 1991	IARC cohort—exposed subcohort	30	1.1 (0.8–1.6)
NIOSH Mortality Cohort (12 US plants, production 1942–1984) (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Steenland et al., 1999	US chemical production workers	28	1.2 (0.8–1.7)
Fingerhut et al., 1991	NIOSH—entire cohort	17	1.2 (0.7–2.0)
	≥ 1-yr exposure, ≥ 20-yr latency	9	1.5 (0.7–2.9)
Monsanto Plant—Nitro, WV (included in IARC and NIOSH cohort)			**Dioxin, phenoxy herbicides**
Collins et al., 1993	Monsanto Company workers	9	1.6 (0.7–3.0)

continued

TABLE 7-28 Prostate Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Dow Chemical Company—Midland, MI (included in IARC and NIOSH cohorts)			**Dioxin, phenoxy herbicides**
Collins et al., 2009a	Trichlorophenol workers	21	1.4 (0.9–2.2)
Collins et al., 2009b	Pentachlorophenol workers	8	1.0 (0.4–1.9)
Bodner et al., 2003	Dow chemical production workers (included in IARC cohort, NIOSH Dioxin Registry)	nr	1.7 (1.0–2.6)
Burns et al., 2001	Dow 2,4-D production workers (included in IARC cohort, NIOSH Dioxin Registry)	7	1.3 (0.5–2.8)
Bond et al., 1988	Dow 2,4-D production workers (included in IARC cohort, NIOSH Dioxin Registry)	1	1.0 (0.0–5.8)
BASF Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Ott and Zober, 1996	BASF employees—incidence		
	TCDD < 0.1 µg/kg of body weight	4	1.1 (0.3–2.8)
	TCDD 0.1–0.99 µg/kg of body weight	1	1.1 (0.0–5.9)
Zober et al., 1990	BASF employees—basic cohort	0	*90% CI* nr (0.0–6.1)
Danish Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Lynge, 1985	Danish production workers—incidence	9	0.8 (nr)
Dutch Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Boers et al., 2010	Dutch chlorophenoxy workers		
	Factory A (HR for exposed vs unexposed)	6 vs 2	2.9 (0.6–14.2)
	Factory B (HR for exposed vs unexposed)	4 vs 2	2.7 (0.5–14.9)
Bueno de Mesquita et al., 1993	Dutch phenoxy herbicide workers (included in IARC cohort)	3	2.6 (0.5–7.7)
German Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Becher et al., 1996	German production workers	9	1.3 (nr)
Manz et al., 1991	German production workers—men, women	7	1.4 (0.6–2.9)
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)			**Dioxin, phenoxy herbicides**
McBride et al., 2009a	1,599 production workers (male and female) vs national rates—mortality 1969 through 2004		
	Ever-exposed workers	1	0.2 (0.0–1.2)
	Never-exposed workers	2	1.9 (0.2–6.7)
't Mannetje et al., 2005	Phenoxy herbicide producers	1	0.4 (0.0–2.1)
	Phenoxy herbicide sprayers (> 99% men)	2	0.6 (0.1–2.2)

TABLE 7-28 Prostate Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
United Kingdom Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Coggon et al., 1986	British MCPA production workers	18	1.3 (0.8–2.1)
Agricultural Health Study			**Herbicides**
Samanic et al., 2006	Pesticide applicators in AHS—prostate cancer incidence from enrollment through 2002		
	Dicamba—lifetime days exposure		
	None	343	1.0
	1– < 20	106	1.0 (0.8–1.3)
	20– < 56	102	0.9 (0.7–1.2)
	56– < 116	76	1.0 (0.7–1.3)
	≥ 116	67	1.1 (0.8–1.5)
			p-trend = 0.45
Alavanja et al., 2005	US AHS—incidence		
	Private applicators	1,046	1.3 (1.2–1.3)
	Spouses of private applicators (> 99% women)	5	1.2 (0.4–2.8)
	Commercial applicators	41	1.4 (1.0–1.9)
Blair et al., 2005a	US AHS		
	Private applicators	48	0.7 (0.5–0.8)
	Spouses of private applicators (> 99% women)	0	0.0 (0–1.6)
Alavanja et al., 2003	US AHS—pesticide appliers in Iowa and North Carolina—incidence	566	1.1 (1.1–1.2)
Other Agricultural Workers			**Herbicides**
Hansen et al., 2007	Danish gardeners (male genital organs, ICD-7 177–178)—incidence		
	10-yr follow-up (1975–1984) reported in Hansen et al. (1992)	20	1.2 (0.7–1.8)
	25-yr follow-up (1975–2001)		
	Born before 1915 (high exposure)	39	1.3 (1.0–1.8)
	Born 1915–1934 (medium exposure)	35	0.9 (0.6–1.2)
	Born after 1934 (low exposure)	3	0.4 (0.1–1.3)
Sharma-Wagner et al., 2000	Swedish citizens		
	Agriculture, stock raising	6,080	1.1 (1.0–1.1) ($p < 0.01$)
	Farmers, foresters, gardeners	5,219	1.1 (1.0–1.1) ($p < 0.01$)
	Paper-mill workers	304	0.9 (0.8–1.0)
	Pulp grinding	39	1.4 (1.0–1.9) ($p < 0.05$)
Gambini et al., 1997	Italian rice growers	19	1.0 (0.6–1.5)
Blair et al., 1993	US farmers in 23 states		
	Whites	3,765	1.2 (1.1–1.2)
	Nonwhites	564	1.1 (1.1–1.2)

continued

TABLE 7-28 Prostate Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Morrison et al., 1993	Canadian farmers, 45–69 yrs of age, no employees, or custom workers, sprayed ≥ 250 acres	20	2.2 (1.3–3.8)
Ronco et al., 1992	Danish farm workers—incidence		
	Self-employed	399	0.9 ($p < 0.05$)
	Employee	63	0.8 ($p < 0.05$)
Alavanja et al., 1988	USDA agricultural extension agents	nr	1.0 (0.7–1.5)
Burmeister et al., 1983	Iowa residents—farm exposures	4, 827	1.2 ($p < 0.05$)
Wiklund, 1983	Swedish male agricultural workers		*99% CI*
		3,890	1.0 (0.9–1.0)
Burmeister, 1981	Iowa farmers	1,138	1.1 ($p < 0.01$)
Dutch Pesticide Applicators			**Herbicides**
Swaen et al., 2004	Dutch licensed herbicide applicators	6	1.0 (0.4–2.2)
Swaen et al., 1992	Dutch licensed herbicide applicators	1	1.3 (0.0–7.3)
Other Studies of Herbicide and Pesticide Applicators			**Herbicides**
Fleming et al., 1999a	Florida pesticide appliers	353	1.9 (1.7–2.1)
Fleming et al., 1999b	Florida pesticide appliers	64	2.4 (1.8–3.0)
Dich and Wiklund, 1998	Swedish pesticide appliers	401	1.1 (1.0–1.2)
	Born 1935 or later	7	2.0 (0.8–4.2)
	Born before 1935	394	1.1 (1.0–1.2)
Zhong and Rafnsson, 1996	Icelandic pesticide users	10	0.7 (0.3–1.3)
Asp et al., 1994	Finnish herbicide applicators		
	Incidence	6	0.4 (0.1–0.8)
	Mortality	5	0.8 (0.3–1.8)
Torchio et al., 1994	Italian licensed pesticide users	66	1.0 (0.7–1.2)
Blair et al., 1983	Florida pesticide applicators		*Expected number of exposed cases (95% CI)*
		2	3.8 (nr)
Forestry Workers			**Herbicides**
Thörn et al., 2000	Swedish lumberjacks exposed to phenoxyacetic herbicides		
	Foremen—incidence	2	4.7 (nr)
	Male lumberjacks—incidence	3	0.9 (nr)

TABLE 7-28 Prostate Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Hertzman et al., 1997	Canadian sawmill workers		
	Morbidity	282	1.0 (0.9–1.1)
	Mortality from male genital tract cancers	116	1.2 (1.0–1.4)
Alavanja et al., 1989	USDA forest conservationists	nr	1.6 (0.9–3.0)
	Soil conservationists	nr	1.0 (0.6–1.8)
Reif et al., 1989	New Zealand forestry workers—nested case–control —incidence	12	0.7 (0.4–1.3)
Paper and Pulp Workers			**Dioxin**
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	117	0.9 (0.7–1.0)
	Ever	84	0.9 (0.7–1.2)
Henneberger et al., 1989	New Hampshire pulp and paper workers	9	1.0 (0.5–1.9)
Solet et al., 1989	US paper and pulp workers	4	1.1 (0.3–2.9)
Robinson et al., 1986	Northwestern US paper and pulp workers	17	*90% CI* 1.2 (0.7–1.7)
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Consonni et al., 2008	Seveso residents—25-yr follow-up to 2001—men, women		
	Zone A	1	0.9 (0.1–6.2)
	Zone B	8	0.9 (0.4–1.8)
	Zone R	65	1.1 (0.8–1.4)
Pesatori et al., 2009	Seveso—20-yr follow-up to 1996—incidence		
	Zone A	0	
	Zone B	7	0.9 (0.5–2.0)
	Zone R	39	0.8 (0.5–1.1)
Bertazzi et al., 2001	Seveso residents—20-yr follow-up		
	Zones A, B—men	8	1.1 (0.5–2.2)
Bertazzi et al., 1997	Seveso residents—15-yr follow-up		
	Zone B—men	6	1.2 (0.5–2.7)
	Zone R—men	39	1.2 (0.8–1.6)
Bertazzi et al., 1993	Seveso residents—10-yr follow-up—incidence		
	Zone R—men	16	0.9 (0.5–1.5)
Pesatori et al., 1992	Seveso residents—incidence		
	Zones A, B—men	4	1.4 (0.5–3.9)
	Zone R—men	17	0.9 (0.6–1.5)
Bertazzi et al., 1989a	Seveso residents—10-yr follow-up		
	Zones A, B, R—men	19	1.6 (1.0–2.7)

continued

TABLE 7-28 Prostate Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Bertazzi et al., 1989b	Seveso residents—10-yr follow-up		
	Zone B—men	3	2.2 (0.7–6.9)
	Zone R—men	16	1.6 (0.9–2.7)
Other Environmental Studies			**Serum dioxin**
Turunen et al., 2008	Finnish fishermen and spouses	36	0.99 (0.7–1.4)
Svensson et al., 1995	Swedish fishermen—mortality		
			Organochlorine compounds
	East coast	12	1.0 (0.5–1.8)
	West coast	123	1.1 (0.9–1.3)
	Swedish fishermen—incidence		
	East coast	38	1.1 (0.8–1.5)
	West coast	224	1.0 (0.9–1.1)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; ACC, Army Chemical Corps; AFHS, Air Force Health Study; AHS, Agricultural Health Study; AO, Agent Orange; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MI, Michigan; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; NZ, New Zealand; OR, odds ratio; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PM, proportionate mortality; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; USDA, US Department of Agriculture; VA, US Department of Veterans Affairs; VES, Vietnam Experience Study; WV, West Virginia.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

[c]Statistically significant with the 95% CI not including 1.0.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

Among Australian Vietnam veterans, O'Toole et al. (2009) extended follow-up to 36 years after the war. The relative prevalence of prostate cancer (compared with that in the general population) was 1.29 (95% CI 0.34–6.73) on the basis of a sample size of 450 veterans.

Cypel and Kang (2010) studied 2,872 ACC veterans and compared them with 2,737 non-Vietnam veterans or US men. When Cox adjusted analyses were used, the prostate-cancer mortality in ACC veterans compared with non-Vietnam veterans was 1.02 (95% CI 0.19–5.64); there were five observed deaths in the Vietnam cohort and two in the non-Vietnam cohort. The Cox proportional hazards survival analysis adjusted for race, rank, duration of military service, and age at

entry into follow-up. In the analysis in which the ACC veterans were compared with US men, the result was 1.05 (95% CI 0.34–2.45) for five observed cases.

Shah et al. (2009) investigated the association of Agent Orange exposure with prostate-cancer clinicopathologic characteristics, rates of biochemical progression after treatment, and PSA doubling time after recurrence of prostate cancer in patients that had radical prostatectomy (RP). The study population consisted of 1,495 veterans who had undergone RP during 1988–2007 at Veterans Affairs Health Care Facilities in West Los Angeles and Palo Alto, California, Augusta, Georgia, and Durham, North Carolina; veteran's data was abstracted from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. The authors noted that the men were grouped by the presence or absence of Agent Orange exposure, but a detailed explanation of the criteria used to determine the presence of exposure was not given. After adjustment for clinical variables, there was no significant association of Agent Orange exposure with odds of a pathologic Gleason sum, positive surgical margins, extracapsular extension, or seminal vesicle invasion. During a mean follow-up of 60 months (with a standard deviation of 46 months), men who were exposed to Agent Orange were more likely to progress than men who were not exposed; after adjustment for clinicopathologic findings, they had an increased RR of biochemical progression of 1.47 (95% CI 1.08–2.00). In the 501 men who had PSA recurrence, the PSA doubling time (PSADT) was available for 298 men. Agent Orange exposure was associated with a significantly shorter mean adjusted PSADT (8.2 vs 18.6 months). Study limitations include the potential for more aggressive screening for prostate cancer in men who had been exposed to Agent Orange, which led to earlier diagnosis. A second limitation is that only men with RP were included; that is, men who had more advanced disease were excluded, so an association of Agent Orange with more advanced disease could not be studied. A final limitation is that Agent Orange exposure was not quantified and was assessed subjectively. The authors note that there is potential concern with exposure assignment because there are financial incentives to associate their diagnosis with a history of Agent Orange exposure; this limits the relevance of the results.

Occupational Studies

Boers et al. (2010) published results of the third follow-up of the retrospective Dutch cohort study in two chlorophenoxy herbicide manufacturing factories (Plant A and Plant B). The authors extended follow-up an additional 15 years through the end of 2006 and included data from Plant B that had previously not been included, because of the small number of deaths reported at the last follow-up. The data from the two plants were analyzed separately because exposure to phenoxy herbicides and dioxins was considered to differ between factories. In Plant A, there were 539 exposed male workers and 482 unexposed workers. In Plant B, there were 411 male workers classified as exposed and 626 classified as unexposed. Although the follow-up period is long, the cohort is moderate in size and would have limited

power to detect increases in rare cancers. The authors reported increased HRs for prostate cancer that were consistent with earlier published analyses. Specifically, the risk in Plant A (HR = 2.93, 95% CI 0.61–14.15) was based on six and two deaths in the exposed and unexposed workers, respectively. The risk in Plant B (HR = 2.68, 95% CI 0.48–14.85) was based on four and two deaths in exposed and unexposed workers, respectively. For all genital cancers, the HR was increased, but not significantly (HR = 3.28, 95% CI 0.63–17.15).

Collins et al. (2009a) published updated results from a Dow Chemical Company site in Michigan. They followed 1,615 workers who were exposed to dioxins in a TCP production plant. Serum dioxin measurements in a set of 280 (17%) workers were used to estimate historical TCDD exposure of all workers. Serum TCDD concentrations were higher than in the unexposed and the general population. Workers were followed from 1942 to 2003. There was an increase (but not a statistically significant increase) in SMR for prostate cancer (SMR = 1.4, 95% CI 0.9–2.2 in all TCP workers; SMR = 1.5, 95% CI 0.9–2.4 when 196 workers who also had PCP exposure were excluded).

Collins et al. (2009b) examined mortality rates among 773 workers in a PCP manufacturing facility who were exposed to dioxins during PCP manufacturing during 1937–1980. Serum dioxin measurements were used to estimate exposure to five dioxins, including TCDD. In all PCP workers, the SMR was 1.0 (95% CI 0.4–1.9), and the number of observed deaths was eight. When they excluded 196 workers who also had TCP exposure, the SMR was 1.0 (95% CI 0.4–2.1) on the basis of seven observed deaths.

McBride et al. (2009a,b) extended their earlier analyses by including additional exposed and unexposed workers, constructing exposure estimates based on serum dioxin (TCDD) in exposed and unexposed workers, and extending follow-up for 4 additional years. The authors reported on the mortality experience of 1,599 workers employed during 1969–1988 at a New Zealand site that manufactured TCP and a nearby field station where 2,4,5-T was occasionally used and tested (McBride et al., 2009a). Serum measurements from 346 blood samples confirmed higher exposure than New Zealand background. The study was limited by a high loss of follow-up (21%). The SMR for ever-exposed workers was 0.2 (95% CI 0.0–1.2) on the basis of one observed death. The SMR for never-exposed workers was 1.9 (95% CI 0.2–6.7) on the basis of two observed deaths. It should be noted that the authors reported increased SMRs for other cancers previously found to be associated with dioxins. The results in McBride et al. (2009b) have not been included because they were diluted by inclusion of a set of workers who had no opportunity for TCDD exposure and no observed deaths.

Environmental Studies

Pesatori et al. (2009) updated cancer-incidence results for the study of residents of Seveso. Poisson regression models were used to calculate sex-, age-, and

period-adjusted rate ratios. The use of exposure zones (A, B, and R) to define individual exposure introduces misclassification, which is likely to be random and to attenuate associations. However, later serum measurements on a subset confirmed the utility of using zone of residence as a proxy for exposure to TCDD. For prostate cancer, none of the RRs (95% CI) were increased: for Zones A, B, and R the RRs were not calculable, 0.94 (95% CI 0.45–1.99), and 0.75 (95% CI 0.54–1.05), respectively.

Turunen et al. (2008) conducted a mortality study of Finnish fishermen and their wives. The cohort consisted of 6,410 Finnish professional fishermen and 4,260 wives. The cohort was linked with Statistics Finland's national cause-of-death data for 1980–2005. SMRs were calculated by using national mortality figures. The SMR for prostate cancer was 0.99 (95% CI 0.69–1.36) on the basis of 36 observed deaths.

Biologic Plausibility

Prostate cells and prostatic-cancer cell lines are responsive to TCDD in induction of various genes, including those involved in drug metabolism. Simanainen et al. (2004a) used different rat lines (TCDD-resistant Hans/Wistar and TCDD-sensitive Long Evans) and showed that TCDD treatment resulted in a significant decrease in the weight of prostate lobes, but the effect did not appear to be line-specific. In contrast, the TCDD-related reduction in sperm appears to be line-specific and not fully related to the effects of TCDD on serum testosterone (Simanainen et al., 2004b). TCDD effects appear to occur through actions on the urogenital sinus (Lin et al., 2004). In utero and lactational exposure to TCDD appears to retard the aging process in the prostate (Fritz et al., 2005). In a follow-up, progeny mice of a genetic cross between AHR-null mice and the transgenic adenocarcinoma of the mouse prostate (TRAMP) strain that models prostate cancer showed that the presence of the AHR inhibited the formation of prostate tumors that have a neuroendocrine phenotype (Fritz et al., 2008). In agreement with a possible protective role, negative associations were found in the AFHS between the risk of benign prostate hyperplasia and both TCDD exposure and serum testosterone concentration (Gupta et al., 2006).

The biologic plausibility of the carcinogenicity of the chemicals of interest is discussed in general at the beginning of this chapter.

Synthesis

The results on Australian and US ACC Vietnam veterans are weak but consistent with the previous finding of suggestive evidence of an association between the chemicals of interest and prostate cancer. The few occupational and environmental studies published since *Update 2008* do not provide substantial evidence for or against the earlier conclusion. The previously existing body of epidemio-

logic evidence supporting an association between exposure to the chemicals of interest and prostate cancer is robust enough that the committee's judgment that there is limited or suggestive evidence of an association is not reversed by the largely negative results in experimental systems.

Analysis of data from VA medical facilities by Shah et al. (2009) found indicators of poor prognosis were associated with self-reported Agent Orange exposure of veterans who had already had radical prostatectomies for diagnosed prostate cancer. The committee had some reservations about possible bias associated with self-reporting of Agent Orange exposure. Furthermore, this interesting finding does not directly address a role of Agent Orange in the occurrence of prostate cancer.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there remains limited or suggestive evidence of an association between exposure to at least one of the chemicals of interest and prostate cancer.

TESTICULAR CANCER

ACS estimated that 8,480 men would receive diagnoses of testicular cancer (ICD-9 186.0–186.9) in the United States in 2010 and that 350 men would die from it (Jemal et al., 2010). Other cancers of the male reproductive system that are infrequently reported separately are cancers of the penis and other male genital organs (ICD-9 187). The average annual incidence of testicular cancer is shown in Table 7-29.

Testicular cancer occurs more often in men younger than 40 years old than in older men. On a lifetime basis, the risk in white men is about 4 times that in black men. Cryptorchidism (undescended testes) is a major risk factor for testicular cancer. Family history of the disease also appears to be a risk factor. Several other hereditary, medical, and environmental risk factors have been suggested, but the results of research are inconsistent (Bosl and Motzer, 1997).

TABLE 7-29 Average Annual Incidence (per 100,000) of Testicular Cancer in United States[a]

55–59 Years Old			60–64 Years Old			65–69 Years Old		
All Races	White	Black	All Races	White	Black	All Races	White	Black
2.8	3.3	0.3	1.5	1.6	0.8	1.3	1.4	0.6

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2004–2008 (NCI, 2010).

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the chemicals of interest and testicular cancer. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008* did not change that conclusion. Table 7-30 summarizes the results of the relevant studies.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

Cypel and Kang (2010) studied 2,872 ACC veterans and compared them with 2,737 non-Vietnam veterans or US men. Using Cox adjusted analyses, the testicular-cancer mortality for ACC veterans compared with non-Vietnam veterans was not calculable; there were two observed deaths in the Vietnam cohort and none in the non-Vietnam cohort. When the ACC veterans were compared with US men, the SMR was 3.63 (95% CI 0.44–13.1) on the basis of two observed cases.

Occupational Studies

Collins et al. (2009a) published updated results from a Dow Chemical Company site in Michigan. They followed 1,615 workers who had been exposed to dioxins in a TCP production plant. Serum dioxin measures in a set of 280 (17%) workers were used to estimate historical TCDD exposure of all workers. Serum TCDD concentrations were higher than in the unexposed and the general population. Workers were followed from 1942 to 2003. There was an increase in SMR (but not a statistically significant one) for testicular cancer in all TCP workers (SMR = 1.6, 95% CI 0.0–8.9). When workers who also had PCP exposure were excluded, the SMR was 1.8 (95% CI 0.0–10.1).

Collins et al. (2009b) examined mortality in 773 workers who had been exposed to dioxins during PCP manufacturing during 1937–1980. Serum dioxin concentrations were used to estimate exposure to five dioxins, including TCDD. No deaths from testicular cancer were observed.

McBride et al. (2009a,b) extended their earlier analyses by including additional exposed and unexposed workers, constructing exposure estimates based on serum dioxin (TCDD) concentrations in exposed and unexposed workers, and extending follow-up for 4 additional years. The authors reported on the mortality experience of 1,599 workers employed during 1969–1988 at a New Zealand site that manufactured TCP and at a nearby field station where 2,4,5-T was occasionally used and tested (McBride et al., 2009a). Serum measurements from 346 blood samples confirmed higher exposure than New Zealand background. The

TABLE 7-30 Selected Epidemiologic Studies—Testicular Cancer

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans			**All COIs**
AFHS, 2000	Air Force Ranch Hand veterans	3	nr
US VA Cohort of Army Chemical Corps			**All COIs**
Cypel and Kang, 2010	ACC veterans (deployed vs nondeployed) vs US men		
	Vietnam cohort	2	3.6 (0.4–13.1)
Dalager and Kang, 1997	Army Chemical Corps veterans	2	4.0 (0.5–14.5)
US VA Mortality Study of Army and Marine Veterans (ground troops serving July 4, 1965–March 1, 1973)			**All COIs**
Watanabe and Kang, 1996	Army Vietnam service	114	1.1 (nr)
	Marine Vietnam service	28	1.0 (nr)
Watanabe et al., 1991	Army Vietnam veterans	109	1.2 (ns)
	Marine Vietnam veterans	28	0.8 (ns)
Breslin et al., 1988	Army Vietnam veterans	90	1.1 (0.8–1.5)
	Marine Vietnam veterans	26	1.3 (0.5–3.6)
VA Case–Control Studies			**All COIs**
Bullman et al., 1994	Navy veterans	12	2.6 (1.1–6.2)
Australian Vietnam Veterans vs Australian Population			**All COIs**
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence	54	0.9 (0.6–1.1)
	Navy	17	1.2 (0.7–1.8)
	Army	34	0.8 (0.5–1.0)
	Air Force	3	0.8 (0.2–2.3)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—mortality	14	0.9 (0.4–1.4)
	Navy	3	0.8 (0.2–2.4)
	Army	10	0.9 (0.4–1.7)
	Air Force	0	0.0 (0.0–3.3)
AIHW, 1999	Australian Vietnam veterans—incidence (validation study)		*Expected number of exposed cases (95% CI)*
		59	110 (89–139)
CDVA, 1998a	Australian Vietnam veterans—self-reported incidence	151	110 (89–131)
CDVA, 1997a	Australian military Vietnam veterans	4	ns

TABLE 7-30 Testicular Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
Australian Conscripted Army National Service (deployed vs nondeployed)			**All COIs**
ADVA, 2005c	Australian male conscripted Army National Service Vietnam-era veterans—deployed vs non-deployed		
	Incidence	17	0.7 (0.4–1.2)
	Mortality	4	0.8 (0.2–2.0)
CDVA, 1997b	Australian National Service Vietnam veterans	1	1.3
State Studies of US Vietnam Veterans			**All COIs**
Clapp, 1997	Massachusetts Vietnam veterans—incidence	30	1.2 (0.4–3.3)
Anderson et al., 1986	Wisconsin Vietnam veterans	9	1.0 (0.5–1.9)
Other Studies of US Vietnam Veterans			**All COIs**
Tarone et al., 1991	Patients in three Washington, DC, area hospitals	31	2.3 (1.0–5.5)
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			
Kogevinas et al., 1997	IARC cohort, workers exposed to any phenoxy herbicide or chlorophenol	68	1.1 (0.9–1.4)
	Exposed to highly chlorinated PCDDs	43	1.1 (0.8–1.5)
	Not exposed to highly chlorinated PCDDs	25	1.1 (0.3–1.6)
Saracci et al., 1991	IARC cohort—exposed subcohort	7	2.3 (0.9–4.6)
Dow Chemical Company—Midland, MI (included in IARC and NIOSH cohorts)			**Dioxin, phenoxy herbicides**
Collins et al., 2009a	Trichlorophenol workers		
	Testes and other male genital	1	1.6 (0.0–8.9)
Collins et al., 2009b	Pentachlorophenol workers		
	Testes and other male genital	0	0.0 (0.0–12.5)
Burns et al., 2001	Dow chemical production workers	1	2.2 (0.0–12.5)
Ramlow et al., 1996	Dow pentachlorophenol production workers	0	nr

continued

TABLE 7-30 Testicular Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
Bond et al., 1988	Dow 2,4-D production workers	1	4.6 (0.0–25.7)
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)			**Dioxin, phenoxy herbicides**
McBride et al., 2009a	1,599 production workers (male and female) vs national rates—mortality 1969 through 2004		
	Ever-exposed workers	0	0.0 (0.0–15.6)
United Kingdom Production Workers (included in IARC cohort)			
Coggon et al., 1986	British MCPA production workers	4	2.2 (0.6–5.7)
Agricultural Health Study			**Herbicides**
Alavanja et al., 2005	US AHS—incidence		
	Private applicators	23	1.1 (0.7–1.6)
	Spouses of private applicators (> 99% women)	nr	0.0 (0.0–50.2)
	Commercial applicators	4	1.2 (0.3–3.2)
Blair et al., 2005a	US AHS		
	Private applicators	0	nr
	Spouses of private applicators (> 99% women)	0	nr
Other Agricultural Workers			**Herbicides**
Blair et al., 1993	US farmers in 23 states		
	White men	32	0.8 (0.6–1.2)
	Nonwhite men	6	1.3 (0.5–2.9)
Ronco et al., 1992	Danish farm workers—incidence		
	Men—self-employed	74	0.9 (nr)
	employee	23	0.6 ($p < 0.05$)
Wiklund, 1983	Swedish male agricultural workers—incidence	101	*99% CI* 1.0 (0.7–1.2)
Other Studies of Herbicide and Pesticide Applicators			**Herbicides**
Flemming et al., 1999b	Florida pesticide appliers	23	2.5 (1.6–3.7)
Zhong and Rafnsson, 1996	Icelandic pesticide users	2	1.2 (0.1–4.3)
Forestry Workers			**Herbicides**
Reif et al., 1989	New Zealand forestry workers—nested case–control—incidence	6	1.0 (0.4–2.6)
Hertzman et al., 1997	British Columbia sawmill workers		
	Mortality (male genital cancers)	116	1.0 (0.8–1.1)
	Incidence	18	1.0 (0.6–1.4)

TABLE 7-30 Testicular Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Paper and Pulp Workers			**Dioxin**
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	2	1.1 (0.1–4.1)
	Ever	5	3.6 (1.2–8.4)
Other Occupational Workers			**Herbicides**
Hardell et al., 1998	Swedish workers exposed to herbicides	4	0.3 (0.1–1.0)
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Pesatori et al., 2009	Seveso—20-yr follow-up to 1996—incidence		
	Zone A	0	
	Zone B	2	0.8 (0.2–3.3)
	Zone R	22	1.4 (0.9–2.3)
Bertazzi et al., 2001	Seveso residents—20-yr follow-up		
	Zone A, B—men	17	1.0 (0.6–1.7)
Bertazzi et al., 1998	Seveso residents—15-yr follow-up (genitourinary tract)—incidence		
	Zone B—men	10	1.0 (0.5–1.8)
	Zone R—men	73	1.0 (0.8–1.3)
Bertazzi et al., 1993	Seveso residents—10-yr follow-up—incidence		
	Zone B—men	1	1.0 (0.1–7.5)
	Zone R—men	9	1.4 (0.7–3.0)
Pesatori et al., 1992	Seveso residents—incidence		
	Zones A, B—men	1	0.9 (0.1–6.7)
	Zone R—men	9	1.5 (0.7–3.0)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; ACC, Army Chemical Corps; AHS, Agricultural Health Study; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MI, Michigan; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; ns, not significant; NZ, New Zealand; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; VA, US Department of Veterans Affairs.

[a]Subjects are male, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

study was limited by a high loss of follow-up (21%). No testicular-cancer deaths were reported in the study. The results in McBride et al. (2009b) have not been included because they were diluted by inclusion of a set of workers who had no opportunity for TCDD exposure and no observed deaths.

Environmental Studies

Pesatori et al. (2009) updated mortality and cancer-incidence results for the study conducted among residents of Seveso. Poisson regression models were used to calculate rate ratios adjusted for sex, age, and period. The use of exposure zones (A, B, and R) to define individual exposure introduces misclassification, which is likely to be random and to attenuate associations. However, later serum measurements of a subset confirmed the utility of assigning zone of residence as a proxy for exposure to TCDD. For testicular cancer, none of the RRs was significantly increased; that for Zone A was noncalculable, and those for Zones B and R were 0.82 (95% CI 0.20–3.32) and 1.44 (95% CI 0.9–2.31), respectively.

Biologic Plausibility

No animal studies of the incidence of testicular cancer after exposure to any of the chemicals of interest have been published since *Update 2008*. The biologic plausibility of the carcinogenicity of the chemicals of interest is discussed in general at the beginning of this chapter.

Synthesis

The evidence from epidemiologic studies is inadequate to link herbicide exposure and testicular cancer. The relative rarity of this cancer makes it difficult to develop risk estimates with any precision. Most cases occur in men 25–35 years old, and men who have received such a diagnosis could be excluded from military service; this could explain the slight reduction in risk observed in some veteran studies.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and testicular cancer.

BLADDER CANCER

Urinary bladder cancer (ICD-9 188) is the most common urinary tract cancer. Cancers of the urethra, and paraurethral glands and other and unspecified urinary cancers (ICD-9 189.3–189.9) are infrequently reported separately; any findings on these cancers would be reported in this section. ACS estimated that 52,760 men and 17,770 women would receive a diagnosis of bladder cancer in the United States in 2010 and that 10,410 men and 4,270 women would die from it (Jemal et al., 2010). In males, in whom this cancer is about twice as common as it is in females, those numbers represent about 7% of new cancer diagnoses and 3% of cancer deaths. Overall, bladder cancer is fourth in incidence in men in the United States.

Bladder-cancer risk rises rapidly with age. In men in the age groups that characterize most Vietnam veterans, bladder-cancer incidence is about twice as high in whites as in blacks. The average annual incidence of urinary bladder cancer is shown in Table 7-31.

The most important known risk factor for bladder cancer is tobacco use, which accounts for about half the bladder cancers in men and one-third of them in women (Miller et al., 1996). Occupational exposure to aromatic amines (also called arylamines), polycyclic aromatic hydrocarbons (PAHs), and some other organic chemicals used in the rubber, leather, textile, paint-products, and printing industries is associated with higher incidence. In some parts of Africa and Asia, infection with the parasite *Schistosoma haematobium* contributes to the high incidence.

Exposure to inorganic arsenic is also a risk factor for bladder cancer. Although cacodylic acid is a metabolite of inorganic arsenic, as discussed in Chapter 4, the data are insufficient to conclude that studies of inorganic-arsenic exposure are directly relevant to exposure to cacodylic acid, so the literature on inorganic arsenic is not considered in this section.

TABLE 7-31 Average Annual Incidence (per 100,000) of Bladder Cancer in United States[a]

	55–59 Years Old			60–64 Years Old			65–69 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Men	44.2	47.7	27.1	77.7	85.4	47.3	130.2	141.3	95.3
Women	12.4	13.8	7.5	21.2	23.2	14.5	34.0	37.4	27.9

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2004–2008 (NCI, 2010).

Conclusions from *VAO* and Previous Updates

The committees responsible for *VAO* and *Update 1996* concluded that there was limited or suggestive evidence of *no* association between exposure to the chemicals of interest and urinary bladder cancer. Additional information available to the committee responsible for *Update 1998* led it to change that conclusion to one of inadequate or insufficient information to determine whether there is an association. The committee responsible for *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008* did not change that conclusion.

Table 7-32 summarizes the results of the relevant studies.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

No Vietnam-veteran studies concerning exposure to the chemicals of interest and bladder cancer have been published since *Update 2008*.

Occupational Studies

Boers et al. (2010) published results from the third follow-up of the retrospective Dutch study of a cohort in two chlorophenoxy herbicide manufacturing factories (Plant A and Plant B). The authors extended follow-up an additional 15 years through the end of 2006 and included data from Plant B that had previously not been included, because of the small number of deaths reported at the last follow-up. The data from the two plants were analyzed separately because exposure to phenoxy herbicides and dioxins was considered to differ between factories. In Plant A, there were 539 exposed male workers and 482 unexposed workers. In Plant B, there were 411 male workers classified as exposed and 626 classified as unexposed. Although the follow-up period is long, the cohort is moderate in size and would have limited power to detect increases in rare cancers. The authors reported an increased hazard ratio for bladder cancer in Plant A of 2.27 (95% CI 0.5–10.28) on the basis of nine deaths in exposed and two deaths in unexposed workers. Plant B had an HR of 1.05 (95% CI 0.15–7.21) on the basis of two deaths in exposed and two deaths in unexposed workers.

Collins et al. (2009a) published updated results from a Dow Chemical Company site in Michigan. They followed 1,615 workers who were exposed to dioxins in a TCP production plant. Serum dioxin measures of a set of 280 (17%) workers were used to estimate historical TCDD exposure of all workers. Serum TCDD concentrations were higher than those in unexposed people and the general population. Workers were followed from 1942 to 2003. The SMR for bladder cancer was 1.2 (95% CI 0.5–2.7) in all TCP workers and 1.2 (95% CI 0.4–2.7) when 196 workers who also had TCP exposure were excluded. Collins et al. (2009b)

TABLE 7-32 Selected Epidemiologic Studies—Urinary Bladder Cancer

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
Air Force Ranch Hands—Ranch Hand veterans vs SEA veterans			**All COIs**
Akhtar et al., 2004	AFHS subjects vs national rates		
	White AFHS Ranch Hand veterans		
	Incidence	14	1.1 (0.6–1.7)
	With tours between 1966–1970	14	1.3 (0.7–2.1)
	Mortality	1	0.9 (nr)
	White AFHS comparison veterans		
	Incidence	8	0.4 (0.2–0.8)
	With tours in 1966–1970	4	0.3 (0.1–0.7)
	Mortality	1	0.6 (nr)
AFHS, 2000	Air Force Ranch Hand veterans		
	Bladder, kidney	11	3.1 (0.9–11.0)
Centers for Disease Control and Prevention			**All COIs**
Boehmer et al., 2004	Follow-up of CDC Vietnam Experience Cohort	1	nr
US Department of Veterans Affairs			**All COIs**
Breslin et al., 1988	Army Vietnam veterans	9	0.6 (0.3–1.2)
	Marine Vietnam veterans	4	2.4 (0.1–66.4)
State Studies of US Vietnam Veterans			**All COIs**
Clapp, 1997	Massachusetts Vietnam veterans	80	0.6 (0.2–1.3)
Anderson et al., 1986	Wisconsin Vietnam veterans	1	nr
Australian Vietnam Veterans vs Australian Population			**All COIs**
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence	164	1.0 (0.9–1.2)
	Navy	34	1.0 (0.7–1.4)
	Army	104	1.0 (0.8–1.2)
	Air Force	26	1.3 (0.8–1.8)
ADVA, 2005b	Australian military Vietnam veterans vs Australian population—mortality	22	0.7 (0.4–1.0)
	Navy	4	0.6 (0.2–1.6)
	Army	13	0.7 (0.3–1.1)
	Air Force	5	1.1 (0.4–2.5)
CDVA, 1997a	Australian military Vietnam veterans	11	1.1 (0.6–1.9)
Australian Conscripted Army National Service (deployed vs nondeployed)			
ADVA, 2005c	Australian male conscripted Army National Service Vietnam-era veterans		
	Incidence	19	0.7 (0.4–1.1)
	Mortality	1	0.3 (0.0–1.7)
CDVA, 1997b	Australian National Service Vietnam veterans	1	0.6 (nr)

continued

TABLE 7-32 Urinary Bladder Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort			**Dioxin, phenoxy herbicides**
Kogevinas et al., 1997	IARC cohort, male and female workers exposed to any phenoxy herbicide or chlorophenol	34	1.0 (0.7–1.5)
	Exposed to highly chlorinated PCDDs	24	1.4 (0.9–2.1)
	Not exposed to highly chlorinated PCDDs	10	0.7 (0.3–1.2)
Saracci et al., 1991	IARC cohort—exposed subcohort (men and women)	13	0.8 (0.4–1.4)
NIOSH Mortality Cohort (12 US plants, production 1942–1984) (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Steenland et al., 1999	US chemical production workers		
	Total cohort	16	2.0 (1.1–3.2)
	High-exposure cohort	6	3.0 (1.4–8.5)
Fingerhut et al., 1991	NIOSH—entire cohort (bladder, other)	9	1.6 (0.7–3.0)
	≥ 1-yr exposure, ≥ 20-yr latency	4	1.9 (0.5–4.8)
Monsanto Plant—Nitro, WV (accident and workers) (included in IARC and NIOSH cohort)			**Dioxin, phenoxy herbicides**
Collins et al., 1993	Monsanto Company workers (many also exposed to 4-aminobiphenyl, a known bladder carcinogen)		
	Bladder, other urinary	16	6.8 (3.9–11.1)
Dow Chemical Company—Midland, MI (included in IARC and NIOSH cohorts)			**Dioxin, phenoxy herbicides**
Collins et al., 2009a	Trichlorophenol workers	6	1.2 (0.5–2.7)
Collins et al., 2009b	Pentachlorophenol workers	2	0.7 (0.1–2.7)
Bodner et al., 2003	Dow chemical production workers	nr	0.7 (0.1–2.0)
Burns et al., 2001	Dow 2,4-D production workers	1	0.5 (0.1–2.8)
Bond et al., 1988	Dow 2,4-D production workers	0	nr (0.0–7.2)
BASF Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Ott and Zober, 1996	BASF employees (bladder, kidney)—incidence	2	1.4 (0.4–3.2)
Zober et al., 1990	BASF employees—basic cohort	0	*90% CI* nr (0.0–15.0)
Danish Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Lynge, 1985	Danish production workers—incidence	11	0.8 (nr)
Dutch Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Boers et al., 2010	Dutch chlorophenoxy workers		
	Factory A (HR for exposed vs unexposed)	9 vs 2	2.3 (0.5–10.3)
	Factory B (HR for exposed vs unexposed)	2 vs 2	1.1 (0.2–7.2)

TABLE 7-32 Urinary Bladder Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
Hooiveld et al., 1998	Dutch chemical production workers		
	Total cohort	4	3.7 (1.0–9.5)
	Accidentally exposed subcohort	1	2.8 (0.1–15.5)
Bueno de Mesquita et al., 1993	Dutch phenoxy herbicide workers	1	1.2 (0.0–6.7)
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)			**Dioxin, phenoxy herbicides**
McBride et al., 2009a	1,599 production workers (male and female) vs national rates—mortality 1969 through 2004		
	Ever-exposed workers	0	0.0 (0.0–2.9)
't Mannetje et al., 2005	New Zealand phenoxy herbicide producers, sprayers		
	Phenoxy herbicide producers (men and women)	0	nr
	Phenoxy herbicide sprayers (> 99% men)	0	nr
United Kingdom Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Coggon et al., 1986	British MCPA production workers	8	0.9 (0.4–1.7)
Paper and Pulp Workers			**Dioxin**
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	50	1.0 (0.7–1.3)
	Ever	43	1.1 (0.8–1.5)
Henneberger et al., 1989	New Hampshire pulp and paper workers	4	1.2 (0.3–3.2)
Robinson et al., 1986	Northwestern US paper and pulp workers	8	1.2 (0.6–2.6)
Agricultural Health Study			**Herbicides**
Samanic et al., 2006	Pesticide applicators in AHS—bladder-cancer incidence from enrollment through 2002		
	Dicamba—lifetime days exposure		
	None	43	1.0
	1– < 20	6	0.5 (0.2–1.3)
	20– < 56	9	0.7 (0.3–1.4)
	56– < 116	6	0.6 (0.3–1.5)
	≥ 116	8	0.8 (0.4–1.9)
			p-trend = 0.66
Alavanja et al., 2005	US AHS (urinary system)—incidence		
	Private applicators (men and women)	184	0.7 (0.6–0.8)
	Spouses of private applicators (> 99% women)	17	0.7 (0.4–1.1)
	Commercial applicators (men and women)	13	1.1 (0.6–1.8)

continued

TABLE 7-32 Urinary Bladder Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
Blair et al., 2005a	US AHS		
	Private applicators (men and women)	7	0.4 (0.1–0.7)
	Spouses of private applicators (> 99% female)	2	0.8 (0.1–2.7)
Other Agricultural Workers			**Herbicides**
Hansen et al., 2007	Danish gardeners (urinary system, ICD-7 180–181)—incidence		
	10-yr follow-up (1975–1984) reported in Hansen et al. (1992)	18	0.9 (0.7–1.8)
	25-yr follow-up (1975–2001)		
	Born before 1915 (high exposure)	25	1.1 (0.7–1.6)
	Born 1915–1934 (medium exposure)	23	0.5 (0.4–0.8)
	Born after 1934 (low exposure)	1	0.2 (0.0–1.1)
Ronco et al., 1992	Danish workers—incidence		
	Men—self-employed	300	0.6 ($p < 0.05$)
	employee	70	0.7 ($p < 0.05$)
	Women—self-employed	1	0.2 (nr)
	employee	2	0.6 (nr)
	family worker	25	0.6 ($p < 0.05$)
Alavanja et al., 1988	USDA agricultural extension agents	8	0.7 (0.4–1.4)
Burmeister, 1981	Iowa farmers	274	0.9 (nr)
Forestry Workers			**Herbicides**
Hertzman et al., 1997	Canadian sawmill workers		
	Mortality	33	0.9 (0.7–1.2)
	Incidence	94	1.0 (0.8–1.2)
Alavanja et al., 1989	USDA forest, soil conservationists	8	0.8 (0.3–1.6)
Reif et al., 1989	New Zealand forestry workers—nested case–control—incidence	4	0.7 (0.3–1.8)
Other Studies of Herbicide and Pesticide Applicators			**Herbicides**
Swaen et al., 2004	Dutch licensed herbicide applicators	2	0.7 (0.1–2.4)
Asp et al., 1994	Finnish herbicide applicators—incidence	12	1.6 (0.8–2.8)
Torchio et al., 1994	Italian licensed pesticide users	31	0.5 (0.4–0.8)
Green, 1991	Herbicide sprayers in Ontario		
	Diseases of genitourinary system	1	1.0 (0.0–5.6)
Blair et al., 1983	Florida pesticide applicators	3	1.6 (nr)
ENVIRONMENTAL			
Chapaevsk, Russia Cohort			**TCDD**
Revich et al., 2001	Residents of Chapaevsk, Russia (urinary organs)		
	Men	31	2.6 (1.7–3.6)
	Women	17	0.8 (0.5–1.3)

TABLE 7-32 Urinary Bladder Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Seveso, Italy Residential Cohort			**TCDD**
Consonni et al., 2008	Seveso residents—25-yr follow-up—men and women		
	Zone A	1	1.0 (0.2–7.4)
	Zone B	6	0.9 (0.4–2.0)
	Zone R	42	0.9 (0.6–1.2)
Pesatori et al., 2009	Seveso—20-yr follow-up to 1996—incidence		
	Zone A	3	1.4 (0.5–4.5)
	Zone B	17	1.3 (0.8–2.2)
	Zone R	84	0.9 (0.8–1.2)
Bertazzi et al., 2001	Seveso residents—20-yr follow-up		
	Zone A, B—men	6	1.2 (0.5–2.7)
Bertazzi et al., 1998	Seveso residents—15-yr follow-up		
	Zone B—men	1	2.4 (0.3–16.8)
	women	3	0.9 (0.3–3.0)
	Zone R—men	21	0.9 (0.6–1.5)
	women	4	0.6 (0.2–1.8)
Pesatori et al., 1992	Seveso residents—incidence		
	Zones A, B—men	10	1.6 (0.9–3.1)
	women	1	0.9 (0.1–6.8)
	Zone R—men	39	1.0 (0.7–1.4)
	women	4	0.6 (0.2–1.5)
Other Environmental Studies			**Phenoxy herbicides, chlorophenols**
Gambini et al., 1997	Italian rice growers	12	1.0 (0.5–1.8)
Svensson et al., 1995	Swedish fishermen (men and women)—mortality		**Organochlorine compounds**
	East coast	5	1.3 (0.4–3.1)
	West coast	20	1.0 (0.6–1.6)
	Swedish fishermen (men and women)—incidence		
	East coast	10	0.7 (0.4–1.3)
	West coast	55	0.9 (0.7–1.1)
Lampi et al., 1992	Finnish community exposed to chlorophenol contamination (men and women)	14	**Chlorophenols** 1.0 (0.6–1.9)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; AFHS, Air Force Health Study; AHS, Agricultural Health Study; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemicals of interest; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MI, Michigan; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; NZ, New Zealand; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; USDA, US Department of Agriculture; WV, West Virginia.

[a]Subjects are male, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

described the mortality experience of 773 workers who were exposed to chlorinated dioxins in the production of PCP; 75% of the cohort have been followed for more than 27 years. SMRs were calculated by comparing the PCP workers with the general US population and the state of Michigan. The SMR for bladder cancer was 0.7 (95% CI 0.1–2.7) in all PCP workers on the basis of two deaths and 0.5 (95% CI 0.0–2.6) on the basis of one death when 196 workers who also had TCP exposure were excluded.

McBride et al. (2009a,b) extended their earlier publications by including additional exposed and unexposed workers, constructing exposure estimates based on serum dioxin (TCDD) concentrations in exposed and unexposed workers, and extending follow-up for 4 additional years. The authors reported on the mortality experience of 1,599 workers who were employed during 1969–1988 at a New Zealand site that manufactured TCP and a nearby field station where 2,4,5-T was occasionally used and tested (McBride et al., 2009a). Serum measurements from 346 blood samples confirmed higher exposure than New Zealand background. The study was limited by a high loss of follow-up (21%). The SMR (95% CI) for bladder cancer in ever-exposed workers was 0 (0.0–2.9) on the basis of no observed deaths. The results in McBride et al. (2009b) have not been included, because they were diluted by inclusion of a set of workers who had no opportunity for TCDD exposure and no observed deaths.

Environmental Studies

Pesatori et al. (2009) updated cancer-incidence results of the study of residents of Seveso. Poisson regression models were used to calculate sex-, age-, and period-adjusted rate ratios. The use of exposure zones (A, B, and R) to define individual exposure introduces misclassification, which is likely to be random and to attenuate associations. However, later serum measurements of a subset confirmed the utility of using zone of residence as a proxy for exposure to TCDD. For bladder cancer, RRs for Zones A, B, and R were 1.44 (95% CI 0.46–4.49), 1.33 (95% CI 0.82–2.16), and 0.94 (95% CI 0.75–1.19), respectively.

In a 12-year follow-up study in Taiwan, Huang et al. (2008) found significantly higher levels of MMA^V and lower levels of DMA^V in patients with urothelial carcinoma than among the healthy residents. After adjustment for age, gender, educational level, and smoking status, the incidence of urinary DMA^V was inversely associated with the risk of urothelial carcinoma, having relative risks across the low, medium, and high strata of 1.0, 0.3, and 0.3, respectively ($p < 0.05$ for the trend test).

Biologic Plausibility

In laboratory animals, cacodylic acid has been shown to induce primarily bladder tumors (Cohen et al., 2006; Wang et al., 2009). In a study of male F344

rats, cacodylic acid administered in drinking water resulted in formation of bladder tumors at the highest concentrations (50 and 200 ppm) (Wei et al., 2002). In another report (Arnold et al., 2006), administration of cacodylic acid in the diet resulted in formation of papillomas and carcinomas in the bladders of female and male F344 rats but not B6C3F1 mice. Experimental work since *Update 2006* has shown that cacodylic acid (dimethyl arsenic acid, DMA) is cytotoxic at high concentrations in rat urothelial cells in vitro (Nascimento et al., 2008); such concentrations are unlikely to be environmentally relevant. Other recent studies have shown DMA concentrations to be lower in bladder-cancer patients than in matched controls (Pu et al., 2007) and to be associated with a lower incidence of urinary cancer (Huang et al., 2008). In contrast, greater oxidative DNA damage has been found in association with higher DMA concentrations in urothelial-cancer patients (Chung et al., 2008), although this was not the case in primary human hepatocytes (Dopp et al., 2008). In a study that used a rat cancer initiation–promotion model, DMA was found to be a weak cancer-initiator but a tumor-promoter at high dose (Fukushima et al., 2005).

No studies have reported an increased incidence of urinary bladder cancer in TCDD-treated animals, but activation of the AHR pathway with TCDD enhances cancer-cell invasion by upregulating the matrix metalloproteinase (MMP)-1 and MMP-9 expression and is associated with poor prognosis in upper urinary tract urothelial cancer (Ishida et al., 2010).

The biologic plausibility of the carcinogenicity of the chemicals of interest is discussed in general at the beginning of this chapter.

Synthesis

Available analyses of an association between exposure to the chemicals of interest and bladder-cancer risk are characterized by low precision because of the small numbers, low exposure specificity, and lack of ability to control for confounding. The data that have emerged over the last several updates suggest that DMA may be a bladder-tumor–promoter and that DMA concentrations are lower in patients who have urinary cancer. The evidence in either direction remains too preliminary to alter the conclusion that the cumulative evidence of such an association is inadequate or insufficient.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and bladder cancer.

RENAL CANCER

Cancers of the kidney (ICD-9 189) and renal pelvis (ICD-9 189.1) are often grouped in epidemiologic studies; cancer of the ureter (ICD-9 189.2) is sometimes also included. Although diseases of those organs have different characteristics and could have different risk factors, there is some logic to grouping them: the structures are all exposed to filterable chemicals, such as PAHs, that appear in urine. ACS estimated that 35,370 men and 22,870 women would receive diagnoses of renal cancer (ICD-9 189, 189.1) in the United States in 2010 and that 8,210 men and 4,830 women would die from it (Jemal et al., 2010). Those figures represent 2–4% of all new cancer diagnoses and cancer deaths. The average annual incidence of renal cancer is shown in Table 7-33.

Renal cancer is twice as common in men as in women. In the age groups that include most Vietnam veterans, black men have a higher incidence than white men. With the exception of Wilms tumor, which is more likely to occur in children, renal cancer is more common in people over 50 years old.

Tobacco use is a well-established risk factor for renal cancer. People who have some rare syndromes—notably, von Hippel–Lindau syndrome and tuberous sclerosis—are at higher risk. Other potential risk factors include obesity, heavy acetaminophen use, kidney stones, and occupational exposure to asbestos, cadmium, and organic solvents. Firefighters, who are routinely exposed to numerous pyrolysis products, are in a known higher-risk group.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the chemicals of interest and renal cancer. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008* did not change that conclusion. Table 7-34 summarizes the results of the relevant studies.

TABLE 7-33 Average Annual Incidence (per 100,000) of Kidney and Renal Pelvis Cancer in United States[a]

	55–59 Years Old			60–64 Years Old			65–69 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Men	40.7	39.2	61.1	60.3	60.2	77.4	77.8	78.6	95.3
Women	20.0	20.2	23.8	27.8	29.2	30.0	36.2	35.6	45.2

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2004–2008 (NCI, 2010).

TABLE 7-34 Selected Epidemiologic Studies—Renal Cancer

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans			**All COIs**
AFHS, 2000	Air Force Ranch Hand veterans	11	3.1 (0.9–11.0)
US CDC Vietnam Experience Study			**All COIs**
Boehmer et al., 2004	Follow-up of CDC VES	1	nr
US VA Mortality Study of Army and Marine Veterans (ground troops serving July 4, 1965–March 1, 1973)			**All COIs**
Breslin et al., 1988	Army Vietnam veterans	55	0.9 (0.5–1.5)
	Marine Vietnam veterans	13	0.9 (0.5–1.5)
State Studies of US Vietnam Veterans			**All COIs**
Visintainer et al., 1995	PM study of deaths (1974–1989) of Michigan Vietnam-era veterans—deployed vs nondeployed	21	1.4 (0.9–2.2)
Kogan and Clapp, 1988	Massachusetts Vietnam veterans	9	1.8 (1.0–3.5)
Anderson et al., 1986	Wisconsin Vietnam veterans	2	nr
Australian Vietnam Veterans vs Australian Population			**All COIs**
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence	125	1.0 (0.8–1.2)
	Navy	34	1.3 (0.9–1.7)
	Army	77	0.9 (0.7–1.1)
	Air Force	14	1.1 (0.6–1.8)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—mortality	50	1.0 (0.7–1.2)
	Navy	12	1.1 (0.6–1.9)
	Army	33	0.9 (0.6–1.3)
	Air Force	5	0.8 (0.3–1.8)
CDVA, 1997a	Australian military Vietnam veterans	22	1.2 (0.7–1.8)
Australian Conscripted Army National Service (deployed vs nondeployed)			**All COIs**
ADVA, 2005c	Australian male conscripted Army National Service Vietnam-era veterans—deployed vs nondeployed		
	Incidence	19	0.7 (0.4–1.0)
	Mortality	4	0.4 (0.1–1.1)
CDVA, 1997b	Australian National Service Vietnam veterans	3	3.9 (nr)

continued

TABLE 7-34 Renal Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			**Dioxin, phenoxy herbicides**
Kogevinas et al., 1997	IARC cohort, male and female workers exposed to any phenoxy herbicide or chlorophenol	29	1.1 (0.7–1.6)
	Exposed to highly chlorinated PCDDs	26	1.6 (1.1–2.4)
	Not exposed to highly chlorinated PCDDs	3	0.3 (0.1–0.9)
Saracci et al., 1991	IARC cohort—exposed subcohort (men and women)	11	1.0 (0.5–1.7)
NIOSH Mortality Cohort (12 US plants, production 1942–1984) (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Steenland et al., 1999	US chemical workers	13	1.6 (0.8–2.7)
Fingerhut et al., 1991	NIOSH cohort—entire cohort	8	1.4 (0.6–2.8)
	≥ 1-yr exposure, ≥ 20-yr latency	2	1.1 (0.1–3.8)
Dow Chemical Company—Midland, MI (included in IARC and NIOSH cohorts)			**Dioxin, phenoxy herbicides**
Collins et al., 2009a	Trichlorophenol workers	2	0.4 (0.1–1.5)
Collins et al., 2009b	Pentachlorophenol workers	4	1.7 (0.5–4.4)
Burns et al., 2001	Dow 2,4-D production workers	2	0.9 (0.1–3.3)
Bond et al., 1988	Dow 2,4-D production workers	0	nr (0.0–6.2)
Danish Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Lynge, 1985	Danish production workers—incidence	3	0.6 (nr)
Dutch Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Boers et al., 2010	Dutch chlorophenoxy workers Plant A—exposed workers	8	HR = "infinitively large"
Hooiveld et al., 1998	Dutch chemical production workers		
	Total cohort—kidney cancer	4	4.1 (1.1–10.4)
	Total cohort—"urinary organs"	8	3.9 (1.7–7.6)
German Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Manz et al., 1991	German production workers—men, women	3	1.6 (0.3–4.6)
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)			**Dioxin, phenoxy herbicides**
McBride et al., 2009a	1,599 production workers (male and female) vs national rates—mortality 1969 through 2004		
	Ever-exposed workers	3	2.3 (0.5–6.7)
't Mannetje et al., 2005	Phenoxy herbicide producers (men and women)	1	1.2 (0.0–6.6)
	Phenoxy herbicide sprayers (> 99% men)	3	2.7 (0.6–8.0)

TABLE 7-34 Renal Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
United Kingdom Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Coggon et al., 1986	British MCPA production workers	5	1.0 (0.3–2.3)
Agricultural Studies			**Herbicides**
Hansen et al., 2007	Danish gardeners—incidence (urinary system, ICD-7 180–181)	18	0.9 (0.7–1.8)
	10-yr follow-up (1975–1984) reported in Hansen et al. (1992)		
	25-yr follow-up (1975–2001)		
	Born before 1915 (high exposure)	25	1.1 (0.7–1.6)
	Born 1915–1934 (medium exposure)	23	0.5 (0.4–0.8)
	Born after 1934 (low exposure)	1	0.2 (0.0–1.1)
Mellemgaard et al., 1994	Danish Cancer Registry patients		
	Occupational herbicide exposure, men	13	1.7 (0.7–4.3)
	Occupational herbicide exposure, women	3	5.7 (0.6–58.0)
Blair et al., 1993	US farmers in 23 states		
	White men	522	1.1 (1.0–1.2)
	White women	6	0.8 (0.3–1.7)
Ronco et al., 1992	Danish workers—incidence		
	Men—self-employed	141	0.6 ($p < 0.05$)
	employee	18	0.4 ($p < 0.05$)
	Women—self-employed	4	0.9 (nr)
	employee	3	1.0 (nr)
	family worker	30	0.8 (nr)
Alavanja et al., 1988	USDA agricultural extension agents	nr	1.7 (0.9–3.3)
Wiklund, 1983	Swedish male and female agricultural workers—incidence	775	*99% CI* 0.8 (0.7–0.9)
Burmeister, 1981	Iowa farmers	178	1.1 (ns)
Magnani et al., 1987	UK case–control		**Herbicides**
	Herbicides	nr	1.3 (0.6–3.1)
	Chlorophenols	nr	0.9 (0.4–1.9)
Other Studies of Herbicide and Pesticide Applicators			
Herbicides			
Swaen et al., 2004	Dutch licensed herbicide applicators	4	1.3 (0.4–3.4)
Torchio et al., 1994	Italian licensed pesticide users	16	0.6 (0.4–1.0)
Blair et al., 1983	Florida pesticide applicators	1	0.5 (nr)
Forestry Workers			**Herbicides**
Reif et al., 1989	New Zealand forestry workers—nested case–control—incidence	2	0.6 (0.2–2.3)

continued

TABLE 7-34 Renal Cancer, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Alavanja	USDA forest conservationists	nr	1.7 (0.5–5.5)
et al., 1989	Soil conservationists	nr	2.4 (1.0–5.9)
Paper and Pulp Workers			**Dioxin**
McLean	IARC cohort of pulp and paper workers		
et al., 2006	Exposure to nonvolatile organochlorine compounds		
	Never	41	0.9 (0.7–1.3)
	Ever	18	0.5 (0.3–0.8)
Henneberger et al., 1989	New Hampshire paper and pulp workers	3	1.5 (0.3–4.4)
Robinson et al., 1986	Northwestern US paper and pulp workers	6	1.2 (0.5–3.0)
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Consonni	Seveso residents—25-yr follow-up—men,		
et al., 2008	women		
	Zone A	0	nr
	Zone B	3	0.6 (0.2–2.0)
	Zone R	39	1.2 (0.8–1.6)
Pesatori	Seveso—20-yr follow-up to 1996—incidence		
et al., 2009	Zone A	0	
	Zone B	6	0.9 (0.4–2.0)
	Zone R	43	0.9 (0.7–1.2)
Bertazzi	Seveso residents—20-yr follow-up		
et al., 2001	Zone A, B—men	3	0.8 (0.3–2.6)
	women	3	1.8 (0.6–5.8)
Bertazzi	Seveso residents—10-yr follow-up (kidney,		
et al., 1993	other urinary organs)—incidence		
	Zone R—men	10	0.9 (0.4–1.7)
	women	7	1.2 (0.5–2.7)
Pesatori	Seveso residents—incidence		
et al., 1992	Zones A, B—men	0	nr
	women	1	1.1 (0.2–8.1)
	Zone R—men	11	0.9 (0.5–1.7)
	women	7	1.2 (0.5–2.6)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MI, Michigan; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; NZ, New Zealand; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PM, proportionate mortality; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; UK, United Kingdom; USDA, US Department of Agriculture; VA, US Department of Veterans Affairs; VES, Vietnam Experience Study.

[a]Subjects are male, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

No Vietnam-veteran studies concerning exposure to the chemicals of interest and renal cancer have been published since *Update 2008*.

Occupational Studies

Boers et al. (2010) published results from the third follow-up of the retrospective Dutch cohort study in two chlorophenoxy herbicide manufacturing factories (Plant A and Plant B). The authors extended follow-up an additional 15 years through the end of 2006 and included data from Plant B that had previously not been included, because of the small number of deaths reported at the last follow-up. The data from the two plants were analyzed separately because exposure to phenoxy herbicides and dioxins was considered to differ between factories. In Plant A, there were 539 exposed male workers and 482 unexposed workers. In Plant B, there were 411 male workers who were classified as exposed and 626 classified as unexposed. Although the follow-up period is long, the cohort is moderate in size and would have limited power to detect increases in rare cancers. The authors reported the HR as infinitively large for renal cancer in Plant A on the basis of eight deaths in the exposed and no deaths in the unexposed workers. Plant B had an HR of 0 on the basis of no deaths in the exposed and no deaths in the unexposed workers.

Collins et al. (2009a) published updated results from a Dow Chemical Company site in Michigan. They followed 1,615 workers who were exposed to dioxins in a TCP production plant. Serum dioxin measures of a set of 280 (17%) workers were used to estimate historical TCDD exposure of all workers. Serum TCDD concentrations were higher than those in unexposed people and the general population. Workers were followed from 1942 to 2003. The SMR for renal cancer was 0.4 (95% CI 0.1–1.5) in all TCP workers and 0.5 (95% CI 0.1–1.7) when 196 workers who also had TCP exposure were excluded.

Collins et al. (2009b) described the mortality experience of 773 workers who were exposed to chlorinated dioxins in the production of PCP; 75% of the cohort have been followed for more than 27 years. SMRs were calculated to compare the PCP workers with the general US population and the state of Michigan. The SMR for renal cancer was 1.7 (95% CI 0.5–4.4) in all PCP workers on the basis of four deaths and 2.3 (95% CI 0.6–5.8) on the basis of four deaths when 196 workers who also had TCP exposure were excluded.

McBride et al. (2009a,b) extended their earlier research by including additional exposed and unexposed workers, constructing exposure estimates based on the basis of serum dioxin (TCDD) concentrations in exposed and unexposed workers, and extending follow-up for 4 additional years. The authors reported the

mortality experience of 1,599 workers who were employed during 1969–1988 at a New Zealand site that manufactured TCP and a nearby field station where 2,4,5-T was occasionally used and tested (McBride et al., 2009a). Serum measurements from 346 blood samples confirmed higher exposure than New Zealand background. The study was limited by a high loss of follow-up (21%). The SMR for renal-cancer death in ever-exposed workers was 2.3 (95% CI 0.5–6.7) on the basis of three observed deaths. The results in McBride et al. (2009b) have not been included, because they were diluted by inclusion of a set of workers who had no opportunity for TCDD exposure and no observed deaths.

Environmental Studies

Pesatori et al. (2009) published updated mortality and cancer incidence results of the study of residents of Seveso. Poisson regression models were used to calculate sex-, age-, and period-adjusted rate ratios. The use of exposure zones (A, B, and R) to define individual exposure introduces misclassification, which is likely to be random and to attenuate associations. However, later serum measurements of a subset confirmed the utility of assigning zone of residence as a proxy for exposure to TCDD. No renal cancers were observed in Zone A, and risks were not elevated in Zone B (RR = 0.87, 95% CI 0.39–1.96) or Zone R (RR = 0.90, 95% CI 0.65–1.24).

Biologic Plausibility

No animal studies have reported an increased incidence of renal cancer after exposure to the chemicals of interest. The biologic plausibility of the carcinogenicity of the chemicals of interest is discussed in general at the beginning of this chapter.

Synthesis

Available analyses of an association between exposure to the chemicals of interest and renal-cancer risk are limited by the small number of cases and lack of exposure specificity. No data have emerged since *Update 2008* to alter the committee's conclusion that the evidence is inadequate or insufficient to determine whether there is an association.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and renal cancer.

BRAIN CANCER

Brain and other nervous-system cancers (ICD-9 191–192) involve the central nervous system (CNS) and include tumors of the brain and spinal cord, the cranial nerves, and the meninges (the outer coverings of the brain and spinal cord). Any of the cell types in the CNS can produce cancer. Tumors of the peripheral nerves and autonomic nervous system are considered soft-tissue tumors (ICD-9 171). Most cancers in the CNS originate in other parts of the body, such as the lung or breast, but have metastasized to the brain or spinal cord. This section focuses on cancers that originate in the CNS.

Cancer of the eye (ICD-9 190) was considered retrospectively in *Update 2006*, but the present committee decided that findings concerning cancer of the eye would be tracked with results on brain cancer because, when it is reported, it is often grouped with brain cancer.

The average annual incidence of primary CNS cancer is shown in Table 7-35. About 95% of cases derive from the brain, cranial nerves, and cranial meninges. In people over 45 years old, about 90% of tumors that originate in the brain are gliomas—astrocytoma, ependymoma, oligodendroglioma, or glioblastoma multiforme. Astrocytoma is the most common; glioblastoma multiforme has the worst prognosis. Meningiomas make up 20–40% of CNS cancers; they tend to occur in middle age and are more common in women than in men. Most meningiomas are benign and can be removed surgically.

ACS estimated that about 11,980 men and 10,040 women would receive diagnoses of brain and other nervous-system cancers in the United States in 2010 and that 7,420 men and 5,720 women would die from them (Jemal et al., 2010). Those numbers represent about 1.5% of new cancer diagnoses and 2.3% of cancer deaths. ACS estimated that 1,240 men and 1,240 women would receive diagnoses of cancers of the eye and orbit in the United States in 2010 and that 120 men and 110 women would die from them (Jemal et al., 2010).

In reviewing the descriptive epidemiology of these cancers, it is important to recognize the variation with which specific cancers are included in published reports, many of which distinguish between benign and malignant cancers. Another

TABLE 7-35 Average Annual Incidence (per 100,000) of Brain and Other Nervous System Cancers in United States[a]

	55–59 Years Old			60–64 Years Old			65–69 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Men	13.3	14.8	8.9	16.4	18.4	8.7	19.6	21.6	14.0
Women	7.9	8.9	4.5	11.3	12.3	7.0	13.2	14.7	8.9

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2004–2008 (NCI, 2010).

variation is whether cancer derived from related tissues (such as the pituitary or the eye) is included. Various types of cancer are usually grouped; although this may bias results in unpredictable ways, the most likely consequence is dilution of risk estimates toward the null.

The only well-established environmental risk factor for brain tumors is exposure to high doses of ionizing radiation (ACS, 2007d; Wrensch et al., 2002). Other environmental exposures—such as to vinyl chloride, petroleum products, and electromagnetic fields—are unproved as risk factors. The causes of most cancers of the brain and other portions of the nervous system are not known.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was limited or suggestive evidence of *no* association between exposure to the chemicals of interest and brain cancer. The committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion.

The committee responsible for *Update 2006* changed the classification for brain cancer (formally expanded to include cancers of the eye and orbit) to inadequate or insufficient evidence to determine an association between exposure to the chemicals of interest and brain cancer. That committee considered one study that suggested a relationship between adult gliomas and phenoxy acid herbicides (Lee et al., 2005), studies that reported slightly but not statistically significantly higher risks of brain cancer in deployed than in nondeployed Australian Vietnam-era veterans (ADVA, 2005a,b) and in pesticide applicators in the AHS (Alavanja et al., 2005), and several studies that had essentially neutral findings (Carreon et al., 2005; Magnani et al., 1987; McLean et al., 2006; Ruder et al., 2004; Torchio et al., 1994). Overall, the studies discussed in *Update 2006* suggested that a conclusion of *no* association between exposure to the chemicals of interest and brain cancer had been too definitive.

The committee for *Update 2008* agreed that brain cancers should remain in the inadequate or insufficient category following review of two new studies. The relevance of the largely null findings of association with occupational exposure to herbicides from a case–control study (Samanic et al., 2008) of gliomas and meningiomas was limited because no specific compounds were addressed. In evaluating mortality through 2001 in the Seveso cohort, Consonni et al. (2008) found no increase in mortality from brain cancer in any of the three exposure zones with increasing exposure and no indication of a dose–response relationship.

Table 7-36 summarizes the results of the relevant studies.

TABLE 7-36 Selected Epidemiologic Studies—Brain Tumors

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans			**All COIs**
Akhtar et al., 2004	White AFHS subjects vs national rates		
	Ranch Hand veterans		
	Incidence (brain and nervous system)	5	1.8 (0.7–4.1)
	With tours in 1966–1970	5	2.2 (0.8–4.8)
	Mortality (CNS)	3	1.3 (0.3–3.6)
	Comparison veterans		
	Incidence (brain and nervous system)	2	0.5 (0.1–1.8)
	With tours in 1966–1970	2	0.7 (0.1–2.3)
	Mortality (CNS)	1	0.3 (nr)
US VA Cohort of Army Chemical Corps			**All COIs**
Cypel and Kang, 2010	ACC veterans (deployed vs nondeployed) vs US men		
	Vietnam cohort	4	0.9 (0.2–2.2)
	Non-Vietnam cohort	2	0.5 (0.1–2.0)
Dalager and Kang, 1997	ACC veterans (crude rate ratio vs nondeployed)	2	1.9 (nr)
Thomas and Kang, 1990	ACC Vietnam veterans	2	nr
US CDC Vietnam Experience Study			**All COIs**
Boehmer et al., 2004	Follow-up of CDC Vietnam Experience Cohort (meninges, brain, other CNS)	9	1.2 (0.4–3.2)
Boyle et al., 1987	VES cohort	3	nr
US VA Mortality Study of Army and Marine Veterans (ground troops serving July 4, 1965–March 1, 1973			**All COIs**
Breslin et al., 1988	Army Vietnam veterans	116	1.0 (0.3–3.2)
	Marine Vietnam veterans	25	1.1 (0.2–7.1)
US VA Cohort of Female Vietnam Veterans			**All COIs**
Cypel and Kang, 2008	US Vietnam veterans (brain and CNS)—women	8	2.0 (0.7–5.9)
	Vietnam veteran nurses	8	3.6 (0.9–14.5)
Dalager et al., 1995	US Vietnam veterans—women	4	1.4 (0.4–3.7)
Australian Vietnam Veterans vs Australian Population			**All COIs**
ADVA, 2005a	Australian male Vietnam veterans vs Australian population (brain)—incidence	97	1.1 (0.9–1.2)
	Navy	24	1.2 (0.7–1.7)
	Army	63	1.0 (0.8–1.3)
	Air Force	10	1.1 (0.6–2.1)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population (brain, CNS)—mortality	99	1.0 (0.8–1.1)
	Navy	23	1.0 (0.6–1.4)
	Army	66	0.9 (0.7–1.2)
	Air Force	9	0.9 (0.4–1.6)

continued

TABLE 7-36 Brain Tumors, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
CDVA, 1997a	Australian military Vietnam veterans	39	1.1 (0.7–1.4)
Australian Conscripted Army National Service (deployed vs nondeployed)			**All COIs**
ADVA, 2005c	Australian male conscripted Army National Service Vietnam-era veterans—deployed vs nondeployed (brain, CNS)		
	Incidence (1982–2000)	23	1.4 (0.7–2.6)
	Mortality (1966–2001)	27	1.6 (0.9–3.1)
CDVA, 1997b	Australian National Service Vietnam veterans	13	1.4 (nr)
State Studies of US Vietnam Veterans			**All COIs**
Visintainer et al., 1995	PM study of deaths (1974–1989) of Michigan Vietnam-era veterans—deployed vs nondeployed	36	1.1 (0.8–1.5)
Anderson et al., 1986	Wisconsin Vietnam veterans	8	0.8 (0.3–1.5)
Lawrence et al., 1985	New York Vietnam veterans (brain and CNS)	4	0.5 (0.2–1.5)
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			**Dioxin, phenoxy herbicides**
Kogevinas et al., 1997	IARC cohort, male and female workers exposed to any phenoxy herbicide or chlorophenol	22	0.7 (0.4–1.0)
	Exposed to highly chlorinated PCDDs	12	0.6 (0.3–1.1)
	Not exposed to highly chlorinated PCDDs	10	0.8 (0.4–1.5)
Saracci et al., 1991	IARC cohort (men and women)—exposed subcohort	6	0.4 (0.1–0.8)
NIOSH Mortality Cohort (12 US plants, production 1942–1984) (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Steenland et al., 1999	US chemical workers (brain and CNS)	8	0.8 (0.4–1.6)
Fingerhut et al., 1991	NIOSH cohort—entire cohort (brain and CNS)		
	≥ 1-yr exposure, ≥ 20-yr latency	2	1.1 (0.1–3.8)
Dow Chemical Company—Midland, MI (included in IARC and NIOSH cohorts)			**Dioxin, phenoxy herbicides**
Collins et al., 2009a	Trichlorophenol workers	3	0.6 (0.1–1.7)
Collins et al., 2009b	Pentachlorophenol workers	1	0.4 (0.0–2.3)
Bodner et al., 2003	Dow chemical production workers (brain and CNS)	nr	0.6 (0.1–1.8)
Burns et al., 2001	Dow 2,4-D production workers	3	1.1 (0.2–3.2)

TABLE 7-36 Brain Tumors, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Ramlow et al., 1996	Dow pentachlorophenol production workers (brain and CNS)		
	0-yr latency	1	nr
	15-yr latency	1	nr
Bond et al., 1988	Dow 2,4-D production workers		
	Brain, other system tissues	0	nr (0.0–4.1)
Danish Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Lynge, 1985	Danish production workers—incidence	4	0.7 (nr)
German Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Becher et al., 1996	German production workers—cohort I	3	2.3 (0.5–6.8)
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)			**Dioxin, phenoxy herbicides**
McBride et al., 2009a	1,599 production workers (male and female) vs national rates—mortality 1969 through 2004		
	Ever-exposed workers	4	2.0 (0.6–5.2)
't Mannetje et al., 2005	New Zealand phenoxy herbicide workers		
	Phenoxy herbicide producers (men and women)	1	0.8 (0.0–4.6)
	Phenoxy herbicide sprayers (> 99% men)	1	0.6 (0.0–3.4)
United Kingdom Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Coggon et al., 1986	British MCPA chemical workers (brain and CNS)	11	1.2 (0.6–2.2)
Agricultural Health Study			**Herbicides**
Alavanja et al., 2005	US AHS—incidence		
	Private applicators (men and women)	33	0.8 (0.6–0.8)
	Spouses of private applicators (> 99% women)	15	0.9 (0.5–1.4)
	Commercial applicators (men and women)	5	1.9 (0.6–4.3)
Blair et al., 2005a	US AHS		
	Private applicators (men and women)	19	0.7 (0.4–1.1)
	Years handled pesticides		
	≥ 10 years	5	0.9 (ns)
	> 10 years	12	0.6 (ns)
	Spouses of private applicators (> 99% women)	11	1.1 (0.5–1.8)
NIOSH Upper Midwest Health Study			**Herbicides**
Carreon et al., 2005	NIOSH UMHS—case–control		
	Women		
	Arsenicals	13	1.0 (0.5–1.9)
	Phenoxy herbicides	25	0.9 (0.5–1.5)
	2,4-D	24	0.9 (0.5–1.6)

continued

TABLE 7-36 Brain Tumors, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Ruder et al., 2004	NIOSH UMHS—case–control		
	Men		
	Arsenicals	15	0.7 (0.4–1.4)
	Phenoxy herbicides	67	0.9 (0.6–1.2)
	2,4-D	nr	nr
Other Agricultural Studies			**Herbicides**
Gambini et al., 1997	Italian rice growers (brain and CNS)	4	0.9 (0.2–2.3)
Dean, 1994	Irish farmers, farm workers		
	Men	195	nr
	Women	72	nr
Blair et al., 1993	US farmers in 23 states		
	White men	447	1.2 (1.1–1.3)
	White women	9	1.1 (0.5–2.1)
Morrison et al., 1992	Farmers in Canadian prairie province		
	250+ acres sprayed with herbicides	24	0.8 (0.5–1.2)
Ronco et al., 1992	Danish farmers (brain and CNS)—incidence		
	Men	194	1.1 (nr)
	Women	5	1.0 (nr)
Wigle et al., 1990	Canadian farmers	96	1.0 (0.8–1.3)
Alavanja et al., 1988	USDA agricultural extension agents	nr	1.0 (0.4–2.4)
Musicco et al., 1988	Brain-tumor patients in Milan, Italy (male, female farmers)	61	1.6 (1.1–2.4)
Burmeister, 1981	Iowa farmers	111	1.1 (ns)
Other Studies of Herbicide and Pesticide Applicators			**Herbicides**
Swaen et al., 2004	Dutch licensed herbicide applicators	4	1.6 (0.4–4.1)
Asp et al., 1994	Finnish herbicide applicators (eye, brain)		
	Incidence	3	0.7 (0.1–2.0)
	Mortality	3	1.2 (0.3–3.6)
Torchio et al., 1994	Italian licensed pesticide users		
	Brain, nervous system	15	0.5 (0.3–0.9)
	Eye	4	2.4 (0.7–6.1)
Swaen et al., 1992	Dutch licensed herbicide applicators	3	3.2 (0.6–9.3)
Blair et al., 1983	Florida pesticide applicators	5	2.0 (nr)

TABLE 7-36 Brain Tumors, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Agricultural Case–Control Studies			**Herbicides**
Samanic et al., 2008	US hospital-based case–control study Cumulative lifetime occupational exposure to herbicides vs unexposed		
	Gliomas		
	Men	65	0.9 (0.6–1.3)
	Low quartile	20	1.0 (0.5–1.9)
	Second quartile	16	1.0 (0.5–2.1)
	Third quartile	12	0.6 (0.3–1.3)
	Fourth quartile	17	0.8 (0.4–1.6)
			p-trend = 0.50
	Women	35	1.3 (0.8–2.0)
	Below median	23	1.5 (0.8–2.7)
	Above median	12	1.0 (0.5–2.1)
			p-trend = 0.91
	Meningiomas (women only)	33	2.4 (1.4–4.3)
	Below median	16	2.1 (1.0–4.4)
	Above median	17	2.9 (1.3–6.2)
			p-trend = 0.01
Lee et al., 2005	Nebraska case–control study (gliomas)—incidence		
	Phenoxy herbicides—combined reports (identical with results for 2,4-D specifically)	32	1.8 (1.0–3.3)
	By self	7	0.6 (0.2–1.6)
	By proxy	25	3.3 (1.5–7.2)
	2,4,5-T—combined reports	7	1.3 (0.5–3.6)
	By self	2	0.4 (0.1–2.3)
	By proxy	5	2.7 (0.7–9.8)
Reif et al., 1989	Case–control study, all men with occupation entered into New Zealand Cancer Registry 1980–1984 (brain, CNS cancers)		
	Forestry workers	4	1.2 (0.4–3.3)
Magnani et al., 1987	UK case–control, JEM used on occupation given on death certificate		
	Herbicides	nr	1.2 (0.7–2.1)
	Chlorophenols	nr	1.1 (0.7–1.8)
Forestry Workers			**Herbicides**
Thörn et al., 2000	Swedish lumberjacks exposed to phenoxy acetic herbicides		
	Foreman—incidence	0	nr
Alavanja et al., 1989	USDA forest, soil conservationists	6	1.7 (0.6–3.7)

continued

TABLE 7-36 Brain Tumors, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Paper and Pulp Workers			**Dioxin**
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	44	1.0 (0.7–1.4)
	Ever	28	0.8 (0.5–1.2)
Henneberger et al., 1989	New Hampshire pulp and paper workers	2	1.2 (0.1–4.2)
Robinson et al., 1986	Northwestern US paper and pulp workers	4	0.6 (0.2–2.1)
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Consonni et al., 2008	Seveso residents—25-yr follow-up—men, women		
	Zone A	0	nr
	Zone B	3	0.7 (0.2–2.1)
	Zone R	34	1.1 (0.8–1.6)
Pesatori et al., 2009	Seveso—20-yr follow-up to 1996—incidence		
	Zone A	2	2.4 (0.6–9.8)
	Zone B	4	0.8 (0.3–2.1)
	Zone R	37	1.0 (0.7–1.5)
Bertazzi et al., 2001	Seveso residents—20-yr follow-up		
	Zone A, B—men	1	0.4 (0.1–3.0)
	women	3	1.9 (0.6–6.0)
Bertazzi et al., 1998	Seveso residents—15-yr follow-up		
	Zone B—men	1	0.8 (0.1–5.5)
	women	3	3.2 (1.0–10.3)
	Zone R—men	12	1.3 (0.7–2.5)
	women	8	1.1 (0.5–2.4)
Bertazzi et al., 1993	Seveso residents—10-yr follow-up—incidence		
	Zone R—men	6	0.6 (0.3–1.4)
	women	6	1.4 (0.6–3.4)
Pesatori et al., 1992	Seveso residents—incidence		
	Zones A, B—women	1	1.5 (0.2–11.3)
	Zone R—men	6	0.6 (0.3–1.4)
	women	5	1.2 (0.4–3.0)
Bertazzi et al., 1989a	Seveso residents—10-yr follow-up		
	Zones A, B, R—men	5	1.2 (0.4–3.1)
	women	5	2.1 (0.8–5.9)
Other Environmental Studies			
Svensson et al., 1995	Swedish fishermen (men and women)—mortality		**Organochlorine compounds**
	East coast	2	0.6 (0.1–2.1)
	West coast	15	1.1 (0.6–1.7)

TABLE 7-36 Brain Tumors, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
	Swedish fishermen (men and women)—incidence		
	East coast	3	0.5 (0.1–1.5)
	West coast	24	0.9 (0.6–1.4)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; ACC, Army Chemical Corps; AFHS, Air Force Health Study; AHS, Agricultural Health Study; CDC, Centers for Disease Control and Prevention; CI, confidence interval; CNS, central nervous system; COI, chemical of interest; IARC, International Agency for Research on Cancer; JEM, job–exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MI, Michigan; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; ; ns, not significant; NZ, New Zealand; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PM, proportionate mortality; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; UK, United Kingdom; UMHS, Upper Midwest Health Study; USDA, US Department of Agriculture; VA, US Department of Veterans Affairs; VES, Vietnam Experience Study.

[a]Subjects are male, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

Cypel and Kang (2010) compared death rates in 2,800 deployed and 2,800 nondeployed Vietnam-era veterans. There were no differences in deaths from brain cancers between the two groups.

Occupational Studies

Collins et al. (2009a) evaluated a previously known cohort of workers at the Dow Chemical Company site in Midland, Michigan, who were exposed to TCP or 2,4,5-T during 1948–1982. Of those workers, 12% had been previously documented to have experienced chloracne. Serum dioxin measures of a set of 280 (17%) workers were used to estimate historical TCDD exposure for all workers. Serum TCDD concentrations were higher than those of unexposed people and the general population. Workers were followed from 1942 to 2003. The SMR for cancer of the central nervous system was 0.6 (95% CI 0.1–1.7) in all TCP workers and 0.4 (95% CI 0.1–1.6) when 196 workers who also had TCP exposure were excluded.

Collins et al. (2009b) described the mortality experience of 773 workers who were exposed to chlorinated dioxins in the production of PCP during 1937–1980, 20% of whom had experienced chloracne; 75% of the cohort have been followed

for more than 27 years. SMRs were calculated to compare the PCP workers with the general US population and the population of the state of Michigan. No clear risk of brain cancer was noted in association with either short-term or long-term exposure.The SMR for brain cancer was 0.4 (95% CI 0.0–2.3) in all PCP workers on the basis of one death; however, it appears that the death occurred in the group of workers who also had TCP exposure.

McBride et al. (2009a,b) extended their earlier research by including additional exposed and unexposed workers, constructing exposure estimates based on serum dioxin (TCDD) concentrations in exposed and unexposed workers, and extending follow-up for 4 additional years. The authors reported the mortality experience of 1,599 workers who were employed during 1969–1988 at a New Zealand site that manufactured TCP and a nearby field station where 2,4,5-T was occasionally used and tested (McBride et al., 2009a). Serum measurements from 346 blood samples confirmed higher exposure than New Zealand background. The study was limited by a high loss of follow-up (21%). The SMR for death from cancer of the central nervous system for ever-exposed workers was 2.0 (95% CI 0.6–5.2), on the basis of four observed deaths. No deaths were reported in the never-exposed workers. The results in McBride et al. (2009b) have not been included, because they were diluted by inclusion of a set of workers who had no opportunity for TCDD exposure and no observed deaths.

Environmental Studies

The well-documented exposure that occurred in Seveso was again queried; Pesatori et al. (2009) in a 20-year follow-up study noted no increase in brain cancers in any of the exposure zones around the accident site. For brain cancer, RRs for Zones A, B, and R were 2.43 (95% CI 0.60–9.79), 0.76 (95% CI 0.28–2.05), and 1.04 (95% CI 0.73–1.48), respectively.

Biologic Plausibility

No animal studies have reported an association between exposure to the chemicals of interest and brain cancer. The biologic plausibility of the carcinogenicity of the chemicals of interest is discussed in general at the beginning of this chapter.

Synthesis

Since *Update 2008*, several studies relevant to the possibility of an association between the chemicals of interest and brain cancer have been identified, including cohort and case–control studies. All recent studies are consistent in identifying no relationship between exposure to the chemicals of interest and the development of gliomas.

Conclusion

On the basis of the epidemiologic evidence from new and previously reported studies of populations that had potential exposure to the chemicals of interest, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and brain cancer and other nervous system cancers.

ENDOCRINE CANCERS

Cancers of the endocrine system as grouped by the SEER program (see Table B-2 in Appendix B) have a disparate group of ICD codes: thymus cancer (ICD-9 164.0), thyroid cancer (ICD-9 193), and other endocrine cancer (ICD-9 194).

ACS estimated that 10,740 men and 33,930 women would receive diagnoses of thyroid cancer in the United States in 2010 and that 730 men and 960 women would die from it and estimated that 1,150 men and 1,110 women would receive diagnoses of other endocrine cancers in 2010 and that 410 men and 470 women would die from them (Jemal et al., 2010). Incidence data on cancers of the endocrine system are presented in Table 7-37.

Thyroid cancer is the most prevalent endocrine cancer. Many types of tumors can develop in the thyroid gland; most are benign. The thyroid gland contains two main types of cells: follicular cells make and store thyroid hormones and make thyroglobulin, and C cells make the hormone calcitonin, which helps to regulate calcium metabolism. Different cancers with varying degrees of seriousness can develop from each kind of cell, and the classification of thyroid cancer is still evolving (Liu et al., 2006; Nikiforov, 2011). Papillary carcinoma is the most common and usually affects women of childbearing age; it metastasizes slowly and is the least malignant type of thyroid cancer. Follicular carcinoma accounts for about 15% of all cases and has a greater rate of recurrence and metastasis. Medullary carcinoma is a cancer of nonthyroid cells in the thyroid gland and tends to occur in families; it requires treatment different from other types of thyroid cancer. Anaplastic carcinoma (also called giant-cell cancer and spindle-cell cancer) is rare but is the most aggressive form of thyroid cancer; it does not respond to

TABLE 7-37 Average Annual Incidence (per 100,000) of Endocrine System Cancer in United States[a]

	55–59 Years Old			60–64 Years Old			65–69 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Men	13.9	14.3	11.2	15.2	15.5	12.3	17.8	18.1	15.1
Women	29.7	30.3	20.2	29.4	30.4	18.6	31.1	30.9	24.4

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2004–2008 (NCI, 2010).

radioiodine therapy and metastasizes quickly, invading such nearby structures as the trachea and causing compression and breathing difficulties.

Thyroid cancer can occur in all age groups. Radiation exposure is recognized as a risk factor for thyroid cancer, so increased incidence is observed among people who received radiation therapy directed at the neck (a common treatment in the 1950s for enlarged thymus glands, adenoids, and tonsils and for skin disorders) or who were exposed to I^{125} from the Chernobyl nuclear powerplant accident. If radiation exposure occurred in childhood, the risk of thyroid cancer is further increased. Other risk factors are a family history of thyroid cancer and chronic goiter.

Conclusions from *VAO* and Previous Updates

The committees responsible for *VAO*, *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not consider endocrine cancers separately and therefore reached no conclusion as to whether there was an association between exposure to the chemicals of interest and endocrine cancers. The committees responsible for *Update 2006* and *Update 2008* considered endocrine cancers separately and concluded that there was inadequate or insufficient evidence to determine whether there was an association between the chemicals of interest and endocrine cancers. Table 7-38 summarizes the pertinent results of the relevant studies.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

No studies concerning exposure to the chemicals of interest and thyroid or other endocrine cancers in Vietnam veterans have been published since *Update 2008*.

Occupational Studies

McBride et al. (2009a,b) published an occupational mortality study of workers in the Dow AgroSciences plant in New Plymouth, New Zealand, who were potentially exposed to TCDD. Workers employed during January 1969–October 2003 were followed to the end of 2004, and SMRs were calculated by using national mortality figures (McBride et al., 2009a). A total of 1,754 workers were included in the study, but 22% were lost to follow-up. No deaths from cancers of the thyroid or other endocrine glands was observed. The results in McBride et al. (2009b) have not been included, because they were diluted by inclusion of a set of workers who had no opportunity for TCDD exposure and no observed deaths.

TABLE 7-38 Selected Epidemiologic Studies—Endocrine Cancers (Thyroid, Thymus, and Other)

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US VA Mortality Study of Army and Marine Veterans (ground troops serving July 4, 1965–March 1, 1973)			**All COIs**
Breslin et al., 1988	Veterans with service in Vietnam vs era veterans (thyroid and other endocrine, ICD-9 193–194)		**All COIs**
	Army	15	0.6 (0.3–1.2)
	Marine Corps	4	0.6 (0.1–3.4)
Australian Vietnam Veterans vs Australian Population			
ADVA, 2005a	Australian male Vietnam veterans vs Australian population (thyroid)—incidence	17	0.6 (0.3–0.9)
	Navy	3	0.5 (0.1–1.3)
	Army	11	0.5 (0.3–1.0)
	Air Force	3	1.2 (0.2–3.5)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population (thyroid)—mortality	2	0.5 (0.0–1.8)
	Navy	1	1.2 (0.0–6.5)
	Army	1	0.4 (0.0–2.0)
	Air Force	0	0.0 (0.0–7.8)
Australian Conscripted Army National Service (deployed vs nondeployed)			**All COIs**
ADVA, 2005c	Australian male conscripted Army National Service Vietnam-era veterans—deployed vs nondeployed		
	Thyroid—incidence	4	0.6 (0.1–2.2)
	Thyroid—mortality	1	1.2 (0.0–91.7)
State Study of US Vietnam Veterans			**All COIs**
Clapp, 1997	Massachusetts male Vietnam veterans vs era veterans (thyroid)—incidence 1988–1993	4	1.2 (0.3–4.5)
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			**Dioxin, phenoxy herbicides**
Kogevinas et al., 1997	IARC cohort, male and female workers exposed to any phenoxy herbicide or chlorophenol		
	Thyroid (ICD-9 193)	4	1.7 (0.5–4.3)
	Exposed to highly chlorinated PCDDs	2	1.4 (0.2–4.9)
	Not exposed to highly chlorinated PCDDs	2	2.2 (0.3–7.9)
	Other endocrine organs (ICD-9 194)	5	3.6 (1.2–8.4)
	Exposed to highly chlorinated PCDDs	2	2.3 (0.3–8.1)
	Not exposed to highly chlorinated PCDDs	3	6.4 (1.3–18.7)
Dow Chemical Company—Midland, MI (included in IARC and NIOSH cohorts)			**Dioxin, phenoxy herbicides**
Ramlow et al.,1996	Dow cohort of pentachlorophenol factory workers employed in 1940–1989 in Michigan Division	0	nr

continued

TABLE 7-38 Endocrine Cancers (Thyroid, Thymus, and Other), continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Bond et al., 1988	Dow 2,4-D production workers	0	nr
New Zealand Production Workers—Dow plant in Pymouth, NZ (included in IARC and NIOSH cohorts)			**Dioxin, phenoxy herbicides**
McBride et al., 2009a	1,599 production workers (male and female) vs national rates—mortality 1969 through 2004		
	Thyroid, other endocrine		
	Ever-exposed workers	0	0.0 (0.0–19.8)
't Mannetje et al., 2005	Phenoxy herbicide producers (men and women)	0	nr
	Phenoxy herbicide sprayers (> 99% men)	0	nr
United Kingdom Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Coggon et al., 1986	British MCPA procuction workers (thyroid)	1	1.8 (0.4–9.8)
Agricultural Health Study			**Herbicides**
Alavanja et al., 2005	US AHS (thyroid, other endocrine)—incidence		
	Private applicators (men and women)	29	1.3 (0.8–1.8)
	Spouses of private applicators (> 99% women)	24	0.9 (0.5–1.4)
	Commercial applicators (men and women)	3	1.6 (0.3–5.0)
Blair et al., 2005a	US AHS (thyroid)—mortality		
	Private applicators (men and women)	3	1.8 (0.4–5.3)
	Spouses of private applicators (> 99% women)	0	0.0 (0.0–2.2)
Other Agricultural Studies			**Herbicides**
Zhong and Rafnsson, 1996	Icelandic men, women exposed to agricultural pesticides, primarily 2,4-D (other endocrine organs, ICD-9 194)—incidence	2	1.3 (0.1–4.7)
Blair et al., 1993	US farmers in 23 states (thyroid)		
	White men	39	1.3 (1.0–1.8)
	White women	1	0.8 (0.0–4.4)
Hallquist et al., 1993	Case–control study of male, female thyroid cancers from Swedish Cancer Registry, 1980–1989		
	Phenoxy herbicide exposure	3	0.5 (0.0–2.0)
	Chlorophenol exposure	4	2.8 (0.5–18)
Ronco et al., 1992	Danish workers—incidence		
	Men—self-employed	13	0.7 (nr)
	employee	5	1.1 (nr)
	Women—self-employed	1	1.3 (nr)
	employee	1	1.4 (nr)
	family worker	15	1.7 ($p < 0.05$)
Wiklund, 1983	Swedish male and female agricultural workers—incidence		*99% CI*
	Thyroid	126	0.9 (0.7–1.1)
	Other endocrine gland	117	0.7 (0.5–0.9)

TABLE 7-38 Endocrine Cancers (Thyroid, Thymus, and Other), continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Other Studies of Herbicide and Pesticide Applicators			**Herbicides**
Asp et al., 1994	Finnish phenoxy herbicide applicators (thyroid, other endocrine)—incidence		
	No latency	2	1.9 (0.3–7.0)
	10-yr latency	2	2.4 (0.3–8.6)
	15-yr latency	2	3.4 (0.4–12.2)
	Mortality (thyroid)		
	No latency	1	3.8 (0.1–21.3)
	10-yr latency	1	4.7 (0.1–26.4)
	15-yr latency	1	6.5 (0.2–36.2)
Wiklund et al., 1989a	Cancer risk in licensed pesticide applicators in Sweden	6	1.1 (0.4–2.4)
Forestry Workers			**Herbicides**
Green, 1991	Cohort mortality study of forestry workers exposed to phenoxy acid herbicides	1	nr
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Pesatori et al., 2009	Seveso—20-yr follow-up to 1996—incidence (ICD-9 193)		
	Zone A	1	2.6 (0.4–18.9)
	Zone B	4	1.6 (0.6–4.4)
	Zone R	19	1.2 (0.7–1.9)
Pesatori et al., 2008	Seveso population (1976–1996); incidence cases identified by hospital discharge records		
	Zone A (prolactinoma)	1	6.2 (0.9–45.5)
	Zone B (nonfunctioning pituitary tumors)	2	1.9 (0.5–7.7)
	Zone R (2 nonfunctioning pituitary adenomas and 3 prolactinomas)	5	0.7 (0.3–1.8)
Bertazzi et al., 1998	Cancer mortality after Seveso incident		
	Zone A	nr	nr
	Zone B—men	1	4.9 (0.6–39.0)
	women	1	3.2 (0.4–24.5)
	Zone R—men	0	nr
	women	2	0.8 (0.2–3.6)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; AHS, Agricultural Health Study; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MI, Michigan; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; NZ, New Zealand; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; VA, US Department of Veterans Affairs.

[a]Subjects are male, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

Environmental Studies

Thyroid-cancer cases were reported in the cancer-incidence study of the population (males and females combined) exposed to dioxin after the Seveso accident in 1976 (Pesatori, 2009). One thyroid-cancer case was observed in residents of Zone A (RR = 2.63, 95% CI 0.37–18.86), 4 thyroid-cancer cases in residents of Zone B (RR = 1.60, 95% CI 0.59–4.36), and 19 in residents of Zone R (RR = 1.15, 95% CI 0.70–1.89).

Pesatori et al. (2008) published a report on benign pituitary adenomas in the Seveso cohort. Incident cases were obtained from the hospital discharge-registration system, and 42 pituitary adenomas were identified among residents of the entire area. The noncontaminated area with 34 cases was used as the referent; Zone A had one prolactinoma (pituitary adenoma that secrets prolactin) (RR = 6.2, 95% CI 0.9–45.5), Zone B had two nonfunctioning pituitary adenomas (RR = 1.9, 95% CI 0.5–7.7), and Zone R had two nonfunctioning pituitary adenomas and three prolactinomas (RR = 0.7, 95% CI 0.3–1.8).

Biologic Plausibility

The NTP conducted carcinogenesis bioassays in Osborne-Mendel rats and B6C3F1 mice that were exposed to TCDD by gavage (NTP, 1982a). The incidence of follicular-cell adenoma, but not of carcinoma, increased with increasing TCDD dose in male and female rats; the increase was significant in male but not in female rats. There was a significant increase in follicular-cell adenoma in female but not in male mice. The NTP carried out a similar study in female Sprague-Dawley rats more recently (NTP, 2006), and Walker et al. (2006) compared the data from that study and the results of the Dow Chemical assessment of TCDD carcinogenicity (Kociba et al., 1978). In the NTP and Dow studies, the incidence of thyroid cancer (C-cell adenoma and carcinoma) decreased with increasing dose of TCDD. However, an increased incidence of minimal thyroid follicular-cell hypertrophy was noted in rats given TCDD at 22 ng/kg of body weight or more.

As indicated in Chapter 4, 2,4-D and 2,4,5-T are weakly mutagenic or carcinogenic at most. No studies that addressed a possible association between exposure to those herbicides and thyroid cancer in animal models have been identified.

The biologic plausibility of the carcinogenicity of the chemicals of interest is discussed in general at the beginning of this chapter.

Synthesis

The studies reviewed previously did not provide sufficient evidence to determine whether there is an association between exposure to the chemicals of interest and thyroid cancer or other endocrine cancers, and no new additional information that would alter this judgment was found by the present committee.

Conclusion

On the basis of the epidemiologic evidence reviewed here, the committee concludes that there is insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and thyroid or other endocrine cancers.

LYMPHOHEMATOPOIETIC CANCERS

Lymphohematopoietic cancers (LHCs) constitute a heterogeneous group of clonal hematopoietic and lymphoid-cell disorders, including leukemias, lymphomas, and multiple myeloma. They are among the most common types of cancer induced by environmental and therapeutic agents. As in the case of other cancers that are subject to idiosyncratic grouping in the results reported from epidemiologic studies (notably, head and neck cancers and gastrointestinal cancers), the conclusions that the VAO committees have drawn about associations between herbicide exposure and specific LHCs have been complicated and curtailed by the lack of specificity and by inconsistencies in groupings in the available evidence. For LHCs, that has been a function not only of epidemiologists' seeking to combine related cancers to produce categories that have enough cases to permit statistical analysis but also of alterations in the prevailing system used by the medical community to classify these malignancies. Categorization of cancers of the lymphatic and hematopoietic systems has continued to evolve, guided by growing information about gene expression and lineage of the clonal cancer cells that characterize each of a broad spectrum of neoplasms arising in these tissues (Jaffe, 2009). The World Health Organization (WHO) categorization presented in the *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissue* (WHO, 2008) makes its primary partition depending on whether the cancer cells are of myeloid or lymphoid origin (see Figure 7-1).

Stem cells arising in the bone marrow generate two major lineages of leukocytes: myeloid and lymphoid. Myeloid cells include monocytes and three types of granulocytes (neutrophils, eosinophils, and basophils). Lymphoid cells include T and B lymphocytes and a smaller set of cells called natural killer (NK) cells. All those cells circulate in the blood and are collectively referred to as white blood cells. Monocytes move out of the bloodstream into inflamed tissues, where they differentiate into macrophages or dendritic cells. Stem cells that are destined to become T lymphocytes migrate from the bone marrow to the thymus, where they acquire antigen-specific receptors. Antigen stimulation induces the T cells to differentiate into the several types involved in cell-mediated immunity. Pre-B cells mature in the bone marrow into antigen-specific B cells. On encountering their cognate antigens, B cells differentiate into antibody-secreting plasma cells involved in humoral immunity, which result in multiple myeloma when they undergo malignant transformation.

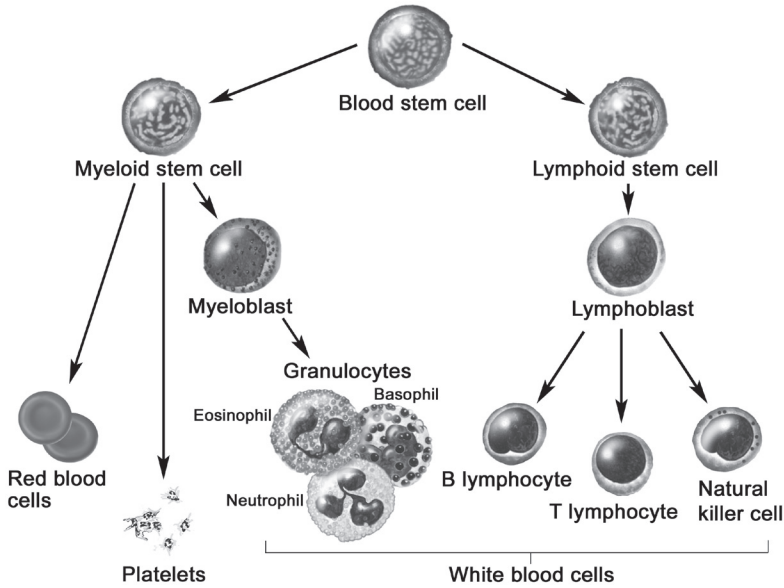

FIGURE 7-1 Hematopoiesis of stem cell differentiation.
SOURCE: ©Winslow, 2007, US government has certain rights.

LHCs originate in specific pluripotent or lineage-restricted cells at different stages in hematopoiesis and immune-cell development. The normal cells are transformed into a malignant tumor through multistep processes that involve genetic and epigenetic alterations. Traditionally, LHCs have been divided into leukemias, lymphomas, myelomas, and so on, according to their cell and site of origin (Figure 7-1). That information and morphologic, cytochemical, and immunophenotypic data are used to characterize LHCs further by their distinct subtypes.

Leukemias occurs when a cell residing in the bone marrow becomes cancerous and its daughter cells crowd normal cells in the bone marrow or are released from the bone marrow and circulate in the blood. Leukemias have generally been classified as myeloid or lymphoid, depending on the lineage of the original mutated cell. If the original mutated cell of a cancer of the blood arises in a lymphocytic cell line, the cancer is called lymphocytic leukemia; lymphocytic leukemias have been further partitioned into acute (ALL) forms if they are derived from precursor B or T lymphoid cells and chronic (CLL) forms derived from more mature lymphoid cells, which tend to replicate less rapidly. Similarly, myeloid leukemias arise from the myeloid cell lineage and are classified into acute and chronic forms, AML and CML, respectively.

Lymphoma is a general term for cancers that arise from lymphocytes (B, T, or NK cells). Lymphomas generally present as solid tumors at lymphoid proliferative sites, such as lymph nodes and spleen. As stem cells mature into B or T cells, they pass through several developmental stages, each with unique functions. The developmental stage at which a cell becomes malignant defines the kind of lymphoma. About 85% of lymphomas are of B-cell origin, and 15% of T- or NK-cell origin. There are two major types of lymphoma: Hodgkin lymphoma (HL), previously referred to as Hodgkin disease and non-Hodgkin lymphoma (NHL). B cells give rise to a number of types of neoplasms that are given names based on the stage at which B-cell development was arrested when the cells became cancerous. Follicular, large-cell, and immunoblastic lymphomas result when a malignancy develops *after* a B cell has been exposed to antigens (such as bacteria and viruses). CLL is now believed to be a tumor of antigen-experienced (memory) B cells, not naive B cells (Chiorazzi et al., 2005); small lymphocytic lymphoma (SLL), which presents primarily in lymph nodes rather than in the bone marrow and blood, is now considered to be the same disease as CLL at a different stage (Jaffe et al., 2008).

Myeloma is another type of lymphohematopoietic malignancy derived from antibody-secreting plasma cells, which also have a B-cell lineage, that accumulate in the marrow of various bones. In most cases (90%), tumors are formed at multiple sites, and the disease is called multiple myeloma. The related premalignant condition AL amyloidosis also arises from B-cell–derived plasma cells. It occurs in 5–15% of patients who have multiple myeloma and causes abnormal deposition of antibody fragments.

The ICD system partitioned these malignancies into leukemias and lymphomas primarily on the basis of whether cancer cells circulated in the blood (disseminated) or appeared in the lymphatic system (solid tissue), respectively, before subdividing according to cell type. The emerging WHO classification of lymphohematopoietic malignancies (Campo et al., 2008; Jaffe, 2009) stratifies cancers of the blood and lymph nodes into disease categories according to their cell lineages, lymphoid or myeloid, as shown in Figure 7-1. It represents a substantial advance in understanding of the biologic paths by which these cancers develop. The current committee decided, however, that it would not be productive to reformulate this entire section to correspond to the WHO categories. In practice, results on LHCs have routinely been reported in a variety of groupings, so it is a continuing challenge to parse out results, noting when results for broader groupings are presented in the results tables for several more specific diagnoses, while recognizing that the specific results will be muted by being "misclassified" with other entities. Most epidemiologic studies already in the evidentiary database that did specify diseases precisely used ICD-9 or earlier versions. Furthermore, the existing records that will serve as the basis of many ongoing and even future studies will use earlier and evolving classifications, so this is likely to remain the case even in new literature for a considerable period. The nomenclature has become more

uniform in recent studies, but the possibility of ambiguity remains if earlier researchers did not use a unique code in accordance with some established system.

Because it has been the objective of VAO committees to address disease entities in as great specificity as possible with the available data, the coarser grouping of LHCs has little effect on the entities about which conclusions of association have been drawn. The present committee notes, however, that the commonality of biologic origin of LHCs that have been judged to have a substantial amount of evidence supporting association with the chemicals of interest (HL, NHL, CLL, hairy-cell leukemia [HCL], multiple myeloma, and AL amyloidosis) means that the WHO approach is supportive of and consistent with these decisions.

VA has asked previous VAO committees to address CLL, AML, and then HCL individually. Scrutiny of the entire body of epidemiologic results on leukemia for findings on particular types (as had been the most common manner of grouping) revealed several studies that showed increased risks specifically of CLL but did not provide support for an association of AML with herbicide exposure. The committee for *Update 2002* advised VA that CLL is recognized as a form of the already recognized-as-service-related condition NHL, whereas the committee for *Update 2006* did not recognize an association with AML. Later, the committee responsible for *Update 2008* advised VA that HCL is a form of CLL. In light of the history and in accord with the current WHO classification, the current committee has incorporated data specifically on CLL and HCL into the section on NHL. The more common cancers of the lymphatic system are described in the sections below on HL, NHL, and multiple myeloma (with a section on the related condition, AL amyloidosis), followed by discussion of evidence on leukemias in general but with a focus on information regarding those of myelocytic origin.

Hodgkin Lymphoma

Hodgkin lymphoma (ICD-9 201), also known as Hodgkin disease, is distinguished from NHL primarily on the basis of its neoplastic cells, mononucleated Hodgkin cells, and multinucleated Reed–Sternberg cells originating in germinal-center B cells (Küppers et al., 2002). HL's demographics and genetics are also characteristic. ACS estimated that 4,670 men and 3,820 women would receive diagnoses of HL in the United States in 2010 and that 740 men and 580 women would die from it (Jemal et al., 2010). The average annual incidence is shown in Table 7-39.

The possibility that HL has an infectious etiology has been a topic of discussion since its earliest description. An increased incidence in people who have a history of infectious mononucleosis has been observed in some studies, and a link with Epstein–Barr virus has been proposed. In addition to the occupational associations discussed below, higher rates of the disease have been observed in people who have suppressed or compromised immune systems.

TABLE 7-39 Average Annual Incidence (per 100,000) of Hodgkin Disease in United States[a]

	55–59 Years Old			60–64 Years Old			65–69 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Men	4.0	4.0	2.4	3.8	4.0	4.4	4.5	4.8	4.7
Women	2.0	1.9	3.6	2.2	2.3	1.6	3.4	3.8	3.1

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2004–2008 (NCI, 2010).

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* determined that there were sufficient epidemiologic data to support an association between exposure to the chemicals of interest and HL. Additional studies available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008* did not change that conclusion. Table 7-40 summarizes the results of the relevant studies.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies No studies concerning exposure to the chemicals of interest and HL specifically in the Vietnam-veteran population have been published since *Update 2008*.

In their update of mortality in the ACC cohort through 2005, Cypel and Kang (2010) presented estimates of association between the chemicals of interest and all LHCs and leukemias in deployed and nondeployed veterans but no results for specific lymphoid cancers.

Occupational Studies The Dow Chemical Company site in Midland, Michigan, produced TCP or 2,4,5-T from 1942 to 1982 and PCP from 1937 to 1980. Some of the workers were exposed to both TCP and PCP. Historical exposures were estimated by evaluating serum dioxin in some of the workers (reported in Collins et al., 2008); their vital status was followed from 1942 to 2003 in the TCP study (Collins et al., 2009a) and from 1940 to 2003 in the PCP study (Collins et al., 2009b), and cause-specific death rates and trends with exposure were evaluated. No deaths from HL were identified in the study of PCP workers (Collins et al., 2009b), but the TCP study (Collins et al., 2009a), included in the NIOSH eight-plant cohort, found that the SMR of HL was 1.8 (95% CI 0.2–6.4); the finding was not statistically significant.

McBride et al. (2009a,b) published an occupational mortality study of workers in the Dow AgroSciences plant in New Plymouth, New Zealand, who

TABLE 7-40 Selected Epidemiologic Studies—Hodgkin Lymphoma

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans			**All COIs**
Akhtar et al., 2004	White Air Force Ranch Hand veterans vs national rates (lymphopoietic cancer[c])—incidence		
	Ranch Hand veterans	10	0.9 (0.4–1.5)
	Comparison Air Force veterans	9	0.6 (0.3–1.0)
AFHS, 2000	Air Force Ranch Hand veterans	1	0.3 (0.0–3.2)
Michalek et al., 1990; Wolfe et al., 1990	Air Force Ranch Hand veteran	0	nr
US CDC Vietnam Experience Study			**All COIs**
Boehmer et al., 2004	Follow-up of CDC VES cohort	2	0.9 (nr)
Boyle et al., 1987	Vietnam Experience Study	0	nr
US CDC Selected Cancers Study			**All COIs**
CDC, 1990a	US men born 1921–1953		
	Vietnam veterans	28	1.2 (0.7–2.4)
	Army	12	1.0 (0.5–2.0)
	Marine Corps	4	1.7 (0.5–5.9)
	Air Force	5	1.7 (0.6–4.9)
	Navy	7	1.1 (0.4–2.6)
US VA Mortality Study of Army and Marine Veterans (ground troops serving July 4, 1965–March 1, 1973)			**All COIs**
Watanabe and Kang, 1996	Marine Vietnam veterans	25	1.9 (1.2–2.7)
Watanabe et al., 1991	Army Vietnam veterans		
	vs Army non-Vietnam veterans	116	1.0 (nr)
	vs all non-Vietnam veterans	116	1.1 (nr)
	Marine Vietnam veterans		
	vs Marine non-Vietnam veterans	25	1.9 (nr)
	vs all non-Vietnam veterans	25	1.0 (nr)
Breslin et al., 1988	Vietnam-era veterans—deployed vs nondeployed		
	Army	92	1.2 (0.7–1.9)
	Marine Corps	22	1.3 (0.7–2.6)
US VA Cohort of Female Vietnam Veterans			**All COIs**
Cypel and Kang, 2008	US Vietnam veterans (lymphopoietic cancers[c])—women	18	0.7 (0.4–1.3)
	Vietnam-veteran nurses	14	0.7 (0.3–1.3)
State Studies of Vietnam Veterans			**All COIs**
Visintainer et al., 1995	PM study of deaths (1974–1989) of Michigan Vietnam-era veterans—deployed vs nondeployed	20	1.1 (0.7–1.8)

TABLE 7-40 Hodgkin Lymphoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Anderson et al., 1986	Wisconsin Vietnam veterans	4	nr
Holmes et al., 1986	West Virginia Vietnam veterans compared with West Virginia Vietnam-era veterans	5	8.3 (2.7–19.5)
Lawrence et al., 1985	New York Vietnam veterans compared with New York Vietnam-era veterans (lymphoma and HD)	10	*99% CI* 1.0 (0.4–2.2)
Australian Vietnam Veterans vs Australian Population			**All COIs**
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence	51	2.1 (1.5–2.6)
	Navy	7	1.3 (0.5–2.6)
	Army	40	2.3 (1.6–3.0)
	Air Force	4	2.1 (0.6–5.3)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—mortality	13	0.9 (0.5–1.5)
	Navy	2	0.6 (0.1–2.1)
	Army	11	1.1 (0.5–1.9)
	Air Force	0	0.0 (0.0–2.9)
Australian Conscripted Army National Service (deployed vs nondeployed)			**All COIs**
ADVA, 2005c	Australian male conscripted Army National Service Vietnam era veterans: deployed vs non-deployed		
	Incidence	12	0.9 (0.4–2.0)
	Mortality	4	1.7 (0.3–11.8)
Fett et al., 1987	Australian Vietnam veterans	0	nr
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			**Dioxin, phenoxy herbicides**
Kogevinas et al., 1997	IARC cohort, male and female workers exposed to any phenoxy herbicide or chlorophenol	10	1.0 (0.5–1.8)
	Exposed to highly chlorinated PCDDs	8	1.3 (0.6–2.5)
	Not exposed to highly chlorinated PCDDs	1	0.3 (0.0–1.5)
Kogevinas et al., 1993	IARC cohort, females—incidence	1	nr
Kogevinas et al., 1992	IARC cohort (men and women)	3	0.6 (0.1–1.7)
Saracci et al., 1991	IARC cohort, exposed subcohort (men and women)	2	0.4 (0.1–1.4)
NIOSH Mortality Cohort (12 US plants, production 1942–1984) (included in IARC and NIOSH cohorts)			**Dioxin, phenoxy herbicides**
Steenland et al., 1999	US chemical production workers	3	1.1 (0.2–3.2)
Fingerhut et al., 1991	NIOSH cohort—entire cohort	3	1.2 (0.3–3.5)
	≥ 1-yr exposure, ≥ 20-yr latency	1	2.8 (0.1–15.3)

continued

TABLE 7-40 Hodgkin Lymphoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
BASF Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Zober et al., 1990	BASF employees—basic cohort	0	nr
Dow Chemical Company—Midland, MI (included in IARC and NIOSH cohorts)			**Dioxin, phenoxy herbicides**
Collins et al., 2009a	Trichlorophenol workers	0	0.0 (0.0–6.4)
Collins et al., 2009b	Pentachlorophenol workers	2	1.8 (0.2–6.4)
Burns et al., 2001	Dow 2,4-D production workers	1	1.5 (0.0–8.6)
Ramlow et al., 1996	Dow pentachlorophenol production workers	0	nr
Bond et al., 1988	Dow 2,4-D production workers	1	2.7 (0.0–14.7)
Danish Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Hooiveld et al., 1998	Dutch chemical production workers	1	3.2 (0.1–17.6)
German Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Becher et al., 1996	German production workers	0	nr
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)			**Dioxin, phenoxy herbicides**
McBride et al., 2009a	1,599 Production workers (men and women) vs national rates—mortality 1969 through 2004		
	Ever exposed	1	4.2 (0.1–23.3)
	Never exposed	0	0.0 (0.0–47.1)
't Mannetje et al., 2006	New Zealand phenoxy herbicide producers, sprayer		
	Phenoxy herbicide producers (men and women)	1	5.6 (0.1–31.0)
	Phenoxy herbicide sprayers (> 99% men)	0	0.0 (0.0–16.1)
Agricultural Health Study			**Herbicides**
Alavanja et al., 2005	US AHS—incidence		
	Private applicators (men and women)	11	0.9 (0.4–1.6)
	Spouses of private applicators (> 99% women)	4	0.7 (0.2–1.9)
	Commercial applicators (men and women)	1	0.8 (0.1–4.2)
Blair et al., 2005a	US AHS	3	1.1 (0.2–3.3)
	Private applicators (men and women)	3	1.7 (0.3–4.8)
	Spouses of private applicators (> 99% women)	0	0.0 (0.0–2.5)
Torchio et al., 1994	Italian licensed pesticide users	11	1.0 (0.5–1.7)

TABLE 7-40 Hodgkin Lymphoma, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
Other Agricultural Workers			**Herbicides**
Orsi et al., 2009	Hospital-based case–control study in France—incidence (males only)		
	Occupational use of herbicides	7	1.5 (0.6–4.1)
	Phenoxy herbicides	6	2.5 (0.8–7.7)
	Domestic use of herbicides	19	0.8 (0.4–1.6)
Gambini et al., 1997	Italian rice growers	1	0.7 (0.0–3.6)
Blair et al., 1993	US farmers in 23 states	56	1.0 (0.8–1.3)
Alavanja et al., 1988	USDA agricultural extension agents		
	PM analysis	6	2.7 (1.2–6.3)
	Case–control analysis	6	1.1 (0.3–3.5)
Dubrow et al., 1988	Hancock County, Ohio, residents—farmers	3	2.7 (nr)
Wiklund et al., 1988	Swedish agricultural and forestry workers (men and women)		
	Workers in land or in animal husbandry	242	1.0 (0.9–1.2)
	Workers in silviculture	15	2.3 (1.3–3.7)
Hoar et al., 1986	Kansas residents		
	All farmers	71	0.8 (0.5–1.2)
	Farm use of herbicides (phenoxy acids and others)	28	0.9 (0.5–1.5)
	Farmers using herbicides > 20 days/yr	3	1.0 (0.2–4.1)
	Farmers using herbicides > 15 yrs	10	1.2 (0.5–2.6)
Pearce et al., 1985	New Zealand residents with agricultural occupations, 20–64 yrs of age	107	1.1 (0.6–2.0)
Wiklund, 1983	Swedish male and female agricultural workers—incidence	226	*99% CI* 1.0 (0.9–1.2)
Burmeister, 1981	Iowa farmers	47	1.2 (ns)
Other Studies of Herbicide and Pesticide Applicators			**Herbicides**
Swaen et al., 2004	Dutch licensed herbicide applicators	0	nr
Asp et al., 1994	Finnish herbicide applicators	2	1.7 (0.2–6.0)
Swaen et al., 1992	Dutch licensed herbicide applicators	1	3.3 (0.04–18.6)
Green, 1991	Ontario herbicide sprayers	0	nr
Wiklund et al., 1989b	Swedish pesticide applicators	15	1.5 (0.8–2.4)
Riihimaki et al., 1982	Finnish herbicide applicators	0	nr

continued

TABLE 7-40 Hodgkin Lymphoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Forestry Workers			**Herbicides**
Eriksson et al., 1992	Swedish Cancer Registry patients (men and women)		
	Male sawmill workers	10	2.2 (nr)
	Male farmers	97	1.2 (nr)
	Male forestry workers	35	1.2 (nr)
	Male horticulture workers	11	1.2 (nr)
Alavanja et al., 1989	USDA forest, soil conservationists	4	2.2 (0.6–5.6)
Paper and Pulp workers			**Dioxin**
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	7	0.6 (0.2–1.2)
	Ever	17	1.8 (1.0–2.8)
Rix et al., 1998	Danish paper-mill workers—incidence		
	Men	18	2.0 (1.2–3.2)
	Women	2	1.1 (0.1–3.8)
Other Occupational Studies			
Waterhouse et al., 1996	Residents of Tecumseh, Michigan	13	**Herbicides/** 2.0 (1.1–3.4) **Phenoxy herbicides/***90% CI*
Persson et al., 1993	Swedish NHL patients—exposure to phenoxy herbicides	5	7.4 (1.4–40.0)
Ronco et al., 1992	Danish workers—incidence		**Herbicides**
	Men—self-employed	27	0.6 ($p < 0.05$)
	employee	13	1.0 (nr)
	Female—self-employed	1	1.1 (nr)
	employee	1	1.2 (nr)
	family worker	9	0.9 (nr)
LaVecchia et al., 1989	Residents of the Milan, Italy, area (men and women)		**Herbicides, dioxin**
	Agricultural occupations	nr	2.1(1.0–3.8)
	Chemical-industry occupations	nr	4.3 (1.4–10.2)
Persson et al., 1989	Orebro (Sweden) Hospital patients (men and women)		**Phenoxys/***90% CI*
	Farming	6	1.2 (0.4–3.5)
	Exposed to phenoxy acids	4	3.8 (0.7–21.0)
Hardell and Bengtsson, 1983	Umea (Sweden) Hospital patients—incidence		**Phenoxys, chlorophenols**
	Exposed to phenoxy acids	14	5.0 (2.4–10.2)
	Exposed to high-grade chlorophenols	6	6.5 (2.2–19.0)
	Exposed to low-grade chlorophenols	5	2.4 (0.9–6.5)
Hardell et al., 1981	Umea (Sweden) Hospital patients (all lymphomas)—incidence		**Phenoxys, chlorophenols**
	Exposed to phenoxy acids	41	4.8 (2.9–8.1)
	Exposed to chlorophenols	50	4.3 (2.7–6.9)

TABLE 7-40 Hodgkin Lymphoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Consonni et al., 2008	Seveso residents (men and women)—25-yr follow-up		
	Zone A	0	nr
	Zone B (Bertazzi et al. [2001, 1997] reported four HD cases in Zone B)	3	2.2 (0.7–6.9)
	Zone R	9	0.9 (0.5–1.9)
Pesatori et al., 2009	Seveso—20-yr follow-up to 1996—incidence		
	Zone A	0	nr
	Zone B	3	1.2 (0.4–3.8)
	Zone R	23	1.5 (0.9–2.3)
Bertazzi et al., 2001	Seveso residents—20-yr follow-up		
	Zone A, B—men	2	2.6 (0.6–10.9)
	women	2	3.7 (0.9–16.0)
Bertazzi et al., 1997	Seveso residents—15-yr follow-up		
	Zone B—men	2	3.3 (0.4–11.9)
	women	2	6.5 (0.7–23.5)
	Zone R—women	4	1.9 (0.5–4.9)
Bertazzi et al., 1993	Seveso residents—10-yr follow-up—incidence		
	Zone B—men	1	1.7 (0.2–12.8)
	women	1	2.1 (0.3–15.7)
	Zone R—men	4	1.1 (0.4–3.1)
	women	3	1.0 (0.3–3.2)
Other Environmental Studies			**2,4,5-T**
Read et al., 2007	Residents of New Plymouth Territorial Authority, New Zealand near plant manufacturing 2,4,5-T (1962–1987)		
	Incidence	49	1.1 (0.8–1.5)[d]
	1970–1974	9	1.2 (0.6–2.3)
	1975–1979	9	1.1 (0.5–2.2)
	1980–1984	8	1.1 (0.5–2.1)
	1985–1989	9	1.3 (0.6–2.5)
	1990–1994	7	1.3 (0.5–2.7)
	1995–1999	4	0.7 (0.2–1.7)
	2000–2001	3	1.0 (0.2–3.1)
	Mortality	22	1.3 (0.8–2.0)[d]
	1970–1974	7	1.6 (0.7–3.3)
	1975–1979	4	1.2 (0.3–3.0)
	1980–1984	6	2.1 (0.8–4.5)
	1985–1989	3	1.2 (0.2–3.5)
	1990–1994	1	0.6 (0.0–3.5)
	1995–1999	1	0.6 (0.0–3.6)
	2000–2001	0	nr

continued

TABLE 7-40 Hodgkin Lymphoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Miligi et al., 2006	Italian case–control study—herbicide exposure in men, women with diagnosis of HD	6	**Herbicides** 0.4 (0.2–1.2)
Pahwa et al., 2006	Canadian men (at least 19 years old) in any of 6 provinces		**Phenoxy Herbicides**
	Any phenoxy herbicide	65	1.0 (0.7–1.4)
	2,4-D	57	1.0 (0.7–1.4)
	Mecoprop	20	1.3 (0.7–2.2)
	MCPA	11	1.2 (0.6–2.6)
Viel et al., 2000	Residents around French municipal solid-waste incinerator—incidence	9	**Dioxin** 1.5 (nr)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; AHS, Agricultural Health Study; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; HD, Hodgkin disease; IARC, International Agency for Research on Cancer; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MI, Michigan; NHL, non-Hodgkin lymphoma; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; ns, not significant; NZ, New Zealand; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PM, proportionate mortality; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; USDA, US Department of Agriculture; VA, US Department of Veterans Affairs; VES, Vietnam Experience Study.

[a]Subjects are male, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

[c]Lymphopoietic cancers comprise all forms of lymphoma (including Hodgkin disease and non-Hodgkin lymphoma) and leukemia (ALL, AML, CLL, CML).

[d]Committee computed total SMR and SIR by dividing sum of observed values by sum of expected values over all years, 95% CIs on these total ratios were computed with exact methods.

were potentially exposed to TCDD. Workers employed during January 1969–October 2003 were followed to the end of 2004, and SMRs were calculated by using national mortality figures. McBride et al. (2009a) examined overall mortality in TCP manufacturing workers (1,599, employed during 1969–1988) at the New Plymouth plant. The SMR and proportional hazards models were used to evaluate risk posed by exposure. The study reported an increased point estimate for the risk of HL (SMR = 4.2); however, this finding was statistically insignificant and inconclusive, because the confidence interval was very wide and uninformative (95% CI 0.1–23.3; only one death was observed). The results in McBride et al. (2009b) have not been included, because they were diluted by inclusion of a set of workers who had no opportunity for TCDD exposure and no observed deaths.

Orsi et al. (2009) conducted a hospital-based case–control study in six counties in France in 2000–2004 to investigate the relationship between exposure to pesticides and the risk of lymphoid neoplasms. Exposures to pesticides—including insecticides, fungicides, and herbicides—were determined through

case-by-case expert reviews of responses to self-administered and face-to-face interviews. The exposure assessment was specific for particular pesticide groups (such as organochlorine insecticides and phenoxy herbicides). The risk of HL was somewhat increased after occupational exposure to herbicides in general (OR = 1.5, 95% CI 0.6–4.1) and increased by more after occupational exposure to phenoxy herbicides in particular (OR = 2.5, 95% CI 0.8–7.7). No association was observed, however, between HL and domestic use of herbicides (OR = 0.8, 95% CI 0.4–1.6). Those findings were consistent with the findings of previous studies.

Environmental Studies Pesatori et al. (2009) examined long-term effects of TCDD exposure in the 1976 accident in Seveso through mortality and cancer-incidence studies that covered the 20-year follow-up to 1996 and examined effects on males and females combined in three exposure zones. No cases of HL were identified in Zone A; there was a modest increase in HL risk in Zone R (RR = 1.46, 95% CI 0.91–2.29) and a less clear increase in risk in Zone B (RR = 1.20, 95% CI 0.38–3.78).

The grouped results for mortality from cancer of "lymphoid, haematopoietic and related tissue" in Finnish fishermen (33 cases) and their wives (10 cases) in the study by Turunen et al. (2008) are too nonspecific to be of use in evaluating an association with particular types of lymphohematopoietic malignancy.

Biologic Plausibility

HL arises from the malignant transformation of a germinal-center B cell and is characterized by malignant cells that have a distinctive structure and phenotype; these binucleate cells are known as Reed–Sternberg cells (Jaffe et al., 2008). No animal studies have shown an increase in HL after exposure to the chemicals of interest. Reed–Sternberg cells have not been demonstrated in mice or rats, so there is no good animal model of HL. Thus, there are no specific animal data to support the biologic plausibility of an association between the chemicals of interest and HL.

The biologic plausibility of the carcinogenicity of the chemicals of interest is discussed in general at the beginning of this chapter.

Synthesis

The relative rarity of HL complicates the evaluation of epidemiologic studies because their statistical power is generally low. Earlier studies (Eriksson et al., 1992; Hardell et al., 1981; Holmes et al., 1986; LaVecchia et al., 1989; Persson et al., 1993; Rix et al., 1998; Waterhouse et al., 1996; Wiklund et al., 1988) were generally well conducted and included excellent characterization of exposure, and they formed the basis of previous committees' conclusions. Later findings have not contradicted those findings, especially given that most studies have had

low statistical power. The present committee notes that the four new studies for this update had uniformly increased risk estimates for HL—but with imprecise confidence intervals. Although it has not been demonstrated as clearly as for NHL, a positive association between the chemicals of interest and the development of HL is biologically plausible because of the common lymphoreticular origin of HL and NHL and their common risk factors.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is sufficient evidence of an association between exposure to at least one of the chemicals of interest and HL.

Non-Hodgkin Lymphoma

Non-Hodgkin lymphoma (ICD-9 200–200.8, 202–202.2, 202.8–202.9) is a general name for cancers of the lymphatic system other than HL or multiple myeloma. NHL comprises a large group of lymphomas that can be partitioned into acute and aggressive (fast-growing) or chronic and indolent (slow-growing) types of either B-cell or T-cell origin. B-cell NHL includes Burkitt lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, large-cell lymphoma, precursor B-lymphoblastic lymphoma, and mantle-cell lymphoma. T-cell NHL includes mycosis fungoides, anaplastic large-cell lymphoma, and precursor T-lymphoblastic lymphoma.

As noted in earlier VAO updates, in response to requests from VA, CLL and HCL have been recognized as sharing many traits with NHL (including B-cell origin and immunohistochemical properties) and may progress to an acute aggressive form of NHL. The proposed WHO classification of NHL notes that CLL (ICD-9 204.1) and its lymphomatous form, SLL, are both derived from mature B cells (Chiorazzi et al., 2005; IARC, 2001). The current VAO committee has determined that it is more appropriate to consider these lymphatic malignancies with other forms of NHL. Therefore, discussion of CLL and HCL will no longer follow the general section on leukemia but have been moved into the NHL grouping.

ACS estimated that 35,380 men and 30,160 women would receive diagnoses of NHL in the United States in 2010 and that 10,710 men and 9,500 women would die from it (Jemal et al., 2010). The incidence of NHL is uniformly higher in men than in women and typically higher in whites than in blacks. In the groups that characterize most Vietnam veterans, incidence increases with age. In addition, ACS estimated that about 8,870 men and 6,120 women would receive diagnoses of CLL in the United States in 2010 and that 2,650 men and 1,740 women would die from it (Jemal et al., 2010). Nearly all cases occur after the age of 50 years. Average annual incidences of NHL are shown in Table 7-41 with the additional incidences of CLL.

TABLE 7-41 Average Annual Incidence (per 100,000) of Non-Hodgkin Lymphoma in United States[a]

	55–59 Years Old			60–64 Years Old			65–69 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Men	37.8	38.7	37.1	56.5	59.3	40.9	77.9	81.8	53.5
Women	27.7	29.5	21.7	40.0	41.9	35.7	53.0	56.8	35.9

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2004–2008 (NCI, 2010).

The causes of NHL are poorly understood. People who have suppressed or compromised immune systems are known to be at higher risk, and some studies show an increased incidence in people who have HIV, human T-cell leukemia virus type I, Epstein–Barr virus, or gastric *Helicobacter pylori* infections. The human retrovirus HTLV-1 causes adult T-cell lymphoma, but early reports that HTLV-2 might play a role in the etiology of HCL have not been substantiated. A broad spectrum of behavioral, occupational, and environmental risk factors have been proposed as contributors to the occurrence of NHL, but given the diversity of malignancies included under this name it is not too surprising that, aside from infectious agents, immune problems, and particular chemotherapies, specific risk factors have not been definitively established (Morton et al., 2008; Wang and Nieter, 2010).

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was sufficient evidence to support an association between exposure to at least one of the chemicals of interest and NHL. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008* did not change that conclusion. Table 7-42 summarizes the results of the relevant studies.

Update 2002 was the first to discuss CLL separately from other leukemias. The epidemiologic studies indicated that farming, especially with exposure to 2,4-D and 2,4,5-T, is associated with significant mortality from CLL. Many more studies support the hypothesis that herbicide exposure can contribute to NHL risk. Most cases of CLL and NHL reflect malignant transformation of germinal-center B cells, so these diseases could have a common etiology. Studies reviewed in *Update 2002*, *Update 2004*, *Update 2006*, *Update 2008*, and the present update are summarized in Table 7-43.

TABLE 7-42 Selected Epidemiologic Studies—Non-Hodgkin Lymphoma

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans			**All COIs**
Akhtar et al., 2004	White Air Force Ranch Hand veterans (lymphopoietic cancer[c])—incidence		
	Ranch Hand veterans	10	0.9 (0.4–1.5)
	Comparison Air Force veterans	9	0.6 (0.3–1.0)
AFHS, 2000	Air Force Ranch Hand veterans—incidence	1	0.2 (0.0–2.6)
Michalek et al., 1990	Air Force Ranch Hand veterans—mortality		
	Lymphatic and hematopoietic tissue	0	nr
Wolfe et al., 1990	Air Force Ranch Hand veterans—incidence	1	nr
US CDC Cohort of Army Chemical Corps			**All COIs**
Boehmer et al., 2004	Vietnam Experience Cohort	6	0.9 (0.3–2.9)
US CDC Vietnam Experience Study			**All COIs**
O'Brien et al., 1991	Army enlisted Vietnam veterans (all lymphomas)	7	1.8 (nr)
US CDC Selected Cancers Study			**All COIs**
CDC, 1990b	US Vietnam veterans born 1921–1953—incidence	99	1.5 (1.1–2.0)
	Army Vietnam veterans	45	1.2 (0.8–1.8)
	Marine Vietnam veterans	10	1.8 (0.8–4.3)
	Air Force Vietnam veterans	12	1.0 (0.5–2.2)
	Navy Vietnam veterans	32	1.9 (1.1–3.2)
	Blue Water Navy Vietnam veterans	28	2.2 (1.2–3.9)
US VA Mortality Study of Army and Marine Veterans (ground troops serving July 4, 1965–March 1, 1973)			**All COIs**
Watanabe and Kang, 1996	Marine Vietnam veterans (ICDA-8 200, 202)	46	1.7 (1.2–2.2)
Watanabe et al., 1991	Army Vietnam veterans vs non-Vietnam veterans (ICD-8 200, 202)	140	0.8 (nr)
	Army Vietnam veterans vs combined Army and Marine Vietnam-era veterans (ICD-8 200, 202)	140	0.9 (nr)
	Marine Vietnam veterans vs non-Vietnam veterans (ICD-8 200, 202)	42	1.8 (1.3–2.4)
	Marine Vietnam veterans vs combined Army and Marine Vietnam-era veterans (ICDA-8 200, 202)	42	1.2 (nr)
Breslin et al., 1988	Army Vietnam veterans (ICDA-8 200, 202)	108	0.8 (0.6–1.0)
	Marine Vietnam veterans (ICDA-8 200, 202)	35	2.1 (1.2–3.8)
State Studies of US Vietnam Veterans			**All COIs**
Visintainer et al., 1995	PM study of deaths (1974–1989) of Michigan Vietnam-era veterans—deployed vs nondeployed	32	1.5 (1.0–2.1)

TABLE 7-42 Non-Hodgkin Lymphoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Clapp et al., 1991	Massachusetts Vietnam veterans		1.2 (0.6–2.4)
Anderson et al., 1986	Wisconsin Vietnam veterans (includes lymphosarcoma, reticulosarcoma)	4	nr
Holmes et al., 1986	West Virginia Vietnam veterans vs West Virginia Vietnam-era veterans	2	1.1 (nr)
Lawrence et al., 1985	New York Vietnam veterans vs New York Vietnam-era veterans (all lymphomas)	10	1.0 (0.4–2.2)
US VA Cohort of Female Vietnam Veterans			**All COIs**
Cypel and Kang, 2008	US Vietnam veterans—women (lymphopoietic cancers[c])	18	0.7 (0.4–1.3)
	Vietnam-veteran nurses	14	0.7 (0.3–1.3)
Thomas et al., 1991	US Vietnam veterans—women (NHL, ICD-8 200, 200–203, 208)	3	1.3 (0.3–1.8)
VA Case–Control Studies			**All COIs**
Dalager et al., 1991	US Vietnam veterans—incidence	100	1.0 (0.7–1.5)
US Navy Enlisted Personnel (January 1, 1974–December 31, 1983)			**All COIs**
Garland et al., 1988	Navy enlisted personnel (white males)—incidence	68	0.7 (0.5–0.9)
US VA Marine Post-Service Mortality Study (ground troops serving July 4, 1965–March 1, 1973)			**All COIs**
Burt et al., 1987	Army combat Vietnam veterans	39	1.1 (0.7–1.5)
	Marine combat Vietnam veterans	17	3.2 (1.4–7.4)
	Army Vietnam veterans (service 1967–1969)	64	0.9 (0.7–1.3)
	Marine Vietnam veterans (service 1967–1969)	17	2.5 (1.1–5.8)
Fett et al., 1987	Australian Vietnam veterans (ICD-8 200, 202)	4	1.8 (0.4–8.0)
Australian Vietnam Veterans vs Australian Population			**All COIs**
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence	126	0.7 (0.6–0.8)
	Navy	31	0.8 (0.5–1.0)
	Army	86	0.7 (0.5–0.8)
	Air Force	9	0.5 (0.2–0.9)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—mortality	70	0.8 (0.6–1.0)
	Navy	10	0.5 (0.3–0.9)
	Army	52	0.9 (0.6–1.1)
	Air Force	8	0.9 (0.4–1.6)
AIHW, 1999	Australian Vietnam veterans—incidence (validation study)		*Expected number of exposed cases (95% CI)*
		62	48 (34–62)
CDVA, 1998a	Australian Vietnam veterans—self-reported incidence	137	48 (34–62)

continued

TABLE 7-42 Non-Hodgkin Lymphoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
CDVA, 1998b	Australian Vietnam veterans (women)—self-reported incidence	2	0 (0–4)
CDVA, 1997a	Australian military Vietnam veterans		
	NHL deaths, 1980–1994	33	0.9 (0.6–1.2)
Australian Conscripted Army National Service (deployed vs nondeployed)			**All COIs**
ADVA, 2005c	Australian male conscripted Army National Service Vietnam-era veterans: deployed vs nondeployed		
	Incidence	35	1.1 (0.7–1.9)
	Mortality	21	1.4 (0.7–2.8)
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			**Dioxin, phenoxy herbicides**
Kogevinas et al., 1997	IARC cohort, male and female workers exposed to any phenoxy herbicide or chlorophenol	34	1.3 (0.9–1.8)
	Exposed to highly chlorinated PCDDs	24	1.4 (0.9–2.1)
	Not exposed to highly chlorinated PCDDs	9	1.0 (0.5–1.9)
Kogevinas et al., 1995	IARC cohort (men and women)—incidence		
	Exposed to 2,4,5-T	10	1.9 (0.7–4.8)
	Exposed to TCDD	11	1.9 (0.7–5.1)
Kogevinas et al., 1992	IARC cohort (men and women)		
	Workers exposed to any phenoxy herbicide or chlorophenol	11	1.0 (0.5–1.7)
NIOSH Mortality Cohort (12 US plants, production 1942–1984) (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Steenland et al., 1999	US chemical production workers	12	1.1 (0.6–1.9)
Dow Chemical Company—Midland, MI (included in IARC and NIOSH cohorts)			**Dioxin, phenoxy herbicides**
Collins et al., 2009a	Trichlorophenol workers	9	1.3 (0.6–2.5)
Collins et al., 2009b	Pentachlorophenol workers	8	2.4 (1.0–4.7)
Bodner et al., 2003	Dow chemical production workers	nr	1.4 (0.6–2.7)
Burns et al., 2001	Dow 2,4-D production workers	3	1.0 (0.2–2.9)

TABLE 7-42 Non-Hodgkin Lymphoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Ramlow et al., 1996	Dow pentachlorophenol production workers		
	All lymphopoietic cancer (ICDA-8 200–209)		
	0-yr latency	7	1.4 (0.6–2.9)
	15-yr latency	5	1.3 (0.4–3.1)
	Other, unspecified lymphopoietic cancer (ICDA-8 200, 202–203, 209)		
	0-yr latency	5	2.0 (0.7–4.7)
	15-yr latency	4	2.0 (0.5–5.1)
Bloemen et al., 1993	Dow 2,4-D production workers	2	2.0 (0.2–7.1)
Danish Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Lynge, 1993	Danish male and female production workers—updated incidence		
	Exposure to phenoxy herbicides (men)	10	1.7 (0.5–4.5)
Dutch Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Boers et al., 2010	Dutch chlorophenoxy workers		
	Factory A (HR for exposed vs unexposed)	4 vs 3	0.9 (0.2–4.5)
	Factory B (HR for exposed vs unexposed)	1 vs 0	nr
Hooiveld et al., 1998	Dutch phenoxy herbicide workers	3	3.8 (0.8–11.0)
Bueno de Mesquita et al., 1993	Dutch phenoxy herbicide workers	2	3.0 (0.4–10.8)
German Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Becher et al., 1996	German production workers	6	3.3 (1.2–7.1)
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)			**Dioxin, phenoxy herbicides**
McBride et al., 2009a	1,599 production workers (men and women) vs national rates—mortality 1969 through 2004		
	Ever exposed	3	1.6 (0.3–4.7)
	Never exposed	1	1.6 (0.0–8.7)
't Mannetje et al., 2005	New Zealand phenoxy herbicide producers, sprayers		
	Phenoxy herbicide producers (men and women)	1	0.9 (0.0–4.9)
	Phenoxy herbicide sprayers (> 99% men)	1	0.7 (0.0–3.8)

continued

TABLE 7-42 Non-Hodgkin Lymphoma, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
Agricultural Health Study			**Herbicides**
Samanic et al., 2006	Pesticide applicators in AHS—NHL incidence from enrollment through 2002		
	Dicamba—lifetime days exposure		
	None	39	1.0
	1– < 20	18	1.8 (1.0–3.2)
	20– < 56	14	1.3 (0.7–2.5)
	56– < 116	7	0.9 (0.4–2.2)
	≥ 116	7	1.2 (0.5–2.9)
			p-trend = 0.92
Alavanja et al., 2005	US AHS—incidence		
	Private applicators (men and women)	114	1.0 (0.8–1.2)
	Spouses of private applicators (> 99% women)	42	0.9 (0.6–1.2)
	Commercial applicators (men and women)	6	1.0 (0.4–2.1)
Blair et al., 2005a	US AHS		
	Private applicators (men and women)	33	0.9 (0.6–1.2)
	Spouses of private applicators (> 99% women)	16	1.2 (0.7–2.0)
California United Farm Workers			**Herbicides**
Mills et al., 2005	Nested case–control analyses of Hispanic workers in cohort of 139,000 California United Farm Workers		
	Ever used 2,4-D	nr	3.8 (1.9–7.8)
Other Agricultural Studies			**Herbicides**
Orsi et al., 2009	Hospital-based case–control study in France—incidence (males only)		
	Occupational use of herbicides	25	1.3 (0.7–2.2)
	Phenoxy herbicides	11	0.9 (0.4–1.9)
	Domestic use of herbicides	86	1.0 (0.7–1.5)
Hansen et al., 2007	Danish gardeners (lymphohematopoietic, ICD-7 200–205)—incidence		
	10-yr follow-up (1975–1984) reported in Hansen et al. (1992)	15	1.4 (0.8–2.4)
	NHL (ICD-7 200, 202, 205)	6	1.7 (0.6–3.8)
	HD (ICD-7 201)	0	nr
	Multiple myeloma (ICD-7 203)	0	nr
	CLL (ICD-7 204.0)	6	2.8 (1.0–6.0)
	Other leukemias (ICD-7 204.1–204.4)	3	1.4 (0.3–4.2)
	25-yr follow-up (1975–2001)		
	Born before 1915 (high exposure)	16	1.4 (0.9–2.3)
	Born 1915–1934 (medium exposure)	25	1.2 (0.8–1.8)
	Born after 1934 (low exposure)	1	0.2 (0.0–1.0)

TABLE 7-42 Non-Hodgkin Lymphoma, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
Chiu et al., 2004	Herbicide use—incidence		
	Farmers (no herbicide use)	294	1.2 (1.0–1.5)
	Farmers (herbicide use)	273	1.0 (0.8–1.2)
Lee et al., 2004b	Asthmatics—incidence		
	Herbicide exposure—phenoxyacetic acid	17	1.3 (0.7–2.4)
	Exposures among farmers		
	2,4-D	17	1.3 (0.7–2.5)
	2,4,5-T	7	2.2 (0.8–6.1)
	Nonasthmatics—incidence		
	Herbicide exposure—phenoxyacetic acid	176	1.0 (0.8–1.3)
	Exposures among farmers		
	2,4-D	172	1.0 (0.8–1.3)
	2,4,5-T	36	1.1 (0.7–1.8)
Gambini et al., 1997	Italian rice growers	4	1.3 (0.3–3.3)
Keller-Byrne et al., 1997	Farmers in central United States	nr	1.3 (1.2–1.6)
Nanni et al., 1996	Italian farming and animal-breeding workers (men and women) (NHL other than lymphosarcoma and reticulosarcoma)—incidence		
	Exposure to herbicides	3	1.4 (0.4–5.7)
Amadori et al., 1995	Italian farming, animal-breeding workers (men and women)—incidence		
	NHL, CLL combined	164	1.8 (1.2–2.6)
Dean, 1994	Irish farmers and farm workers		
	Other malignant neoplasms of lymphoid and histiocytic tissue (including some types of NHL) (ICD–9 202)		
	Men	244	nr
	Women	84	nr
Morrison et al., 1994	Farm operators in three Canadian provinces		
	All farm operators	nr	0.8 (0.7–0.9)
	Highest quartile of herbicides sprayed	19	2.1 (1.1–3.9)
	Highest quartile of herbicides sprayed relative to no spraying	6	3.0 (1.1–8.1)
Blair et al., 1993	US farmers in 23 states (white men)	843	1.2 (1.1–1.3)
Zahm et al., 1993	Females on eastern Nebraska farms	119	1.0 (0.7–1.4)
Ronco et al., 1992	Danish farm workers—incidence	147	1.0 (nr)
	Italian farm workers—mortality	14	1.3 (nr)
Wigle et al., 1990	Canadian farmers		
	All farmers	103	0.9 (0.8–1.1)
	Spraying herbicides on 250+ acres	10	2.2 (1.0–4.6)

continued

TABLE 7-42 Non-Hodgkin Lymphoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Zahm et al., 1990	Eastern Nebraska residents—incidence		
	Ever done farm work	147	0.9 (0.6–1.4)
	Ever mixed or applied 2,4-D	43	1.5 (0.9–2.5)
Corrao et al., 1989	Italian farmers licensed to apply pesticides		
	Lymphatic tissue (ICD-8 200–202.9)		
	Licensed pesticide users and nonusers	45	1.4 (1.0–1.9)
	Farmers in arable land areas	31	1.8 (1.2–2.5)
LaVecchia et al., 1989	Residents of Milan, Italy, area (men and women)—incidence		
	Agricultural occupations	nr	2.1 (1.3–3.4)
Alavanja et al., 1988	USDA agricultural extension agents	nr	1.2 (0.7–2.3)
Dubrow et al., 1988	Hancock County, Ohio, residents—farmers	15	1.6 (0.8–3.4)
Hoar et al., 1986	Kansas residents—incidence		
	Farmers compared with nonfarmers	133	1.4 (0.9–2.1)
	Farmers using herbicides at least 21 days/year	7	6.0 (1.9–19.5)
Burmeister et al., 1983	Iowa residents—farming exposures	1,101	1.3 (nr)
Wiklund, 1983	Swedish male and female agricultural workers—incidence	476	*99% CI* 1.1 (0.9–1.2)
Cantor, 1982	Wisconsin residents—farmers (ICD-8 200.0, 200.1, 202.2)	175	1.2 (1.0–1.5)
Other Studies of Herbicide and Pesticide Applicators			**Herbicides**
Torchio et al., 1994	Italian licensed pesticide users (ICD-8 202.0–202.9)	15	0.9 (0.5–1.5)
Asp et al., 1994	Finnish herbicide applicators—incidence		
	No latency	1	0.4 (0.0–2.0)
	10-yr latency	1	0.4 (0.0–2.4)
Swaen et al., 1992	Dutch herbicide applicators	0	nr
Wiklund et al., 1989b	Swedish pesticide applicators (men and women)—incidence	27	1.1 (0.7–1.6)
Pearce et al., 1987	New Zealand residents—incidence		
	Farming occupations	33	1.0 (0.7–1.5)
	Fencing work	68	1.4 (1.0–2.0)
Woods et al., 1987	Washington state residents—incidence		
	Phenoxy herbicide use	nr	1.1 (0.8–1.4)
	Chlorophenol use	nr	1.0 (0.8–1.2)
	Farming occupations	nr	1.3 (1.0–1.7)
	Forestry herbicide appliers	nr	4.8 (1.2–19.4)
Pearce et al., 1986	New Zealand residents (ICD-9 202 only)—incidence		
	Agricultural sprayers (phenoxy herbicides)	19	1.5 (0.7–3.3)

TABLE 7-42 Non-Hodgkin Lymphoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Pearce et al., 1985	New Zealand residents with agricultural occupations, 20–64 yrs of age—incidence	nr	1.4 (0.9–2.0)
Riihimaki et al., 1982	Finnish herbicide applicators	0	nr
Forestry Workers			**Herbicides**
Thörn et al., 2000	Swedish lumberjacks exposed to phenoxyacetic herbicides—incidence	2	2.3 (0.3–8.5)
Persson et al., 1993	Swedish NHL patients		
	Exposure to phenoxy herbicides	10	2.3 (0.7–7.2)
	Occupation as lumberjack	9	6.0 (1.1–31.0)
Alavanja et al., 1989	USDA forest, soil conservationists	22	2.4 (1.5–3.6)
Reif et al., 1989	New Zealand forestry workers—nested case–control (ICD-9 200, 202)—incidence	7	1.8 (0.9–4.0)
Wiklund et al., 1988	Swedish agricultural, forestry workers (men and women)		
	Workers in land, animal husbandry		1.0 (0.9–1.1)
	Timber cutters		0.9 (0.7–1.1)
Paper and Pulp Workers			**Dioxin**
McLean et al., 2006	IARC cohort of pulp and paper workers—men, women (ICD-9 200, 202)		
	Exposure to nonvolatile organochlorine compounds		
	Never		0.9 (0.7–1.3)
	Ever		0.9 (0.6–1.3)
	Exposed to chlorophenols	50	4.3 (2.7–6.9)
Occupational Case–Control Studies			**TCDD, Herbicides**
Richardson et al., 2008	German case–control study, occupational factors associated with NHL		
	Chlorophenols		
	NHL—high-grade malignancy	61	2.0 (1.3–2.9)
	NHL—low-grade malignancy	77	1.3 (1.0–1.8)
	CLL	44	0.9 (0.6–1.3)
	Herbicides		
	NHL—high-grade malignancy	56	2.2 (1.4–3.3)
	NHL—low-grade malignancy	79	1.4 (1.0–1.9)
	CLL	43	1.2 (0.8–1.7)
Fritschi et al., 2005	Population-based case–control study in New South Wales, Australia, 2000–2001		**Herbicides**
	Phenoxy herbicides		
	Nonsubstantial exposure	10	0.7 (0.3–1.7)

continued

TABLE 7-42 Non-Hodgkin Lymphoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Hardell et al., 2002	Pooled analysis of Swedish case–control studies of NHL, hairy-cell leukemia		**Herbicides**
	Herbicide exposure	77	1.8 (1.3–2.4)
	Phenoxyacetic acids	64	1.7 (1.2–2.3)
	MCPA	21	2.6 (1.4–4.9)
	2,4-D, 2,4,5-T	48	1.5 (1.0–2.2)
	Other	15	2.9 (1.3–6.4)
	Substantial exposure	5	1.8 (0.4–7.4)
Other Occupational Studies			**Herbicides**
Chiu et al., 2006	Nebraska residents (men and women), NHL reclassified according to specific chromosomal translocation (t[14;18][q32;q21])—incidence		
	Translocation present in cases		
	Herbicides	25	2.9 (1.1–7.9)
	Translocation absent in cases		
	Herbicides	22	0.7 (0.3–1.2)
Miligi et al., 2003	Residents of 11 areas in Italy (NHL other than lymphosarcoma and reticulosarcoma)—incidence		**Herbicides**
	Phenoxy acid herbicides exposure		
	Men	18	1.0 (0.5–2.0)
	Women	11	1.3 (0.5–3.7)
	2,4-D exposure		
	Men	6	0.7 (0.3–1.9)
	Women	7	1.5 (0.4–5.7)
Hardell et al., 1994	Umea (Sweden) Hospital patients—incidence		**Herbicides**
	Exposure to phenoxy herbicides	25	5.5 (2.7–11.0)
	Exposure to chlorophenols	35	4.8 (2.7–8.8)
Smith and Christophers, 1992	Australian residents		**Herbicides**
	Exposure > 1 day	15	1.5 (0.6–3.7)
	Exposure > 30 days	7	2.7 (0.7–9.6)
Vineis et al., 1991	Residents of selected Italian provinces		
	Male residents of contaminated areas	nr	2.2 (1.4–3.5)
Persson et al., 1989	Örebro (Sweden) Hospital (men and women)—incidence		**Herbicides**
	Exposed to phenoxy acids	6	4.9 (1.0–27.0)
Olsson and Brandt, 1988	Lund (Sweden) Hospital patients—incidence		**Herbicides**
	Exposed to herbicides	nr	1.3 (0.8–2.1)
	Exposed to chlorophenols	nr	1.2 (0.7–2.0)
Hardell et al., 1981	Umea (Sweden) Hospital patients (lymphoma and HD)—incidence		**Phenoxy herbicides**
	Exposed to phenoxy acids	41	4.8 (2.9–8.1)

TABLE 7-42 Non-Hodgkin Lymphoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Consonni et al., 2008	Seveso residents—25-yr follow-up—men, women		
	Zone A	3	3.4 (1.1–10.5)
	Zone B	7	1.2 (0.6–2.6)
	Zone R	40	1.0 (0.7–1.4)
Pesatori et al., 2009	Seveso—20-yr follow-up to 1996—incidence		
	Zone A	1	0.8 (0.1–5.7)
	Zone B	12	1.5 (0.9–2.7)
	Zone R	49	0.9 (0.7–1.2)
Bertazzi et al., 2001	Seveso residents—20-yr follow-up		
	Zone A, B—men	3	1.2 (0.4–3.9)
	women	4	1.8 (0.7–4.9)
Bertazzi et al., 1997	Seveso residents—15-yr follow-up		
	Zone B—men	2	1.5 (0.2–5.3)
	Zone R—men	10	1.1 (0.5–2.0)
	women	8	0.9 (0.4–1.7)
Bertazzi et al., 1993	Seveso residents—10-yr follow-up—incidence		
	Zone B—men	3	2.3 (0.7–7.4)
	women	1	0.9 (0.1–6.4)
	Zone R—men	12	1.3 (0.7–2.5)
	women	10	1.2 (0.6–2.3)
Pesatori et al., 1992	Seveso residents—incidence		
	Zones A, B—men	3	1.9 (0.6–6.1)
	women	1	0.8 (0.1–5.5)
	Zone R—men	13	1.4 (0.7–2.5)
	women	10	1.1 (0.6–2.2)
Bertazzi et al., 1989b	Seveso residents—10-yr follow-up		
	Zone B—women (ICD-9 200–208)	2	1.0 (0.3–4.2)
	Zone R—men (ICD-9 202)	3	1.0 (0.3–3.4)
	women (ICD-9 202)	4	1.6 (0.5–4.7)
Populations with Residential Proximity to Chemical Plant or Incinerator			**TCDD**
Viel et al., 2008	Residents near French solid-waste incinerator—incidence		
	Highly exposed census group vs slightly exposed		1.1 (1.0–1.3)
Read et al., 2007	Residents of New Plymouth Territorial Authority, New Zealand near plant manufacturing 2,4,5-T (1962–1987)		**All COIs**
	Incidence	223	1.0 (0.9–1.1)[d]
	1970–1974	33	1.8 (1.2–2.5)
	1975–1979	29	1.3 (0.9–1.9)
	1980–1984	22	0.8 (0.5–1.3)
	1985–1989	24	0.7 (0.5–1.1)

continued

TABLE 7-42 Non-Hodgkin Lymphoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
	1990–1994	35	0.8 (0.6–1.1)
	1995–1999	61	1.1 (0.8–1.4)
	2000–2001	19	0.8 (0.5–1.3)
	Mortality	138	1.1 (0.9–1.3)[d]
	1970–1974	19	1.6 (0.9–2.4)
	1975–1979	24	1.6 (1.0–2.4)
	1980–1984	14	1.0 (0.5–1.6)
	1985–1989	25	1.3 (0.9–2.0)
	1990–1994	23	0.9 (0.6–1.4)
	1995–1999	21	0.7 (0.4–1.1)
	2000–2001	12	1.0 (0.5–1.8)
Floret et al., 2003	Residents near French municipal solid-waste incinerator—incidence		**TCDD**
	High exposure category	31	2.3 (1.4–3.8)
Viel et al., 2000	Residents near French solid-waste incinerator—incidence		**TCDD**
	Spatial cluster	286	1.3 (p = 0.00003)
	1991–1994	109	1.8 (p = 0.00003)
Environmental Case–Control Studies			**Pesticides, herbicides**
Eriksson et al., 2008	NHL case–control study of exposure to pesticides in Sweden (men and women)—incidence		
	Herbicides, total	74	1.7 (1.2–2.5)
	≤ 20 days	36	1.6 (1.0–2.7)
	> 20 days	38	1.9 (1.1–3.2)
	Phenoxyacetic acids	47	2.0 (1.2–3.4)
	≤ 45 days	32	2.8 (1.5–5.5)
	> 45 days	15	1.3 (0.6–2.7)
	MCPA	21	2.8 (1.3–6.2)
	≤ 32 days	15	3.8 (1.4–10.5)
	> 32 days	6	1.7 (0.5–6.0)
	2,4,5-T, 2,4-D	33	1.6 (0.9–3.0)
	≤ 29 days	21	2.1 (1.0–4.4)
	> 29 days	12	1.3 (0.6–3.1)
Spinelli et al., 2007	Case–control study in British Columbia, Canada		**dl-PCBs**
	Total dioxin-like PCBs		
	Lowest quartile	82	1.0
	Second quartile	96	1.4 (0.9–2.2)
	Third quartile	82	1.6 (1.0–2.5)
	Highest quartile	143	2.4 (1.5–3.7)
			p-trend < 0.001

TABLE 7-42 Non-Hodgkin Lymphoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Miligi et al., 2006	Italian case–control study of hematolymphopoietic malignancies		**Herbicides, pesticides**
	NHL or CLL—ever exposed to herbicides		
	Men and women	73	1.0 (0.7–1.4)
	Men	49	0.8 (0.5–1.3)
	Women	24	1.3 (0.7–2.5)
	NHL (men and women)		
	Phenoxy herbicides—ever	32	1.1 (0.6–1.8)
	Probability of use more than "low," lack of protective equipment	13	2.4 (0.9–7.6)
	2,4-D—ever	17	0.9 (0.5–1.8)
	Probability of use more than "low," lack of protective equipment	9	4.4 (1.1–29.1)
	MCPA—ever	18	0.9 (0.4–1.8)
	Probability of use more than "low," lack of protective equipment	7	3.4 (0.8–23.2)
Xu et al., 2006	Case–control study of nasal NK/T-cell lymphomas in East Asia (men and women)—incidence		**Herbicides, pesticides**
	Pesticide use	23	4.0 (2.0–8.1)
	Herbicide	13	3.2 (1.4–7.4)
	Insecticide	20	3.5 (1.7–7.1)
	Fungicide	10	6.1 (2.0–18.5)
Hartge et al., 2005	NCI SEER case–control study (Iowa, Los Angeles County, Detroit, Seattle) 1998–2000		**2,4-D**
	Exposures to 2,4-D in carpet dust (ng/g)		
	Under detection limit	147	1.0
	< 500	257	1.1 (0.8–1.6)
	500–999	86	0.9 (0.6–1.5)
	1,000–9,999	165	0.7 (0.5–1.0)
	> 10,000	24	0.8 (0.4–1.7)
Kato et al., 2004	Population-based case–control study in upstate New York, women, 20–79 years old, 1995–1998		**Pesticides**
	Home use only of herbicides, pesticides (times)		
	0	231	1.0
	1–4	33	0.9 (0.5–1.5)
	5–17	30	0.7 (0.4–1.3)
	18–39	27	1.0 (0.6–1.7)
	≥ 40	40	0.9 (0.5–1.5)
Hardell et al., 2001	Case–control study of NHL—TEQ > 27.8, EA > 80	8	**Dioxin** 2.8 (0.5–18.0)

continued

TABLE 7-42 Non-Hodgkin Lymphoma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
McDuffie et al., 2001	Case–control study of NHL in Canada		**Pesticides**
	Exposed to phenoxy herbicides	131	1.4 (1.1–1.8)
	2,4-D	111	1.3 (1.0–1.7)
	Mecoprop	53	2.3 (1.6–3.4)
Lampi et al., 1992	Finnish community exposed to chlorophenol contamination (men and women)—incidence	16	**Chlorophenols/** 2.8 (1.4–5.6)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; AHS, Agricultural Health Study; CDC, Centers for Disease Control and Prevention; CI, confidence interval; CLL, chronic lymphocytic leukemia; COI, chemical of interest; EA, Epstein–Barr virus early antigen; HD, Hodgkin disease; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; ICDA, International Classification of Diseases, Adapted for Use in the United States; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MI, Michigan; NCI, National Cancer Institute; NHL, non-Hodgkin lymphoma; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; NZ, New Zealand; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PM, proportionate mortality; SEA, Southeast Asia; SEER, Surveillance, Epidemiology, and End Results; SIR, standard incidence ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEQ, toxicity equivalent quotient; USDA, US Department of Agriculture; VA, US Department of Veterans Affairs.

[a]Subjects are male, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

[c]Lymphopoietic cancers comprise all forms of lymphoma (including Hodgkin disease and non-Hodgkin lymphoma) and leukemia (ALL, AML, CLL, CML).

[d]Committee computed total SMR and SIR by dividing sum of observed values by sum of expected values over all years; 95% CIs on these total ratios were computed with exact methods.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies No studies concerning exposure to the chemicals of interest and NHL specifically in the Vietnam-veteran population have been published since *Update 2008*.

In their update of mortality in the ACC cohort through 2005, Cypel and Kang (2010) presented estimates of association between the chemicals of interest and all LHCs and leukemias in deployed and nondeployed veterans but no results for specific lymphoid cancers.

Occupational Studies Boers et al. (2010) followed up the mortality experience of retrospective cohorts in two Dutch chlorophenoxy herbicide manufacturing factories, which are included in the IARC cohort of phenoxy herbicide workers (Saracci et al., 1991). During 1955–1985, 1,167 workers in Factory A produced mainly 2,4,5-T. In Factory B, 1,143 workers produced 2,4-D, MCPA, and MCPP during 1965–1985. Determination of vital status through 2006 added

TABLE 7-43 Selected Epidemiologic Studies—Chronic Lymphocytic Leukemia

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
Australian Vietnam Veterans vs Australian Population			**All COIs**
ADVA, 2005a	Australian Vietnam veterans vs Australian population—incidence		
	All branches	58	1.2 (0.7–1.7)
	Navy	12	1.5 (0.8–2.6
	Army	42	1.7 (1.2–2.2)
	Air Force	4	0.9 (0.2–2.2)
OCCUPATIONAL			
Residential Populations			**Herbicides/pesticides**
Richardson et al., 2008	German residents, occupational factors associated with CLL—incidence		
	Chlorophenols	44	0.9 (0.6–1.3)
	Lowest tertile cumulative exposure	12	0.9 (0.4–1.8)
	Middle tertile	15	0.9 (0.5–1.8)
	Highest tertile	17	0.9 (0.5–1.6)
			p-trend = 0.770
	Herbicides	43	1.2 (0.8–1.7)
	Lowest tertile cumulative exposure	13	1.3 (0.7–2.7)
	Middle tertile	15	1.3 (0.7–2.5)
	Highest tertile	15	1.0 (0.5–1.9)
			p-trend = 0.755
Waterhouse et al., 1996	Residents of Tecumseh, Michigan (men and women)—incidence	10	1.8 (0.8–3.2)
Brown et al., 1990	Residents of Iowa, Minnesota		
	Ever farmed	156	1.4 (1.1–1.9)
	Any herbicide use	74	1.4 (1.0–2.0)
	Ever used 2,4,5-T	10	1.6 (0.7–3.4)
	Use at least 20 yrs before interview	7	3.3 (1.2–8.7)
Other Agricultural Workers			**Herbicides**
Orsi et al., 2009	Hospital-based case–control study in France—incidence (males only)		
	Occupational use of herbicides	5	0.5 (0.2–1.3)
	Phenoxy herbicides	3	0.4 (0.1–1.7)
Amadori et al., 1995	Workers in northeast Italy (men and women)	15	2.3 (0.9–5.8)
	Farming workers only	5	1.6 (0.5–5.2)
	Breeding workers only	10	3.1 (1.1–8.3)
Hansen et al., 1992	Danish gardeners (men and women)		
	All gardeners	6	2.5 (0.9–5.5)
	Male gardeners	6	2.8 (1.0–6.0)
Blair and White, 1985	1,084 leukemia deaths in Nebraska 1957–1974		
	Farmer usual occupation on death certificate	nr	1.3 ($p < 0.05$)
	248 CLL cases	nr	1.7 ($p < 0.05$)

continued

TABLE 7-43 Chronic Lymphocytic Leukemia, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Burmeister et al., 1982	1,675 leukemia deaths in Iowa 1968–1978		
	Farmer usual occupation on death certificate		1.2 ($p < 0.05$)
	CLL	132	1.7 (1.2–2.4)
	Lived in 33 counties with highest herbicide use	nr	1.9 (1.2–3.1)
Forestry Workers			**Herbicides**
Hertzman et al., 1997	British Columbia sawmill worker with chlorophenate process (more hexa-, hepta-, and octa-chlorinated dibenzo-*p*-dioxins than TCDD), all leukemias—incidence	47	1.2 (0.9–1.5)
	ALL	2	1.0 (0.2–3.1)
	CLL	24	1.7 (1.2–2.4)
	AML	5	0.8 (0.3–1.7)
	CML	7	1.1 (0.5–2.0)
	Other, unspecified	5	0.5 (0.2–1.0)
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Consonni et al., 2008	Seveso residents (men and women)—25-yr follow-up		
	Lymphatic leukemia (ICD-9 204)		
	Zone A	0	nr
	Zone B	3	1.3 (0.4–4.1)
	Zone R	23	1.4 (0.9–2.2)
Pesatori et al., 2009	Seveso—20-yr follow-up to 1996—incidence		
	Lymphatic leukemia (ICD-9 204)		
	Zone A	1	2.8 (0.4–19.9)
	Zone B	0	nr
	Zone R	13	0.8 (0.5–1.5)
Bertazzi et al., 2001	Seveso residents—20-yr follow-up		
	Lymphatic leukemia		
	Zones A, B—men	2	1.6 (0.4–6.8)
	women	0	nr
Other Environmental Studies			**2,4,5-T**
Read et al., 2007	Residents of New Plymouth Territorial Authority, New Zealand near plant manufacturing 2,4,5-T (1962–1987)		
	Incidence	104	1.3 (1.1–1.6)[c]
	1970–1974	16	2.5 (1.4–4.1)
	1975–1979	7	0.9 (0.4–1.8)
	1980–1984	21	2.6 (1.6–3.9)
	1985–1989	16	1.4 (0.8–2.3)
	1990–1994	13	0.9 (0.5–1.6)
	1995–1999	19	0.9 (0.5–1.4)
	2000–2001	12	1.1 (0.6–1.9)

TABLE 7-43 Chronic Lymphocytic Leukemia, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
	Mortality	40	1.3 (0.9–1.8)[c]
	1970–1974	7	1.7 (0.7–3.5)
	1975–1979	7	1.8 (0.7–3.6)
	1980–1984	6	1.4 (0.5–3.0)
	1985–1989	4	0.8 (0.2–2.2)
	1990–1994	6	1.1 (0.4–2.5)
	1995–1999	8	1.3 (0.6–2.6)
	2000–2001	2	0.8 (0.1–2.8)

ABBREVIATIONS: 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; CI, confidence interval; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; COI, chemical of interest; ICD, International Classification of Diseases; nr, not reported; SIR, standard incidence ratio; SMR, standardized mortality ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

[a]Subjects are male, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

[c]The total SMR/SIR were computed by dividing sum of observed values by sum of expected values over all years; 95% CIs on these total ratios were computed with exact methods.

15 years of follow-up to results reported previously (Bueno de Mesquita et al., 1993; Hooiveld et al., 1998). HRs were derived by using Cox proportional hazard models with attained age as the timescale. The two previous studies of this group had shown increased risks of death from NHL. Although increased risks of all cancers were observed previously in both Factory A (HR = 1.31, 95% CI 0.86–2.01) and Factory B (HR = 1.54, 95% CI 1.00–2.37), the later analysis no longer confirmed the increased risk of death from NHL (HR = 0.92, 95% CI 0.19–4.47) in Factory A. Only one case of NHL was observed in exposed workers in Factory B and none in the unexposed workers. That finding could not be attributed to the different statistical models that were used, inasmuch as the HR generated from Cox regression model was similar to the reported RR from the Poisson regression model that had been used in the second followup study. Perhaps an unknown latent period for NHL associated with the exposures has passed, and cases that would normally occur with increasing age of the controls now mask the previous finding.

Collins et al. (2008) estimated historical exposures by an evaluating serum dioxin in some of the workers exposed to dioxins at the Dow Chemical Company site that produced TCP and PCP in Midland, Michigan. There were 1,615 workers in the TCP cohort (Collins et al., 2009a) and 773 in the PCP cohort (Collins et al., 2009b), and 196 of the workers were exposed to both TCP and PCP. The vital status of the TCP workers was followed from 1942 to 2003 and that of the

PCP workers from 1940 to 2003, and cause-specific death rates and trends with exposure were evaluated. A modest or slight increase in NHL risk (SMR = 1.3, 95% CI 0.6–2.5) was observed in TCP production-site workers (Collins et al., 2009a), but a larger and almost statistically significant increase in risk was identified (SMR = 2.4, 95% CI 1.0–4.7) in PCP-plant workers (Collins et al., 2009b). As stated before, the potential chemicals of interest have been considered by the present committee in evaluating study findings.

McBride et al. (2009a,b) published an occupational mortality study of workers in the Dow AgroSciences plant in New Plymouth, New Zealand, who were potentially exposed to TCDD. Workers employed during January 1969–October 2003 were followed to the end of 2004, and SMRs were calculated by using national mortality figures. McBride et al. (2009a) examined the overall mortality in TCP manufacturing workers (1,599, employed during 1969–1988). The SMR and proportional hazards models were used to evaluate risk from exposure. The study reported a 60% increase in NHL risk (SMR = 1.6, 95% CI 0.3–4.7; three deaths in exposed workers); the wide confidence interval, including values substantially below 1, makes this finding inconclusive. The results in McBride et al. (2009b) have not been included because they were diluted by inclusion of a set of workers who had no opportunity for TCDD exposure and no observed deaths.

Orsi et al. (2009) conducted a hospital-based case–control study in six counties in France in 2000–2004 to investigate the relationship between occupational exposures to pesticides and the risk of lymphoid neoplasms categorized according to the WHO system, ICD-O-3 (*International Classification of Diseases for Oncology*, 3rd edition). The lymphoid neoplasms analyzed included HL, NHL, lymphoproliferative syndromes (CLL and HCL), and multiple myeloma. Exposures (both occupational and domestic) to pesticides—including insecticides, fungicides, and herbicides—were evaluated through specific interviews and case-by-case expert reviews. The exposure assessment specified particular pesticide groups (such as organochlorine insecticides and phenoxy herbicides). The risk of NHL was somewhat increased after occupational exposure to herbicides in general (OR = 1.3, 95% CI 0.7–2.2), but no association was observed between occupational exposure to phenoxy herbicides and NHL risk (OR = 0.9, 95% CI 0.4–1.9). A modest association was observed between garden pesticide use and NHL (OR = 1.4, 95% CI 1.0–2.0) but not between domestic use of herbicides and NHL (OR = 1.0, 95% CI 0.7–1.5). No association was observed between occupational exposure to herbicides and CLL (OR = 0.5, 95% CI 0.2–1.3) or between phenoxy herbicides and CLL (OR = 0.4, 95% CI 0.1–1.7).

Environmental Studies Pesatori et al. (2009) examined long-term effects of TCDD exposure in the 1976 accident in Seveso through a cancer-incidence study that covered the 20-year follow-up to 1996 and examined effects on males and females separately in three exposure zones. A positive association was not identified in Zone A (RR = 0.80, 95% CI 0.11–5.69) or in Zone R (RR = 0.90, 95% CI

0.66–1.22), but a modest, statistically nonsignificant increase in NHL risk was detected in Zone B (RR = 1.51, 95% CI 0.85–2.69). Nonsignificant increases in lymphatic leukemia (ICD-9 204) were seen in Zone A (RR = 2.78, 95% CI 0.39–19.9) and Zone R (RR = 0.83, 95% CI 0.46–1.48) on the basis of 1 and 13 cases, respectively. No cases of lymphatic leukemia were reported in Zone B.

Viel et al. (2008) studied exposure to dioxin emissions from municipal solid-waste incinerators, the major source of dioxin exposure of public concern in France. The study examined an association of dioxin exposure and NHL incidence in 3,974 people in 1990–1999 in the populations residing in the vicinity of 13 French municipal waste incinerators. The study area incorporated four French administrative departments, comprising a total of 2,270 block groups, and the cumulative ground-level dioxin concentrations were calculated for each block group on the basis of modeling of sparse 1972–1985 emmisions data. A statistically significant relationship was found at the block-group level between dioxin exposure and risk of NHL (RR = 1.12, 95% CI 1.00–1.25) in persons who lived in highly exposed census blocks compared with those who lived in slightly exposed block groups. Although the observed increase in RR is small, a dose–response relationship with increased exposure to dioxin was observed.

Additional analyses of NHL in several previously studied populations have been published since *Update 2008*, but they did not present new information with sufficient specificity for the chemicals of interest in the VAO series. McDuffie et al. (2009) investigated the interaction of family history with pesticide exposure in the Canadian case–control study reported on earlier by McDuffie et al. (2001) and Pahwa et al. (2006). Ng et al. (2010) explored the role of AHR polymorphisms in response to several dioxin-like PCBs in another Canadian case–control study of NHL reported on by Spinelli et al. (2007). Colt et al. (2009) reported on the influence of polymorphisms in 36 immune genes and toxic equivalents in the National Cancer Institute SEER case–control study of NHL (De Roos et al., 2005a; Hartge et al., 2005).

The grouped results for mortality from cancer of "lymphoid, haematopoietic and related tissue" in Finnish fishermen (33 cases) and their wives (10 cases) in the study by Turunen et al. (2008) are too nonspecific to be of use in evaluating an association with particular types of lymphohematopoietic malignancy.

The temporal correspondence of the years of greatest PCB use with marked increase and then plateauing in NHL incidence and several epidemiology studies reporting association of NHL with total serum concentrations of PCB motivated a series of nested case–control studies on NHL analyzing the levels of individual PCB congeners and other organochlorines (not including dioxins or furans) in existing biologic samples from prospective cohorts (Bertrand et al., 2010; Engel et al., 2007; Laden et al., 2010). Engel et al. (2007) conducted parallel nested analyses on three cohorts: more than 87,000 Norwegian men and women assembled in the 1970s; almost 24,000 residents of Washington County, Maryland, gathered in 1974; and a pilot sample from the Nurses' Health Study with bloods

drawn in 1989. PCB-118, a dioxin-like PCB, is among the congeners most consistently detected in human samples; it and the two other PCBs measured most reliably in these three cohorts (PCB-138 and -153) were the targets of statistical analysis. Significant dose–response relationships were found for each of these congeners in all three cohorts, with the results being strongest for PCB-118. Working from the cohort established in 1982 for the Physicians' Health Study, Bertrand et al. (2010) found less pronounced results for PCB-118 and a set of six "immunotoxic PCBs" (PCB-66, -74, -105, -118, -156, and -167, of which four are dioxin-like) suggested by Wolff et al. (1997) as a suitable hypothesis-driven group for analysis in epidemiology studies. The findings of Laden et al. (2010) from an analogous nested case–control study on the full Nurses' Health Study were not supportive of an association. The findings of these PCB-focused studies are consistent with the associations with NHL repeatedly observed for the chemicals of interest in the VAO series, but the extent of intercorrelation of these persistent organic pollutants greatly curtails the degree to which any effect could be specifically attributed to "dioxin-like activity."

Biologic Plausibility

The diagnosis of NHL encompasses a wide variety of lymphoma subtypes. In humans, about 85% are of B-cell origin and 15% of T-cell origin. In commonly used laboratory mice, the lifetime incidence of spontaneous B-cell lymphomas is about 30% in females and about 10% in males. Although researchers seldom note the subtypes of B lymphomas observed, lymphoblastic, lymphocytic, follicular, and plasma-cell lymphomas are seen in mice and are similar to types of NHL seen in humans. Laboratory rats are less prone to develop lymphomas, but Fisher 344 rats have an increased incidence of spontaneous mononuclear-cell leukemia of nonspecific origin. The lifetime incidence of leukemia is about 50% in male rats and about 20% in female rats. Neither mice nor rats develop T-cell lymphomas spontaneously at a predictable incidence, but T-cell–derived tumors can be induced by exposure to some carcinogens.

Several long-term feeding studies of various strains of mice and rats have been conducted over the past 30 years to determine the effects of TCDD on cancer incidence. Few of them have shown effects of TCDD on lymphoma or leukemia incidence. The NTP (1982a) reported no increase in overall incidence of lymphoma in female B6C3F1 mice exposed to TCDD at 0.04, 0.2, or 2.0 µg/kg per week for 104 weeks but found that histiocytic lymphomas (now considered to be equivalent to large B-cell lymphomas) were more common in the high-dose group. No effects on lymphoma incidence were seen in Osborne–Mendel rats treated with TCDD at 0.01, 0.05, or 0.5 µg/kg per week. Sprague–Dawley rats treated with TCDD at 0.003, 0.010, 0.022, 0.046, or 0.100 µg/kg per day showed no change in incidence of malignant lymphomas. Long-term exposure to phenoxy herbicides or cacodylic acid also has not resulted in an increased incidence

of lymphomas in laboratory animals. Thus, few laboratory animal data support the biologic plausibility of promotion of NHL by TCDD or other chemicals of interest.

In contrast, more recent studies at the cellular level indicate that activation of the AHR by TCDD inhibits apoptosis, a mechanism of cell death that controls the growth of cancer cells. Vogel et al. (2007) studied human cancer cells in tissue culture and showed that addition of TCDD inhibited apoptosis in histiocytic-lymphoma cells, Burkitt-lymphoma cells, and NHL cell lines. The reduction in apoptosis was associated with an increase in the expression of *Cox-2*, *C/EBP* β, and *Bcl-xL* mRNA in the cells. Those expressed genes code for proteins that protect cells from apoptosis. The effects of TCDD on apoptosis were blocked when an AHR antagonist or a Cox-2 inhibitor was added to the culture; this demonstrated the underlying AHR-dependent mechanism of the effects. More important, when C57Bl/10J mice were given multiple doses of TCDD over a period of 140 days, premalignant lymphoproliferation of B cells was induced in the TCDD-treated mice before the appearance of any spontaneous lymphomas in the control mice. When the B cells were examined, they were found to manifest changes in gene expression similar to those induced by TCDD in the human cell lines, which provided support for this mechanism of lymphoma promotion by TCDD.

Recent evidence has shown that AHR activation by TCDD in human breast and endocervical cell lines induces sustained high concentrations of the IL-6 cytokine, which has tumor-promoting effects in numerous tissues (Hollingshead et al., 2008). IL-6 plays a roll in B-cell maturation and induces a transcriptional inflammatory response. It is known to be increased in B-cell neoplasms, including multiple myeloma and various lymphomas, especially diffuse large B-cell lymphomas (Hussein et al., 2002; Kato et al., 1998; Kovacs, 2006).

An alternative link that could help to explain the association between TCDD and NHL has been explored in human studies. Chromosomal rearrangements, with consequent expression dysregulation of various genes, are prevalent in B-cell lymphomas, and the t(14;18) reciprocal translocation, which juxtaposes the BCL2 with the locus of the immunoglobin heavy chain, is found in tumor cells in most cases of follicular lymphoma. Roulland et al. (2004) investigated the prevalence of the t(14;18) translocation that is characteristic of most cases of follicular lymphoma in 53 never-smoking and pesticide-using men in a cohort of French farmers whose pesticide exposures and confounding information had previously been well characterized; 21 blood samples had been gathered during periods of high pesticide use, and samples from the other 32 were drawn during a period of low pesticide use. The authors found a higher prevalence of cells carrying this translocation in the farmers whose blood had been drawn during a period of high pesticide use than in those whose blood had been drawn during a low-use period. Baccarelli et al. (2006) reported an increase in t(14;18) chromosomal translocation in lymphocytes from humans exposed to TCDD in the Seveso accident. In most cases of follicular lymphoma, tumor cells carry the t(14;18) chromosomal

translocation, and there is evidence to suggest that an increased frequency of lymphocytes from the peripheral blood carrying this tumor marker may be a necessary but not sufficient step toward development of follicular lymphoma (Roulland et al., 2006).

Synthesis

The first VAO committee found the evidence to be sufficient to support an association between exposure to at least one of the chemicals of interest and NHL. The evidence was drawn from occupational and other studies in which subjects were exposed to a variety of herbicides and herbicide components. As has generally been the case in previous updates, the new studies were largely concordant with the conclusion that there is an association with the chemicals of interest. For the present update, with the exception of the case–control study by Orsi et al. (2009), the new occupational studies of herbicide production workers (Boers et al., 2010; Collins et al., 2009a,b; McBride et al., 2009a) were largely supportive of earlier conclusions. Much of the earlier epidemiologic evidence suggests that 2,4-D or 2,4,5-T, rather than TCDD, might be responsible for the associations observed in occupational cohorts, but the new positive findings for NHL in residents around a municipal waste incinerator (Viel et al., 2008) support an association with TCDD exposure. The nonpositive findings on the incidence of NHL in the 20-year follow-up of the Seveso population (Pesatori et al., 2009) are contrary to the increasingly strong association with NHL mortality observed in the 25-year follow-up of the same population (Consonni et al., 2008) reviewed in *Update 2008*.

Individual findings on CLL are fairly few compared with the considerable number of studies supporting an association between exposure to the chemicals of interest and NHL. Some high-quality studies show that exposure to 2,4-D and 2,4,5-T appears to be associated with CLL, including the incidence study of Australian veterans (ADVA, 2005a), the case–control study by Hertzman et al. (1997) of British Columbia sawmill workers exposed to chlorophenates, the Danish-gardener study (Hansen et al., 1992), and the population-based case–control study in two US states by Brown et al. (1990) that showed increased risks associated with any herbicide use and specifically use of 2,4,5-T for at least 20 years before interview. Other studies that showed positive associations but do not contribute greatly to the overall conclusion include the population-based case–control study by Amadori et al. (1995) that made use of occupational titles but did not include specific assessments of exposure to the chemicals; the cancer-incidence study in Tecumseh County, Michigan, in which no exposure assessments were available (Waterhouse et al., 1996); and proportionate-mortality studies by Blair and White (1985) and Burmeister et al. (1982).

Conclusions

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is sufficient evidence of an association between exposure to at least one of the chemicals of interest and NHL.

Multiple Myeloma

Multiple myeloma (ICD-9 203) is characterized by proliferation of bone-marrow stem cells that results in an excess of neoplastic plasma cells and in the production of excess abnormal proteins, usually fragments of immunoglobulins. Multiple myeloma is sometimes grouped with other immunoproliferative neoplasms (ICD-9 203.8). ACS estimated that 11,170 men and 9,010 women would receive diagnoses of multiple myeloma in the United States in 2010 and that 5,760 men and 4,890 women would die from it (Jemal et al., 2010). The average annual incidence of multiple myeloma is shown in Table 7-44.

The incidence of multiple myeloma is highly age-dependent and is relatively low in people under 40 years old. The incidence is slightly higher in men than in women, and the difference becomes more pronounced with age.

An increased incidence of multiple myeloma has been observed in several occupational groups, including farmers and other agricultural workers and those with workplace exposure to rubber, leather, paint, and petroleum (Riedel et al., 1991). People who have high exposure to ionizing radiation and those who suffer from other plasma-cell diseases, such as monoclonal gammopathy of unknown significance or solitary plasmacytoma, are also at greater risk.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was limited or suggestive evidence of an association between exposure to the chemicals of interest and multiple myeloma. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update*

TABLE 7-44 Average Annual Incidence (per 100,000) of Multiple Myeloma in United States[a]

	55–59 Years Old			60–64 Years Old			65–69 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
Men	11.7	10.8	23.0	18.7	17.1	43.7	27.8	26.1	59.9
Women	8.0	7.3	15.1	13.0	11.2	31.6	18.5	16.6	39.5

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2004–2008 (NCI, 2010).

2004, *Update 2006*, and *Update 2008* did not change that conclusion. Table 7-45 summarizes the results of the relevant studies.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies No studies concerning exposure to the chemicals of interest and multiple myeloma specifically in the Vietnam-veteran population have been published since *Update 2008*.

In their update of mortality in the ACC cohort through 2005, Cypel and Kang (2010) presented estimates of an association between the chemicals of interest and all LHCs and leukemias in deployed and nondeployed veterans but gave no results for specific lymphoid cancers.

Occupational Studies McBride et al. (2009a,b) published an occupational mortality study of workers in the Dow AgroSciences plant in New Plymouth, New Zealand, who were potentially exposed to TCDD. Workers who were employed during January 1969–October 2003 were followed to the end of 2004, and SMRs were calculated by using national mortality figures. McBride et al. (2009a) examined overall mortality in 1,599 TCP manufacturing workers who were employed during 1969–1988. The SMR and proportional hazards models were used to evaluate risk posed by exposure. The study reported an increase in multiple myeloma (SMR = 2.2) that is statistically nonsignificant and inconclusive (95% CI 0.2–8.1; two deaths in the exposed). The results in McBride et al. (2009b) have not been included because they were diluted by inclusion of a set of workers who had no opportunity for TCDD exposure and no observed deaths.

Orsi et al. (2009) conducted a hospital-based case–control study in six counties in France in 2000–2004 to investigate the relationship between exposures to pesticides and the risk of various lymphoid neoplasms, including multiple myeloma. Exposures to pesticides were evaluated through specific interviews and case-by-case expert reviews. The exposure assessment specified particular pesticide groups (such as organochlorine insecticides and phenoxy herbicides). The risk of multiple myeloma was significantly increased in association with total occupational herbicide use (OR = 2.9, 95% CI 1.3–6.5), and a positive association was observed between exposure to phenoxy herbicides and multiple myeloma (OR = 2.6, 95% CI 0.9–7.1). However, no association between domestic use of herbicides and multiple myeloma was observed (OR = 1.0, 95% CI 0.6–2.0).

A nested case–control study of male pesticide applicators in the AHS (Landgren et al., 2009) found a statistically nonsignificant increase in monoclonal gammopathy of undetermined significance (MGUS) in association with exposure to 2,4-D (OR = 1.8, 95% CI 0.7–4.8) but not dicamba (OR = 0.9, 95% CI 0.5–1.8). MGUS is a benign clonal expansion of plasma cells that converts into multiple myeloma in a modest proportion of cases.

TABLE 7-45 Selected Epidemiologic Studies—Multiple Myeloma

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans			**All COIs**
Akhtar et al., 2004	White Air Force Vietnam veterans (lymphopoietic cancers)—incidence		
	Ranch Hand veterans—incidence	10	0.9 (0.4–1.5)
	Comparison Air Force veterans—incidence	9	0.6 (0.3–1.0)
AFHS, 2000	Air Force Ranch Hand veterans	2	0.7 (0.1–5.0)
US CDC Vietnam Experience Study			**All COIs**
Boehmer et al., 2004	Follow-up of CDC VES cohort	1	0.4 (nr)
US VA Mortality Study of Army and Marine Veterans (ground troops serving July 4, 1965–March 1, 1973)			**All COIs**
Watanabe and Kang, 1996	Army Vietnam veterans	36	0.9 (nr)
	Marine Vietnam veterans	4	0.6 (nr)
Breslin et al., 1988	Army Vietnam veterans	18	0.8 (0.2–2.5)
	Marine Vietnam veterans	2	0.5 (0.0–17.1)
US VA Cohort of Female Vietnam Veterans			**All COIs**
Cypel and Kang, 2008	US Vietnam veterans—women (lymphopoietic cancers) vs nondeployed	18	0.7 (0.4–1.3)
	Vietnam-veteran nurses only	14	0.7 (0.3–1.3)
Australian Vietnam Veterans vs Australian Population			**All COIs**
ADVA, 2005a	Australian male Vietnam veterans vs Australian population—incidence	31	0.7 (0.4–0.9)
	Navy	4	0.4 (0.1–1.0)
	Army	21	0.7 (0.4–1.0)
	Air Force	6	1.1 (0.4–2.4)
ADVA, 2005b	Australian male Vietnam veterans vs Australian population—mortality	24	0.9 (0.5–1.2)
	Navy	3	0.5 (0.1–1.5)
	Army	15	0.8 (0.4–1.3)
	Air Force	6	1.7 (0.6–3.6)
CDVA, 1997a	Australian military Vietnam veterans	6	0.6 (0.2–1.3)
Australian Conscripted Army National Service (deployed vs nondeployed)			**All COIs**
ADVA, 2005c	Australian male conscripted Army National Service Vietnam-era veterans—deployed vs nondeployed		
	Incidence	8	2.1 (0.7–6.0)
	Mortality	5	0.9 (0.2–3.4)
CDVA, 1997b	Australian military Vietnam veterans	0	

continued

TABLE 7-45 Multiple Myeloma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			**Dioxin, phenoxy herbicides**
Kogevinas et al., 1997	IARC cohort, male and female workers exposed to any phenoxy herbicide or chlorophenol	17	1.3 (0.8–2.1)
	Exposed to highly chlorinated PCDDs	9	1.2 (0.6–2.3)
	Not exposed to highly chlorinated PCDDs	8	1.6 (0.7–3.1)
Saracci et al., 1991	IARC cohort (men and women)—exposed subcohort	4	0.7 (0.2–1.8)
NIOSH Mortality Cohort (12 US plants, production 1942–1984) (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Steenland et al., 1999	US chemical production workers	10	2.1 (1.0–3.8)
Fingerhut et al., 1991	NIOSH cohort—entire cohort	5	1.6 (0.5–3.9)
	≥ 1-yr exposure, ≥ 20-yr latency	3	2.6 (0.5–7.7)
Dow Chemical Company—Midland, MI (included in IARC and NIOSH cohorts)			**Dioxin, phenoxy herbicides**
Burns et al., 2001	Dow 2,4-D production workers	1	0.8 (0.0–4.5)
Danish Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Lynge, 1993	Danish production workers—updated incidence		
	Men	0	nr
	Women	2	12.5 (1.5–45.1)
Dutch Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Hooiveld et al., 1998	Dutch phenoxy herbicide workers	0	0.0 (nr)
German Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Becher et al., 1996	German production workers—Plant I	3	5.4 (1.1–15.9)
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)			**Dioxin, phenoxy herbicides**
McBride et al., 2009a	1,599 production workers (male and female) vs national rates—mortality 1969 through 2004		
	Ever exposed	2	2.2 (0.2–8.1)
	Never exposed	0	0.0 (0.0–12.2)
't Mannetje et al., 2005	New Zealand phenoxy herbicide producers, sprayers		
	Phenoxy herbicide producers (men and women)	3	5.5 (1.1–16.1)
	Phenoxy herbicide sprayers (> 99% men)	0	0.0 (0.0–5.3)

TABLE 7-45 Multiple Myeloma, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
Agricultural Health Study			**Herbicides**
Landgren et al., 2009	US AHS—nested case–control study of MGUS among male private and commercial applicators		
	2,4-D	33	1.8 (0.7–4.8)
	Dicamba	17	0.9 (0.5–1.8)
Alavanja et al., 2005	US AHS—incidence		
	Private applicators (men and women)	43	1.3 (1.0–1.8)
	Spouses of private applicators (> 99% women)	13	1.1 (0.6–1.9)
	Commercial applicators (men and women)	0	0.0 (0.0–2.7)
Blair et al., 2005a	US AHS		
	Private applicators (men and women)	11	0.6 (0.3–1.2)
	Spouses of private applicators (> 99% women)	5	0.9 (0.3–2.1)
Other Agricultural Workers			**Herbicides**
Orsi et al., 2009	Hospital-based case–control study in France—incidence (males only)		
	Occupational use of herbicides	12	2.9 (1.3–6.5)
	Phenoxy herbicides	7	2.6 (0.9–7.0)
	Domestic use of herbicides	22	1.0 (0.6–2.0)
Gambini et al., 1997	Italian rice growers	0	nr
Dean, 1994	Irish farmers and farm workers (men and women)		
	Men	171	1.0 (nr)
Semenciw et al., 1994	Farmers in Canadian prairie provinces	160	0.8 (0.7–1.0)
Blair et al., 1993	US farmers in 23 states	413	1.2 (1.0–1.3)
Boffetta et al., 1989	ACS Prevention Study II subjects	12	2.1 (1.0–4.2)
	Farmers using herbicides, pesticides	8	4.3 (1.7–10.9)
LaVecchia et al., 1989	Residents (men and women) of Milan, Italy, area		
	Agricultural occupations	nr	2.0 (1.1–3.5)
Cantor and Blair, 1984	Wisconsin residents—farmers in counties with highest herbicide use	nr	1.4 (0.8–2.3)
Burmeister et al., 1983	Iowa residents—farming exposures		
	Born 1890–1900	nr	2.7 ($p < 0.05$)
	Born after 1900	nr	2.4 ($p < 0.05$)
Other Herbicide and Pesticide Applicators			**Herbicides**
Swaen et al., 2004	Dutch licensed herbicide applicators (included in IARC cohort, NIOSH Dioxin Registry)	3	2.1 (0.4–6.1)
Asp et al., 1994	Finnish herbicide applicators		
	Incidence	2	1.5 (0.2–5.2)
	Mortality	3	2.6 (0.5–7.7)
Torchio et al., 1994	Italian licensed pesticide users	5	0.4 (0.1–1.0)

continued

TABLE 7-45 Multiple Myeloma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Swaen et al., 1992	Dutch herbicide applicators	3	8.2 (1.6–23.8)
Pearce et al., 1986	New Zealand residents—agricultural sprayers		
	Use of agricultural spray	16	1.3 (0.7–2.5)
	Likely sprayed 2,4,5-T	14	1.6 (0.8–3.1)
Riihimaki et al., 1982	Finnish herbicide applicators		*Expected number of exposed cases*
		1	0.2 (nr)
Forestry Workers			**Herbicides**
Thörn et al., 2000	Swedish lumberjacks exposed to phenoxyacetic herbicides—incidence	0	nr
Alavanja et al., 1989	USDA forest, soil conservationists	6	1.3 (0.5–2.8)
Reif et al., 1989	New Zealand forestry workers—nested case–control—incidence	1	0.5 (0.1–3.7)
Paper and Pulp Workers			**Dioxin**
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	21	0.8 (0.5–1.3)
	Ever	20	1.1 (0.7–1.7)
Residential Studies			
Brown et al., 1993	Iowa residents who used pesticides or herbicides	111	1.2 (0.8–1.7)
Zahm et al., 1992	Eastern Nebraska users of herbicides		
	Men	8	0.6 (0.2–1.7)
	Women	10	2.3 (0.8–7.0)
	Eastern Nebraska users of insecticides		
	Men	11	0.6 (0.2–1.4)
	Women	21	2.8 (1.1–7.3)
Eriksson and Karlsson, 1992	Residents of northern Sweden		*90% CI*
		20	2.2 (1.2–4.7)
Morris et al., 1986	Residents of four SEER program areas		2.9 (1.5–5.5)
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Consonni et al., 2008	Seveso residents—25-yr follow-up—men, women		
	Zone A	2	4.3 (1.1–17.5)
	Zone B	5	1.7 (0.7–4.1)
	Zone R	24	1.1 (0.7–1.7)

TABLE 7-45 Multiple Myeloma, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Pesatori	Seveso—20-yr follow-up to 1996—incidence		
et al., 2009	Zone A	1	2.9 (0.4–20.7)
	Zone B	6	2.8 (1.2–6.3)
	Zone R	18	1.2 (0.7–1.9)
Bertazzi	Seveso residents—20-yr follow-up		
et al., 2001	Zone A, B—men	1	0.6 (0.1–4.3)
	women	4	3.2 (1.2–8.8)
Bertazzi	Seveso residents—15-yr follow-up		
et al., 1997	Zone B—men	1	1.1 (0.0–6.2)
	women	4	6.6 (1.8–16.8)
	Zone R—men	5	0.8 (0.3–1.9)
	women	5	1.0 (0.3–2.3)
Bertazzi	Seveso residents—10-yr follow-up—incidence		
et al., 1993	Zone B—men	2	3.2 (0.8–13.3)
	women	2	5.3 (1.2–22.6)
	Zone R—men	1	0.2 (0.0–1.6)
	women	2	0.6 (0.2–2.8)
Pesatori	Seveso residents—incidence		
et al., 1992	Zones A, B—men	2	2.7 (0.6–11.3)
	women	2	4.4 (1.0–18.7)
	Zone R—men	1	0.2 (0.0–1.5)
	women	3	0.9 (0.3–3.1)
Other Environmental Studies			
Miligi	Italian case–control study—herbicide exposure		
et al., 2006	among men, women with diagnosis of multiple		**Herbicides**
	myeloma	11	1.6 (0.8–3.5)
Pahwa	Canadian men (at least 19 yrs of age) in any of 6		**Phenoxy herbicides**
et al., 2006	provinces		
	Any phenoxy herbicide	62	1.2 (0.8–1.8)
	2,4-D	59	1.3 (0.9–1.9)
	Mecoprop	16	1.2 (0.7–2.8)
	MCPA	7	0.5 (0.2–1.2)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; ACS, American Cancer Society; AHS, Agricultural Health Study; CDC, Centers of Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MGUS, monoclonal gammopathy of undetermined significance; MI, Michigan; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; NZ, New Zealand; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); SEA, Southeast Asia; SEER, Surveillance, Epidemiology, and End Results; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; USDA, US Department of Agriculture; VA, US Department of Veterans Affairs; VES, Vietnam Experience Study.

[a]Subjects are male, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

Environmental Studies Pesatori et al. (2009) reported cancer incidence through 1996 in combined males and females exposed to TCDD in the 1976 accident in Seveso in three exposure Zones. The magnitude of multiple-myeloma risk increased with degree of exposure; the increases identified in Zone A (RR = 2.88, 95% CI 0.40–20.70) and Zone R (RR = 1.15, 95% CI 0.70–1.91) were not significant, but a statistically significant increase was observed in Zone B (RR = 2.77, 95% CI 1.2–6.32).

McDuffie et al. (2009) conducted additional analyses in the Canadian case–control study of multiple myeloma reported on earlier by McDuffie et al. (2001) and Pahwa et al. (2006). The investigation concerning the interaction of family history with pesticide exposure did not present new information with sufficient specificity for the chemicals of interest in the VAO series.

The grouped results for mortality from cancer of "lymphoid, haematopoietic and related tissue" among Finnish fishermen (33 cases) and their wives (10 cases) in the study by Turunen et al. (2008) are too nonspecific to be of use in evaluating an association between the chemicals of interest and particular types of lymphohematopoietic malignancy.

Biologic Plausibility

No animal studies have reported an association between exposure to the chemicals of interest and multiple myeloma. Thus, there are no specific animal data to support the biologic plausibility of an association between exposure to the chemicals of interest and multiple myeloma.

Recent evidence has shown that AHR activation by TCDD in human breast and endocervical cell lines induces sustained high concentrations of the IL-6 cytokine, which has tumor-promoting effects in numerous tissues (Hollingshead et al., 2008). IL-6 plays a roll in B-cell maturation and induces a transcriptional inflammatory response. It is known to be increased in B-cell neoplasms, including multiple myeloma and various lymphomas (Hussein et al., 2002; Kovacs, 2006).

In comparing the frequency of specific variants of several metabolic genes between multiple-myeloma cases and controls, Gold et al. (2009) found some indication of differences, particularly for *CYP1B1* and *AHR* alleles, that might reflect increased suspectibility to myeloma after exposure to particular chemicals. A biochemical link to the chemicals of interest, however, is far from being established.

The biologic plausibility of the carcinogenicity of the chemicals of interest is discussed in general at the beginning of this chapter.

Synthesis

The three studies providing new information on an association between exposure to the components of the herbicides used in Vietnam and multiple my-

eloma had findings consistent with the conclusion of the first and all later VAO committees that there is evidence suggesting an association. The study of New Zealand production workers (McBride et al., 2009a) showed an increase in estimated risk with very wide confidence limits due to the fairly small sample. The incidence of multiple myeloma in the 20-year update of the Seveso population (Pesatori et al., 2009) was increased in all three exposure zones and achieved significance in the intermediate zone (Zone B). A well-conducted case–control study (Orsi et al., 2009) found an association between occupational exposure to herbicides in general and phenoxy herbicides in particular, but not domestic use of herbicides, and multiple myeloma. The nested case–control study of the precursor condition MGUS in the AHS male applicators (Landgren et al., 2009) also was consistent with the existing assigned category for multiple myeloma.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is limited or suggestive evidence of an association between exposure to at least one of the chemicals of interest and multiple myeloma.

AL Amyloidosis

The committee responsible for *Update 2006* moved the discussion of AL amyloidosis from the chapter on miscellaneous nonneoplastic health conditions to the cancer chapter to put it closer to related neoplastic conditions, such as multiple myeloma and some types of B-cell lymphoma. The conditions share several biologic features, most notably clonal hyperproliferation of B-cell–derived plasma cells and production of abnormal amounts of immunoglobulins.

The primary feature of amyloidosis (ICD-9 277.3) is the accumulation and deposition in various tissues of insoluble proteins that were historically denoted by the generic term *amyloid*. Amyloid protein accumulates in the extracellular spaces of various tissues. The pattern of organ involvement depends on the nature of the protein; some amyloid proteins are more fibrillogenic than others. Amyloidosis is classified according to the biochemical properties of the fibril-forming protein. Excessive amyloid protein can have modest clinical consequences or can produce severe, rapidly progressive multiple–organ-system dysfunction. The annual incidence is estimated at 1/100,000; there are about 2,000 new cases each year in the United States. Amyloidosis occurs mainly in people 50–70 years old and occurs more often in males than in females.

AL amyloidosis is the most common form of systemic amyloidosis; the *A* stands for *amyloid*, and the *L* indicates that the amyloid protein is derived from immunoglobin *light* chains. That links AL amyloidosis with other B-cell disorders that involve overproduction of immunoglobin, such as multiple myeloma

and some types of B-cell lymphomas. AL amyloidosis results from the abnormal overproduction of immunoglobulin light-chain protein from a monoclonal population of plasma cells. Clinical findings can include excessive AL protein or immunoglobulin fragments in the urine or serum, renal failure with nephrotic syndrome, liver failure with hepatomegaly, heart failure with cardiomegaly, marcroglossia, carpal tunnel syndrome, and peripheral neuropathy. Bone marrow biopsies commonly show an increased density of plasma cells, which suggests a premalignant state. Historically, that test emphasized routine histochemical analysis, but modern immunocytochemistry and flow cytometry now commonly identify monoclonal populations of plasma cells with molecular techniques. AL amyloidosis can progress rapidly and is often far advanced by the time it is diagnosed (Buxbaum, 2004).

Conclusions from *VAO* and Previous Updates

VA identified AL amyloidoisis as of concern after the publication of *Update 1998*. The committees responsible for *Update 2000*, *Update 2002*, and *Update 2004* concluded that there was inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and AL amyloidosis. Although there are few epidemiologic data specifically on AL amyloidosis, the committee responsible for *Update 2006* changed the categorization to limited or suggestive evidence of an association on the basis of commonalities in its cellular lineage with multiple myeloma and B-cell lymphomas. The committee responsible for *Update 2008* did not change that categorization.

Update of the Epidemiologic Literature

No studies concerning exposure to the chemicals of interest and amyloidosis of any sort have been published since *Update 2008*.

Biologic Plausibility

A 1979 study reported the dose-dependent development of a "generalized lethal amyloidosis" in Swiss mice that were treated with TCDD for 1 year (Toth et al., 1979). That finding has not been validated in 2-year carcinogenicity studies of TCDD in mice or rats. Thus, few animal data support an association between TCDD exposure and AL amyloidosis in humans, and no animal data support an association between the other chemicals of interest and AL amyloidosis.

It is known, however, that AL amyloidosis is associated with B-cell diseases, and 15–20% of cases of AL amyloidosis occur with multiple myeloma. Other diagnoses associated with AL amyloidosis include B-cell lymphoma (Cohen et al., 2004), monoclonal gammopathy, and agammaglobulinemia (Rajkumar et al., 2006).

Synthesis

AL amyloidosis is very rare, and it is not likely that population-based epidemiology will ever provide substantial direct evidence regarding its causation. However, the biologic and pathophysiologic features linking AL amyloidosis, multiple myeloma, and some types of B-cell lymphoma—especially clonal hyperproliferation of plasma cells and abnormal immunoglobulin production—indicate that AL amyloidosis is pathophysiologically related to these conditions.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is limited or suggestive evidence of an association between exposure to the chemicals of interest and AL amyloidosis.

Leukemia

Leukemias (ICD-9 202.4, 203.1, 204–204.9, 205–205.9, 206–206.9, 207–207.2, 207.8, 208–208.9) have traditionally been divided into four primary types: acute and chronic lymphocytic leukemia and acute and chronic myeloid leukemia. There are numerous subtypes of AML (ICD-9 205), which is also called acute myelogenous leukemia, granulocytic leukemia, or acute nonlymphocytic leukemia.

ACS estimated that 24,690 men and 18,360 women would receive diagnoses of some form of leukemia in the United States in 2010 and that 12,660 men and 9,180 women would die from it (Jemal et al., 2010). Collectively, leukemia was expected to account for 3.1% of all new diagnoses of cancer and 3.8% of deaths from cancer in 2010. The different forms of leukemia have different patterns of incidence and in some cases different risk factors. The incidences of the various forms of leukemia are presented in Table 7-46.

Myeloid Leukemias

In adults, acute leukemia is nearly always in the form of AML (ICD-9 205, 207, 207.2). ACS estimated that about 6,590 men and 5,740 women would receive new diagnoses of AML in the United States in 2010 and that 5,280 men and 3,670 women would die from it (Jemal et al., 2010). In the age groups that include most Vietnam veterans, AML makes up roughly one-fourth of cases of leukemia in men and one-third in women. Overall, AML is slightly more common in men than in women. Risk factors associated with AML include high doses of ionizing radiation, occupational exposure to benzene, and exposure to some medications used in cancer chemotherapy (such as melphalan). Fanconi anemia and Down syndrome are associated with an increased risk of AML, and tobacco use is thought to account for about 20% of AML cases.

TABLE 7-46 Average Annual Incidence (per 100,000) of Leukemias in United States[a]

	55–59 Years Old			60–64 Years Old			65–69 Years Old		
	All Races	White	Black	All Races	White	Black	All Races	White	Black
All leukemias:									
Men	20.5	21.4	17.0	31.3	33.0	31.0	48.3	51.8	30.8
Women	12.8	13.4	10.2	18.4	19.5	15.5	27.1	29.0	22.6
Acute lymphocytic leukemia:									
Men	0.9	1.0	0.3	1.1	1.2	0.4	1.5	1.5	1.2
Women	0.8	0.9	0.6	1.0	1.0	0.6	1.2	1.1	1.3
Acute myeloid leukemia:									
Men	4.9	4.9	5.0	6.9	7.0	7.2	10.1	10.5	6.4
Women	4.3	4.4	3.6	4.6	4.8	4.4	7.9	8.2	6.2
Chronic lymphocytic leukemia:									
Men	9.8	10.4	6.8	16.8	17.4	14.7	26.1	28.8	14.5
Women	5.1	5.6	2.8	9.2	10.3	5.4	12.5	13.8	8.4
Chronic myeloid leukemia:									
Men	2.5	2.4	3.1	3.3	3.4	4.4	5.7	6.0	4.1
Women	1.5	1.5	1.1	1.8	1.8	3.2	2.8	3.1	1.8
All other leukemia:[b]									
Men	0.6	0.6	0.8	1.2	1.1	2.0	2.0	2.0	2.3
Women	0.4	0.4	0.6	0.8	0.6	1.6	1.4	1.2	3.6

[a]Surveillance, Epidemiology, and End Results program, nine standard registries, crude age-specific rates, 2004–2008 (NCI, 2010).

[b]Includes leukemic reticuloendotheliosis (hairy cell leukemia), plasma-cell leukemia, monocytic leukemia, and acute and chronic erythremia and erythroleukemia.

Vietnam veterans have expressed concern about whether myelodysplastic syndromes, most often precursors to AML, are associated with Agent Orange exposure. However, no results on those conditions in conjunction with the chemicals of interest have been found by VAO literature searches. Epidemiologic research on those hematologic disorders has been undertaken fairly recently; for instance, the LATIN Case–Control Study (Maluf et al., 2009) has undertaken investigation of aplastic anemia in South America, but the reported exposures have been only as specific as "herbicides" and "agricultural pesticides."

The incidence of CML increases steadily with age in people over 30 years old. Its lifetime incidence is roughly equal in whites and blacks and is slightly higher in men than in women. CML accounts for about one-fifth of cases of leukemia in people in the age groups that include most Vietnam veterans. It is associated with an acquired chromosomal abnormality known as the Philadelphia chromosome, for which exposure to high doses of ionizing radiation is a known risk factor.

Lymphoid Leukemias

ALL is a disease of young children (peak incidence at 2–5 years old) and of people over 70 years old. It is relatively uncommon in the age groups that include most Vietnam veterans. The lifetime incidence of ALL is slightly higher in whites than in blacks and higher in men than in women. Exposure to high doses of ionizing radiation is a known risk factor for ALL, but there is little consistent evidence on other factors.

CLL shares many traits with lymphomas (such as immunohistochemistry, B-cell origin, and progression to an acute, aggressive form of NHL), so the committee now considers it in the section above on NHL, as classified in the WHO system.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the chemicals of interest and all types of leukemia. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008* did not change that conclusion. The committee responsible for *Update 2002*, however, considered CLL separately and judged that there was sufficient evidence of an association with the herbicides used in Vietnam and CLL alone, and *Update 2008* noted that HCL is closely related to CLL. The committee responsible for *Update 2006* and *Update 2008* considered AML individually but did not find evidence to suggest that its occurrence is associated with exposure to the chemicals of interest, so it was retained with other non-CLL leukemias in the category of inadequate and insufficient evidence. Table 7-47 summarizes the results of the relevant studies.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies Cypel and Kang (2010) examined the risk of disease-related mortality in the ACC veterans (2,872) who handled or sprayed herbicides in Vietnam and in nondeployed Vietnam-era ACC veterans (2,737). Vital status was determined through December 31, 2005. As would be consistent with a healthy-warrior effect, deployed veterans had a lower rate of leukemia than males in the US population (SMR = 0.42, 95% CI 0.05–1.51) and significantly lower mortality from all LHCs (SMR = 0.46, 95% CI 0.17–0.99). Comparing Vietnam veterans with nondeployed Vietnam veterans and adjusting for race, rank, duration of military service, and age at entry into follow-up, the study found that mortality was not significantly increased for all LHCs (ARR = 1.10, 95% CI 0.35–3.48) or more specifically for leukemia (adjusted RR = 0.56, 95% CI 0.10–3.20).

TABLE 7-47 Selected Epidemiologic Studies—Leukemia

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans			**All COIs**
Akhtar et al., 2004	White Air Force Ranch Hand veterans—lymphopoietic cancers[c]		
	All Ranch Hand veterans		
	Incidence	10	0.9 (0.4–1.5)
	Mortality	6	1.0 (0.4–2.0)
	Veterans with tours in 1966–1970—incidence	7	0.7 (0.3–1.4)
	White Air Force Comparison veterans—lymphopoietic cancers[c]		
	All comparison veterans		
	Incidence	9	0.6 (0.3–1.0)
	Mortality	5	0.6 (0.2–1.2)
	Veterans with tours in 1966–1970—incidence	4	0.3 (0.1–0.8)
AFHS, 2000	Air Force Ranch Hand veterans	2	0.7 (0.1–5.0)
US VA Cohort of Army Chemical Corps			**All COIs**
Cypel and Kang, 2010	ACC—deployed vs nondeployed and vs US men (Vietnam-service status through 2005)		
	All Lymphopoietic		
	Deployed vs nondeployed	6 vs 6	1.1 (0.4–2.5)
	ACC veterans vs US men		
	Vietnam cohort	6	0.5 (0.2–0.99)
	Non-Vietnam cohort	6	0.6 (0.2–1.4)
	Leukemia		
	Deployed vs nondeployed	2 vs 4	0.6 (0.1–3.2)
	ACC veterans vs US men		
	Vietnam cohort	2	0.4 (0.1–1.5)
	Non-Vietnam cohort	4	1.2 (0.3–3.0)
Dalager and Kang, 1997	ACC veterans		1.0 (0.1–3.8)
US CDC Vietnam Experience Study			**All COIs**
Boehmer et al., 2004	Vietnam Experience Cohort	8	1.0 (0.4–2.5)
US VA Cohort of Female Vietnam Veterans			**All COIs**
Cypel and Kang, 2008	US Vietnam veterans (women)—lymphopoietic cancers[c]	18	0.7 (0.4–1.3)
	Deployed vs nondeployed		
	Nurses only	14	0.7 (0.3–1.3)
State Studies of US Vietnam Veterans			
Visintainer et al., 1995	PM study of deaths (1974–1989) of Michigan Vietnam-era veterans—deployed vs nondeployed	30	1.0 (0.7–1.5)

TABLE 7-47 Leukemia, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Australian Vietnam Veterans vs Australian Population			**All COIs**
ADVA, 2005a	Australian Vietnam veterans vs Australian population—incidence		
	All branches	130	1.1 (1.0–1.4)
	Lymphocytic leukemia	72	1.4 (1.1–1.7)
	Myeloid leukemia	54	1.0 (0.8–1.3)
	Navy	35	1.5 (1.0–2.0)
	Lymphocytic leukemia	14	1.3 (0.7–2.1)
	Myeloid leukemia	19	1.7 (1.0–2.6)
	Army	80	1.1 (0.8–1.3)
	Lymphocytic leukemia	50	1.4 (1.0–1.8)
	Myeloid leukemia	28	0.8 (0.5–1.1)
	Air Force	15	1.2 (0.7–2.0)
	Lymphocytic leukemia	8	1.4 (0.6–2.7)
	Myeloid leukemia	7	1.3 (0.5–2.6)
ADVA, 2005b	Australian Vietnam veterans vs Australian population—mortality		
	All branches	84	1.0 (0.8–1.3)
	Lymphocytic leukemia	24	1.2 (0.7–1.7)
	Myeloid leukemia	55	1.1 (0.8–1.3)
	Navy	17	1.3 (0.8–1.8)
	Lymphocytic leukemia	4	0.2 (0.0–1.2)
	Myeloid leukemia	11	1.6 (0.9–2.5)
	Army	48	0.1 (0.7–1.2)
	Lymphocytic leukemia	17	1.3 (0.7–2.0)
	Myeloid leukemia	30	0.8 (0.5–1.1)
	Air Force	14	1.6 (0.8–2.6)
	Lymphocytic leukemia	6	2.7 (1.0–5.8)
	Myeloid leukemia	8	1.3 (0.5–2.5)
AIHW, 1999	Australian Vietnam veterans—incidence (validation study)		*Expected number of exposed cases (95% CI)*
		27	26 (16–36)
CDVA, 1998a	Australian Vietnam veterans (men)—self-reported incidence	64	26 (16–36)
CDVA, 1998b	Australian Vietnam veterans (women)—self-reported incidence	1	0 (0–4)
CDVA, 1997a	Australian military Vietnam veterans	33	1.3 (0.8–1.7)

continued

TABLE 7-47 Leukemia, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
Australian Conscripted Army National Service (deployed vs nondeployed)			**All COIs**
ADVA, 2005c	Australian male conscripted Army National Service Vietnam-era veterans: deployed vs nondeployed		
	Incidence	16	0.6 (0.3–1.1)
	Lymphocytic leukemia	9	0.8 (0.3–2.0)
	Myeloid leukemia	7	0.5 (0.2–1.3)
	Mortality	11	0.6 (0.3–1.3)
	Lymphocytic leukemia	2	0.4 (0.0–2.4)
	Myeloid leukemia	8	0.7 (0.3–1.7)
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			**Dioxin, phenoxy herbicides**
Kogevinas et al., 1997	IARC cohort, male and female workers exposed to any phenoxy herbicide or chlorophenol	34	1.0 (0.7–1.4)
	Exposed to highly chlorinated PCDDs	16	0.7 (0.4–1.2)
	Not exposed to highly chlorinated PCDDs	17	1.4 (0.8–2.3)
Kogevinas et al., 1993	IARC cohort (women only, myeloid leukemia)	1	2.0 (0.2–7.1)
Saracci et al., 1991	IARC cohort—exposed subcohort (men and women)	18	1.2 (0.7–1.9)
NIOSH Mortality Cohort (12 US plants, production 1942–1984) (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Steenland et al., 1999	US chemical production workers	10	0.8 (0.4–1.5)
Fingerhut et al., 1991	NIOSH—entire cohort	6	0.7 (0.2–1.5)
BASF Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Zober et al., 1990	BASF employees at plant with 1953 explosion		*90% CI*
	All 3 cohorts (n = 247)	1	1.7 (nr)
	Cohort 3	1	5.2 (0.4–63.1)
	Incident case of AML in Cohort 1		
Dow Chemical Company—Midland, MI (included in IARC and NIOSH cohorts)			**Dioxin, phenoxy herbicides**
Collins et al., 2009a	Trichlorophenol workers—leukemia, aleukemia	13	1.9 (1.0–3.2)
	Excluding subset with pentachlorophenol exposure	2	1.9 (1.0–3.4)
	Trichlorophenol workers—other lymphopoietic	2	0.6 (0.1–2.3)
	Excluding subset with pentachlorophenol exposure	2	0.7 (0.1–2.6)

TABLE 7-47 Leukemia, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
Collins et al., 2009b	Pentachlorophenol workers—leukemia, aleukemia	2	0.6 (0.1–2.0)
	Excluding subset with TCP exposure	1	0.4 (0.0–2.0)
	Pentachlorophenol workers—other lymphopoietic	2	1.3 (0.2–4.6)
	Excluding subset with TCP exposure	2	1.7 (0.2–6.0)
Burns et al., 2001	Dow 2,4-D production workers		
	Lymphopoietic mortality in workers with high 2,4-D exposure	4	1.3 (0.4–3.3)
Ramlow et al., 1996	Dow pentachlorophenol production workers		
	0-yr latency	2	1.0 (0.1–3.6)
	15-yr latency	1	nr
Bond et al., 1988	Dow 2,4-D production workers	2	3.6 (0.4–13.2)
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)			**Dioxin, phenoxy herbicides**
McBride et al., 2009a	1,599 production workers (male and female) vs national rates—mortality 1969 through 2004		
	Leukemia, aleukemia		
	Ever-exposed workers	1	0.6 (0.0–3.1)
	Never-exposed workers	0	0.0 (0.0–6.0)
't Mannetje et al., 2005	Phenoxy herbicide producers (men and women)	0	0.0 (0.0–5.3)
	Phenoxy herbicide sprayers (> 99% men) (myeloid leukemia)	1	1.2 (0.0–6.4)
Dutch Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Boers et al., 2010	Dutch chlorophenoxy workers		
	LHC		
	Factory A (HR for exposed vs unexposed)	11 vs 7	0.9 (0.3–2.6)
	Factory B (HR for exposed vs unexposed)	3 vs 3	1.5 (0.3–7.5)
	Leukemia		
	Factory A (HR for exposed vs unexposed)	2 vs 3	0.3 (0.0–2.6)
	Factory B (HR for exposed vs unexposed)	2 vs 2	1.5 (0.2–10.8)
Hooiveld et al., 1998	Dutch chemical production workers	1	1.0 (0.0–5.7)
German Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Becher et al., 1996	German chemical production workers—Cohort I	4	1.8 (0.5–4.7)
Agricultural Health Study			**Herbicides**
Alavanja et al., 2005	US AHS—incidence		
	Private applicators (men and women)	70	0.9 (0.7–1.2)
	Spouses of private applicators (> 99% women)	17	0.7 (0.4–1.2)
	Commercial applicators (men and women)	4	0.9 (0.3–2.4)
Blair et al., 2005a	US AHS		
	Private applicators (men and women)	27	0.8 (0.5–1.1)
	Spouses of private applicators (> 99% women)	14	1.4 (0.8–2.4)

continued

TABLE 7-47 Leukemia, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
United Farm Workers			**Herbicides**
Mills et al., 2005	Cohort study of 139,000 United Farm Workers, with nested case–control analyses restricted to Hispanic workers in California		
	Ever used 2,4-D		
	Total leukemia	nr	1.0 (0.4–2.6)
	Lymphocytic leukemia	nr	1.5 (0.3–6.6)
	Granulocytic (myeloid) leukemia	nr	1.3 (0.3–5.4)
Other Agricultural Workers			**Herbicides**
Hansen et al., 2007	Danish gardeners (all hematopoietic, ICD-7 200–205—incidence)		
	10-yr follow-up (1975–1984) reported in Hansen et al. (1992)	15	1.4 (0.8–2.4)
	NHL (ICD-7 200, 202, 205)	6	1.7 (0.6–3.8)
	HD (ICD-7 201)	0	nr
	Multiple myeloma (ICD-7 203)	0	nr
	CLL (ICD-7 204.0)	6	2.8 (1.0–6.0)
	Other leukemias (204.1–204.4)	3	1.4 (0.3–4.2)
	25-yr follow-up (1975–2001)	42	1.1 (0.8–1.4)
	Leukemia (ICD-7 204)	22	1.4 (0.9–2.1)
	Born before 1915 (high exposure)	16	1.4 (0.9–2.3)
	Leukemia (ICD-7 204)	12	2.3 (1.3–4.1)
	Born 1915–1934 (medium exposure)	25	1.2 (0.8–1.8)
	Leukemia (ICD-7 204)	9	1.0 (0.5–2.0)
	Born after 1934 (low exposure)	1	0.2 (0.0–1.0)
	Leukemia (ICD-7 204)	1	0.5 (0.0–3.4)
Gambini et al., 1997	Italian rice growers	4	0.6 (0.2–1.6)
Amadori et al., 1995	Italian farming, animal-breeding workers—CLL	15	2.3 (0.9–5.8)
	Farmers	5	1.6 (0.5–5.2)
	Breeders	10	3.1 (1.1–8.3)
Semenciw et al., 1994	Farmers in Canadian prairie provinces	357	0.9 (0.8–1.0)
	Lymphatic	132	0.9 (0.8–1.1)
	Myeloid	127	0.8 (0.7–0.9)
Blair et al., 1993	US farmers in 23 states		
	White men	1,072	1.3 (1.2–1.4)
	White women	24	1.5 (0.9–2.2)
Hansen et al., 1992	Danish gardeners—incidence		
	All gardeners—CLL	6	2.5 (0.9–5.5)
	all other types of leukemia	3	1.2 (0.3–3.6)
	Men—CLL	6	2.8 (1.0–6.0)
	all other types of leukemia	3	1.4 (0.3–4.2)

TABLE 7-47 Leukemia, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Ronco	Danish workers—incidence		
et al., 1992	Men—self-employed	145	0.9 (nr)
	employee	33	1.0 (nr)
	Women—self-employed	8	2.2 ($p < 0.05$)
	employee	3	1.3 (nr)
	family worker	27	0.9 (nr)
Brown	Case–control study on white men in Iowa,	578	
et al., 1990	Minnesota, all types of leukemia—incidence		
	Ever farmed	335	1.2 (1.0–1.5)
	AML	81	1.2 (0.8–1.8)
	CML	27	1.1 (0.6–2.0)
	CLL	156	1.4 (1.1–1.9)
	ALL	7	0.9 (0.3–2.5)
	Myelodysplasias	32	0.8 (0.5–1.4)
	Any herbicide use	157	1.2 (0.9–1.6)
	AML	39	1.3 (0.8–2.0)
	CML	16	1.3 (0.7–2.6)
	CLL	74	1.4 (1.0–2.0)
	ALL	2	0.5 (0.1–2.2)
	Myelodysplasias	10	0.7 (0.3–1.5)
	Phenoxy acid use	120	1.2 (0.9–1.6)
	2,4-D use	98	1.2 (0.9–1.6)
	2,4,5-T use	22	1.3 (0.7–2.2)
	First use > 20 years before	11	1.8 (0.8–4.0)
	MCPA	11	1.9 (0.8–4.3)
	First use > 20 years before	5	2.4 (0.7–8.2)
Wigle	Canadian farmers	138	0.9 (0.7–1.0)
et al., 1990			
Alavanja	USDA agricultural extension agents	23	1.9 (1.0–3.5)
et al., 1988	Lymphatic	nr	2.1 (0.7–6.4)
	Trend over years worked		($p < 0.01$)
	Myeloid	nr	2.8 (1.1–7.2)
	Trend over years worked		($p < 0.01$)
Blair and	1,084 leukemia deaths in Nebraska in 1957–1974		
White,	Farmer–usual occupation on death certificate		1.3 ($p < 0.05$)
1985	99 ALL cases	nr	1.3 (nr)
	248 CLL cases	nr	1.7 ($p < 0.05$)
	105 unspecified lymphatic cases	nr	0.9 (nr)
	235 AML cases	nr	1.2 (nr)
	96 CML cases	nr	1.1 (nr)
	39 unspecified myeloid cases	nr	1.0 (nr)
	39 acute monocytic cases	nr	1.9 (nr)
	52 acute unspecified leukemia cases	nr	2.4 (nr)
	65 unspecified leukemia cases	nr	1.2 (nr)

continued

TABLE 7-47 Leukemia, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
Burmeister et al., 1982	1,675 leukemia deaths in Iowa 1968–1978		
	Farmer-usual occupation on death certificate		1.2 ($p < 0.05$)
	ALL	28	0.7 (0.4–1.2)
	CLL	132	1.7 (1.2–2.4)
	Lived in one of 33 counties with highest herbicide use	nr	1.9 (1.2–3.1)
	Unspecified lymphatic	64	1.7 (1.0–2.7)
	AML	86	1.0 (0.8–1.5)
	CML	46	1.0 (0.7–1.7)
	Unspecified myeloid	36	0.8 (0.5–1.4)
	Acute monocytic	10	1.1 (0.4–2.6)
	Unspecified leukemia	31	1.1 (0.6–2.0)
Other Herbicide and Pesticide Applicators			**Herbicides**
Swaen et al., 2004	Dutch licensed herbicide applicators—mortality	3	1.3 (0.3–3.7)
Asp et al., 1994	Finnish herbicide applicators		
	Mortality	2	nr
	Lymphatic	1	0.9 (0.0–5.1)
	Myeloid	1	0.7 (0.0–3.7)
	Incidence		
	Lymphatic	3	1.0 (0.2–3.0)
Torchio et al., 1994	Italian licensed pesticide users	27	0.8 (0.5–1.1)
Bueno de Mesquita et al., 1993	Dutch phenoxy herbicide workers (included in IARC cohort)		
	Leukemia, aleukemia (ICD-9 204–207)	2	2.2 (0.3–7.9)
	Myeloid leukemia (ICD-8 205)	2	4.2 (0.5–15.1)
Forestry Workers			**Herbicides**
Thörn et al., 2000	Swedish lumberjacks exposed to phenoxyacetic herbicides	0	nr
Hertzman et al., 1997	British Columbia sawmill workers with chlorophenate process (more hexa-, hepta-, octa-chlorinated dibenzodioxins than TCDD), all leukemias—incidence	47	1.2 (0.9–1.5)
	ALL	2	1.0 (0.2–3.1)
	CLL	24	1.7 (1.2–2.4)
	AML	5	0.8 (0.3–1.7)
	CML	7	1.1 (0.5–2.0)
	Other, unspecified	5	0.5 (0.2–1.0)
Reif et al., 1989	Case–control study of all men with occupation indicated entered into New Zealand Cancer Registry 1980–1984 (all leukemias)		
	Forestry workers	4	1.0 (0.4–2.6)
	AML	3	2.2 (nr)

TABLE 7-47 Leukemia, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Paper and Pulp Workers			**Dioxin**
McLean et al., 2006	IARC cohort of pulp and paper workers		
	Exposure to nonvolatile organochlorine compounds		
	Never	49	1.0 (0.7–1.3)
	Ever	35	0.9 (0.6–1.2)
Rix et al., 1998	Danish paper-mill workers—incidence		
	Men	20	0.8 (0.5–1.2)
	Women	7	1.3 (0.5–2.7)
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Consonni et al., 2008	Seveso residents—25-yr follow-up—men, women		
	Leukemia (ICD-9 204–208)		
	Zone A	1	0.9 (0.1–6.3)
	Zone B	13	1.7 (1.0–3.0)
	Zone R	51	1.0 (0.7–1.3)
	Lymphatic leukemia (ICD-9 204)		
	Zone A	0	nr
	Zone B	3	1.3 (0.4–4.1)
	Zone R	23	1.4 (0.9–2.2)
	Myeloid leukemia (ICD-9 205)		
	Zone A	1	2.1 (0.3–15.2)
	Zone B	6	2.0 (0.9–4.5)
	Zone R	16	0.7 (0.4–1.2)
	Monoccytic leukemia (ICD-9 206)	0	nr
	Leukemia, unspecified (ICD-9 208)		
	Zone A	0	nr
	Zone B	4	2.4 (0.9–6.5)
	Zone R	10	0.8 (0.4–1.6)
Pesatori et al., 2009	Seveso—20-yr follow-up to 1996—incidence		
	Leukemia (ICD-9 204–208)		
	Zone A	2	2.2 (0.5–8.8)
	Zone B	8	1.4 (0.7–2.7)
	Zone R	31	0.8 (0.5–2.1)
	Lymphatic leukemia (ICD-9 204)		
	Zone A	1	2.8 (0.4–19.9)
	Zone B	0	nr
	Zone R	13	0.8 (0.5–1.5)
	Myeloid leukemia (ICD-9 205)		
	Zone A	1	2.2 (0.3–16.0)
	Zone B	7	2.4 (1.1–5.2)
	Zone R	15	0.8 (0.4–1.3)

continued

TABLE 7-47 Leukemia, continued

Reference	Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
	Leukemia, unspecified (ICD-9 208)		
	Zone A	0	nr
	Zone B	1	2.2 (0.3–16.1)
	Zone R	2	0.6 (0.1–2.6)
Bertazzi et al., 2001	Seveso residents—20-yr follow-up		
	Zones A, B—men	9	2.1 (1.1–4.1)
	women	3	1.0 (0.3–3.0)
Bertazzi et al., 1998	Seveso residents—15-yr follow-up		
	Zone B—men	7	3.1 (1.4–6.7)
	women	1	0.6 (0.1–4.0)
	Zone R—males	12	0.8 (0.4–1.5)
	women	12	0.9 (0.5–1.6)
Bertazzi et al., 1997	Seveso residents—15-yr follow-up		
	Zone B—men	7	3.1 (1.3–6.4)
	women	1	0.6 (0.0–3.1)
	Zone R—men	12	0.8 (0.4–1.4)
	women	12	0.9 (0.4–1.5)
Bertazzi et al., 1993	Seveso residents—10-yr follow-up—incidence		
	Zone B—men	2	1.6 (0.4–6.5)
	Myeloid leukemia (ICD-9 205)	1	2.0 (0.3–14.6)
	women	2	1.8 (0.4–7.3)
	Myeloid leukemia (ICD-9 205)	2	3.7 (0.9–15.7)
	Zone R—men	8	0.9 (0.4–1.9)
	Myeloid leukemia (ICD-9 205)	5	1.4 (0.5–3.8)
	women	3	0.4 (0.1–1.2)
	Myeloid leukemia (ICD-9 205)	2	0.5 (0.1–2.1)
Bertazzi et al., 1992	Seveso residents—10-yr follow-up		
	Zones A, B, R—men	4	2.1 (0.7–6.9)
	women	1	2.5 (0.2–27.0)
Chapaevsk, Russia Residential Cohort			**TCDD**
Revich et al., 2001	Residents of Chapaevsk, Russia		
	Mortality standardized to Samara Region		
	Men	11	1.5 (0.8–2.7)
	Women	15	1.5 (0.8–2.4)
Other Environmental Studies			**Herbicides**
Miligi et al., 2003	Case–control study of residents of 11 areas in Italy—incidence of leukemia excluding CLL		
	Exposure to phenoxy herbicides	6	2.1 (0.7–6.2)
Waterhouse et al., 1996	Residents of Tecumseh, Michigan—incidence		**Herbicides**
	All leukemias		
	Men	42	1.4 (1.0–1.9)
	Women	32	1.2 (0.9–1.8)
	CLL	10	1.4 (1.0–1.9)

TABLE 7-47 Leukemia, continued

Reference	Study Population[a]	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Svensson et al., 1995	Swedish fishermen		**Organochlorine compounds**
	All leukemias—mortality		
	East coast (higher serum TEQs)	5	1.4 (0.5–3.2)
	West coast (lower serum TEQs)	24	1.0 (0.6–1.5)
	Lymphocytic—incidence		
	East coast (higher serum TEQs)	4	1.2 (0.3–3.3)
	West coast (lower serum TEQs)	16	1.3 (0.8–2.2)
	Myeloid—incidence		
	East coast (higher serum TEQs)	2	0.9 (0.1–3.1)
	West coast (lower serum TEQs)	6	0.5 (0.2–1.1)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; ACC, Army Chemical Corps; AHS, Agricultural Health Study; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CDC, Centers for Disease Control and Prevention; CI, confidence interval; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; COI, chemical of interest; HD, Hodgkin disease; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; LHC, lymphohematopoietic cancers; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MI, Michigan; NHL, non-Hodgkin lymphoma; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; NZ, New Zealand; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PM, proportionate mortality; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEQ, toxicity equivalent quotient; USDA, US Department of Agriculture; VA, US Department of Veterans Affairs.

[a]Subjects are male, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

[c]Lymphopoietic cancers comprise all forms of lymphoma (including Hodgkin lymphoma and non-Hodgkin lymphoma) and leukemia (ALL, AML, CLL, CML).

Occupational Studies Boers et al. (2010) presented results of an additional 15 years of follow-up of a retrospective cohort of workers in two Dutch chlorophenoxy herbicide manufacturing factories (2,4,5-T in Factory A and 2,4-D in Factory B). Analyses of HR were performed using the Cox proportional hazard models with attained age as the timescale. As in the results on all LHCs (HR = 0.89, 95% CI 0.31–2.61 in Factory A; HR = 1.52, 95% CI 0.31–7.45 in Factory B), associations for the smaller group of only leukemias differed considerably between Factory A (HR = 0.28, 95% CI 0.03–2.61) and Factory B (HR = 1.53, 95% CI 0.22–10.82), but were even less certain.

Collins et al. (2008) reported historical exposures estimated on the basis of serum dioxin measurements in some of the workers who were exposed to dioxins at the Dow Chemical Company site producing TCP and PCP in Midland, Michigan. There were 1,615 workers in the TCP cohort and 773 in the PCP cohort, and 196 of the workers were exposed to both TCP and PCP. The vital status

of the TCP workers was followed from 1942 to 2003, and that of the PCP workers from 1940 to 2003. Aleukemia, which can occur in any of the four major types of leukemia but presents with normal WBC counts, was grouped with leukemia. A significant increase in observed deaths from leukemia and aleukemia (SMR = 1.9, 95% CI 1.0–3.2) was observed in the TCP production workers (Collins et al., 2009a) but not in the PCP workers (SMR = 0.6, 95% CI 0.1–2.0) (Collins et al., 2009b).

McBride et al. (2009a,b) published two occupational mortality studies of workers in the Dow AgroSciences plant in New Plymouth, New Zealand, who were potentially exposed to TCDD. McBride et al. (2009a) examined the overall mortality in 1,599 TCP manufacturing workers who were employed during 1969–1988. The SMR and proportional hazards model were used to evaluate risk posed by exposure. The study did not detect any increase in leukemia or aleukemia risk (SMR = 0.6, 95% CI 0.0–3.1). The results in McBride et al. (2009b) have not been included because they were diluted by inclusion of a set of workers who had no opportunity for TCDD exposure and no observed deaths.

Environmental Studies Pesatori et al. (2009) examined cancer incidence through 1996 in the 20-year follow-up of TCDD exposure during the 1976 accident in Seveso. Effects in males and females combined in the three exposure zones were estimated. Nonsignificant positive associations with leukemia were identified in Zone A (RR = 2.18, 95% CI 0.54–8.76) and Zone B (RR=1.35, 95% CI 0.66-2.73), but there was no increase in leukemia risk in Zone R (RR = 0.77, 95% CI 0.53–2.12). When the leukemia cases were divided into myeloid leukemia (ML) and lymphoid leukemia (LL), a statistically significant increase in ML was detected in Zone B (seven cases; RR = 2.41, 95% CI 1.12–5.18), but the increased in risk in Zone A (RR = 2.23, 95% CI 0.31–15.99) was nonsignificant. That might be the first report of a positive association of TCDD exposure with ML. However, no association with ML (RR = 0.76, 95% CI 0.44–1.30) was observed in Zone R. Similarly, a nonsignificant increase in LL was detected in Zone A (1 case; RR = 2.78, 95% CI 0.39–19.9), but no association with LL (13 cases; RR = 0.83, 95% CI 0.46–1.48) was observed in Zone R. No cases were reported in Zone B.

The grouped results on mortality from cancer of "lymphoid, haematopoietic and related tissue" in Finnish fishermen (33 cases) and their wives (10 cases) in the study by Turunen et al. (2008) are too nonspecific to be of use in evaluating an association between the chemicals of interest and particular types of lymphohematopoietic malignancy.

Biologic Plausibility

Leukemia is a relatively rare spontaneous tumor in mice, but it is less rare in some strains of rats. A small study reported that 5 of 10 male rats fed TCDD at 1

ng/kg per week for 78 weeks showed an increased incidence of various cancers, one of which was lymphocytic leukemia (Van Miller et al., 1977). Later studies of TCDD's carcinogenicity have not shown an increased incidence of lymphocytic leukemia in mice or rats.

Two recent studies that used cells in tissue culture suggested that TCDD exposure does not promote leukemia. Proliferation of cultured human bone marrow stem cells (the source of leukemic cells) was not influenced by addition of TCDD to the culture medium (van Grevenynghe et al., 2005). Likewise, Mulero-Navarro et al. (2006) reported that the AHR promoter is silenced in ALL—an effect that could lead to reduced expression of the receptor, which binds TCDD and mediates its toxicity. No reports of animal studies have noted an increased incidence of leukemia after exposure to the phenoxy herbicides or other chemicals of interest.

The biologic plausibility of the carcinogenicity of the chemicals of interest is discussed in general at the beginning of this chapter.

Synthesis

The findings of Pesatori et al. (2009) on the incidence of myeloid leukemias in the 20-year follow-up of the Seveso cohort tracked the atypical results reported for myeloid leukemia mortality in the same population at the 25-year follow-up (Consonni et al., 2008), as reviewed in *Update 2008*. The committee has some concern about misclassification of leukemia types and finds the correspondence between intensity of exposure and magnitude of risk to be erratic, so it does not regard this isolated finding adequate to alter prior conclusions.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and leukemias in general. An exception is the specific leukemia subtypes of chronic B-cell hematoproliferative diseases, including CLL and HCL, which are more appropriately grouped with lymphomas.

SUMMARY

The committee had four categories available to classify the strength of the evidence from the veteran, occupational, and environmental studies that were reviewed regarding an association between exposure to the chemicals of interest and each kind of cancer. In categorizing diseases according to the strength of the evidence, the committee applied the same criteria (discussed in Chapter 2) that were used in *VAO*, *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008*. To be consistent with the charge

to the committee from the Secretary of Veterans Affairs in Public Law 102-4 and with accepted standards of scientific review, the committee distinguished among the four categories on the basis of statistical association, not causality.

Health Outcomes with Sufficient Evidence of an Association

For outcomes in this category, a positive association with at least one of the chemicals of interest must be observed in studies in which chance, bias, and confounding can be ruled out with reasonable confidence. The committee regarded evidence from several small studies that were free of bias and confounding and that showed an association that was consistent in magnitude and direction as sufficient evidence of an association.

Previous VAO committees found sufficient evidence of an association between exposure to at least one of the chemicals of interest and soft-tissue sarcoma, Hodgkin lymphoma, and non-Hodgkin lymphoma broadened to include chronic lymphocytic leukemia, hairy-cell leukemia, and other chronic B-cell neoplasms. The scientific literature continues to support the classification of those cancers in the category of sufficient evidence.

Health Outcomes with Limited or Suggestive Evidence of an Association

For outcomes in this category, the evidence must suggest an association with at least one of the chemicals of interest that could be limited because chance, bias, or confounding could not be ruled out with confidence. A high-quality study may have demonstrated a strong positive association amid a field of less convincing positive findings, or, more often, several studies yielded positive results but the results of other studies were inconsistent.

Previous VAO committees found limited or suggestive evidence of an association between exposure to at least one of the chemicals of interest and laryngeal cancer; cancer of the lung, bronchus, or trachea; prostatic cancer; multiple myeloma; and AL amyloidosis. The literature continues to support the classification of those diseases in the category of limited or suggestive evidence.

Health Outcomes with Inadequate or Insufficient Evidence to Determine Whether There Is an Association

This is the default category for any disease outcome for which there is not enough information on which to base a decision. For many of the kinds of cancer reviewed by the committee, scientific data were available but were inadequate or insufficient in quality, consistency, or statistical power to support a conclusion as to the presence or absence of an association. Some studies failed to control for confounding or failed to provide adequate exposure assessment. In addition to any specific kinds of cancer that have not been directly addressed in the

present report, this category includes hepatobiliary cancer (cancer of the liver, gallbladder, and bile ducts); cancer of the oral cavity, pharynx, and nasal cavity; cancer of the pleura, mediastinum, and other unspecified sites in the respiratory system and intrathoracic organs; cancer of the colon, rectum, esophagus, stomach, and pancreas; bone and joint cancer; melanoma and nonmelanoma skin cancer (including basal-cell carcinoma and squamous-cell carcinoma); breast cancer; cancer of the male and female reproductive systems (excluding prostate cancer); urinary bladder cancer; renal cancer (cancer of the kidney and renal pelvis); cancer of the brain and nervous system (including eye); and the various forms of leukemia other than chronic B-cell leukemias, including chronic lymphocytic leukemia and hairy-cell leukemia.

Health Outcomes with Limited or Suggestive Evidence of No Association

For outcomes in this category, several adequate studies covering the full known range of human exposure must be consistent in *not* showing a positive association with exposure to one of the chemicals of interest. The studies have relatively narrow confidence intervals. A conclusion of *no* association would inevitably be limited to the conditions, magnitude of exposure, and length of observation of the available studies. The possibility of a very small increase in risk associated with a given exposure can never be excluded. Inclusion in this category would presume evidence of a lack of association between each of the chemicals of interest and a particular health outcome, but virtually no cancer-epidemiologic studies have specifically evaluated the consequences of exposure to picloram or cacodylic acid.

On the basis of evaluation of the scientific literature, no kinds of cancer satisfy the criteria for inclusion in this category.

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[1]Throughout the report the same alphabetic indicator following year of publication is used consistently for the same article when there were multiple citations by the same first author in a given year. The convention of assigning the alphabetic indicator in order of citation in a given chapter is not followed.

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8

Reproductive Effects and Impacts on Future Generations

This chapter summarizes the scientific literature published since *Veterans and Agent Orange: Update 2008*, hereafter referred to as *Update 2008* (IOM, 2009), on the association between exposure to herbicides and adverse reproductive or developmental effects. (Analogous shortened names are used to refer to the updates for 1996, 1998, 2000, 2002, 2004, and 2006 [IOM, 1996, 1999, 2001, 2003, 2005, 2007] of the original report *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* [*VAO;* IOM, 1994].) The categories of association and the approach to categorizing the health outcomes are discussed in Chapters 1 and 2. The literature considered in this chapter includes studies of a broad spectrum of reproductive effects in Vietnam veterans or other populations occupationally or environmentally exposed to the herbicides sprayed in Vietnam or to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Because some polychlorinated biphenyls (PCBs), some polychlorinated dibenzofurans (PCDFs), and some polychlorinated dibenzodioxins (PCDDs) other than TCDD have dioxin-like biologic activity, studies of populations exposed to PCBs or PCDFs were reviewed if their results were presented in terms of TCDD toxic equivalents (TEQs).

As in previous updates, the adverse outcomes evaluated include impaired fertility (in which declines in sperm quality may be involved), endometriosis, increased fetal loss (spontaneous abortion and stillbirth) or neonatal and infant mortality, and such other adverse birth outcomes as low birth weight, preterm birth, and birth defects. In addition to the more delayed problem of childhood cancer in their offspring, this update also addresses the concern of Vietnam veterans that their military exposures may contribute to other problems that their children experience later in life or that are manifested in later generations. Finally, as suggested in *Update 2008*, endometriosis and pregnancy loss will no

longer be fully evaluated after this update. It is unlikely, given the age of the Vietnam veteran cohort, that any newly published data on those two outcomes will provide additional information that would be directly relevant to that cohort. However, if new research suggests that the two outcomes may be influenced by epigenetic changes, their relevance to transgenerational effects will be assessed in future updates.

To reduce repetition throughout the report, Chapter 5 presented design information on new studies that report findings on multiple health outcomes. To provide context for publications that present new results on study populations that were addressed in publications reviewed in earlier updates, Chapter 5 also discussed the overall characteristics of those populations with details about design and analysis relevant to individual publications. Design information on new studies that report only reproductive health outcomes and are not revisiting previously studied populations is summarized in this chapter with results.

This chapter's primary emphasis is on the potential adverse reproductive effects of herbicide exposure of men because the vast majority of Vietnam veterans are men. However, about 8,000 women served in Vietnam (H. Kang, US Department of Veterans Affairs, personal communication, December 14, 2000), so findings relevant to female reproductive health are also included. Whenever the information was available, an attempt was made to evaluate the effects of maternal and paternal exposure separately. Exposure scenarios in human populations and experimental animals studied differ in their applicability to our population of concern according to whether the exposed parent was a male or female veteran. In addition, for published epidemiologic or experimental results to be fully relevant to evaluation of the plausibility of reproductive effects in Vietnam veterans, whether female or male, the timing of exposure needs to correspond to the veterans' experience (that is, it must have occurred only before conception). With the possible exception of female veterans who became pregnant while serving in Vietnam, pregnancies that might have been affected occurred after deployment, when primary exposure had ceased.

BIOLOGIC PLAUSIBILITY OF REPRODUCTIVE EFFECTS

This chapter opens with a general discussion of factors that influence the plausibility that TCDD and the four herbicides used in Vietnam could have adverse reproductive effects. There have been few reproductive studies of the four herbicides in question, particularly picloram and cacodylic acid, and those studies generally have shown toxicity only at very high doses, so the preponderance of the following discussion concerns TCDD, which outside of controlled experimental circumstances usually occurred in a mixture of dioxins (dioxin congeners in addition to TCDD).

Because TCDD is stored in fat tissue and has a long biologic half-life, internal exposure at generally constant concentrations may continue after episodic,

high-level exposure to external sources has ceased. If a person had high exposure, there may still be high amounts of dioxins stored in fat tissue, which may be mobilized, particularly at times of weight loss. That would not be expected to be the case for nonlipophilic chemicals, such as cacodylic acid.

A father's contribution to a pregnancy is limited to the contents of the sperm that fertilizes an egg and any damage to the embryo or offspring would result from either genetic or epigenetic changes of the sperm DNA. Epigenetic effects are ones that result in permanent (heritable) changes in gene expression without a change in DNA sequence. Dioxins have not been shown to mutate DNA sequence, so any damage to an embryo or offspring from a dioxin-exposed father would be limited to epigenetic effects.

A mother's contribution to a pregnancy is obviously more extensive, and any damage to an embryo or offspring can result from epigenetic changes of the egg DNA or from direct effects of exposure on the fetus during gestation and on the neonate during lactation. Dioxin in the mother's bloodstream can cross the placenta and expose the developing embryo and fetus. Furthermore, mobilization of dioxin during pregnancy or lactation may be increased because the body is drawing on fat stores to supply nutrients to the developing fetus or nursing infant. In humans, TCDD has been measured in circulating maternal blood, cord blood, placenta, and breast milk (Suzuki et al., 2005), and it is estimated that an infant breastfed for 1 year accumulates a dose of TCDD that is 6 times as high as that in an infant not breastfed (Lorber and Phillips, 2002).

On the basis of laboratory animal studies, TCDD can affect reproduction and development, so a connection between TCDD exposure and human reproductive and developmental effects is biologically plausible. However, definitive conclusions based on animal studies about the potential for TCDD to cause reproductive and developmental toxicity in humans are complicated by differences in sensitivity and susceptibility among individual animals, strains, and species; by the lack of strong evidence of organ-specific effects across species; by differences in route, dose, duration, and timing of exposure in experimental protocols and real-world exposure; and by substantial differences in the toxicokinetics of TCDD between laboratory animals and humans. Experiments with 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) indicate that they have subcellular effects that could constitute a biologically plausible mechanism for reproductive and developmental effects. Evidence from animals, however, indicates that they do not have reproductive effects and that they have developmental effects only at very high doses. There is insufficient information on picloram and cacodylic acid to assess the biologic plausibility of their reproductive or developmental effects.

The biologic-plausibility sections on the specific outcomes considered in this chapter present more detailed toxicologic findings that are of particular relevance to the outcomes discussed.

ENDOMETRIOSIS

Endometriosis (*International Classification of Diseases*, *9th revision* [ICD-9], code 617) affects 5.5 million women in the United States and Canada at any given time (National Institute of Child Health and Human Development, 2007). The endometrium is the tissue that lines the inside of the uterus and is built up and shed each month during menstruation. In endometriosis, endometrial cells are found outside the uterus—usually in other parts of the reproductive system, in the abdomen, or on surfaces near the reproductive organs. The ectopic tissue develops into growths or lesions that continue to respond to hormonal changes in the body and break down and bleed each month in concert with the menstrual cycle. Unlike blood released during normal shedding of the endometrium lining the uterus, blood released from endometrial lesions has no way to leave the body, and results in inflammation and internal bleeding. The degeneration of blood and tissue can cause scarring, pain, infertility, adhesions, and intestinal problems.

There are several theories of the etiology of endometriosis, including a genetic contribution, but the cause remains unknown. Estrogen dependence and immune modulation are established features of endometriosis but do not adequately explain its cause. It has been proposed that endometrium is distributed through the body via blood or the lymphatic system; that menstrual tissue backs up into the fallopian tubes, implants in the abdomen, and grows; and that all women experience some form of tissue backup during menstruation but only those with immune-system or hormonal problems experience the tissue growth associated with endometriosis. Despite numerous symptoms that can indicate endometriosis, diagnosis is possible only through laparoscopy or a more invasive surgical technique. Several treatments for endometriosis are available, but there is no cure.

Conclusions from *VAO* and Previous Updates

Endometriosis was first reviewed in this series of reports in *Update 2002*, which identified two relevant environmental studies, and *Update 2004* examined three environmental studies. Three additional environmental studies considered in *Update 2008* did not change the conclusion that the evidence was inadequate or insufficient to support an association with herbicide exposure. Table 8-1 provides a summary of relevant studies that have been reviewed.

Update of the Epidemiologic Literature

No Vietnam-veteran or occupational studies of exposure to the chemicals of interest and endometriosis have been published since *Update 2008*.

TABLE 8-1 Selected Epidemiologic Studies—Endometriosis

Reference	Study Population	Study Results
ENVIRONMENTAL		
Studies Conducted in the United States		
Niskar et al., 2009	Case–control study of women in Atlanta, GA with endometriosis; 60 cases and 64 controls	Results for cases vs controls: Total TEQ (determined by GC/MS): OR = 01.00 (95% CI 0.930–1.07)
Studies Conducted in Belgium		
Heilier et al., 2007	88 matched triads (264 total); patients with deep endometriotic nodules, pelvic endometriosis, controls matched for age, gynecologic practice in Belgium; routes of exposure to DLCs examined	Results for pelvic endometriosis vs controls: Dietary fat: OR = 1.0 (95% CI 1.0–1.0) BMI: OR = 1.0 (95% CI 0.9–1.0) Occupation: OR = 0.5 (95% CI 0.2–1.1) Traffic: OR = 1.0 (95% CI 0.3–2.8) Incinerator: OR = 1.0 (95% CI 1.0–1.1)
Heilier et al., 2006	Serum DLC and aromatase activity in endometriotic tissue from 47 patients in Belgium	No association between TEQs (determined by GC/MS) of DLCs in serum and aromatase activity by regression analyses. p-values = 0.37–0.90 for different endometriosis subgroups
Heilier et al., 2005	Endometriosis in Belgian women with overnight fasting serum levels of PCDD, PCDF, PCB	50 exposed cases, risk of increase of 10 pg/g lipid of TEQ compounds (determined by GC/MS); OR = 2.6 (95% CI 1.3–5.3)
Fierens et al., 2003	Belgian women with environmental exposure to PCDDs, PCDFs; compared analyte concentrations in cases vs controls	Mean concentration of TEQ (determined by GC/MS): Cases (n = 10), 26.2 (95% CI 18.2–37.7) Controls (n = 132), 25.6 (95% CI 24.3–28.9) No significant difference
Pauwels et al., 2001	Patients undergoing infertility treatment in Belgium; compared number of women with, without endometriosis who had serum dioxin levels up to 100 pg TEQ/g of serum lipid (determined by CALUX bioassay)	Six exposed cases: OR = 4.6 (95% CI 0.5–43.6)

TABLE 8-1 Endometriosis, continued

Reference	Study Population	Study Results
Studies Conducted in Italy		
Porpora et al., 2009	Case–control study of Italian women with endometriosis; 80 cases and 78 controls (TEQs determined by CALUX bioassay)	Results for endometriosis vs controls: dl-PCB 118 compared to ≤ 13.2 ng/g: 13.3–24.2 ng/g; OR = 3.17 (95% CI 1.36–7.37) ≥ 24.3 ng/g; OR = 3.79 (95% CI 1.61–8.91) Total TEQ compared to ≤ 15.6 pgC-TEQ/g fat: 15.7–29.5 pgC-TEQs/g fat; OR = 0.52 (95% CI 0.18–1.48) ≥ 29.6 pgC-TEQ/g fat; OR = 0.73 (95% CI 0.26–2.01)
Porpora et al., 2006	Case–control study of Italian women with endometriosis, measured serum PCBs	Mean total PCBs (ng/g) Cases, 410 ng/g Control, 250 ng/g All PCB congeners: OR = 4.0 (95% CI 1.3–13)
De Felip et al., 2004	Pilot study of Italian, Belgian women of reproductive age; compared concentrations of TCDD, total TEQ (determined by GC/MS) in pooled blood samples from women who had diagnosis endometriosis with controls	Mean concentration of TCDD (ppt of lipid): Italy: Controls (10 pooled samples), 1.6 Cases (two sets of 6 pooled samples), 2.1, 1.3 Belgium: Controls (7 pooled samples), 2.5 Cases (Set I, 5 pooled samples; Set II, 6 pooled samples), 2.3, 2.3 Mean concentration of TEQ (ppt of lipid): Italy: Controls (10 pooled samples), 8.9 ± 1.3 (99% CI 7.2–11.0) Cases (two sets of 6 pooled samples), 10.7 ± 1.6; 10.1 ± 1.5 Belgium: Controls (7 pooled samples), 24.7 ± 3.7 (99% CI 20–29) Cases (Set I, 5 pooled samples; Set II, 6 pooled samples), 18.1 ± 2.7; 27.1 ± 4.0
Eskenazi et al., 2002a	Residents of Seveso Zones A and B up to 30 years old in 1976; population-based historical cohort comparing incidence of endometriosis across serum TCDD concentrations	Serum TCDD (ppt): ≤ 20 (n = 2 cases), RR = 1.0 (reference) 20.1–100, (n = 8), RR = 1.2 (90% CI 0.3–4.5) > 100, (n = 9), RR = 2.1 (90% CI 0.5–8.0)

continued

TABLE 8-1 Endometriosis, continued

Reference	Study Population	Study Results
Studies Conducted in Israel		
Mayani et al., 1997	Residents of Jerusalem being evaluated for infertility; compared number of women with high TCDD who had (n = 44), did not have (n = 35) diagnosis of endometriosis	8 exposed cases: OR = 7.6 (95% CI 0.9–169.7)
Studies Conducted in Japan		
Tsuchiya et al., 2007	138 infertility patients in Japan; laproscopically confirmed case–control status, serum dioxin, PCB TEQ (determined by GC/MS); P450 genetic polymorphism	Results for advanced endometriosis: Total TEQ: OR = 0.5 (95% CI 0.2–1.7) Genotype-specific: ORs = 0.3–0.6 No significant interaction between genotype, dioxin TEQ

ABBREVIATIONS: BMI, body mass index; CALUX, chemical activated luciferase gene expression; CI, confidence interval; dl, dioxin-like; DLC, dioxin-like compound; GA, Georgia; GC/MS, gas chromatography/mass spectrometry; OR, odds ratio; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzodioxin; PCDF, polychlorinated dibenzofuran; RR, relative risk or risk ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEQ, (total) toxic equivalent.

Environmental Studies

Niskar et al. (2009) recruited 144 women who lived in Atlanta, Georgia, during 1998–1999 for a case–control study of endometriosis. TCDD TEQs were calculated on the basis of the serum concentration of each of the dioxin-like PCDDs, PCDFs, and PCBs; total PCBs were calculated on the basis of the sum of 36 PCB congeners measured in serum. Persons who had endometriosis (n = 60) and controls who did not (n = 64) were selected from patients seeking consultation at a reproductive-medicine clinic. At the time of enrollment, cases had been recently diagnosed, confirmed with biopsy, and staged as minimal, mild, moderate, or severe. No difference was observed between cases and controls with regard to TEQ or total PCBs on the basis of either lipid-adjusted or non–lipid-adjusted values.

A second case–control study of endometriosis was completed in Rome, Italy (Porpora et al., 2009). Women scheduled for laparoscopy were recruited from a reproductive-medicine clinic. Cases (n = 80) were confirmed and staged with

histologic analyses. Controls (n = 78) were women who had no known infertility and underwent laparoscopy for unrelated gynecologic conditions. An increased risk of endometriosis was observed with increasing serum concentrations of the dioxin-like PCB 118. When they were compared with women who had the lowest concentrations of PCB 118 (≤ 13.3 ng/g serum lipid), the adjusted odds ratios (ORs) for endometriosis were 3.14 (95% confidence interval [CI] 1.36–7.37) and 3.79 (95% CI 1.61–8.91) for women who had serum PCB 118 concentrations of 13.3–24.2 ng/g lipid and more than 24.2 ng/g lipid, respectively. However, no association was observed with total TEQs: an OR of 0.73 (95% CI 0.26–2.01) in women who had the highest concentration of total TEQ (> 29.6 pg TEQ/g lipid).

Biologic Plausibility

Laboratory studies that used animal models and examined gene-expression changes associated with human endometriosis provide evidence of the biologic plausibility of a link between TCDD exposure and endometriosis. The first suggestion that TCDD exposure may be linked to endometriosis came as a secondary finding of a study that exposed female rhesus monkeys (*Macaca mulatta*) chronically to low concentrations of dietary TCDD for 4 years (Rier et al., 1993). Ten years after the exposure ended, the investigators documented an increased incidence of endometriosis in the monkeys that correlated with the TCDD exposure concentration. The small sample prevented a definitive conclusion that TCDD was a causal agent of endometriosis, but it led to numerous studies of the ability of TCDD to promote the growth of pre-existing endometriotic lesions.

A number of proposed mechanisms by which TCDD may promote endometrial lesions provide additional biologic plausibility of the link between TCDD and endometriosis. Human endometrial tissue expresses the aryl hydrocarbon receptor (AHR) and its dimerization partner, the aryl hydrocarbon nuclear translocator (ARNT) (Khorram et al., 2002), and three AHR target genes: CYP1A1, 1A2, and 1B1 (Bulun et al., 2000); this suggests that endometrial tissue is responsive to TCDD. Recently, it was shown that CYP1A1 expression increases in ectopic endometrial tissue from women, compared with eutopic uterine tissue, in the absence of TCDD exposure, and this suggests that CYP1A1 may play a role in disease etiology (Singh et al., 2008). Other mechanisms by which TCDD may promote endometriosis include altering the ratio of progesterone receptor A to B and blocking the ability of progesterone to suppress matrix metalloproteinase (MMP) expression—actions that promote endometrial-tissue invasion and that are observed in women who have endometriosis (Igarashi et al., 2005).

TCDD also induces changes in gene expression that mirror those observed in endometrial lesions. In addition to the induction of CYP1A1 noted above, TCDD can induce expression of histamine-releasing factor, which is increased in endometrial lesions and accelerates their growth (Oikawa et al., 2002, 2003). Similarly, TCDD stimulates expression of RANTES (*r*egulated on *a*ctivation, *n*ormal

T-cell–*e*xpressed, and *s*ecreted) in endometrial stromal cells, and RANTES concentration and bioactivity are increased in women who have endometriosis (Zhao et al., 2002). The two CC-motif chemokines (chemotactic cytokines), RANTES and macrophage-inflammatory protein 1α (MIP-1α), have been identified as potential contributors to the pathogenesis and progression of endometriosis. Previous studies showed that the combination of 17β-estradiol and TCDD increased the secretion of RANTES and MIP-1α in endometrial stromal cells (Yu et al., 2008), and a more recent study showed that the same combination increased expression of the chemokine C receptor 9 (CCR9) and the secretion of its ligand, thymus-expressed chemokine (TECK), in endometriosis-associated cells (Wang et al., 2010). Those results support the idea that TCDD in combination with estradiol may contribute to the development of endometriosis by increasing invasiveness of endometrial cells. Despite that compelling evidence, chronic exposure of rats to TCDD, a dioxin-like PCB, or PCDF or a mixture of the three fails to alter endometrial histology in a consistent manner (Yoshizawa et al., 2009). Differences between the rodent uterus and human endometrium could account for that lack of observed effects in rats.

In summary, experimental studies, particularly those using human eutopic and ectopic endometrial tissue provide evidence of the biologic plausibility of a link between TCDD exposure and endometriosis.

Synthesis

The new epidemiologic studies described above were contradictory in their findings and did not assess dioxin directly. Overall, the studies linking dioxin exposure with endometriosis are few and inconsistent. The association in animal studies is biologically plausible, but it is possible that human exposures are too low to show an association consistently.

Conclusion

On the basis of the evidence reviewed here, in *VAO*, and in the previous VAO updates, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and human endometriosis.

FERTILITY

Male reproductive function is under the control of several components whose proper coordination is important for normal fertility. Several of the components and some health outcomes related to male fertility, including reproductive hormones and sperm characteristics, can be studied as indicators of fertility. The reproductive neuroendocrine axis involves the central nervous system, the an-

terior pituitary gland, and the testis. The hypothalamus integrates neural inputs from the central and peripheral nervous systems and regulates the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Both are secreted into the circulation in episodic bursts by the anterior pituitary gland and are necessary for normal spermatogenesis. In the testis, LH interacts with receptors on Leydig cells, where it stimulates increased testosterone synthesis. FSH and the testosterone from the Leydig cells interact with Sertoli cells in the seminiferous tubule epithelium to regulate spermatogenesis. More detailed reviews of the male reproductive hormones can be found elsewhere (Knobil et al., 1994; Yen and Jaffe, 1991). Several agents, such as lead and dibromochloropropane, affect the neuroendocrine system and spermatogenesis (for reviews, see Bonde and Giwercman, 1995; Tas et al., 1996).

Studies of the relationship between chemicals and fertility are less common in women than in men. Some chemicals may disrupt the female hormonal balance necessary for proper functioning. Normal menstrual-cycle functioning is also important in the risk of hormonally related diseases, such as osteopenia, breast cancer, and cardiovascular disease. Chemicals can have multiple effects on the female system, including modulation of hormone concentrations that result in menstrual-cycle or ovarian-cycle irregularities, changes in menarche and menopause, and impairment of fertility (Bretveld et al., 2006a,b).

Conclusions from *VAO* and Previous Updates

The committee responsible for the original *VAO* report (IOM, 1994) concluded that there was inadequate or insufficient evidence of an association between exposure to 2,4-D, 2,4,5-T, TCDD, picloram, or cacodylic acid and altered sperm characteristics or infertility. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008* did not change that conclusion. Reviews of the relevant studies are presented in the earlier reports. Tables 8-2 and 8-3 summarize the studies related to male and female fertility, respectively.

Update of the Epidemiologic Literature

Male Fertility

No Vietnam-veteran or occupational studies of exposure to the chemicals of interest and male fertility have been published since *Update 2008*.

Environmental Studies Since *Update 2008*, two studies published on semen quality and exposure to organochlorine compounds have been published. The first, by Cok et al. (2010), explored associations between PCBs measured in adipose tissue and fertility status in 25 infertile men and 21 healthy men. Infertile

TABLE 8-2 Selected Epidemiologic Studies—Male Fertility (Altered Hormone Concentrations, Decreased Sperm Counts or Quality, Subfertility, or Infertility)

Reference	Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Risk (95% CI)[a]
VIETNAM VETERANS			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans			**All COIs**
Gupta et al., 2006			*Coefficient (p-value)* for ln(Testosterone) vs ln(TCDD) in 1987
	AFHS (964 Ranch Hands, 1,259 comparison)		
	Comparison TCDD quartile I (mean, 2.14 ppt)	nr	0 (referent)
	Comparison TCDD quartile II (mean, 3.54 ppt)	nr	–0.063 (0.004)
	Ranch Hand TCDD quartile I (mean, 4.14 ppt)	nr	0.002 (0.94)
	Comparison TCDD quartile III (mean, 4.74 ppt)	nr	–0.048 (0.03)
	Comparison TCDD quartile IV (mean, 7.87 ppt)	nr	–0.079 (< 0.001)
	Ranch Hand TCDD quartile II (mean, 8.95 ppt)	nr	–0.052 (0.03)
	Ranch Hand TCDD quartile III (mean, 18.40 ppt)	nr	–0.029 (0.22)
	Ranch Hand TCDD quartile IV (mean, 76.16 ppt)	nr	–0.056 (0.02)
Henriksen et al., 1996	Effects on specific hormone concentrations or sperm count in Ranch Hands		
	Low testosterone		
	High dioxin (1992)	18	1.6 (0.9–2.7)
	High dioxin (1987)	3	0.7 (0.2–2.3)
	Low dioxin (1992)	10	0.9 (0.5–1.8)
	Low dioxin (1987)	10	2.3 (1.1–4..9)
	Background (1992)	9	0.5 (0.3–1.1)
	High FSH		
	High dioxin (1992)	8	1.0 (0.5–2.1)
	Low dioxin (1992)	12	1.6 (0.8–3.0)
	Background (1992)	16	1.3 (0.7–2.4)
	High LH		
	High dioxin (1992)	5	0.8 (0.3–1.9)
	Low dioxin (1992)	5	0.8 (0.5–3.3)
	Background (1992)	8	0.8 (0.4–1.8)
	Low sperm count		
	High dioxin	49	0.9 (0.7–1.2)
	Low dioxin	43	0.8 (0.6–1.0)
	Background	66	0.9 (0.7–1.2)

TABLE 8-2 Male Fertility, continued

Reference	Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Risk (95% CI)[a]
US CDC Vietnam Experience Study			**All COIs**
CDC, 1989a	Vietnam Experience Study		
	Lower sperm concentration	42	2.3 (1.2–4.3)
	Proportion of abnormal sperm	51	1.6 (0.9–2.8)
	Reduced sperm motility	83	1.2 (0.8–1.8)
American Legion Cohort			**All COIs**
Stellman et al., 1988	American Legionnaires who served in SEA		
	Difficulty in having children	349	1.3 ($p < 0.01$)
OCCUPATIONAL			
US Chemical Workers			**Dioxin**
Oh et al., 2005	Male waste incinerator workers (n = 6) vs controls (n = 8), dioxin measured by air monitoring		
	Reduced number of sperm (10^6/ml)		($p = 0.050$)
	Workers		42.9 ± 18.0
	Controls		56.1 ± 44.5
	DNA damaged sperm (%)		($p = 0.001$)
	Workers		1.40 ± 0.08
	Controls		1.26 ± 0.03
Egeland et al., 1994	Male chemical workers exposed to dioxin vs neighborhood controls in New Jersey, Missouri measured in 1987		Risk of extreme hormone concentration
	Testosterone (< 10.4 nmol/L)		
	Referents (TCDD < 20 ppt)	11	1.0
	Workers	25	2.1 (1.0–4.6)
	Quartile I (TCDD < 20 ppt)	2	0.9 (0.2–4.5)
	Quartile II (TCDD 20–75 ppt)	7	3.9 (1.3–11.3)
	Quartile III (TCDD 76–240 ppt)	6	2.7 (0.9–8.2)
	Quartile IV (TCDD 241–3,400 ppt)	10	2.1 (0.8–5.8)
	FSH (> 31 IU/L)	20	1.5 (0.7–3.3)
	LH (> 28 IU/L)	23	1.6 (0.8–3.3)
Agricultural Workers			**Herbicides**
Larsen et al., 1998	Danish farmers who used any potentially spermatotoxic pesticides, including 2,4-D		
	Farmers using pesticides vs organic farmers	523	1.0 (0.8–1.4)[b]
	Used three or more pesticides	nr	0.9 (0.7–1.2)[b]
	Used manual sprayer for pesticides	nr	0.8 (0.6–1.1)[b]
Lerda and Rizzi, 1991	Argentinean farmers exposed to 2,4-D	32	
	Sperm count (millions/mL)	exposed: 49.0 vs control: 101.6	
	Motility (%)	exposed: 24.8 vs control: 70.4	
	Sperm death (%)	exposed: 82.9 vs control: 37.1[d]	
	Anomalies (%)	exposed: 72.9 vs control: 33.4	
Forestry Workers			**Herbicides**
Heacock et al., 1998	Workers at sawmills using chlorophenates		

continued

TABLE 8-2 Male Fertility, continued

Reference	Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Risk (95% CI)[a]
	Standardized fertility ratio	18,016 (births)	0.7 (0.7–0.8)[c]
	Mantel–Haenszel rate-ratio estimator	18,016 (births)	0.9 (0.8–0.9)[c]
	Cumulative exposure (hours)		
	120–1,999	7,139	0.8 (0.8–0.9)[c]
	2,000–3,999	4,582	0.9 (0.8–1.0)[c]
	4,000–9,999	4,145	1.0 (0.9–1.1)[c]
	≥ 10,000	1,300	1.1 (1.0–1.2)[c] ($p < 0.01$ overall)
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**Dioxin**
Mocarelli et al., 2008	Men exposed in Seveso, Zone A vs age-matched men residing outside the contamination zone, measured semen characteristics, estradiol, FSH, testosterone, LH, inhibin B		*Authors' evaluation* (data not shown)
	Age at 1976 exposure:		Sensitive
	Infant/prepuberty (1–9 years), n = 71 vs 176		Intermediate response
	Puberty (10–17 years), n = 44 vs 136		No associations
	Adult (18–26 years), n = 20 vs 60		
Ankara, Turkey Case–Control Study of Infertile Men			**DLCs**
Cok et al., 2010	Adipose-tissue samples assayed for PCB-118	21 fertile 25 infertile	68.6 ng/g lipid 21.7 ng/g lipid ($p = 0.003$)
Cok et al., 2008	Adipose-tissue samples assayed for dioxins, furans, dl PCBs	22 fertile 23 infertile	9.4 TEQ pg/g lipid 12.5 TEQ pg/g lipid ($p = 0.065$)
US Environmental Study			**2,4-D**
Swan et al., 2003	Men in Missouri, US with or without low sperm quality		
	Increased urinary metabolite marker for 2,4-D	5	0.8 (0.2–3.0)
International Environmental Studies			
Krüger et al., 2008	DNA sperm integrity among Inuit men from Greenland (n = 53) and European men (n = 247)		**POPs**
	Median % DNA fragmentation index		
	Inuits		6.8
	Europeans		12
	Median % DNA stainability		
	Inuits		11
	Europeans		8.9

TABLE 8-2 Male Fertility, continued

Reference	Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Risk (95% CI)[a]
Polsky et al., 2007	Case–control study of erectile dysfunction in urology patients patients in Ontario, Canada		**PCBs/**Highest vs lowest PCB groups
	PCB-118 (TEF = 0.0001)		1.0 (0.5–2.1)
	PCB-156 (TEF = 0.0005)		0.9 (0.5–1.6)
	PCB-170		0.6 (0.3–1.2)
	PCB-180		0.7 (0.4–1.4)
Toft et al., 2007	Men in general population of Poland, Greenland, Ukraine, Sweden; AHR binding measured with CALUX assay		**Dioxin-like activity**
	Measurements of semen quality (concentration, motility, percentage normal)		No consistent associations
Dhooge et al., 2006	Men in general population of Belgium		**PCBs, dioxin**
	Association with 2-fold increase in CALUX-TEQ		Change (p–value)
	Sperm concentration		25.2% (p = 0.07)
	Semen volume		–16.0% (p = 0.03)
	Total testosterone		–7.1% (p = 0.04)
	Free testosterone		–6.8% (p = 0.04)
Staessen et al., 2001	Adolescents in communities close to industrial sources of heavy metals, PCBs, VOCs, and PAHs—delays in sexual maturity		**PCBs, DLCs**
	In Hoboken, Belgium	8	4.0 (nr)
	In Wilrik, Belgium	15	1.7 (nr)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; AFHS, Air Force Health Study; AHR, aryl hydrocarbon receptor; CALUX, assay for determination of dioxin-like activity; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; dl, dioxin-like; DLC, dioxin-like chemical; FSH, follicle-stimulating hormone; IU, international unit; LH, luteinizing hormone; nr, not reported; PAH, polycyclic aromatic hydrocarbon; PCB, polychlorinated biphenyl; POP, persistent organic pollutants; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEF, toxicity equivalency factor; TEQ, (total) toxic equivalent; VOC, volatile organic compound.

[a]Given when available; results other than estimated risk explained individually.

[b]For this study, relative risk has been replaced with fecundability ratio, for which value less than 1.0 indicates adverse effect.

[c]For this study, relative risk has been replaced with standardized fertility ratio, for which value less than 1.0 indicates adverse effect.

[d]Table 1 in reference reverses these figures—control, 82.9%; exposed, 37.1%—but text ("The percentages of asthenospermia, mobility, necrosperma and teratospermia were greater in the exposed group than in controls. . .") suggests that this is a typographical error.

TABLE 8-3 Selected Epidemiologic Studies—Female Fertility (Altered Hormone Concentrations, Subfertility, or Infertility)

Reference	Study Population	Exposed Cases	Exposure of Interest/ Estimated Risk (95% CI)[a]
OCCUPATIONAL			
Agricultural Health Study			**Herbicides**
Farr et al., 2006	8,038 premenopausal women aged 35–55 at enrollment		
	Later menopause		
	Pesticide exposure	5,013	0.9 (0.8–1.0)
	Herbicide exposure	3,725	0.9 (0.7–1.1)
	Phenoxy herbicide exposure	1,379	0.9 (0.7–1.1)
Farr et al., 2004	Menstrual-cycle characteristics of 3,103 premenopausal women aged 21–40		
	Reported at enrollment had used herbicides	1,291	
	Short menstrual cycle		0.6 (0.4–1.0)
	Long menstrual cycle		1.0 (0.5–2.0)
	Irregular		0.6 (0.3–0.9)
	Missed period		1.4 (1.0–2.0)
	Intermenstrual bleeding		1.1 (0.8–1.7)
ENVIRONMENTAL			
Seveso Women's Health Study			**TCDD**
Eskenazi et al., 2010	Time to pregnancy and infertility in women from Zones A and B who attempted pregnancy after 1976		
	Time to pregnancy (adjusted fecundability OR)		
	Log_{10} TCDD	278	0.8 (0.6–1.0)
	Categorical TCDD (ppt)		
	≤ 20	52	1.0 (reference)
	20.1–44.4	76	0.8 (0.5–1.3)
	44.5–100	75	0.7 (0.5–1.1)
	> 100	75	0.6 (0.4–1.0)
	Infertility (adjusted OR)		
	Log_{10} TCDD	49	1.9 (1.1–3.2)
	Categorical TCDD (ppt)		
	≤ 20	6	1.0 (reference)
	20.1–44.4	9	1.1 (0.4–3.6)
	44.5–100	16	2.5 (0.8–7.3)
	> 100	18	2.8 (1.0–8.1)
Eskenazi et al., 2007	Fibroids among women from Zones A and B who were newborn to age 40 in 1976		
	Uterine fibroids (age-adjusted HR)		
	Log_{10} TCDD (ppt)	251	0.8 (0.7–1.1)
	Categorical TCDD (ppt)		
	≤ 20.0	62	1.0 (reference)
	20.1–75.0	110	0.6 (0.4–0.8)
	> 75.0	79	0.6 (0.4–0.9)

TABLE 8-3 Female Fertility, continued

Reference	Study Population	Exposed Cases	**Exposure of Interest/** Estimated Risk (95% CI)[a]
Warner et al., 2007	Ovarian function in women from Zones A and B who were newborn to age 40 in 1976; results are for a 10-fold increase in serum TCDD		
	Ovarian follicles (age-adjusted OR)		
	in follicular phase	65	1.0 (0.4–2.2)
	Ovulation (age-adjusted OR)		
	in luteal phase	87	1.0 (0.5–1.9)
	in midluteal phase	55	1.0 (0.4–2.7)
	Estradiol (age-adjusted ß)		Slopes for log TCDD
	in luteal phase	87	−1.8 (−10.4–6.8)
	in midluteal phase	55	−3.1 (−14.1–7.8)
	Progesterone (age-adjusted ß)		
	in luteal phase	87	−0.7 (−2.4–1.0)
	in midluteal phase	55	−0.8 (−3.7–2.0)
Eskenazi et al., 2005	Age at menopause in women from Zones A and B who were newborn to age 40 in 1976	616	
	Onset of natural menopause (unadjusted HR)		
	Log_{10} TCDD	169	1.0 (0.8–1.3)
	Menopause category		Serum TCDD median (IQR)
	Premenopause	260	43.6 (0.2–0.9)
	Natural menopause	169	45.8 (0.3–1.0)
	Surgical menopause	83	43.4 (0.3–1.0)
	Impending menopause	13	43.8 (0.2–1.1)
	Perimenopause	33	36.5 (0.2–0.9)
	Other	58	39.6 (0.2–0.9)
Warner et al., 2004	Age at menarche in women from Zones A and B who were premenarcheal in 1976	282	1.0 (0.8–1.1)
	All premenarcheal women in 1976 (unadjusted HR)		
	Log_{10} TCDD	282	1.0 (0.8–1.1)
	Women < 8 years in 1976 (unadjusted HR)		
	Log_{10} TCDD	158	1.1 (0.9–1.3)
Eskenazi et al., 2002b	Menstrual cycle characteristics in women from Zones A and B who were premenopausal, less than age 44, and not recently pregnant, breastfeeding, or using hormonal medications		
	Menstrual cycle length (adjusted ß)		
	Log_{10} TCDD	277	0.4 (−0.1–0.9)
	Premenarcheal at explosion		0.9 (0.0–1.9)
	Postmenarcheal at explosion		0.0 (−0.6–0.5)

continued

TABLE 8-3 Female Fertility, continued

Reference	Study Population	Exposed Cases	**Exposure of Interest/** Estimated Risk (95% CI)[a]
	Days of menstrual flow (adjusted ß)		
	Log_{10} TCDD	301	0.2 (−0.1–0.4)
	Premenarcheal at explosion		0.2 (−0.2–0.5)
	Postmenarcheal at explosion		0.2 (−0.2–0.5)
	Heaviness of flow (scanty vs moderate/heavy; adjusted OR)		
	Log_{10} TCDD	30	0.8 (0.4–1.6)
	Premenarcheal at explosion		0.3 (0.1–1.1)
	Postmenarcheal at explosion		1.4 (0.7–2.6)
	Irregular cycle (vs regular; adjusted OR)		
	Log_{10} TCDD	24	0.5 (0.2–1.0)
	Premenarcheal at explosion		0.5 (0.2–1.4)
	Postmenarcheal at explosion		0.4 (0.2–1.2)
Other Environmental Studies			
Chao et al., 2007	Pregnant women in Taiwan; measured placental dioxin TEQ, PCB TEQ		**Dioxin**/Regression adjusted for maternal age, BMI, parity
	Older of "regular menstrual cycle"		
	Dioxin TEQ		p = 0.032
	PCB TEQ		p = 0.077
	Longer "longest menstrual cycle"		
	Dioxin TEQ		p = 0.269
	PCB TEQ		p = 0.006
Greenlee et al., 2003	Women in Wisconsin, US with or without infertility (maternal exposure)		**Phenoxy herbicides**
	Mixed or applied herbicides	21	2.3 (0.9–6.1)
	Used 2,4,5-T	9	9 cases (2.7%) 11 controls (3.4%)
	Used 2,4-D	4	4 cases (1.2%) 4 controls (1.2%)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; BMI, body mass index; CI, confidence interval; HR, hazard ratio; IQR, inter-quartile range; OR, odds ratio; PCB, polychlorinated biphenyl; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEQ, (total) toxic equivalent.

[a]Given when available; results other than estimated risk explained individually.

men had higher adipose-tissue concentrations of PCB 52 and PCB 180 but lower concentrations of the one dioxin-like PCB congener measured, PCB 118.

The second study included 53 men in Greenland (Inuits) and 247 Europeans (in Sweden, Poland, and Ukraine) whose sperm DNA integrity was measured using flow cytometry to assess the integrity of sperm chromatin structure (Krüger et al., 2008). Total TCDD TEQs were calculated from serum samples analyzed with the AHR-CALUX assay; analogous CALUX assays were used to determine

estrogenic and androgenic activity in the samples. Results for none of the three measured outcomes showed a coherent pattern across sub-populations. The fraction of sperm showing DNA breaks was negatively associated with serum TEQs for Greenland Inuits, while it was positively associated for the groups of European men. Thus, neither study provides convincing evidence of an association between dioxin exposure and reduced semen quality.

Female Fertility

No Vietnam-veteran or occupational studies of exposure to the chemicals of interest and female fertility have been published since *Update 2008*.

Environmental Studies Since *Update 2008*, Eskenazi et al. (2010) examined the relationship between serum TCDD level around the time of the Seveso accident and time to pregnancy (TTP) in 472 Seveso Women's Health Study (SWHS) participants who attempted pregnancy since the accident. Participants were eligible for this study if they were newborn to 40 years old at the time of the accident, lived in the contaminated area at the time of the accident, and had adequate stored sera available for analyses. Nine women were excluded due to fertility-related problems, leaving 463 eligible women in the analysis sample. The main analysis was restricted to women whose pregnancies were not the result of contraceptive failure and resulted in a live birth (n = 278). Additional analyses of subgroups included women who conceived after contraceptive failure and pregnancies not resulting in a live birth. TTP for the first post-accident pregnancy was determined from interviews conducted between 1996 and 1998 using the question "How many months did it take to become pregnant? In other words, for how many months had you been having sexual intercourse without doing anything to prevent pregnancy?" Women whose TTP was 12 months or more were classified as infertile.

Initial serum TCDD levels at the time of the accident were measured using stored samples for 444 participants (431 collected in 1976 or 1977, 13 collected between 1978 and 1981). For 19 participants with insufficient stored samples, new samples were collected in 1996 or 1997. For women with detectable post-1977 TCDD measurements (n = 27), the TCDD level was back-extrapolated to 1976, using the Filser Model (Kreuzer et al., 1997). Initial serum TCDD levels were extrapolated to the time each woman initiated her attempt to become pregnant using a toxicokinetic model (Kreuzer et al., 1997) for women 16 years old or younger at the time of the accident, and a first-order kinetic model assuming a 9-year half-life (Pirkle et al., 1989).

The association between serum TCDD and TTP was assessed using a Cox proportional hazards model to estimate the fecundability odds ratios (fOR) and 95% confidence intervals. The association between serum TCDD and infertility was assessed using multiple logistic regression. Both models were adjusted for

maternal age, maternal smoking in the year before conception, parity, menstrual cycle irregularity, oral contraceptive use in the year before attempt, paternal age near the time of conception, and history of reproductive and endocrine conditions including pelvic infection, or thyroid or urogenital problems. A variety of sensitivity analyses were conducted to investigate the consistency of study findings and to check for possible bias.

Serum TCDD was specified both as a continuous variable on the logarithmic scale, and as categorical variables. The fOR was calculated to evaluate the odds of conceiving in a given cycle for each 10-fold increase in TCDD (on the continuous scale) or each exposure category. A fOR less than 1 represents increased TTP for those designated as exposed. In these analyses, TTP increased with increasing exposure on both the continuous and categorical scales. For example, for every 10-fold increase in TCDD, a 25% decrease in fecundability was observed (fOR = 0.75, 95% CI 0.60–0.95). Seventeen percent of the women in this study were classified as infertile (a TTP of longer than 12 months). As with TTP, the odds of infertility increased with every 10-fold increase in exposure (adjusted OR 1.92, 95% CI 1.14–3.22). The results did not substantively change when different eligibility criteria and exposure models were considered.

Biologic Plausibility

There is little evidence that 2,4-D or 2,4,5-T has substantial effects on reproductive organs or fertility. In contrast, many diverse laboratory studies have provided evidence that TCDD can affect reproductive-organ function and reduce fertility in both males and females.

The administration of TCDD to male animals elicits reproductive toxicity by affecting testicular, epididymal, and seminal vesicle weight and function and by decreasing the rate of sperm production. The mechanisms of those effects are not known, but a primary hypothesis is that they are mediated through dysregulation of testicular steroidogenesis. Studies published since *Update 2008* have reinforced those findings. Single intraperitoneal injections of TCDD induced marked histologic changes in the testis, impaired spermatogenesis, increased serum estradiol, decreased testosterone in male rats (Choi et al., 2008; Park et al., 2008), and impaired epididymal function (Foster et al., 2010). The effects of TCDD on the reproductive system of the male rat depend heavily on the developmental time of exposure.

Many studies have examined the effects of TCDD on the female reproductive system. Two primary mechanisms that probably contribute to abnormal follicle development and decreased numbers of ova after TCDD exposure are cross-talk of the AHR with the estrogen receptor and dysregulation of the hypothalamic–pituitary–gonadal axis. In addition, oocytes are directly responsive to TCDD. Thus, TCDD's effects on hormone concentrations, hormone-receptor signaling, and ovarian responsiveness to hormones all probably contribute to TCDD-induced

female reproductive toxicity. Since *Update 2008*, additional work addressing TCDD's effects on female reproduction in animal models has been published. The data of Heiden et al. (2008) on zebrafish suggest that TCDD inhibits follicle maturation via attenuated gonadotropin responsiveness or depression of estradiol biosynthesis and that interference of estrogen-regulated signal transduction may also contribute to TCDD's effects on follicular development, possibly by disrupting signaling pathways, such as glucose and lipid metabolism, and disrupting regulation of transcription.

Since the *Update 2008*, studies with TCDD in rodents have suggested that dioxin has a pharmacologic effect on sperm flagellum movement (Yamano et al., 2009) and that TCDD has a greater effect on epididymal function and sperm analysis than on spermatogenesis (Foster et al., 2010). Studies of female reproduction in rats involved the demonstration that a number of PCBs and dioxin compounds have numerous effects on reproductive physiology after 2-year oral treatment, including infertility, and the different actions of the various chemicals suggested that more than one signaling mechanism was involved (Yoshizawa et al., 2009). Another study suggested direct effects on human trophoblast formation in vitro and thus the capacity to influence the developing fetus (Chen et al., 2010). The more recent literature continues to support the biologic plausibility of effects of TCDD on male and female reproduction.

Although it would not constitute an adverse health outcome in an individual veteran, there is fairly strong evidence (see Table 8-4) that paternal exposure to dioxin may result in a lower sex ratio (that is, a smaller than expected proportion of male infants at birth). Pronounced reductions in sex ratio have been observed in the offspring of men exposed to dioxin after the Seveso accident, especially those under 19 years old at the time of the dioxin release (Mocarelli et al., 2000); this phenomenon was not observed in the offspring of young women exposed by the Seveso accident (Baccarelli et al., 2008). Similar results of a depression in the sex ratio concentrated among fathers who were under 20 years old at the time of the incident were following the Yucheng poisoning with oil contaminated with PCBs, PCDFs, and PCDDs (del Rio Gomez et al., 2002). Reductions in the expected number of male offspring have also been reported in several cohorts of men occupationally exposed to dioxin (Moshammer and Neuberger, 2000; Ryan et al., 2002), but other such cohorts did not manifest this relationship (Heacock et al., 1998; Savitz et al., 1997; Schnorr et al., 2001). In the single report relevant to this outcome in Vietnam veterans, however, the sex ratio was increased in the Ranch Hand group that had the highest serum dioxin concentrations (Michalek et al., 1998b).

Chao et al. (2007) mention that they did not find an association between sex ratio of the offspring and the TEQ concentrations of dioxins, furans, or PCBs in the placentas from 119 Taiwanese women. Crude sex ratios for all births in 1994–2005 to women who were less than 18 years old at the time of the Seveso accident are reported in Baccarelli et al. (2008), and the proportion of male births

TABLE 8-4 Selected Epidemiologic Studies—Sex Ratio[a]

Reference	Study Population	Sex Ratio of Offspring (boys/total)[b]	Comments
VIETNAM VETERANS			
US Air Force Health Study			
Michalek et al., 1998b	Births from service through 1993 in AFHS		
	Comparison group	0.504	Not formally analyzed
	Dioxin level in Ranch Hand personnel		
	Background	0.502	
	Low	0.487	
	High	0.535	
OCCUPATIONAL			
NIOSH Cross-Sectional Study			
Schnorr et al., 2001	Workers producing trichlorophenol and derivatives, including 2,4,5-T		No difference on basis of age at first exposure
	Serum TCDD in fathers		
	Neighborhood controls (< 20 ppt)	0.544	Referent
	Worker fathers		
	< 20 ppt	0.507	None significantly decreased (or increased)
	20–255 ppt	0.567	
	255– < 1,120 ppt	0.568	
	≥ 1,120 ppt	0.550	
International Occupational Studies			
Ryan et al., 2002	Russian workers manufacturing 2,4,5,-trichlorophenol (1961–1988) or 2,4,5-T (1964–1967)		
	Either parent exposed	0.401 (91 boys: 136 girls)	$p < 0.001$
	Only father exposed	0.378 (71 boys: 117 girls)	$p < 0.001$
	Only mother exposed	0.513 (20 boys: 19 girls)	ns
Moshammer and Neuberger, 2000	Austrian chloracne cohort—157 men, 2 women; exposed to TCDD during 2,4,5-T production		Fewer sons, especially if father was under 20 years old when exposed: SR = 0.20 (1 boy: 4 girls)
	Children born after starting TCDD exposure in 1971	0.464 (26 boys: 30 girls	
	Children born before 1971	0.613 (19 boys: 12 girls)	

TABLE 8-4 Sex Ratio, continued

Reference	Study Population	Sex Ratio of Offspring (boys/total)[b]	Comments
Heacock et al., 1998	Sawmill workers in British Columbia		
	Chlorophenate-exposed workers	0.515	
	Nonexposed workers	0.519	
	Province overall	0.512	
Savitz et al., 1997	OFFHS fathers' exposure during 3 mo before conception:		
	No chemical activity	0.503	Referent
	Crop herbicides (some phenoxy herbicides)	0.500	ns
	Protective equipment used	0.510	ns
	No protective equipment	0.450	ns
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			
Baccarelli et al., 2008	Births 1994–2005 in women 0–28 yrs of age at time of Seveso accident		
	Zone A	0.571	
	Zone B	0.508	
	Zone R	0.495	
Mocarelli et al., 2000	Births 1977–1996 in people from Zones A, B, R, 3–45 yrs of age at time of 1976 Seveso accident	0.514	Referent
	Neither parent exposed	0.608	ns
	Father exposed (whether or not mother exposed)	0.440	p = 0.03
	Father under 19 yrs of age in 1976	0.382	p = 0.002
	Father at least 19 yrs of age in 1976	0.469	ns
	Only mother exposed	0.545	ns
Mocarelli et al., 1996	Parent (either sex) from Seveso Zone A		
	Births 1977–1984	0.351 (26 boys: 48 girls)	p < 0.001, related to parental TCDD serum
	Births 1985–1994	0.484 (60 boys: 64 girls)	ns
Chapaevsk, Russia Residential Cohort			
Revich et al., 2001	Residents near chemical plant in operation 1967–1987 in Chapaevsk, Russia		
	1983–1997	0.507	No clear pattern
	Minimum in 1989	0.401	
	Maximum in 1987	0.564	
	Maximum in 1995	0.559	

continued

TABLE 8-4 Sex Ratio, continued

Reference	Study Population	Sex Ratio of Offspring (boys/total)[b]	Comments
US Environmental Studies			
Hertz-Picciotto et al.. 2008	San Francisco Bay area—serum concentrations in pregnant women during 1960s	OR for male birth (not SR)	
	90th percentile vs 10th percentile		SRs all < 0.5
	Total PCBs	0.4 (0.3–0.8)	p = 0.007
	dl PCBs		
	PCB 105	0.6 (0.4–0.9)	p = 0.02
	PCB 118	0.7 (0.5–1.2)	p = 0.17
	PCB 170	0.6 (0.4–0.9)	p = 0.02
	PCB 180	0.8 (0.5–1.2)	p = 0.32
Karmaus et al., 2002	Births after 1963 to Michigan fish-eaters with serum PCBs in both parents		ns
	Paternal PCBs > 8.1 µg/L	0.571	p < 0.05
	Maternal PCBs > 8.1 µg/L	0.494	(but for *more* sons) ns
International Environmental Studies			
Chao et al., 2007	Taiwan—placental TEQ concentrations of TCDDs, TCDFs, PCBs	nr	No association
del Rio Gomez et al., 2002	Births in individuals exposed to PCBs, PCDFs, PCDDs in 1979 Yucheng incident		vs unexposed with same demographics
	Father exposed (whether or not mother exposed)	0.490	p = 0.037
	Father under 20 yrs of age in 1979	0.458	p = 0.020
	Father at least 20 yrs of age in 1979	0.541	p = 0.60
	Mother exposed (whether or not father exposed)	0.504	p = 0.45
	Mother under 20 yrs of age in 1979	0.501	p = 0.16
	Mother at least 20 yrs of age in 1979	0.500	p = 0.40
Yoshimura et al., 2001	Parents (one or both) exposed to PCBs, PCDFs in Yusho, Japan		
	All Japan in 1967	0.513	Referent
	Births 1967 (before poisoning incident)	0.516	ns
	Births 1968–1971 (after incident)	0.574	ns

ABBREVIATIONS: 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; AFHS, Air Force Health Study; dl, dioxin-like; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; ns, not significant; OFFHS, Ontario Farm Family Health Study; OR, odds ratio; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzodioxin; PCDF, polychlorinated dibenzofurans; SR, sex ratio; TCDD, 2,3,7,8–tetrachlorodibenzo-*p*-dioxin; TCDF, tetrachlorodibenzofuran; TEQ, (total) toxic equivalent.

[a]*VAO* reports before *Update 1998* did not address association between perturbations in sex ratio of offspring and exposure to chemicals of interest.

[b]Given when available.

exceeds that of female births in Zones A and B. The only new evidence of an effect on sex ratio came from Hertz-Picciotto et al. (2008), who reported on serum concentrations of nine PCB congeners (four of which were dioxin-like: PCB 105, 118, 170, and 180) in blood gathered during the 1960s from 399 pregnant women in the San Francisco Bay area. The adjusted odds of a male birth were significantly decreased when the 90th percentile of the total concentration of all nine PCBs was compared with the 10th percentile (OR = 0.45, 95% CI 0.26–0.80). The proportion of male births was significantly reduced for two of the dioxin-like PCBs analyzed separately, and the decrease in the proportion of male babies was not significant for any of the five non–dioxin-like PCBs.

A population-level finding of a paternally mediated effect would be a strong indicator that dioxin exposure can interfere with the male reproductive process. To date, however, the results for a reduced number of sons for exposed fathers are mixed. James (2006) has interpreted perturbation of sex ratios by dioxins and other agents as being an indicator of parental endocrine disruption. If James' hypothesis were demonstrated to hold, it would be concordant with observing a reduction in testosterone levels among exposed men. Another pathway to an altered sex ratio might involve male embryos experiencing more lethality with induction of mutations due to their unmatched X chromosome. A genotoxic mechanism has not been expected to apply to TCDD, but gender-specific adverse consequences of modified imprinting of gametes might be a possible mechanism leading to observation of altered sex ratios at birth.

There has been no work with experimental animals that specifically examines the effects of TCDD on sex ratios of offspring, nor have any alterations in sex ratio been reported in animal studies that examined developmental effects of TCDD on offspring.

Synthesis

Reproduction is a sensitive toxic endpoint of TCDD and dioxin-like compounds (DLCs) in rodents. It is clear that the fetal rodent is more sensitive to adverse effects of TCDD than the adult rodent. The sensitivity of these endpoints in humans is less apparent. There is little evidence that exposure to dioxin is associated with a reduction in sperm quality or a reduction in fertility. However, the committee notes that the evidence that TCDD exposure reduces serum testosterone in men is consistent across several epidemiologic studies with appropriate consideration of confounders, including one of Vietnam veterans, shows a dose–response relationship and is biologically plausible based on concomitant increases observed in gonadotropins and biologic plausibility from animal studies. Human populations showing evidence of reduced testosterone with exposure to dioxin-like chemicals include a general population sample (Dhooge et al., 2006),

occupationally exposed individuals (Egeland et al., 1994), and Vietnam veterans studies in the AFHS (Gupta et al., 2006). The evidence that dioxin-like chemicals may modify the sex ratio lends credence to the hypothesis that these chemicals do have an impact on male reproductive functioning.

Despite the relative consistency of the findings of a reduction in testosterone level, the testosterone levels observed even in the highest exposed groups studied are well within the normal range. The small reduction in testosterone is not expected to have adverse clinical consequences. There is evidence of compensatory physiological mechanisms coming into play. The occupational study of Egeland et al. (1994) found elevated gonadotropins in addition to reduced testosterone. The gonadotropins stimulate the production of testosterone in men.

The first published study to examine dioxin exposure in women and association with TTP and infertility was reviewed in this update. A dose–response relationship with increasing TCDD exposure and increased TTP and infertility was observed, which is consistent with published observations in the rat model. However, given that this is the first study to observe these associations in women, the continued review of the epidemiology literature will be needed to more fully assess any relationship between dioxin exposure and female-mediated infertility.

Conclusions

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the present committee concludes that there is inadequate or insufficient evidence of an association between exposure to the compounds of interest and decreased sperm counts or sperm quality, subfertility, or infertility.

SPONTANEOUS ABORTION

Spontaneous abortion is the expulsion of a nonviable fetus, generally before 20 weeks of gestation, that is not induced by physical or pharmacologic means. The background risk of recognized spontaneous abortion is generally 7–15% (Hertz-Picciotto and Samuels, 1988), but it is established that many more pregnancies terminate before women become aware of them (Wilcox et al., 1988); such terminations are known as subclinical pregnancy losses and generally are not included in studies of spontaneous abortion. Estimates of the risk of recognized spontaneous abortion vary with the design and method of analysis. Studies have included cohorts of women asked retrospectively about pregnancy history, cohorts of pregnant women (usually those receiving prenatal care), and cohorts of women who are monitored for future pregnancies. The value of retrospective reports can be limited by loss of memory, particularly of spontaneous abortions that took place long before the interview. Studies that enroll women who appear for prenatal care require the use of life tables and specialized statistical techniques to account for differences in the times at which women seek medical care during

pregnancy. Enrollment of women before pregnancy provides the theoretically most valid estimate of risk, but it can attract nonrepresentative study groups because the study protocols are demanding for the women.

Conclusions from *VAO* and Previous Updates

The committee responsible for the original *VAO* report concluded that there was inadequate or insufficient evidence of an association between exposure to 2,4-D, 2,4,5-T, TCDD, picloram, or cacodylic acid and spontaneous abortion. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, and *Update 2000* did not change that conclusion.

The committee responsible for *Update 2002*, however, found that there was enough evidence available concerning paternal exposure to TCDD specifically to conclude that there was suggestive evidence that paternal exposure to TCDD is *not* associated with the risk of spontaneous abortion. That conclusion was based primarily on the National Institute for Occupational Safety and Health study (Schnorr et al., 2001), which investigated a large number of pregnancies fathered by workers whose serum TCDD concentrations were extrapolated back to the time of conception; no association was observed up to the highest exposure group (1,120 ppt of higher). Indications of positive association were seen in studies of Vietnam veterans (CDC, 1989a,b; Field and Kerr, 1988; Stellman et al., 1988), but the committee for *Update 2002* asserted that they might be due to exposure to phenoxy herbicides rather than to TCDD and concluded that there was insufficient information to determine whether there is an association between maternal exposure to TCDD and the risk of spontaneous abortion or between maternal or paternal exposure to 2,4-D, 2,4,5-T, picloram, or cacodylic acid and the risk of spontaneous abortion.

The additional information (none of which concerned paternal exposure) reviewed by the committees responsible for *Update 2004*, *Update 2006*, and *Update 2008* did not change that conclusion. The relevant studies are reviewed in the earlier reports. Table 8-5 summarizes their findings.

Update of the Epidemiologic Literature

No studies of exposure to the chemicals of interest and spontaneous abortion have been published since *Update 2008*.

Biologic Plausibility

Laboratory animal studies have demonstrated that TCDD exposure during pregnancy can alter concentrations of circulating steroid hormones and disrupt placental development and function and thus contribute to a reduction in survival of implanted embryos and to fetal death (Ishimura et al., 2009). There is

TABLE 8-5 Selected Epidemiologic Studies—Spontaneous Abortion[a]

Reference	Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans			**All COIs**
Wolfe et al., 1995	Air Force Ranch Hand veterans	157	
	Background	57	1.1 (0.8–1.5)
	Low exposure	56	1.3 (1.0–1.7)
	High exposure	44	1.0 (0.7–1.3)
US CDC Cohort of Army Chemical Corps			**All COIs**
CDC, 1989a	Vietnam Experience Study		
	Overall	1,566	1.3 (1.2–1.4)
	Self-reported low exposure	489	1.2 (1.0–1.4)
	Self-reported medium exposure	406	1.4 (1.2–1.6)
	Self-reported high exposure	113	1.7 (1.3–2.1)
US VA Cohort of Female Vietnam Veterans			**All COIs**
Kang et al., 2000	Female Vietnam-era veterans (maternal exposure)		1.0 (0.82–1.21)
	Vietnam veterans (1,665 pregnancies)	278	nr
	Vietnam-era veterans who did not serve in Vietnam (1,912 pregnancies)	317	nr
US National Vietnam Veterans			**All COIs**
Schwartz, 1998	Female Vietnam veterans (maternal exposure)		
	Women who served in Vietnam	113	nr
	Women who did not serve in the war zone	124	nr
	Civilian women	86	nr
American Legion Cohort			**All COIs**
Stellman et al., 1988	American Legionnaires with service 1961–1975		
	Vietnam veterans vs Vietnam-era veterans		
	All Vietnam veterans	231	1.4 (1.1–1.6)
	Low exposure	72	1.3 (1.0–1.7)
	Medium exposure	53	1.5 (1.1–2.1)
	High exposure	58	1.7 (1.2–2.4)
	Vietnam-era veterans vs herbicide handlers	9	1.6 (0.7–3.3)
	Vietnam veterans		
	Low exposure	72	1.0
	Medium exposure	53	1.2 (0.8–1.7)
	High exposure	58	1.4 (0.9–1.9)
State Studies of US Vietnam Veterans (wives)			**All COIs**
Aschengrau and Monson, 1989	Wives of Vietnam veterans presenting at Boston Hospital for Women		
	27 weeks of gestation	10	0.9 (0.4–1.9)
	13 weeks of gestation	nr	1.2 (0.6–2.8)
Tasmanian Veterans with Service in Vietnam			**All COIs**
Field and Kerr, 1988	Follow-up of Australian Vietnam veterans	199	1.6 (1.3–2.0)

TABLE 8-5 Spontaneous Abortion, continued

Reference	Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
OCCUPATIONAL			
NIOSH Cohort (12 US plants, production 1942–1984) (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Schnorr et al., 2001	Wives and partners of men in NIOSH cohort		
	Estimated paternal TCDD serum at time of conception		
	< 20 ppt	29	0.8 (0.5–1.2)
	20 to < 255 ppt	11	0.8 (0.4–1.6)
	255 to < 1120	11	0.7 (0.3–1.6)
	≥ 1120 ppt	8	1.0 (0.4–2.2)
Dow Chemical Company—Midland, MI (included in IARC and NIOSH cohorts)			**Dioxin, phenoxy herbicides**
Townsend et al., 1982	Wives of men employed involved in chlorophenol processing at Dow Chemical Co.	85	1.0 (0.8–1.4)
Other Production Workers			**Dioxin, phenoxy herbicides**
Moses et al., 1984	Follow-up of 2,4,5-T production workers	14	0.9 (0.4–1.8)
Suskind and Hertzberg, 1984	Follow-up of 2,4,5-T production workers	69	0.9 (0.6–1.2)
Agricultural Exposures			**Herbicides**
Carmelli et al., 1981	Wives of men occupationally exposed to 2,4-D		
	All reported work exposure to herbicides (high and medium)	63	0.8 (0.6–1.1)[c]
	Farm exposure	32	0.7 (0.4–1.5)[c]
	Forest and commercial exposure	31	0.9 (0.6–1.4)[c]
	Exposure during conception period		
	Farm exposure	15	1.0 (0.5–1.8)[c]
	Forest and commercial exposure	16	1.6 (0.9–1.8)[c]
	Fathers 18–25 yrs of age		
	Farm exposure	1	0.7 (nr)
	Forest and commercial exposure	3	4.3 (nr)
	Fathers 26–30 yrs of age		
	Farm exposure	4	0.4 (nr)
	Forest and commercial exposure	8	1.6 (nr)
	Fathers 31–35 yrs of age		
	Farm exposure	10	2.9 (nr)
	Forest and commercial exposure	5	1.0 (nr)
Other Studies of Herbicide and Pesticide Applicators			**Herbicides**
Smith et al., 1982	Follow-up of 2,4,5-T sprayers vs nonsprayers	43	0.9 (0.6–1.3)[c]
US Forest Service			**Herbicides**
Driscoll et al., 1998	Women employed by US Forest Service—miscarriages (maternal exposure)	141	2.0 (1.1–3.5)

continued

TABLE 8-5 Spontaneous Abortion, continued

Reference	Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
ENVIRONMENTAL			
Seveso Women's Health Study			**TCDD**
Eskenazi et al., 2003	SWHS participants living in exposure Zones A, B in 1976 (maternal exposure)		
	Pregnancies 1976–1998	97	0.8 (0.6–1.2)
	Pregnancies 1976–1984	44	1.0 (0.6–1.6)
Other Environmental Studies			
Tsukimori et al., 2008	Spontaneous abortions among pregnancies (excluding induced abortions) of women in 1968 Yusho incident (maternal exposure)		**PCBs, PCDFs**
	10 yrs after vs 10 yrs before	nr	2.1 (0.8–5.2)
	10-fold increase in maternal blood concentration (drawn 2001–2005) of:		
	PeCDF	nr	1.6 (1.1–2.3)
	PCB 126 (TEF = 0.1)	nr	2.5 (0.9–6.9)
	PCB 169 (TEF = 0.01)	nr	2.3 (1.1–4.8)
Chao et al., 2007	Pregnant Taiwanese women, placental TEQ of dioxins, PCBs (maternal exposure)		**Dioxin, PCBs/** nr, but reported ns
Arbuckle et al., 2001	Ontario farm families (maternal and paternal exposure)		**Phenoxy herbicides**
	Phenoxyacetic acid herbicide exposure in preconception period, spontaneous-abortion risk	48	1.5 (1.1–2.1)
Revich et al., 2001	Residents of Samara Region, Russia (maternal and paternal exposure)		**TCDD**
	Chapaevsk	nr	24.4% (20.0–29.5%)[d]
	Samara	nr	15.2% (14.3–16.1%)[d]
	Toliatti	nr	10.6% (9.8–11.5%)[d]
	Syzran	nr	15.6% (13.4–18.1%)[d]
	Novokuibyshevsk	nr	16.9% (14.0–20.3%)[d]
	Other small towns	nr	11.3% (9.4–13.8%)[d]
Tuyet and Johansson, 2001	Vietnamese women who were or whose husbands were exposed to herbicides sprayed during Vietnam War	nr	**COIs/**nr, anecdotal reports of miscarriage in pilot study

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; MI, Michigan; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; ns, not significant (usually refers to $p < 0.05$); PCB, polychlorinated biphenyl; PCDF, polychlorinated dibenzofuran; PeCDF, 2,3,4,7,8-pentachlorodibenzofuran; SEA, Southeast Asia; SWHS, Seveso Women's Health Study; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEF, toxic equivalency factor; TEQ, (total) toxic equivalent; VA, US Department of Veterans Affairs.

[a]Unless otherwise indicated, results are for paternal exposure.

[b]Given when available; results other than estimated risk explained individually.

[c]90% CI.

[d]Spontaneous abortion rate per 100 full-term pregnancies for 1991–1997.

no evidence of a relationship between paternal or maternal exposure to TCDD and spontaneous abortion. Exposure to 2,4-D or 2,4,5-T causes fetal toxicity and death after maternal exposure in experimental animals. However, that effect occurs only at high doses and in the presence of maternal toxicity. No fetal toxicity or death has been reported to occur after paternal exposure to 2,4-D.

Synthesis

No new epidemiologic evidence concerning the chemicals of interest and spontaneous abortion have been published since *Update 2008*, and toxicologic studies do not provide clear evidence of biologic plausibility of an association between these chemicals and spontaneous abortion. Furthermore, given the ages of the Vietnam-veteran cohort, publication of additional information on this outcome in the target population of the VAO series is not likely.

Conclusions

On the basis of the evidence reviewed to date, the committee concludes that paternal exposure to TCDD is *not* associated with risk of spontaneous abortion and that insufficient information is available to determine whether there is an association between maternal exposure to TCDD or either maternal or paternal exposure to 2,4-D, 2,4,5-T, picloram, or cacodylic acid and the risk of spontaneous abortion.

STILLBIRTH, NEONATAL DEATH, AND INFANT DEATH

Stillbirth or *late fetal death* typically refers to the delivery at or after 20 weeks of gestation of a fetus that shows no signs of life, including fetuses that weigh more than 500 g regardless of gestational age (Kline et al., 1989). *Neonatal death* refers to the death of a liveborn infant within 28 days of birth, and *infant death* to a death that occurs before the first birthday.

Because the causes of stillbirth and early neonatal death overlap considerably, they are commonly analyzed together in a category referred to as perinatal mortality (Kallen, 1988). Stillbirths make up less than 1% of all births (CDC, 2000). The most common causes of perinatal mortality (Kallen, 1988) in low-birth-weight (500–2,500 g) liveborn and stillborn infants are placental and delivery complications—abruptio placenta, placenta previa, malpresentation, and umbilical-cord conditions. The most common causes of perinatal death of infants weighing more than 2,500 g at birth are complications of the cord, placenta, and membranes and congenital malformations (Kallen, 1988).

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient evidence to determine whether there is an association between exposure to 2,4-D, 2,4,5-T, TCDD, picloram, or cacodylic acid and stillbirth, neonatal death, or infant death. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008* did not change that conclusion. Reviews of the relevant studies are presented in the earlier reports.

Update of the Epidemiologic Literature

One study published since *Update 2008* examined pesticide use and infant death in Brazil (Teixeira de Siqueira et al., 2010). However, given that the study defined exposure at the ecologic level (as pesticide-use intensity in agricultural-crop areas) and did not examine specific pesticides separately, it did not meet the level of exposure specificity required for review by the committee. No additional studies of exposure to the chemicals of interest and perinatal death have been published since *Update 2008*.

Biologic Plausibility

Laboratory studies of maternal TCDD exposure during pregnancy have demonstrated the induction of fetal death; neonatal death, however, is only rarely observed and is usually the result of cleft palate, which leads to an inability to nurse. Studies addressing the potential for perinatal death as a result of paternal exposure to TCDD or herbicides are inadequate to support conclusions. One new study demonstrated that TCDD alters vascular remodeling of the placenta in rats leading to an increase in the incidence of fetal death under hypoxic conditions (Ishimura et al., 2009).

Synthesis

No new epidemiologic evidence concerning exposure to the chemicals of interest and stillbirth, neonatal death, and infant death have been published since *Update 2008,* and toxicologic studies do not provide clear evidence of biologic plausibility of an association.

Conclusions

On the basis of the evidence reviewed in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine

whether there is an association between exposure to the chemicals of interest and stillbirth, neonatal death, or infant death. Given the ages of the Vietnam-veteran cohort, publication of additional information on this outcome in the target population of the VAO series is highly unlikely.

BIRTH WEIGHT AND PRETERM DELIVERY

Birth weight and the length of the gestation period can have important effects on neonatal morbidity and mortality and on subsequent health over the lifespan. Defined by the World Health Organization as birth weights under 2,500 g (Alberman, 1984), low birth weight has two distinct causes. Intrauterine growth retardation (IUGR) occurs when fetal growth is diminished and a fetus or baby fails to attain a normal weight or is small for gestational age. The concept of IUGR represents birth weight, adjusted for gestational age, that is lower than average according to local or national fetal-growth graphs (Romo et al., 2009). Low birth weight can also be secondary to preterm delivery (PTD), which is delivery at less than 259 days, or 37 completed weeks, of gestation, calculated on the basis of the date of the first day of the last menstrual period (Bryce, 1991). Low birth weight of either causes occurs in about 7% of live births. When no distinction is made between the causes of low birth weight (IUGR or PTD), the factors most strongly associated with it are maternal tobacco use during pregnancy, multiple births, and race or ethnicity. Other potential risk factors are low socioeconomic status (SES), malnutrition, maternal weight, birth order, maternal complications during pregnancy (such as severe pre-eclampsia or intrauterine infection) and obstetric history, job stress, and cocaine or caffeine use during pregnancy (Alexander and Slay, 2002; Alexander et al., 2003; Ergaz et al., 2005; Kallen, 1988; Peltier, 2003). Established risk factors for PTD include race (black), marital status (single), low SES, previous low birth weight or PTD, multiple gestations, tobacco use, and cervical, uterine, or placental abnormalities (Berkowitz and Papiernik, 1993).

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and low birth weight or PTD. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008* did not change that conclusion. Reviews of the relevant studies are presented in the earlier reports.

Update of the Epidemiologic Literature

No occupational or Vietnam-veteran studies of exposure to the chemicals of interest and low birth weight or PTD have been published since *Update 2008*.

Environmental Studies

Two studies in Japan examined prenatal exposure to dioxin-like PCDDs, PCDFs, and PCBs, calculated as total TEQs, and birth weight. In a prospective cohort study of 514 women in Sapporo, Japan (Konishi et al., 2009), a significant reduction in birth weight was observed in connection with total TEQs (–220.5 g per 10-fold increase in TEQ; 95% CI –399.2 to –41.9). A significant reduction in birth weight was also observed in connection separately with dioxin-like PCDD TEQs and PCDF TEQs and marginally with PCB TEQs. When stratified on infant sex, the association remained statistically significant for male but not female infants. The second study, in a coastal area of Japan (where consumption of seafood is common), measured dioxin-like PCDD and PCDF congeners in maternal breast milk and markers of fetal growth (Tawara et al., 2009). The concentration of several individual dioxin-like PCDD and PCDF congeners was inversely related to newborn length as was total TEQs, but none was related to birth weight. In the Danish National Birth Cohort (Halldorsson et al., 2009), 100 women were enrolled in a nested study on the basis of their reported intake of fatty fish; about one-third of the women were in each of three fish-intake categories (high, medium, and low). Total TEQs were calculated from serum samples analyzed with the AhR-CALUX assay. No association with birth weight was observed.

One study published since *Update 2008* examined pesticide use and birth weight in Brazil (Teixeira de Siqueira et al., 2010). However, given that the study defined exposure at the ecologic level (as pesticide-use intensity in agricultural-crop areas) and did not examine specific pesticides separately, it did not meet the level of exposure specificity required for review by the committee.

Biologic Plausibility

The available experimental evidence on animals indicates that TCDD exposure during pregnancy can reduce body weight at birth but only at high doses. Laboratory studies of the potential male-mediated developmental toxicity of TCDD and herbicides as a result of exposure of adult male animals are inadequate to permit conclusions. TCDD and herbicides are known to cross the placenta, and this leads to direct exposure of the fetus. Data from studies of experimental animals also suggest that the preimplantation embryo and developing fetus are sensitive to the toxic effects of 2,4-D and TCDD after maternal exposure.

Synthesis

The three environmental studies reviewed here did not provide evidence of an association between exposure to the chemicals of interest and the risk of low birth weight or prematurity.

Conclusions

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and low birth weight or preterm delivery.

BIRTH DEFECTS

The March of Dimes defines a birth defect as an abnormality of structure, function, or metabolism, whether genetically determined or resulting from an environmental influence during embryonic or fetal life (Bloom, 1981). Other terms, often used interchangeably, are *congenital anomaly* and *congenital malformation*. Major birth defects, which occur in 2–3% of live births, are abnormalities that are present at birth and are severe enough to interfere with viability or physical well-being. Birth defects are detected in another 5% of babies through the first year of life. The causes of most birth defects are unknown. Genetic factors, exposure to some medications, exposure to environmental contaminants, occupational exposures, and lifestyle factors have been implicated in the etiology of birth defects (Kalter and Warkany, 1983). Most etiologic research has focused on the effects of maternal and fetal exposures, but some work has addressed paternal exposures. Paternally mediated exposures might occur by several routes and exert effects in various ways. One way is through direct genetic damage to the male germ cell transmitted to the offspring and dominantly expressed as a birth defect. A hypothesized route is the transfer of toxic chemicals through a man's body into his seminal fluid that results in intermittent fetal exposure throughout gestation (Chia and Shi, 2002). Another, even more indirect route of paternally mediated exposure could be contact of family members with contamination brought into the home from the workplace, but this would not be applicable to offspring of Vietnam veterans conceived after deployment.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient evidence to determine whether there is an association between exposure to 2,4-D, 2,4,5-T or its contaminant TCDD, picloram, or cacodylic acid and birth defects in offspring. Additional information available to the committee re-

sponsible for *Update 1996* led it to conclude that there was limited or suggestive evidence of an association between at least one of the chemicals of interest and spina bifida in the children of veterans; there was no change in the conclusions regarding other birth defects. The committee for *Update 2002*, which reviewed the study of female Vietnam veterans (Kang et al., 2000) that reported significant increases in birth defects in their offspring, did not find those results adequate to modify prior conclusions. Later VAO committees have not encountered additional data to merit changing the conclusion that the evidence is inadequate to support an association between exposure to the chemicals of interest and birth defects (aside from spina bifida) in the offspring of either male or female veterans.

Summaries of the results of studies of birth defects and specifically neural-tube defects that were reviewed in the current report and in earlier VAO reports are in Tables 8-6 and 8-7, respectively.

Update of the Epidemiologic Literature

No Vietnam-veteran or occupational studies of exposure to the chemicals of interest and birth defects have been published since *Update 2008*.

Environmental Studies

In a retrospective case–control study of births in Washington state, Waller et al. (2010) assessed agricultural exposure and season of conception possible association with gastroschisis, a defect in the abdominal wall usually near the umbilicus. The Washington State Department of Agriculture database was used to classify exposure to surface-water concentrations of atrazine, nitrates, nitrites, and 2,4-D by season. Residential proximity to areas of increased exposure to those chemicals was estimated by using the latitude and longitude of ZIP code for each maternal residence. Although an increased OR was observed for high atrazine exposure, this is not a chemical of interest to the committee; no associations with the remaining chemicals examined were observed.

Cordier et al. (2010) evaluated residence near municipal-waste incinerators and urinary tract birth defects. Infants born with renal defects in 2001–2003 were eligible for a population-based case–control study in southeastern France. Controls were randomly selected from the same region. The mothers of 187 of the located 304 case infants agreed to participate and completed interviews. With stratification on the infant's sex, year of birth, and family address at birth, 226 mothers of qualifying controls were identified, agreed to enroll, and completed telephone interviews. For each of the 21 incinerators in the region, emissions of dioxins were measured for the period of study; on the basis of residential proximity to the incinerators, exposure to emissions for the period from 1 month before conception to the end of the first trimester was modeled for all infants. Women were classified as exposed or not exposed, and the exposed were dichotomized

TABLE 8-6 Selected Epidemiologic Studies—Birth Defects in Offspring of Subjects[a]

Reference	Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans			**All COIs**
Michalek et al., 1998a	Air Force Ranch Hand veterans		
	Before service in SEA	nr	0.7 (nr)
	After service in SEA	nr	1.5 (nr)
Wolfe et al., 1995	High-exposure Ranch Hands relative to comparisons		
	All anomalies	57	1.0 (0.8–1.3)
	Nervous system	3	nr
	Eye	3	1.6 (0.4–6.0)
	Ear, face, neck	5	1.7 (0.6–4.7)
	Circulatory system, heart	4	0.9 (0.3–2.7)
	Respiratory system	2	nr
	Digestive system	5	0.8 (0.3–2.0)
	Genital system	6	1.2 (0.5–3.0)
	Urinary system	7	2.1 (0.8–5.4)
	Musculoskeletal	31	0.9 (0.6–1.2)
	Skin	3	0.5 (0.2–1.7)
	Chromosomal anomalies	1	nr
AFHS, 1992	Air Force Operation Ranch Hand veterans—birth defects in conceptions after service in SEA		
	Congenital anomalies	229	1.3 (1.1–1.6)
	Nervous system	5	1.9 (0.5–7.2)
	Respiratory system	5	2.6 (0.6–10.7)
	Circulatory system, heart	19	1.4 (0.7–2.6)
	Urinary system	21	2.5 (1.3–5.0)
	Chromosomal	6	1.8 (0.6–6.1)
	Other	5	2.6 (0.6–10.7)
US CDC Vietnam Experience Study			**All COIs**
CDC, 1989a	Vietnam Experience Study—interview data		
	Total anomalies	826	1.3 (1.2–1.4)
	Nervous system defects	33	2.3 (1.2–4.5)
	Ear, face, neck defects	37	1.6 (0.9–2.8)
	Integument	41	2.2 (1.2–4.0)
	Musculoskeletal defects	426	1.2 (1.1–1.5)
	Hydrocephalus	11	5.1 (1.1–23.1)
	Spina bifida	9	1.7 (0.6–5.0)
	Hypospadias	10	3.1 (0.9–11.3)
	Multiple defects	71	1.6 (1.1–2.5)
	Children of veterans reporting high exposure	46	1.7 (1.2–2.4)

continued

TABLE 8-6 Birth Defects in Offspring of Subjects, continued[a]

Reference	Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
US VA Cohort of Female Vietnam Veterans			**All COIs**
Kang et al., 2000	Female Vietnam-era veterans—deployed vs nondeployed (maternal exposure)		
	"Likely" birth defects	nr	1.7 (1.2–2.2)
	"Moderate-to-severe" birth defects	nr	1.5 (1.1–2.0)
CDC—General Birth Defects Study			**All COIs**
CDC, 1989b	GBDS—hospital records		
	Birth defects	130	1.0 (0.8–1.3)
	Major birth defects	51	1.2 (0.8–1.9)
	Digestive system defects	18	2.0 (0.9–4.6)
	Birth defects—black Vietnam veterans only	21	3.4 (1.5–7.6)
CDC—Metropolitan Atlanta Congenital Defects Program			**All COIs**
Erikson et al., 1984a	Vietnam veterans identified through CDC Metropolitan Atlanta Congenital Defects Program		
	Any major birth defects	428	1.0 (0.8–1.1)
	Multiple birth defects with reported exposure	25	1.1 (0.7–1.7)
	EOI-5: spina bifida	1	2.7 (1.2–6.2)
	EOI-5: cleft lip with or without cleft palate	5	2.2 (1.0–4.9)
State Studies of US Vietnam Veterans			**All COIs**
Aschengrau and Monson, 1990	Vietnam veterans whose children were born at Boston Hospital for Women		
	All congenital anomalies (crude OR)		
	vs men without known military service	55	1.3 (0.9–1.9)
	vs non-Vietnam veterans	55	1.2 (0.8–1.9)
	One or more major malformations (crude OR)		
	vs men without known military service	18	1.8 (1.0–3.1)
	vs non-Vietnam veterans	18	1.3 (0.7–2.4)
Australian Vietnam Veterans vs Australian Population			**All COIs**
AIHW, 1999	Australian Vietnam veterans—validation study		*Cases expected (95% CI)*
	Down syndrome	67	92 expected (73–111)
	Tracheo-esophageal fistula	10	23 expected (14–32)
	Anencephaly	13	16 expected (8–24)
	Cleft lip or palate	94	64 expected (48–80)
	Absent external body part	22	34 expected (23–45)
	Extra body part	74	74 expected (nr)
Donovan et al., 1984	Australian Vietnam veterans		
	Vietnam veterans vs all other men	127	1.0 (0.8–1.3)
	National Service veterans—Vietnam service vs no Vietnam service	69	1.3 (0.9–2.0)

TABLE 8-6 Birth Defects in Offspring of Subjects, continued[a]

Reference	Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
OCCUPATIONAL			
NIOSH Cohort (12 US plants, production 1942–1984) (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Lawson et al., 2004	Wives of workers with measured serum TCDD in NIOSH cohort	14	nr
Dow Chemical Company—Midland, MI (included in IARC and NIOSH cohorts)			**Dioxin, phenoxy herbicides**
Townsend et al., 1982	Follow-up of Dow Chemical plant workers	30	0.9 (0.5–1.4)
			Dioxin, phenoxy herbicides
Production Workers			
Moses et al., 1984	Follow-up of 2,4,5-T male production workers	11	1.3 (0.5–3.4)
Suskind and Hertzberg, 1984	Follow-up of 2,4,5-T male production workers	18	1.1 (0.5–2.2)
Herbicide and Pesticide Applicators			**Herbicides**
Smith et al., 1982	Follow-up of 2,4,5-T sprayers—sprayers vs non-sprayers	13	*90% CI* 1.2 (0.6–2.5)
Agricultural Workers			**Herbicides**
Weselak et al., 2008	Pregnancies with one or more birth defects in OFFHS	108	
	Use on farm, during 3 months before conception, of:		
	Herbicides	24	0.7 (0.4–1.1)
	Male offspring	19	0.9 (0.5–1.6)
	Direct paternal use	19	0.5 (0.3–1.0)
	Phenoxy herbicides	12	0.6 (0.3–1.1)
	Male offspring	9	0.8 (0.4–1.7)
	Direct paternal use	8	0.4 (0.2–0.9)
	2,4-D	10	1.1 (0.6–2.1)
	Male offspring	7	1.3 (0.6–2.8)
	Direct paternal use	6	0.6 (0.3–1.5)
	Dicamba	8	1.7 (0.8–3.5)
	Male offspring	7	2.4 (1.1–5.5)
	Use on farm, during 3 months after conception, of:		
	Herbicides	7	0.5 (0.2–1.2)
	Phenoxy herbicides	9	0.8 (0.4–1.5)
	2,4-D	7	1.0 (0.4–2.3)
Kristensen et al., 1997	Norwegian farmers (maternal, paternal exposure)	4,189	1.0 (1.0–1.1)

continued

TABLE 8-6 Birth Defects in Offspring of Subjects, continued[a]

Reference	Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Garry et al., 1996	Private pesticide appliers		
	All births with anomalies	125	1.4 (1.2–1.7)
	Circulatory, respiratory	17	1.7 (1.0–2.8)
	Gastrointestinal	6	1.7 (0.8–3.8)
	Urogenital	20	1.7 (1.1–2.6)
	Musculoskeletal, integumental	30	
	Maternal age under 30 yrs	11	0.9 (0.5–1.7)
	Maternal age over 30 yrs	19	2.5 (1.6–4.0)
	Chromosomal	8	1.1 (0.5–2.1)
	Other	48	
	Maternal age under 35 yrs	36	1.1 (0.8–1.6)
	Maternal age over 35 yrs	12	3.0 (1.6–5.3)
Forestry Workers			**Herbicides**
Dimich-Ward et al., 1996	Sawmill workers with exposure in upper three quartiles for any job held up to 3 months before conception		
	Cataracts	11	5.7 (1.4–22.6)
	Genital organs	105	1.3 (0.9–1.5)
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Mastroiacovo et al., 1988	Seveso residents (maternal, paternal, in utero exposure)		*90% CI*
	Zones A, B, R—total defects	137	1.0 (0.8–1.1)
	Zones A and B—total defects	27	1.2 (0.9–1.6)
	Zones A and B—mild defects	14	1.4 (0.9–2.2)
US Environmental Studies			
Meyer et al., 2006	Case–control study in eastern Arkansas of hypospadias as function of mother's residence within 500 m of agricultural pesticide use during gestation weeks 6–16		**Dicamba**
	Dicamba (lb)		
	0	nr	1.0
	> 0– < 0.04	nr	0.5 (0.3–1.0)
	≥ 0.04	nr	0.9 (0.4–2.1)
Schreinemachers, 2003	Rural or farm residents of Minnesota, Montana, North Dakota, South Dakota (maternal, paternal exposure)		**Herbicides**
	Any birth anomaly	213	1.1 (0.9–1.3)
	Central nervous system anomalies	12	0.8 (0.5–1.4)
	Circulatory, respiratory anomalies	39	1.7 (1.1–2.6)
	Digestive system anomalies	24	0.9 (0.6–1.5)
	Urogenital anomalies	44	1.0 (0.7–1.5)
	Musculoskeletal, integumental anomalies	70	1.5 (1.1–2.1)
	Chromosomal anomalies	17	0.9 (0.6–1.6)

TABLE 8-6 Birth Defects in Offspring of Subjects, continued[a]

Reference	Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Loffredo et al., 2001	Mothers in the BWIS exposed to herbicides during first trimester (maternal exposure)	8	**Herbicides** 2.8 (1.2–6.9)
Fitzgerald et al., 1989	Persons exposed to an electric-transformer fire—total birth defects (maternal, paternal exposure)	1	**Chlorophenols** 2.1 (0.1–11.9)
Stockbauer et al., 1988	Persons in Missouri with documented TCDD soil contamination near residence (maternal, paternal, in utero exposure)		**TCDD**
	Total birth defects	17	0.8 (0.4–1.5)
	Major defects	15	0.8 (0.4–1.7)
	Midline defects	4	0.7 (0.2–2.3)
French Studies of Birth Defects Registry in Rhône-Alpes Region			**Dioxin**
Cordier et al., 2010	Case–control study (2001–2003 births) of urinary tract defects (n = 304) vs regional controls (n = 226)		
	Maternal exposure to:		
	Atmospheric dioxin	63	2.0 (1.2–3.4)
	Above median	33	2.8 (1.3–6.1)
	Below median	30	1.4 (0.7–2.9)
	Dioxin deposits	75	1.8 (1.1–3.0)
	Above median	41	3.0 (1.5–5.9)
	Below median	34	1.2 (0.6–2.2).
Cordier et al., 2004	Births (1988–1997): maternal residence in municipality with solid-waste incinerator vs not		
	Minor anomalies	518	0.9 (0.8–1.1)
	Chromosomal anomalies	204	1.0 (0.9–1.2)
	Monogenic anomalies	83	1.1 (0.8-1.4)
	Unknown or multifactoral etiology	964	1.1 (1.0–1.2)
	Specific major anomalies with significant increases reported (of 23 categories reported)		
	Facial clefts	152	1.3 (1.1–1.6)
	Renal dysplasia	60	1.6 (1.1–2.2)
Other International Environmental Studies			
Kuscu et al., 2009	Cross-sectional study of MIH in Turkey; n = 109 from industrialized community with high levels of PCDDs and n = 44 from low industrialized community		**PCDDs** Prevalence of MIH 4/44 and 10/109, no difference

continued

TABLE 8-6 Birth Defects in Offspring of Subjects, continued[a]

Reference	Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Laisi et al., 2008	Follow-up of participants from previous case–control study of cleft lip and palate, n = 167 placenta tissue analyzed for PCDD/Fs and children assessed for MIH		**PCDDs, PCDFs** 24/167 with MIH TEQ of PCDDs not association with MIH; duration of breast feeding not association with MIH
Tango et al., 2004	Investigated multiple pregnancy outcomes in Japan-infant deaths from congenital defects	42	**Dioxin** nr, but ns
Revich et al., 2001	Residents of Chapaevsk, Russia—congenital malformations	nr	**Dioxin** nr, but ns
ten Tusscher et al., 2000	Infants born in Zeeburg, Amsterdam, clinics 1963–1965 with orofacial cleft (maternal exposure)		**Dioxin**
	Births in 1963	5	nr, but said to be significant
	Births in 1964	7	nr, but said to be significant
			Herbicides
García et al., 1998	Residents of agricultural areas in Spain—at least median score on chlorophenoxy-herbicide exposure duration (months) index	14	3.1 (0.6–16.9)
Hanify et al., 1981	Residents of areas of northland New Zealand subject to aerial 2,4,5-T spraying		**2,4,5-T** *90% CI*
	All birth malformations excluding dislocated or dislocatable hip	164	1.7 (1.4–2.1)
	All heart malformations	20	3.9 (2.1–7.4)
	Hypospadias, epispadias	18	5.6 (2.7–11.7)
	Talipes	52	1.7 (1.2–2.3)
	Cleft lip	6	0.6 (0.3–1.3)
	Isolated cleft palate	7	1.4 (0.6–3.2)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; BWIS, Baltimore–Washington Infant Study; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, exposure opportunity index; GBDS, General Birth Defects Study; IARC, International Agency for Research on Cancer; MI, Michigan; MIH, molar incisor hypomineralization; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; ns, not significant; OFFHS, Ontario Farm Family Health Study; OR, odds ratio; PCDD, polychlorinated dibenzodioxins; PCDF, polychlorinated dibenzofurans; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEQ, (total) toxic equivalent; VA, US Department of Veterans Affairs.

[a]Unless otherwise indicated, studies show paternal exposure.

[b]Given when available; results other than estimated risk explained individually.

TABLE 8-7 Selected Epidemiologic Studies—Neural-Tube Defects in Offspring of Subjects[a]

Reference	Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US Air Firce Health Study—Ranch Hand veterans vs SEA veterans			**All COIs**
Wolfe et al., 1995	Air Force Operation Ranch Hand personnel—neural-tube defects	4[c]	nr
US CDC Vietnam Experience Study			**All COIs**
CDC, 1989a	VES cohort		
	Spina bifida		
	Vietnam veterans' children	9	1.7 (0.6–5.0)
	Non-Vietnam veterans' children	5	1.0
	Anencephaly		
	Vietnam Veterans' children	3	nr
	Non-Vietnam veterans' children	0	1.0
US CDC Birth Defects Study			**All COIs**
Erickson et al., 1984a,b	CDC birth defects case–control study		
	Service in Vietnam		
	Spina bifida	19	1.1 (0.6–1.7)
	Anencephaly	12	0.9 (0.5–1.7)
	Military records indicate opportunity for exposure		
	Spina bifida	20	2.7 (1.2–6.2)
	Anencephaly	7	0.7 (0.2–2.8)
Australian Vietnam Veterans vs Australian Population			**All COIs**
AIHW, 1999	Australian Vietnam veterans—validation study		*Cases expected (95% CI)*
	Spina bifida—maximums	50	33 expected (22–44)
	Anencephaly	13	16 expected (8–24)
ADVA, 1983	Australian Vietnam veterans—neural-tube defects	16	0.9 (nr)
OCCUPATIONAL			
Agricultural Workers			
Blatter et al., 1997	Dutch farmers		
	Spina bifida—moderate, heavy exposure		
	Pesticide use	8	1.7 (0.7–4.0)
	Herbicide use	7	1.6 (0.6–4.0)[d]
Kristensen et al., 1997	Norwegian farmers—spina bifida (maternal, paternal exposure)		
	Tractor spraying equipment	28	1.6 (0.9–2.7)
	Tractor spraying equipment, orchards, greenhouses[e]	5	2.8 (1.1–7.1)
Pesticide Applicators			**Pesticides**
Garry et al., 1996	Private pesticide appliers—central nervous system defects	6	1.1 (0.5–2.4)

continued

TABLE 8-7 Neural-Tube Defects in Offspring of Subjects, continued

Reference	Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Forestry Workers			**Herbicides**
Dimich-Ward et al., 1996	Sawmill workers with exposure in upper three quartiles for any job held up to 3 months before conception		
	Spina bifida, anencephaly	22	2.4 (1.1–5.3)
	Spina bifida only	18	1.8 (0.8–4.1)
ENVIRONMENTAL			
US Environmental Studies			**TCDD**
Stockbauer et al., 1988	Persons in Missouri with documented TCDD soil contamination—central nervous system defects (maternal, paternal, in utero exposure)	3	3.0 (0.3–35.9)
International Environmental Studies			
Cordier et al., 2004	Population-based birth defects registry in Rhône-Alpes region of France (1988–1997): Residence in municipality with solid-waste incinerator (maternal, paternal exposure) vs not near—neural tube defects	49	**Dioxin** 0.9 (0.6–1.2)
Hanify et al., 1981	Spraying of 2,4,5-T in New Zealand (all exposures)		**2,4,5-T***/90% CI*
	Anencephaly	10	1.4 (0.7–2.9)
	Spina bifida	13	1.1 (0.6–2.1)

ABBREVIATIONS: 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; nr, not reported; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; VES, Vietnam Experience Study.

[a]Unless otherwise indicated, studies show paternal exposure.

[b]Given when available; results other than estimated risk explained individually.

[c]Of four neural-tube defects reported in Ranch Hand offspring, two were spina bifida (high dioxin exposure), one spina bifida (low dioxin), one anencephaly (low dioxin); no neural-tube defects reported in comparison cohort; 454 postservice births studied in Ranch Hand veterans; 570 in comparison cohort.

[d]Calculated from data presented in the paper.

[e]Greenhouse workers would not have been exposed to chemicals of interest.

at the median exposure: 3.8×10^{-3} pg/m^3 for atmospheric dioxins and 1.7×10^{-5} pg/m^2-s for soil deposits of dioxins. The presence of additional industries (such as the cement industry) with potential dioxin emissions was also considered in the analyses. If there was at least one additional industry in the municipality of the study participant, the participant was considered potentially exposed to other sources of dioxin. Pollutant concentrations more than 10 km away were considered negligible, and such residences were considered not exposed. The procedures for recruitment were not identical, but the response rates did differ by case status, with 62% of eligible cases and more than 85% of eligible controls

participating. Residential addresses were available for the nonparticipating cases but not for the noninterviewed controls; the primary results reported contrasted all 304 located cases, whether or not the mother had been interviewed, with the interviewed control subjects. A higher incidence of urinary tract birth defects was observed in infants of mothers who were exposed to atmospheric dioxin above median concentrations than in infants of women who had no exposure (OR = 2.84, 95% CI 1.32–6.09). A smaller risk was observed for infants of women classified as exposed below the median but not unexposed (OR = 1.44, 95% CI 0.72–2.87). Atmospheric dioxin levels and dioxin soil deposits were highly correlated across the study area ($p < 0.0001$), so the largely parallel results for exposure to dioxin soil deposits (for which some results excluding the noninterviewed case mothers were reported) cannot be considered independent. Proximity to dioxin deposits above the median was also associated with the outcome (OR = 2.95, 95% CI 1.47–5.92; OR = 2.25, 95% CI 1.04–4.87, without noninterviewed cases; OR 2.05, 95% CI 0.92–4.57, with adjustment for geographical origin of parents, family history of urinary tract birth defects, parity, and maternal alcohol consumption), but exposure to deposits below the median was only marginally associated with urinary tract defects (OR = 1.18, 95% CI 0.63–2.19). A similar diminution in significance was said to occur in the analyses of exposure to atmospheric dioxins when only the interviewed case mothers were included and when confounders were considered. Other sources of dioxin emissions were not associated with urinary tract defects. A higher proportion of the noninterviewed case mothers were exposed to atmospheric and dioxin deposits than of those who were interviewed, and they were more likely to live in low-SES areas. It is possible, but not known, that the nonparticipating cases differed in the distribution of additional key confounding variables. If the proportion of exposed controls remained the same, then excluding the noninterviewed cases would have resulted in an underestimate of effect. However, the disparity in participation rates between cases and controls suggests the potential for selection bias, which may explain some of the observed excess risk.

Two studies examined dioxin exposure and molar-incisor hypomineralization (MIH) in children, the enamel hypomineralization of the molars. Kuscu et al. (2009) assessed the prevalence of MIH in children living in two regions in Turkey, one with dense industrialization and the other an agricultural area known for its use of organic techniques and its use of wind farms for energy. Soil PCDD and PCDF concentrations were higher in the urbanized region, but there was no difference in MIH prevalence between the two regions. Laisi et al. (2008) conducted a case–control study of children born in 1995–1999 in Finland. Placenta samples were collected and analyzed for PCDDs, PCDFs, and PCBs. Total exposure to PCDDs and PCDFs and total PCBs was not associated with MIH.

Five other studies of birth defects did not meet the level of exposure specificity required for review by the committee. One study examined pesticide use at the state level and all congenital abnormalities combined (Teixeira de Siqueira

et al., 2010). A second examined maternal exposure to pesticides and neural-tube defects in Mexican Americans (Brender et al., 2010). A third examined parental occupational exposure in agriculture (not the application of pesticides of interest) and oral clefts (Gonzalez et al., 2008), and a fourth evaluated birth defects in pregnancies conceived during months of high surface-water agrichemical concentration (Winchester et al., 2009). Exposure assessments in those studies did not specify individual herbicides and therefore did not present results on the chemicals of interest to the committee. In the fifth study, Giordano et al. (2010) examined hypospadias and maternal exposure to endocrine-disrupting chemicals as defined by parental job title and maternal diet, but the chemicals of interest to this committee were not assessed individually.

Biologic Plausibility

Studies indicate that 2,4-D does not produce fetal abnormalities. Other herbicides of interest can induce fetal malformations but typically only at high doses that are toxic to pregnant women. It is well established that TCDD is a potent teratogen in all laboratory species that have been studied although the pattern of birth defects that are produced is often species-specific. Since *Update 2008*, studies have investigated the mechanism underlying various TCDD-induced birth defects in mice, including hydronephrosis, cleft palate, altered jaw structure, and delayed lung development (Dong et al., 2010; Gan et al., 2009; Imura et al., 2010; Jang et al., 2008; Keller et al., 2008; Kransler et al., 2009). Those mechanisms have not been fully elucidated, but it has been demonstrated that TCDD-induced birth defects require the AHR but do not require induction of cytochrome P4501A1 (Dragin et al., 2006; Jang et al., 2007; Mimura et al., 1997). When pregnant AHR-null mice are exposed to TCDD, the fetuses do not exhibit any of the typical developmental malformations associated with TCDD exposure, but fetuses of TCDD-exposed pregnant CYP1A1 null mice do. In addition, an AHR antagonist can significantly attenuate TCDD-induced birth defects in mice. Thus, activation of the AHR by TCDD during development appears to be a key first step in mediating TCDD's developmental toxicity. Although structural differences in the AHR have been identified among species, it functions similarly in animals and humans. Therefore, a common mechanism mediated by the AHR in which tissue growth and differentiation processes are affected probably underlies the developmental toxicity of TCDD in humans and animals. It has been shown that antioxidant treatment provides protection against some TCDD-induced teratogenicity; this suggests that reactive oxygen species might be involved in the pathways that lead to these structural changes (Jang et al., 2008). Few laboratory studies of potential male-mediated developmental toxicity (and birth defects specifically) attributable to exposure to TCDD and herbicides have been conducted. Feeding of simulated Agent Orange mixtures to male mice produced no adverse effects in offspring; a statistically significant excess of fused

sternebrae in the offspring of the two most highly exposed groups was attributed to an anomalously low rate of this defect in the controls (Lamb et al., 1981).

Synthesis

Embryonic and fetal development is a sensitive toxic outcome of exposure to TCDD and dioxin-like chemicals in rodents. It is clear that the fetal rodent is more sensitive to adverse effects of TCDD than the adult rodent; human data are generally lacking, however, and the sensitivity of this outcome in humans is less apparent.

Overall, one study (Cordier et al., 2010) observed an association between dioxin exposure and urinary tract defects, but the influence of selection bias on the observed results could not be fully assessed. Therefore, the results of the study are insufficient to determine whether there is an association between maternal exposure to dioxin and urinary tract defects.

Conclusions

There were no new relevant studies of the association between parental exposure to 2,4-D, 2,4,5-T, TCDD, cacodylic acid, or picloram and spina bifida in offspring. The committee concludes that the evidence of an association between exposure to the chemicals of interest and spina bifida is still limited or suggestive. The evidence of an association between exposure to the chemicals of interest and other birth defects is inadequate or insufficient.

CHILDHOOD CANCER

The American Cancer Society estimated that 10,700 children under 15 years old would receive a diagnosis of cancer in the United States in 2010 (ACS, 2010). Treatment and supportive care of children with cancer have improved greatly, and mortality has declined by 55% over the past 35 years. Despite those advances, cancer remains the leading cause of death from disease in children under 15 years old, and 1,340 deaths were projected for 2010 (ACS, 2010).

Leukemia is the most common cancer in children. It accounts for about one-third of all childhood cancer cases; leukemia was expected to be diagnosed in nearly 3,317 children in 2010 (ACS, 2010). Of those, nearly 2,000 will have acute lymphocytic leukemia (ALL); most of the rest will have acute myeloid leukemia (AML). AML (ICD-9 205) is also referred to as acute myelogenous leukemia or acute nonlymphocytic leukemia. For consistency, this report uses *acute myeloid leukemia*, or AML, regardless of usage in the source materials. ALL is most common in early childhood, peaking at the ages of 2–3 years, and AML is most common during the first 2 years of life. ALL incidence is consistently higher in boys than in girls; AML incidence is similar in boys and girls (NCI, 2001). Through

early adulthood, ALL rates are about twice as high in whites as in blacks; AML exhibits no consistent pattern in this respect. Chapter 7 contains additional information on leukemia as part of the discussion of adult cancer.

The second-most common group of cancers in children are those of the central nervous system—the brain and the spinal cord. Other cancers in children include lymphomas, bone cancers, soft-tissue sarcomas, renal cancers, eye cancers, and adrenal gland cancers. In contrast with adult cancers, relatively little is known about the etiology of most childhood cancers, especially about potential environmental risk factors and the effects of parental exposures.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient evidence to determine whether there is an association between exposure to 2,4-D, 2,4,5-T, TCDD, picloram, or cacodylic acid and childhood cancers. Additional information available to the committees responsible for *Update 1996* and *Update 1998* did not change that conclusion. The committee responsible for *Update 2000* reviewed the material in earlier VAO reports and newly available published literature and concluded that there was limited or suggestive evidence of an association between exposure to at least one of the chemicals of interest and AML. After the release of *Update 2000*, investigators involved in one study discovered an error in their published data. The *Update 2000* committee reconvened to evaluate the previously reviewed and new literature regarding AML, and it produced *Acute Myelogenous Leukemia* (IOM, 2002). It reclassified AML from "limited/suggestive evidence of an association" to "inadequate evidence to determine whether an association exists." Table 8-8 summarizes the results of the relevant studies. The committees responsible for *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008* reviewed the material in earlier VAO reports and in newly available published literature and agreed that there remained inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and childhood cancers.

Update of Epidemiologic Literature

No occupational or Vietnam-veteran studies of exposure to the chemicals of interest and childhood cancer have been published since *Update 2008*.

Environmental Studies

Two studies were published on the basis of information gathered in the Northern California Childhood Leukemia Study, a case–control study of acute lymphoblastic leukemia in 35 counties. Rull et al. (2009) examined 213 cases and 268 controls (matched on birth date, sex, race, and Hispanic ethnicity) for

TABLE 8-8 Selected Epidemiologic Studies—Childhood Cancers[a]

Reference	Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
VIETNAM VETERANS			
US CDC Vietnam Experience Study			**All COIs**
CDC, 1989a	VES—outcomes in offspring of veterans		
	Cancer	25	1.5 (0.7–2.8)
	Leukemia	12	1.6 (0.6–4.0)
US CDC Birth Defects Study			**All COIs**
Erikson et al., 1984b	Children of Vietnam veterans		
	"Other" neoplasms	87	1.8 (1.0–3.3)
Australian Vietnam Veterans			**All COIs**
AIHW, 2001	Australian Vietnam veterans' children—revised validation study—AML	12[c]	1.3 (0.8–4.0)
AIHW, 2000	*Australian Vietnam veterans' children—validation study—AML*		
	This study, which incorrectly calculated expected number of AML cases, is updated by AIHW, 2001 above.		
Tasmanian Male Veterans with Service in Vietnam			**All COIs**
Field and Kerr, 1988	Cancer in children of Australian Vietnam veterans	4	nr
Other Studies of Vietnam Veterans			**All COIs**
Wen et al., 2000	Case–control study of children's leukemia		
	AML, ALL		
	Father ever served in Vietnam, Cambodia	117	1.2 (0.9–1.6)
	< 1 yr in Vietnam or Cambodia	61	1.4 (0.9–2.0)
	> 1 yr in Vietnam or Cambodia	49	1.2 (0.8–1.7)
	AML only		
	Father ever served in Vietnam, Cambodia	40	1.7 (1.0–2.9)
	< 1 yr in Vietnam, Cambodia	13	2.4 (1.1–5.4)
	> 1 yr in Vietnam, Cambodia	16	1.5 (0.7–3.2)
OCCUPATIONAL			
Agricultural Health Study			**Herbicides**
Flower et al., 2004	Offspring of male pesticide applicators in Iowa from AHS		
	Maternal exposure to chlorophenoxy herbicides	7	0.7 (0.3–1.5)
	Paternal exposure to chlorophenoxy herbicides	28	1.3 (0.6–2.6)
	Maternal exposure to 2,4-D	7	0.7 (0.3–1.6)
	Paternal exposure to 2,4-D	26	1.3 (0.7–2.4)

continued

TABLE 8-8 Childhood Cancers, continued

Reference	Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Risk (95% CI)[b]
Other Parental Agricultural Exposures			**Herbicides**
Monge et al., 2007	Parental occupational exposure to pesticide, childhood leukemia in Costa Rica		
	Paternal exposure in year before conception to:		
	Herbicides	53	1.2 (0.8–1.7)
	Phenoxyacetic acids	28	1.0 (0.6–1.6)
	Picloram (all ALL)	11	1.6 (0.7–3.4)
	High vs low	8	6.3 (1.0–38.6)
	Maternal exposure to:		
	Herbicides		
	In year before conception	9	2.0 (0.8–5.0)
	In 1st trimester	8	5.3 (1.4–20.0)
	In 2nd trimester	8	5.3 (1.4–20.0)
	In 3rd trimester	7	2.3 (0.8–6.8)
	Phenoxyacetic acids in year before conception	4	1.3 (0.4–4.8)
Chen et al., 2005	Parental occupational exposure to pesticide, childhood GCTs		
	Maternal	32	1.1 (0.7–1.6)
	Paternal	39	0.9 (0.6–1.3)
Reynolds et al., 2005b	Maternal exposure to agricultural pesticide in class of "probable human carcinogens" (including cacodylic acid) during 9 months before delivery		
	All sites	223	1.0 (0.9–1.2)
	Leukemias	179	1.2 (0.9–1.5)
	Central nervous system tumors	31	0.9 (0.5–1.4)
Buckley et al., 1989	Children's Cancer Study Group—exposure to pesticides, weed killers—AML		
	Any paternal exposure	27	2.3 (p = 0.5)
	Paternal exposure over 1,000 days	17	2.7 (1.0–7.0)
	Maternal exposure over 1,000 days	7	undefined
Forestry Workers			**Herbicides**
Heacock et al., 2000	Offspring of sawmill workers exposed to fungicides contaminated with PCDDs, PCDFs		
	Leukemia		
	All workers' offspring—incidence	11	1.0 (0.5–1.8)
	Chlorophenate exposure: high- vs low-exposure subjects	5	0.8 (0.2–3.6)
	Brain cancer		
	All workers' offspring—incidence	9	1.3 (0.6–2.5)
	Chlorophenate exposure: high- vs low-exposure subjects	5	1.5 (0.4–6.9)

TABLE 8-8 Childhood Cancers, continued

Reference	Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Pesatori et al., 1993	Seveso residents 0–19 yrs of age—10-yr follow-up, morbidity, all exposure zones		
	All cancers	17	1.2 (0.7–2.1)
	Ovary, uterine adnexa	2	nr (0 cases expected)
	Brain	3	1.1 (0.3–4.1)
	Thyroid	2	4.6 (0.6–32.7)
	HL	3	2.0 (0.5–7.6)
	Lymphatic leukemia	2	1.3 (0.3–6.2)
	Myeloid leukemia	3	2.7 (0.7–11.4)
Bertazzi et al., 1992	Seveso residents 0–19 yrs of age—10-yr follow-up, mortality, all exposure zones		
	All cancers	10	7.9 (3.8–13.6)
	Leukemias	5	3.9 (1.2–1.8)
	Lymphatic leukemia	2	1.6 (0.1–4.5)
	Myeloid leukemia	1	0.8 (0.0–3.1)
	Leukemia, others	2	1.6 (0.1–4.6)
	Central nervous system tumors	2	1.6 (0.1–4.6)
US Environmental Studies			**Herbicides**
Cooney et al., 2007	Case–control study of Wilms' tumor in the United States and Canada		
	Maternal report of household use of herbicides from month before conception through child's diagnosis	112	1.0 (0.7–1.4)
Chen et al., 2006	Childhood GCTs residential exposure to herbicides 6 months before conception, during gestation, through breastfeeding period		
	Maternal exposure	47	1.3 (0.9–1.7)
	Daughters	36	1.4 (1.0–2.0)
	Sons	11	1.0 (0.5–1.8)
	Paternal exposure	90	1.0 (0.7–1.3)
	Daughters	32	1.2 (0.7–2.0)
	Sons	58	(0.7–1.4)
Kerr et al., 2000	Neuroblastoma risk in children		
	Maternal occupational exposure to insecticides	40	2.3 (1.4–3.7)
	Paternal exposure to dioxin	7	6.9 (1.3–68.4)

continued

TABLE 8-8 Childhood Cancers, continued

Reference	Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
International Environmental Studies			**Herbicides**
Rudant et al., 2007	Case–control study of childhood hematopoietic malignancies in France		
	Maternal household herbicide use during pregnancy		
	Acute leukemia	53	1.5 (1.0–2.2)
	Without paternal exposure	4	5.0 (1.3–19.0)
	All ALL	nr	1.7 (1.2–2.5)
	Common B-cell ALL	nr	1.9 (1.3–2.9)
	Mature B-cell ALL	nr	1.5 (0.3–6.4)
	T-cell ALL	nr	0.5 (0.1–2.0)
	AML	nr	1.2 (0.5–2.8)
	HL	9	1.1 (0.5–2.4)
	Without paternal exposure	0	nr
	Nodular sclerosis	nr	1.3 (0.5–3.1)
	Mixed cell	nr	0.8 (0.1–6.6)
	NHL	14	1.5 (0.8–2.7)
	Without paternal exposure	0	nr
	Burkitt's lymphoma	nr	1.7 (0.7–4.0)
	B-cell lymphoblastic	nr	0.7 (0.2–3.0)
	T-cell lymphoblastic	nr	2.6 (0.7–9.0)
	Anaplastic large cell	nr	1.4 (0.3–2.8)
Daniels et al., 2001 (United States and Canada)	Neuroblastoma risk in children (538 cases, 504 controls) from 139 hospitals in United States and Canada (exposures as reported by both parents)		
	Pesticides in home (used ever)	nr	1.6 (1.0–2.3)
	Herbicides in garden	nr	1.9 (1.1–3.2)
	Pesticides in garden	nr	2.2 (1.3–3.6)
Meinert et al., 2000	Childhood cancer—population-based case–control study in Germany		
	Leukemia		
	Paternal exposure year before pregnancy	62	1.5 (1.1–2.2)
	Paternal exposure during pregnancy	57	1.6 (1.1–2.3)
	Maternal exposure year before pregnancy	19	2.1 (1.1–4.2)
	Maternal exposure during pregnancy	15	3.6 (1.5–8.8)
	Lymphomas		
	Paternal exposure year before pregnancy	11	1.5 (0.7–3.1)
	Paternal exposure during pregnancy	10	1.6 (0.7–3.6)
	Maternal exposure year before pregnancy	3	2.9 (0.7–13)
	Maternal exposure during pregnancy	4	11.8 (2.2–64)
Pearce and Parker, 2000	Renal cancer in subjects (1–15 years old) with paternal occupation in agriculture	21	0.9 (0.2–3.8)

TABLE 8-8 Childhood Cancers, continued

Reference	Study Population	Exposed Cases[b]	**Exposure of Interest/** Estimated Risk (95% CI)[b]
Infante-Rivard et al., 1999	Childhood ALL in households using herbicides—population-based case–control study		
	Exposure during pregnancy	118	1.8 (1.3–2.6)
	Exposure during childhood	178	1.4 (1.1–1.9)
Kristensen et al., 1996	Children of agricultural workers in Norway		
	Children with AML whose parents purchased pesticides	12	1.4 (0.6–2.9)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; AHS, Agricultural Health Study; AIHW, Australian Institute for Health and Welfare; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; GCT, germ-cell tumor; HL, Hodgkin lymphoma; nr, not reported; PCDD, polychlorinated dibenzodioxin; PCDF, polychlorinated dibenzofuran; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; VES, Vietnam Experience Study.

[a]Unless otherwise indicated, studies show paternal exposure.

[b]Given when available; results other than estimated risk explained individually.

[c]Of the 12, 9 were observed, 3 additional cases estimated to have occurred in portion of cohort whose data were not validated.

residential proximity to specific pesticide applications accumulated over the life of the child, and they evaluated 191 cases and 244 matched controls for risk associated with applications limited to the first year of life. Residential history was obtained from parental interviews and linked to the comprehensive statewide pesticide-use reporting system to identify potential exposure to specific pesticides during the periods of interest. However, analyses were limited to categories of pesticides; results were not reported for the chemicals of interest to the committee. In the second study (Ward et al., 2009), dust samples collected from carpets in the homes of 184 cases and 212 controls were analyzed for PCBs and organochlorines. No association between DDT or DDE and leukemia was observed. An increased risk in connection with several PCB congeners was observed, but analyses that considered dioxin-like activity were not available. For relevance to the offspring of Vietnam veterans, however, only analyses of parental exposures (prenatal to be applicable for female veterans or preconception for male veterans).

Three other studies of childhood cancer did not meet the level of exposure specificity required for review by the committee. One examined paternal exposures that occurred in working on hobbies during or a month before pregnancy, but exposure was limited to "lawn care using insecticides, bug or weed killer" (Rosso et al., 2008). The two other studies examined maternal exposures during pregnancy, but exposure was limited to any herbicide or pesticide and was not specific to the chemicals of interest (Shim et al., 2009; Spix et al., 2009).

Biologic Plausibility

Paternal or maternal exposure to xenobiotics potentially could increase the susceptibility of offspring to cancer through multiple mechanisms. Susceptibility could be increased by inheriting a genetic predisposition, which by itself could increase the development of cancer or the likelihood of developing cancer after future exposure to a carcinogen; the mother or father would transmit either an acquired genetic defect or an epigenetic alteration that predisposed the child to cancer. Alternatively, a maternally mediated increase in susceptibility to childhood cancer could result from direct exposure of a child in utero or via lactation to a xenobiotic that induces epigenetic alterations that increase cancer susceptibility or is itself carcinogenic.

It has been shown that prenatal TCDD exposure of rats is associated with altered mammary gland differentiation and an increase in the number of mammary adenocarcinomas (Brown et al., 1998). A recent study's demonstration that early postnatal TCDD exposure does not increase mammary-cancer risk (Desaulniers et al., 2004) is consistent with the finding that TCDD-induced changes in utero mediate the increase in cancer susceptibility (Fenton et al., 2000, 2002). Developmental epigenetic alterations may be involved in those prenatal effects. TCDD has been shown to suppress the expression of two tumor-suppressor genes, $p16^{Ink4a}$ and p53, via an epigenetic mechanism that appears to involve DNA methylation (Ray and Swanson, 2004). Similarly, it was reported that prenatal TCDD exposure increases methylation of two growth-related imprinted genes, H19 and Igf2, in the developing fetus (Wu et al., 2004).

Although there is no direct evidence from animal models that TCDD increases the risk of childhood cancers, such as acute leukemia or germ-cell tumors, emerging research suggests that prenatal TCDD exposure can disrupt epigenetic imprinting patterns and alter organ differentiation, which could contribute to an increased susceptibility to cancer later in life. A recent study has shown that chromosomal rearrangements associated with childhood ALL are evident in the neonatal blood spots; this suggests that childhood leukemias begin before birth and that maternal and perinatal exposures to xenobiotics may contribute to genetic mutations (Smith et al., 2005).

Synthesis

No new epidemiologic evidence concerning the chemicals of interest and childhood cancers has been published since *Update 2008*.

Conclusions

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to

determine whether there is an association between exposure to the chemicals of interest and childhood cancers.

EFFECTS OCCURRING LATER IN OFFSPRING'S LIFE OR IN LATER GENERATIONS

In response to a special request from the Department of Veterans Affairs, continuing inquiries from the veterans themselves and their families, and increasing attention in research efforts, the present update addresses whether it is feasible to assess associations between exposure to the herbicides sprayed in Vietnam and health effects in the children and grandchildren of Vietnam veterans that have not been formally reviewed in previous VAO updates. The additional outcomes may include effects (other than cancer) in children that become apparent after the first year of life and that are related to maternal or paternal exposures. In addition, the committee explored the possibility of transgenerational effects resulting from exposure-related epigenetic changes, either in the parents or exposed fetuses, that would lead to adverse health effects in later generations, such as grandchildren.

Conclusions from *VAO* and Previous Updates

The potential impact of maternal and paternal exposure of Vietnam veterans to herbicides on the development of disease in their children after the first year of life or in later generations has not been considered in previous updates for any health outcomes other than cancer. Therefore, no conclusions have been made previously.

Changes Detected in Children after Parental Exposure

Epidemiologic studies that evaluated the potential for effects in offspring as a result of maternal or paternal exposure to the chemicals of interest were identified. Those found did not, however, deal with specific diseases in the offspring, but rather measured physiologic biomarkers that might indicate a potential for disease development later in life. Thus, despite support for measurable changes after maternal exposure as described below, the committee strongly cautions that the *clinical consequences* of the observed changes are highly uncertain. In order to review the studies, the committee broadly categorized them by the physiologic biomarkers that were assessed, including measurements of thyroid hormones, cognitive and motor development, and immune-cell populations. The committee also maintained its standard requirement for exposure specific to components of the herbicides sprayed in Vietnam. Finally, although it may be physiologically possible for paternal exposure to cause changes in offspring that are manifested later in life, as discussed in Chapter 4 and at the beginning of this chapter, none of the published epidemiologic studies assessed the potential for paternal exposure to contribute to outcomes that would be manifested later in their offspring's

lives. Thus, any of the observed changes reported in the studies discussed below would be applicable only to children born to female Vietnam veterans during or after their deployment in Vietnam.

A number of studies have evaluated thyroid hormone concentrations in infants and children after exposure to TCDD and dioxin-like chemicals prenatally and during lactation and had mixed outcomes. For example, Baccarelli et al. (2008) evaluated neonatal thyroid-stimulating hormone (TSH) concentrations in children born to women in the Seveso cohort up to 25 years after the accident. Compared with the reference population, the risk of increased blood TSH was increased in Zone A (OR = 6.60, 95% CI 2.45–17.8) and Zone B (OR = 1.79, 95% CI 0.92–3.50). Neonatal TSH correlated with current maternal plasma TCDD concentration and dioxin-like PCB TEQs. Nagayama et al. (1998) assessed neonatal T3 and T4 concentrations and compared them with the concentrations of PCDDs, PCDFs, and PCBs, expressed as total TCDD-like TEQs, in the breast milk of their mothers. They found that both neonatal T3 and T4 were correlated negatively with total TEQs ($p = 0.037$ and 0.018, respectively). Physiologically, a decrease in T3 and T4 production by the thyroid would stimulate the pituitary to increase the secretion of TSH. Thus, the increase in TSH observed by Baccarelli et al. (2008) is consistent with the reductions in T3 and T4 observed by Nagayama et al. (1998). In studying newborns in Amsterdam, Pluim et al. (1993) found that total T4 levels at 1 and 11 weeks after birth were correlated with dioxin concentrations in maternal serum and breast milk, but the pattern was less clear for TSH, In contrast with those results, Darnerud et al. (2010) failed to find any relationship between neonatal (3 weeks) or infant (3 months) blood TSH and maternal plasma dioxin-like TEQs after adjusting for important confounders, including mother's age, smoking, and alcohol consumption during pregnancy. Those important confounders were not considered by Baccarelli et al. (2008) or Nagayama et al. (1998). Furthermore, changes in thyroid hormone concentrations observed early after birth do not appear to be sustained in the offspring later in life. Su et al. (2010) found a slight increase in T3 in 2-year-old girls after in utero exposure to dioxin-like PCDDs and PCDFs, but this was not evident in either boys or girls at the age of 5 years. Similarly, following the same cohort of Dutch children, neither Ilsen et al. (1996) nor ten Tusscher et al. (2008) found any association between thyroid hormone concentrations and prenatal or lactational exposure to TCDD in children 2 or 7–12 years old, respectively, and none of the children exhibited any clinically pathologic changes in TSH or T4.

A number of studies evaluated cognitive and motor development, using such standard testing methods as the Bayley Scales of Infant Development and self-reporting questionnaires. The results of those studies, like the results of the studies that evaluated thyroid hormone concentrations, reported mixed outcomes relative to an association with prenatal or lactational exposure to TCDD and dioxin-like compounds. For example, Halldorsson et al. (2009) evaluated the attainment of specific milestones by infants, on the basis of maternal reporting,

in relation to maternal plasma dioxin-like activity, assessed as CALUX-TEQs. They found a significant inverse correlation between maternal CALUX-TEQs and a total developmental score (Spearman r = –0.23, p = 0.046), but only one specific outcome, crawling, showed a significant delay (OR = 3.0, 95% CI 1.0–8.6). In another study, Koopman-Esseboom et al. (1996) found a significant negative association between PCB-dioxin TEQs in breast milk and a psychomotor development index at 7 months, but not at 18 months, and neither prenatal nor postnatal PCB-dioxin TEQs were associated with a mental-developmental index at any age. Similarly, Huisman et al. (1995) reported no association between PCB-dioxin TEQs in breast milk and neurologic optimality score, and Ilsen et al. (1996) reported that all psychomotor and neurologic indexes were within normal ranges, although there was an association between PCB-dioxin TEQs in breast milk and enhanced neuromotor maturation. Analyses in other epidemiologic studies reviewed (Boersma and Lanting, 2000; Harari et al., 2010; Vreugdenhil et al., 2002) were based on inadequately specific exposures (such as exposure to pesticides or total PCB concentrations).

Finally, a number of studies have measured immune-cell populations and the prevalence of allergies in children after prenatal and postnatal exposure to TCDD and dioxin-like chemicals; outcomes varied with children's ages. Three studies followed the same cohort of Dutch children as they aged (ten Tusscher et al., 2003; Weisglas-Kuperus et al., 1995, 2000). They found that postnatal exposure to breast-milk PCB-dioxin TEQs was associated with significant decreases in white blood cell counts at 3 months and significant increases in T-cell markers at 18 months, but had no effect on respiratory tract symptoms or antibody production at either age. At 3.5 years, they found that postnatal exposure to breast-milk PCB-dioxin TEQs was associated with a significant increase in recurrent middle ear infections and a slight increase in coughing, chest congestion, and phlegm, but no longer with changes in white blood cell counts or T-cell markers. By 8 years, postnatal exposure to breast-milk PCB-dioxin TEQs was associated with significant increases in T-cell markers and a decrease in allergy. A separate study of offspring of farm families found an association between 2,4-D use and the incidence of allergy in children (Weselak et al., 2007).

Developmental Effects in Later Generations

Epidemiologic studies designed to investigate associations of occupational or environmental exposures with adverse developmental effects manifested in later generations have not been reported in connection with the chemicals of interest or any other chemicals; they will be even more challenging to conduct than research on adverse effects on the first generation. However, recently recognized epigenetic mechanisms that are the focus of intensive research could constitute a mechanism by which such outcomes might occur (Baccarelli and Bollati, 2009; Skinner et al., 2010).

Biological Plausibility

It has been proposed that TCDD could produce adverse effects via epigenetic mechanisms. Research into dioxin's potential as an epigenetic agent is in its early stages, but a few studies have suggested that dioxin has such properties. For instance, Wu et al. (2004) demonstrated that TCDD exposure of mouse embryos before implantation in unexposed females resulted in epigenetic changes, including increased methylation and reduced expression of imprinted genes. Another mode of epigenetic change is modification of the spatial arrangement of chromosomes, which can influence gene expression and cell differentiation. Oikawa et al. (2008) have found that TCDD, through the AHR, modifies the position of chromosomes in the interphase nuclei of human preadipocytes. Those studies suggest that TCDD has the potential to influence the epigenome and therefore could promote changes in offspring that lead to disease later in life. The mechanisms are presented in more detail in Chapter 4.

Synthesis

The epidemiologic studies designed to examine effects of the chemicals of interest in more mature offspring have evaluated a variety of biomarkers pertaining to the neurologic, immunologic, and endocrine systems. However, they have not examined defined clinical health conditions in those or other systems. The animal literature does provide evidence that environmental agents mediated by maternal affect later generations through fetal and germ-line modifications. However, in the case of adult male exposures before conception of the next generation, there is insufficient evidence of generational affects.

Conclusions

There is inadequate or insufficient evidence to determine whether there is an association between exposure of men and women to 2,4-D, 2,4,5-T, TCDD, picloram, or cacodylic acid before conception or during pregnancy and disease in their children as they mature or in later generations. Although laboratory research supports the plausibility of transgenerational clinical conditions, no completed epidemiologic studies have provided data to support an association between the chemicals of interest and such disease states in human offspring.

SUMMARY

Synthesis

The studies reviewed for this update did not find any new significant associations between the relevant exposures and reproductive outcomes. The scientific

evidence supports the biologic plausibility of a connection between exposure to the chemicals of interest and reproductive effects, but the epidemiologic studies of occupational cohorts, exposed communities, and Vietnam veterans have not provided conclusive evidence of any additional associations between exposures and an array of reproductive outcomes and conditions in the offspring of exposed parents beyond neural tube defects. The mechanisms by which the chemicals exert their biologic effects are still subjects of scientific investigation. With the aging of the Vietnam-veteran population, additional studies of endometriosis and pregnancy loss cannot be expected, although there may be additional studies of reproductive outcomes in other populations after exposure to the chemicals of interest. The possibility that structural or functional abnormalities will be manifested in the maturing offspring of exposed people will continue to be of interest. In addition, the committee strongly recommends that careful consideration be given to systematically evaluating whether recently recognized mechanisms of epigenetic modification imply that there could be long-term consequences of herbicide exposure for the health of the progeny of Vietnam veterans in future generations.

Conclusions

There is inadequate or insufficient evidence to determine whether there is an association between exposure to 2,4-D, 2,4,5-T, TCDD, picloram, or cacodylic acid and endometriosis; semen quality; infertility; spontaneous abortion; stillbirth; late fetal, neonatal, or infant death; low birth weight or preterm delivery; birth defects other than spina bifida; childhood cancers; or diseases in more mature offspring or later generations.

There is limited or suggestive evidence of an association between exposure to the chemicals of interest and spina bifida. There is some evidence of altered hormone concentrations, but the degree to which testosterone concentration may be modified is not great enough for clinical consequences to be expected.

There is limited or suggestive evidence of *no* association between paternal exposure to TCDD and spontaneous abortion.

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[1]Throughout the report the same alphabetic indicator following year of publication is used consistently for the same article when there were multiple citations by the same first author in a given year. The convention of assigning the alphabetic indicator in order of citation in a given chapter is not followed.

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9

Neurologic Disorders

The nervous system is a complex organ system that allows human beings to interact with both the internal environment and the external environment. For convenience, we divide the nervous system into the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS comprises the brain and spinal cord, and the PNS includes sensory and motor nerves, which enter or leave the spinal cord and are responsible for our ability to sense the outside world and to move within it, and autonomic nerve fibers, which sense such internal events as changes in blood pressure or temperature and act to control these and other aspects of our internal environment.

Neurologic disorders due to toxicant exposure may result in either immediate or delayed dysfunction of any component of the nervous system; immediate effects of toxicants may involve all aspects of the nervous system, whereas delayed effects are likely to produce more focal problems. Diffuse damage to the CNS may cause alterations in thinking, consciousness, or attention, often in combination with abnormalities in movement. Focal dysfunction can cause myriad syndromes, depending on which area is damaged. Neurologic disorders can cause problems with thinking and emotional dysregulation, but it is important to distinguish them from psychiatric conditions—such as posttraumatic stress disorder, depression, and anxiety—and from systemic conditions of uncertain cause, such as chronic fatigue syndrome. In this chapter, we will consider possible diffuse CNS effects of toxic exposure and specific clinical conditions that result from focal dysfunction. Examples of diseases that result from degeneration of specific brain areas are Parkinson disease (PD), Alzheimer disease (AD), spinocerebellar degeneration, and amyotrophic lateral sclerosis (ALS); all these diseases occur in

the absence of any toxicant exposure but all may be triggered by aspects of the environment, including toxicant exposure.

Disorders of the PNS are generally referred to as neuropathies. Neuropathies may be purely motor and affect only movement or purely sensory; most often, however, both motor and sensory fibers are affected. Neuropathies usually are symmetric and start with symptoms related to dysfunction of fibers that travel the greatest distance to their target organ. For that reason, symptoms of neuropathy generally start in the digits and travel toward the torso. Most neuropathies also affect autonomic fibers and thus can result in changes in blood pressure and heart rate and in symptoms related to the control of digestion. Toxicant exposure can induce immediate damage to peripheral nerves, and previous updates have found limited or suggestive evidence that dioxin exposure caused such short-term effects. Evidence related to rapid onset of these conditions is presented in Appendix B, which deals with short-term adverse health effects. Previously undistilled information concerning persistence of symptoms after early effects is also evaluated in Appendix B. The overall focus of this chapter is *delayed* adverse effects on the PNS and the CNS.

Timing is important in assessing the effects of chemical exposure on neurologic function and must be considered in the design and critique of epidemiologic studies. In the original *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* report, hereafter referred to as *VAO* (IOM, 1994), attention was deliberately focused on persistent neurobehavioral disorders. That focus was maintained in *Update 1996* (IOM, 1996), *Update 1998* (IOM, 1999), *Update 2000* (IOM, 2001), and *Update 2002* (IOM, 2003). A slight change in emphasis toward chronic neurodegenerative disorders was reflected in the change in the name of this chapter to "Neurologic Disorders" in *Update 2004* (IOM, 2005), which was carried forward in *Update 2006* (IOM, 2007) and *Update 2008* (IOM, 2009). The present chapter reviews data pertinent to persistent neurologic disorders of all types.

Case identification in neurologic disorders is often difficult because there are few disorders for which there are specific diagnostic tests. Many disorders involve cellular or molecular biochemical effects, so even the most advanced imaging techniques can miss an abnormality. Because the nervous system is not readily accessible for biopsy, pathologic confirmation usually is not feasible. However, identifiable neurologic disorders always result in objective abnormalities that are reflected in anatomic or functional tests or discovered via clinical examination.

Many studies have addressed the possible contribution of various chemical exposures to neurologic disorders, but the committee's focus is on the health effects of a particular set of chemicals: four herbicides—2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), picloram (4-amino-3,5,6-trichloropicolinic acid), and cacodylic acid (dimethyl arsenic acid)—and a contaminant of 2,4,5-T, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Thus,

the specificity of exposure assessment is an important consideration in weighing evidence relevant to the committee's charge.

This chapter reviews the association between exposure to the chemicals of interest and neurobehavioral disorders, neurodegenerative disorders, and chronic peripheral system disorders. The scientific evidence supporting biologic plausibility is also reviewed here. More complete discussions of the categories of association and of this committee's approach to categorizing health outcomes are presented in Chapters 1 and 2. For citations new to this update that revisit previously studied populations, design information can be found in Chapter 5.

NEUROBEHAVIORAL (COGNITIVE OR NEUROPSYCHIATRIC) DISORDERS

This section summarizes the findings of *VAO* and previous updates on neurobehavioral disorders and incorporates information published in the last 2 years into the evidence database.

Conclusions from *VAO* and Previous Updates

On the basis of the data available at the time, the committees responsible for *VAO*, *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008* concluded that there was inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and neurobehavioral disorders. Many of the data that informed that conclusion came from the Air Force Health Study (AFHS, 1991, 1995, 2000; Barrett et al., 2001, 2003). *VAO* and the updates offer more complete discussions of the results. The AFHS studies (AFHS, 1991, 1995) reviewed in *VAO* revealed no association between serum TCDD concentration and reported sleep disturbance or variables on the Symptom Checklist-90-Revised (SCL-90); in contrast, serum TCDD was significantly associated with responses on some scales of the Millon Clinical Multiaxial Inventory. Observations on 55 highly exposed Czech 2,4,5-T production workers (Pazderova-Vejlupkova et al., 1981) were found to suffer from methodologic problems.

Update 1996 reviewed two not particularly informative studies of Vietnam veterans (Decoufle et al., 1992; Visintainer et al., 1995) and a study of highly exposed German workers (Zober et al., 1994), which found a relationship between "mental disorders" and severity of chloracne but not with blood TCDD concentrations. *Update 1998* considered a report on mental-health problems in Australian Vietnam veterans but not in the context of herbicide exposure (O'Toole et al., 1996).

In *Update 2000*, results from the AFHS (AFHS, 2000) indicated that although the frequency of several self-reported neuropsychiatric symptoms differed between exposure groups, the associations were not significant after adjustment

for covariates. In addition, a repeat psychologic assessment with the SCL-90 in conjunction with self-reported psychologic disorders verified through medical-record review showed that among five diagnostic categories (psychosis, alcohol dependence, drug dependence, anxiety, and other neurosis), a dose–response pattern with serum TCDD concentration was found only for "other neuroses" in the enlisted ground crew. When the entire cohort was evaluated, there were no significant associations between serum TCDD and various psychologic diagnoses.

Update 2002 reviewed three studies. Neuropsychologic tests of cognitive functioning indicated significant group differences on some scales in the AFHS cohort during the 1982 examination, but the findings did not support a dose–response relationship with serum TCDD: poorer performance was seen in groups with background or low exposure, and the lower performance on only one memory test in one subgroup of subjects suggested a chance finding (Barrett et al., 2001). Gauthier et al. (2001) did not find a relationship between AD and exposure to herbicides and insecticides. The poorly documented results of Pelclová et al. (2001) from a 30-year follow-up of 13 of 55 workers in a Czech 2,4,5-T-production cohort were not given much credence.

Update 2004 reviewed five new studies. Among them was a report on the AFHS cohort (Barrett et al., 2003) in which the authors concluded that there were "few consistent differences in psychological functioning" between groups categorized by serum-dioxin concentrations. Kim et al. (2003) described increased prevalence of posttraumatic stress disorder in Korean military who served in Vietnam, but there was no association with estimated exposure to Agent Orange. The remaining three studies (Baldi et al., 2003; Dahlgren et al., 2003; Pelclová et al., 2002) were found to be uninformative because of methodologic limitations.

Update 2006 considered two new studies of limited relevance. Park et al. (2005) analyzed cause of death as a function of subjects' "usual occupation" on 2.8 million death certificates, but the significantly increased odds ratio (OR) for presenile dementia and "pest control" was not sufficiently specific for the chemicals of interest. The increase in mortality from "mental disorders" reported in Australian Vietnam veterans (ADVA, 2005c) was based on such a broad diagnostic category that it was impossible to conclude whether subjects who were investigated had neurologic symptoms or signs.

Update 2008 considered data on subjects who participated in the Agricultural Health Study (Kamel et al., 2007a) and found no relationship between a constellation of neurobehavioral complaints and herbicide exposure. Another large study of rural residents of England failed to demonstrate a clear relationship between herbicide exposure and a variety of neurologic and neurobehavioral symptoms (Solomon et al., 2007). In contrast, the study of Urban et al. (2007) confirmed that acute neurologic symptoms experienced shortly after an acute exposure to TCDD could be sustained more than 30 years after the exposure; this study did not address delayed effects, because the subjects evaluated all had evidence of acute toxicity.

Update of the Epidemiologic Literature

No Vietnam-veteran, occupational, or environmental studies of exposure to the chemicals of interest and neurobehavioral conditions have been published since *Update 2008*.

Biologic Plausibility

Some animal studies have suggested possible involvement of the chemicals of interest in the occurrence of neurobehavioral effects. Akahoshi et al. (2009) produced a mouse neuroblastoma cell line that overexpressed the aryl hydrocarbon receptor, which is important in dopamine synthesis. Treating the line with TCDD increased tyrosine hydroxylase activity and led to increased dopamine expression. The implication of that finding is not clear, although changes in dopamine regulation have been implicated in a number of neurobehavioral syndromes. Other recent studies have focused on perinatal exposure. Haijima et al. (2010) found that perinatal exposure to TCDD impaired memory in male offspring. Mitsui et al. (2006) reported that hippocampus-dependent learning could be impaired in male rats exposed in utero to TCDD and that impairment could have affected fear conditioning. Lensu et al. (2006) examined areas in the hypothalamus for possible involvement in TCDD effects on food consumption, potentially related to wasting syndrome, and suggested that their results were not consistent with a primary role of the hypothalamus. Studies in rodents have also detected molecular effects in cerebellar granule cells or neuroblasts, which are involved in cognitive and motor processes (Kim and Yang, 2005; Williamson et al., 2005). Sturtz et al. (2008) found that 2,4-D affected rat maternal behavior. The specific relevance of those studies and studies cited in earlier updates to neurobehavioral effects is unclear. A general summary of the biologic plausibility of neurologic effects of exposure to the herbicides used in Vietnam is presented at the end of this chapter.

Synthesis

There is not consistent epidemiologic evidence of an association between Agent Orange exposure and neurobehavioral (cognitive or neuropsychiatric) disorders.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and neurobehavioral (cognitive or neuropsychiatric) disorders.

NEURODEGENERATIVE DISEASES

This section summarizes the findings of previous VAO reports on neurodegenerative diseases—specifically PD and ALS—and incorporates information published in the last 2 years into the evidence database.

Parkinson Disease and Parkinsonism

PD is a progressive neurodegenerative disorder that affects millions of people worldwide. Its primary clinical manifestations are bradykinesia, resting tremor, cogwheel rigidity, and gait instability. Those signs were first described in 1817 as a single entity by James Parkinson. In recent years, many nonmotor manifestations of PD have been described, and they can be the presenting symptoms of the disease. These include cognitive dysfunction often progressing to frank dementia, sleep disturbances, hallucinations, psychosis, mood disorders, fatigue, and autonomic dysfunction (Langston, 2006).

In the nearly 2 centuries since the initial description, much has been learned about genetic predisposition and the pathophysiology of the disease. However, the etiology of PD in most patients is unknown, and specific environmental risk factors remain largely unproved. The diagnosis of PD is based primarily on clinical examination; in recent years, magnetic resonance imaging and functional brain imaging have been increasingly useful. PD must be distinguished from a variety of parkinsonian syndromes, including drug-induced parkinsonism, and neurodegenerative diseases, such as multiple systems atrophy, which have parkinsonian features combined with other abnormalities. Ultimately, a diagnosis of PD can be confirmed with postmortem pathologic examination of brain tissue for the characteristic loss of neurons from the substantia nigra and telltale Lewy body intracellular inclusions. Pathologic findings in other causes of parkinsonism show different patterns of brain injury.

Estimates of population-based incidence of PD range from 2 to 22 per 100,000 person–years, and estimates of prevalence range from 18 to 182 per 100,000 person–years. It affects about 1% of all persons over 60 years old and up to 5 million people worldwide. That makes PD the second-most common neurodegenerative disease (after AD). Age is a risk factor for PD; the peak incidence and prevalence are consistently found in people 60–80 years old. A consensus statement from a 2007 meeting of PD experts (Bronstein et al., 2009) concluded that, in addition to firm evidence that the toxicant 1-methyl-4-phenyl-1,2,4,6-tetrahydropyridine (MPTP) can induce PD, there is substantial evidence that men are at greater risk and that smoking and coffee consumption are associated with reduced risk.

Heredity has long been suspected of being an important risk factor for PD; as many as 25% of all PD patients have at least one first-degree relative who has PD. At least 13 gene mutations have been identified in autosomal dominant PD,

including mutations in parkin and α-synuclein (Klein and Lohmann-Hedrich, 2007). Mutations associated with an autosomal recessive inheritance pattern have also been described. Complex genetics may be found to account for an increasing number of PD cases in coming years, but environmental risk factors clearly are also important.

Conclusions from *VAO* and Previous Updates

In *Update 2008*, both new and previous studies referring to specific herbicide exposures and risk of PD were reviewed. Stern et al. (1991) performed a case–control study of 69 cases in people who developed symptoms before the age of 40 years (early onset) and 80 after the age of 60 years (late onset). Herbicide exposure (classified as "any" or "none") was not more prevalent in either early-onset or late-onset cases. However, the study is limited in that the design specifically eliminated cases in the age ranges in which PD is most often diagnosed. In contrast, Semchuk et al. (1992) used a conditional logistic regression model to assess risk in 130 PD cases as compared to 260 controls from Calgary, Alberta, Canada; a statistically significant crude OR of 3.06 (95% confidence interval [CI] 1.34–7.00) was found for herbicide exposure; 7 of the 17 cases reporting herbicide use were able to specify the particular product—1 reported paraquat use, and the rest reported exclusive use of chlorophenoxy and thiocarbamate compounds. Butterfield et al. (1993), in another case–control study, also found a significant association between herbicide exposure and PD (OR = 3.22; $p = 0.033$). In a larger population-based case–control study, Gorell et al. (1998) found a significant association between PD and herbicide exposure, which increased after controlling for other confounding factors (OR = 4.10, $p < 0.012$). PD and control subjects were equally likely to report residential herbicide exposure, which presumably occurs at a lower level than occupational exposure, whereas risk of PD was increased in subjects who reported 10 years or more of occupational herbicide exposure (OR = 5.8, 95% CI 1.99–16.97). In contrast, Taylor et al. (1999) performed a case–control study of 140 cases at Boston City Hospital that showed no association between herbicide use and PD (OR = 1.1, 95% CI 0.7–1.7); this was probably a primarily urban sample, and there is no mention of how many cases or controls reported herbicide use. In addition, controls were identified by PD subjects and contacted by the subjects themselves—an unconventional way of accruing control subjects that may be subject to bias.

Update 2008 reviewed several new epidemiological studies related to PD risk and compounds of interest. Kamel et al. (2007b) studied the large cohort collected by the prospective AHS; this cohort was established from 1993 to 1997 and included 84,738 people of whom 57,259 were reached again 5 years later. Among incident cases, there was a trend toward increased risk of PD in subjects exposed to pesticides (OR = 1.3, 95% CI 0.5–3.3); although the overall relationship did not reach statistical significance, there was a dose effect over the quartiles (p =

0.009), with subjects with the highest number of days of pesticide use showing the greatest risk (OR = 2.3, 95% CI 1.2–4.5). Brighina et al. (2008) performed a large case–control study of 844 case–control pairs, and found that exposure to chlorophenoxy acid or esters chemical class was associated with increased risk of PD in younger subjects (OR = 1.52, 95% CI 1.04–2.22; p = 0.004); 2,4-D was the most commonly reported of the phenoxy herbicides. Another study reported in this Update was that of Hancock et al. (2008), who evaluated specific pesticide exposure and risk of PD by using a family-based case–control series of 319 PD patients and 296 controls. Overall pesticide use was significantly associated with PD (OR = 1.61, 95% CI 1.13–2.29). Exposure to chlorophenoxy acid or esters, including chemicals of interest in this review, were associated with increased ORs but the relationship was not statistically significant (OR = 2.07, 95% CI 0.69–6.23).

On the basis of the preponderance of evidence summarized above, *Update 2008* concluded that there was limited/suggestive evidence relating exposure to the compounds of interest and PD.

These findings are summarized in Table 9-1.

Update of the Epidemiologic Literature

Since the previous update, a number of new epidemiologic studies have been published. Dhillon et al. (2008) evaluated a variety of risk factors in an East Texas cohort of 800 PD patients seen at a local medical center's neurological institute. For the analysis, 100 cases and 87 controls were recruited; no details on the recruitment algorithm were provided. During a structured interview, study participants were queried about their herbicide use in general and about their personal use, mixture, or application of individual products, including 2,4-D, 2,4,5-T, Silvex, or other 2,4,5-TP products. An equal number of cases (34) and controls (34) reported having used herbicides for home or agricultural purposes (OR = 0.8, 95% CI 0.4–1.4). No significant relationship was found between exposure to 2,4-D (OR = 1.2, 95% CI 0,6–2.8), 2,4,5-T (OR = 0.5 (0.1–1.6) or Silvex or other 2,4,5-TP products (OR = 0.3, 95% CI 0.03–2.7) and a diagnosis of PD. Firestone et al. (2010) extended a population based case–control study of incident PD cases in Washington State by adding cases newly diagnosed 2003–2006 to those diagnosed 1992–2002 and analyzed in Firestone et al. (2005). The total of enrolled PD cases increased from 250 to 404, who were compared to 526 unrelated controls. The prevalence of exposure to compounds of interest was low; 8 cases reported exposure to 2,4-D, and there was no suggestion of a difference in exposure between cases and controls (OR = 0.8, 95% CI 0.3–2.0).

In contrast, Tanner et al. (2009) performed a case–control study recruiting consecutive subjects from eight large movement disorders clinics in North America; 519 cases and 521 cases were recruited. Subjects whose occupation included frequent pesticide use had an increased risk of PD (OR = 1.90, 95% CI

TABLE 9-1 Epidemiologic Studies of Herbicide[a] Exposure and Parkinson Disease

Reference and Country	Cases in Study Group	Comparison Group	Exposure Assessment	Exposure(s)[a]	n	OR (95% CI)	Diagnosis of Neurologic Dysfunction
Firestone et al., 2010 (updates and expands Firestone et al., 2005); Washington, US	Enrolled cases increased from 250 (in original study) to 404	526 unrelated controls	Structured face-to-face interviews; demographic information collected, job descriptions (if held for more than 6 months) and workplace exposures to various industrial toxicants identified from a checklist were recorded	2,4-D	8	0.8 (0.3–2.0)	≥ 2 of 4 cardinal signs; must have bradykinesia or resting tremor, may have cogwheel rigidity, or postural reflex impairment
Dhillon et al., 2009; US (University of Texas)	100 PD cases recruited from a medical center's neurological institute in East Texas	84 controls without PD recruited from the same medical center	Professionally administered questionnaire used to determine military history (including spraying herbicides/pesticides), personal use/mixing and average duration of exposure to herbicides and specific pesticides, among other exposures	Ever personally used/mixed or applied: Herbicide use-home or agricultural 2,4-D 2,4,5-T Silvex or other 2,4,5-TP products	 34 17 4 1	 0.8 (0.4–1.4) 1.2 (0.6–2.8) 0.5 (0.1–1.6) 0.3 (0.0–2.7)	PD diagnosed by neurologist specializing in movement disorders using standard clinical/lab diagnostic criteria
Elbaz et al., 2009; France	224 PD cases	557 controls	Initial self-assessment, plus individual interview with occupational specialist	Phenoxy herbicides Age of onset > 65 yrs	na na	1.8 (0.9–3.3) 2.9 (1.1–7.3)	≥ 2 cardinal signs (rest tremor, bradykinesia, rigidity, impaired postural reflexes)

continued

TABLE 9-1 Epidemiologic Studies of Herbicide[a] Exposure and Parkinson Disease, continued

Reference and Country	Cases in Study Group	Comparison Group	Exposure Assessment	Exposure(s)[a]	n	OR (95% CI)	Diagnosis of Neurologic Dysfunction
Tanner et al., 2009; US	519 cases; consecutively eligible subjects between July 1, 2004, and May 31, 2007	521 controls frequency matched to cases by age, sex, and location	Telephone interviewers collected information about exposures before the reference age; employment history—industry, location, processes, materials, and job tasks. Toxicant exposure collected for some jobs	2,4-D	16	2.6 (1.0–6.5)	Enrolling investigator determined diagnosis and type of parkinsonism, Unified Parkinson Disease Rating Scale score, and clinical features
Brighina et al., 2008; US (Mayo Clinic)	833 PD sequential cases from clinic; median age = 67.7 yr, 208 cases ≤ 59.8 yr	472 unaffected siblings and 361 unrelated controls	Self-report down to specific herbicides; 2,4-D said to be most prevalent in cases, but published analysis not that detailed	For *youngest quartile* at diagnosis:			PD diagnosed by movement disorder specialist
				Pesticides (ever):	87	1.8 (1.1–2.9)	
				Herbicides (ever):		2.5 (1.3–4.5)	
				Phenoxy herbicides		1.5 (1.0–2.2)	
				Insecticides (ever):		1.0 (0.6–1.7)	
				Fungicides (ever):		1.0 (0.3–3.2)	
Hancock et al., 2008; US (Duke)	319 cases	296 unaffected relatives and others	All comparisons referent to those who never applied any pesticide	Pesticide application:	200	1.6 (1.1–2.3)	
				Insecticides:		1.8 (1.2–2.8)	
				Botanical:	7	5.9 (0.6–56)	
				Organophosphate:	53	1.9 (1.1–3.6)	
				Herbicides:		1.6 (1.0–2.5)	
				Chlorophenoxy:	15	2.1 (0.7–6.2)	
				Phosophonoglycine:	57	1.5 (0.9–2.5)	
				Triazine:	5	1.1 (0.3–3.6)	

Kamel et al., 2007b; US (Agricultural Health Study) [Updates Kamel et al., 2005]	83 prevalent cases at enrollment; 78 incident cases during follow-up among private applicators and spouses	79,557 without PD at enrollment; 55,931 without PD followed up	Self-report of individual herbicides (2,4-D; 2,4,5-T; 2,4,5-TP) on detailed self-administered questionnaires at enrollment or telephone interview for follow-up	For incident cases:			
				2,4-D:	49	1.0 (0.5–2.1)	
				2,4,5-T:	24	1.8 (1.0–3.3)	
				2,4,5-TP:	7	0.9 (0.4–1.8)	
				Dicamba:	32	1.5 (0.8–2.8)	
				Paraquat:	11	1.0 (0.5–1.9)	
				Trifuralin:	32	1.7 (1.0–3.2)	
				Cyanazine	26	1.0 (0.5–1.8)	
				For prevalent cases:			
				2,4-D:	47	0.9 (0.5–1.8)	
				2,4,5-T:	16	0.9 (0.5–1.7)	
				2,4,5-TP:	4	0.8 (0.3–1.9)	
				Dicamba:	26	0.9 (0.5–1.6)	
				Paraquat:	14	1.8 (1.0–3.4)	
				Trifuralin:	31	0.9 (0.5–1.6)	
				Cyanazine	30	2.6 (1.4–4.9)	
Firestone et al., 2005; Washington, US	250 (156 men) newly diagnosed 1992–2002 at Group Health Cooperative	388 (241 men)	Interview determining occupational and home-based pesticide exposure characterized by chemical name or brand, duration, and frequency	Occupational, men only			Controlled for age, sex, smoking
				Pesticides:	19	1.0 (0.5–1.9)	
				Insecticides:	15	0.9 (0.4–1.8)	
				Fungicides:	2	0.4 (0.1–3.9)	
				Herbicides:	9	1.4 (0.5–3.9)	
				Paraquat:	2	1.7 (0.2–12.8)	
				Home use, all subjects			
				Pesticides:	178	1.0 (0.7–1.4)	
				Insecticides:	141	0.8 (0.6–1.1)	
				Fungicides:	14	0.6 (0.3–1.1)	
				Herbicides:	116	1.1 (0.8–1.5)	
Behari et al., 2001; India	377 (301 men, 76 women)	377 matched for age (± 3 yr), but not sex	Structured interview	McNemar chi-square:		p = 0.010	
				Herbicides:			

continued

TABLE 9-1 Epidemiologic Studies of Herbicide[a] Exposure and Parkinson Disease, continued

Reference and Country	Cases in Study Group	Comparison Group	Exposure Assessment	Exposure(s)[a]	n	OR (95% CI)	Diagnosis of Neurologic Dysfunction
				(protective effect—*not confirmed* by multivariate analysis)			
				Insecticide:		p = 0.169	
				Rodenticide:		p = 0.662	
Engel et al., 2001; US [cross-sectional, but otherwise fairly high-quality design]	238	72	Self-administered questionnaire for occupational exposure	[prevalence ratios]			
				Any pesticide:		0.8 (0.5–1.2)	Neurologic exam by trained nurse
				Herbicides:		0.9 (0.6–1.3)	
				Insecticides:		0.9 (0.6–1.5)	
				Fungicides:		0.8 (0.6–1.3)	
Kuopio et al., 1999; Finland	123 (onset of PD before 1984; 63 men, 60 women)	246 matched on sex, age (± 2 yr), and urban/rural	Interview—pesticides or herbicides regularly or occasionally used	Pesticide use:	39	1.0 (0.6–1.7)	Neurologic exam
				Occasional use:	26	1.2 (0.7–2.0)	
				Regular use:	13	0.7 (0.3–1.3)	
				Herbicide use:	33	1.4 (0.8–2.5)	
				Occasional use:	20	1.7 (0.9–3.2)	
				Regular use:	13	0.8 (0.4–1.7)	
Taylor et al., 1999; Boston Medical Center	140	147 controls referred by cases	Interview—exposure recorded as total days for lifetime	Logistic analysis adjusted for age, sex, family history, education, smoking, water source, head injury, depression			Neurologic exam
				Pesticides:		1.0 (0.9–1.2)	
				Herbicides:		1.1 (0.7–1.7)	
Gorell et al., 1998; US	144 (age > 50 yrs)	464	Interview—herbicide and insecticide use while working on a farm or gardening	All occupations contributing exposure to:			Standard criteria of PD by history
				Herbicides:		4.1 (1.4–12.2)	
				Insecticides:		3.6 (1.8–7.2)	
				Fungicides:		1.6 (0.5–5.5)	

Liou et al., 1997; Taiwan	120	240 hospital controls matched for age (± 2 yr) and sex	Interview—occupational exposures to herbicides or pesticides	Pesticides vs no pesticides: But no paraquat use: Paraquat use: Paraquat use vs no paraquat:		2.9 (2.3–3.7) 2.2 (0.9–5.6) 4.7 (2.0–12)) 3.2 (2.4–4.3)	Neurologic exam
Seidler et al., 1996; Germany	380 (age < 66 yrs with PD after 1987)	755 (379 neighborhood, 376 regional; neighborhood controls may be over-matched)	Interview—dose-years = years of application weighted by use	Pesticides: Herbicides—high dose: Dose trend vs neighbor controls vs regional controls Insecticides—high dose: Dose trend vs neighbor controls vs regional controls		2.1 (1.6–2.6) 2.4 (1.0–6.0) p = 0.06 p < 0.001 2.1 (0.9–4.8) p = 0.12 p < 0.001	Neurologic exam
Hertzman et al., 1994; Canada	127 (71 men and 56 women)	245 (121 with cardiac disease; 124 voters)	Interview—occupation with probable pesticide exposure	Cases vs voters—among men Pesticides: Herbicides: Chlorophenoxys: Paraquat: Insecticides: Fungicides:		 2.3 (1.1–4.9) 1.2 (0.6–2.5) 1.2 (0.6–2.4) 1.3 (0.3–4.6) 0.3 (0.1–0.9)	Neurologic exam
Butterfield et al., 1993; US	63 young onset cases (age < 50 years)	68	Questionnaire—pesticide or insecticide use 10 times in any year	Herbicides: Insecticides: Dwelling fumigated:		3.2 p = 0.033 5.8 p < 0.001 5.3 p = 0.45	Standard criteria of PD by history
Semchuk et al., 1992; Calgary, Alberta, Canada	130 living cases from register of Calgary residents (population-based)	260 community controls matched for age (± 2.5 yr) and sex, identified by RDD	Interview—self-report of exposure for each job held > 1 month	Pesticides: Herbicides: Exposed during age interval: 16–25 yr 26–35 yr 36–45 yr	32 17	2.3 (1.3–4.0) 3.1 (1.3–7.0) 1.4 (0.5–4.3) 4.8 (1.5–15.0) 3.8 (1.2–13.0)	Neurologic exam confirming idiopathic PD without dementia (average 7.8 yr from diagnosis)

continued

TABLE 9-1 Epidemiologic Studies of Herbicide[a] Exposure and Parkinson Disease, continued

Reference and Country	Cases in Study Group	Comparison Group	Exposure Assessment	Exposure(s)[a]	n	OR (95% CI)	Diagnosis of Neurologic Dysfunction
				46–55 yr		4.9 (1.3–19.0)	
				Insecticides:	17	2.1 (1.0–4.1)	
				Fungicides:	16	1.6 (0.8–3.3)	
Stern et al., 1991; NJ and PA, US	69—all young onset cases identified (age < 40 yrs); 80—random selection of old onset cases (age > 59 yrs)	149 nominated by each case or picked from hospital; matched by age (± 6 yr), sex, and race	Interview—self-report of insecticide and pesticide use by self or others in home or garden	Insecticides:		0.7 (0.3–1.4)	Review of medical records, responsive to PD medication (under treatment average of 8.2 yr), without major cognitive impairment
				Onset < 40 years:		0.6 (0.2–1.7)	
				Onset > 59 years:		0.8 (0.3–2.1)	
				Herbicides:		1.1 (0.7–1.7)	
				Onset < 40 years:		0.9 (0.5–1.7)	
				Onset > 59 years:		1.3 (0.7–2.4)	
				Adjusted for smoking, head injury, rural residence:			
				Insecticides:		0.5 (0.2–1.1)	
				Herbicides:		0.9 (0.6–1.5)	
Hertzman et al., 1990; British Columbia, Canada	57 prevalent PD patients (age < 79 yrs) (50–54 had confirmed PD, not clear exactly how many)	122 aged 50–79 who responded from electoral rolls	Questionnaire—ever worked in an orchard	Work in orchards:		3.7 (1.3–10.3)	Neurologic exam confirmed diagnostic criteria in 55 of 69 cases identified by asking physicians in area
				Paraquat:	4/57	(p = 0.01)	

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TP, 2-(2,4,5-trichlorophenoxy) propionic acid or Silvex; CI, confidence interval; OR, odds ratio; PD, Parkinson disease; RDD, random-digit dialing.

[a]For the objective of the VAO review series, only associations with herbicides are of possible relevance; only the phenoxy herbicides, cacodylic acid, and picloram are of specific interest.

1.12–3.21), and exposure to 2,4-D also significantly increased risk (OR = 2.59, 95% CI 1.03–6.48). The strengths of this study were the multicenter recruitment strategy and the careful job ascertainment.

Another well-controlled study was performed investigating 224 PD cases and 557 controls drawn from an agricultural area in France with a high degree of pesticide/herbicide use (Elbaz et al., 2009). Occupational exposure was conducted with a two-stage process that included initial self-assessment followed by individual interviews with an occupational specialist. Farming as an occupation as well as professional pesticide use were significantly associated with an increased risk of PD. Exposure to phenoxy herbicides was associated with a trend toward higher risk of PD (OR = 1.8, 95% CI 0.9–3.3) which became statistically significant when age of onset was restricted to greater than 65 years (OR = 2.9, 95% CI 1.1–7.3).

Progressive Supranuclear Palsy (PSP) is a disorder that overlaps PD with respect to many symptoms. In a small case–control study of 79 patients with PSP and 79 controls, Vidal et al. (2009) found no relationship between risk of PSP and exposure to herbicides in general.

Biologic Plausibility

Several reviews of the literature have addressed the possible involvement of environmental chemicals in the etiology of PD. The very clear PD-like toxicity resulting from human exposure to MPTP has indicated that select compounds can result in the same type of damage to dopaminergic neurons as PD does, and MPTP has become an important toxicant in studies that use animal and in vitro models. It is notable that MPTP's bioactive metabolite, MPP+, is similar in chemical structure to paraquat (a commonly used herbicide although not one used in Vietnam); but it is different from the chemicals of interest in this report. Pesticides that have been shown to produce PD-like toxicity in animal models include paraquat, rotenone, maneb, and dieldrin, and substantial research has gone into understanding the molecular mechanisms responsible for the toxicity, especially in connection with paraquat and rotenone, as reviewed recently by Drechsel and Patel (2008), Hatcher et al. (2008), and Nunomura et al. (2007) and by others in the past, including Di Monte et al. (2002) and Sherer et al. (2002a). The damage done to dopaminergic neurons in PD is probably from oxidative stress and probably also involves damage to mitochondria in the target cells (Liang et al., 2007; Sarnico et al., 2008). In this regard, Bongiovanni et al. (2007) found that rat cerebellar granule cells in culture produce increased levels of reactive oxygen specials when exposed to 2,4-D. The chemicals of interest to this committee are known to be distributed to the CNS, but they have not been investigated in similar experimental systems, so there is no evidence that they could cause inflammation or oxidative stress similar to that caused by the compounds, such as paraquat, that have been investigated.

Research on the neurotoxicity of 2,4-D has been going on for a number of years, but most of it has focused on its effects on the developing rodent nervous system. The studies have often used high doses of 2,4-D that have resulted in adverse changes in the developing nervous system, both neurochemical (such as changes in D2 receptors, tyrosine hydroxylase and dopamine beta-hydroxylase) and behavioral (for example, Bortolozzi et al., 1999, 2002, 2003, 2004; Duffard et al., 1996; Evangelista de Duffard et al., 1990, 1995; Garcia et al., 2004, 2006; Rosso et al., 2000a,b). Injection of 2,4-D directly into the rat brain yielded toxicity in the basal ganglia (Bortolozzi et al., 2001), but this route of administration is highly artificial. Recent studies showed that postpartum dietary exposure of females to 2,4-D resulted in adverse alterations in maternal behavior and neurochemical changes including increases in dopamine and its metabolites 3,4-dihydroxyphenylacetic acid and homovanillic acid (Sturtz et al., 2008). Such an increase in dopamine is the reverse of what is seen in PD, in which degradation of the dopaminergic system occurs. In addition, a study of mice and 2,4-D yielded no evidence of neurochemical damage to the dopaminergic system (Thiffault et al., 2001). One study indicated that 2,4-D, among a variety of pesticides and metals, caused fibrillation of α-synuclein in vitro, but it used purified protein and did not report data on 2,4-D but only a generalized result (Uversky et al., 2002), so little confidence can be placed in it. Because the majority of the studies were on the developing nervous system, not the mature nervous system, and some studies yielded evidence of a lack of a role of 2,4-D in the development of PD, the existing studies are of little use in addressing the question of the etiology of PD.

A general summary of the biologic plausibility of neurologic effects of exposure to the herbicides used in Vietnam is presented at the end of this chapter.

Synthesis

Update 2008 reviewed three recent epidemiological studies (Brighina et al., 2008; Hancock et al., 2008; Kamel et al., 2007) as well as reevaluated older studies that did not specifically investigate relationships between disease and the compounds of interest (COIs). Based on the preponderance of data, the committee concluded that there was limited or suggestive evidence of an association of COIs with PD. This conclusion was arrived at despite concern that no specific studies had been performed on veterans, as well as the fact that a clear biological mechanism underlying a relationship was not known. Since 2008, two well-designed epidemiological studies performed in the United States and France primarily on rural workers have also shown a relationship. There continues to be a dearth of investigation on veterans, and biological plausibility is still lacking. We continue to strongly urge the performance of studies relating PD incidence to exposure in the Vietnam-veteran population. We are also concerned that a biologic mechanism by which the chemicals of interest may cause PD has not been demonstrated. Nevertheless, the preponderance of epidemiologic evidence

continues to support an association between herbicide exposure and PD and specifically implicates the chemicals of interest.

Conclusions

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is limited or suggestive evidence of an association between exposure to the chemicals of interest and PD.

Amyotrophic Lateral Sclerosis

ALS is a progressive, adult-onset, motor neuron disease that presents with muscle atrophy, weakness, and fasciculations and with signs that implicate involvement of motor pathways in the CNS. The cause of most cases of ALS is unknown, but about 10% of cases report an autosomal dominant pattern of inheritance. One-fifth of familial-ALS patients have mutations in the gene that encodes superoxide dismutase-1 (Rosen et al., 1993). The incidence of sporadic ALS is 1–2 per 100,000 person–years, and the incidence of ALS peaks at the ages of 55–75 years (Brooks, 1996). The diagnosis of ALS is made through clinical examination and electrodiagnostic testing and has a high degree of accuracy when made by experienced neurologists (Rowland, 1998; Rowland and Shneider, 2001).

Summary of Previous Updates

ALS was first considered by the committee for *Update 2002*. Although multiple potential etiologic factors have been investigated (Breland and Currier, 1967; Deapen and Henderson, 1986; Gallagher and Sander, 1987; Hanisch et al., 1976; Kurtzke and Beebe, 1980; McGuire et al., 1997; Roelofs-Iverson et al., 1984; Savettieri et al., 1991), associations have not been consistently identified.

Pesticide or herbicide exposure has been associated with increased risk of ALS, including a doubling of the risk after long-term occupational exposure to pesticides (Deapen and Henderson, 1986) and a tripling of the risk after exposure to agricultural chemical products (Savettieri et al., 1991) and after exposure to herbicides (McGuire et al., 1997), although none of the risk estimates was statistically significant. A population-based case–control study demonstrated associations between exposure to agricultural chemical products and ALS in men, with an odds ratio of 2.4 and a trend with duration of exposure that were both statistically significant (McGuire et al., 1997). A mortality study of Dow Chemical Company employees exposed to 2,4-D included three deaths from ALS, with a significant positive association (relative risk, 3.45, 95% CI 1.10–11.11) (Burns et al., 2001).

In *Update 2006*, three additional studies were reviewed. Morahan and Pamphlett (2006) published a case–control study from Australia in which the

cases were self-reported and the controls chosen in nonrandom fashion. The authors found an increased risk of ALS after exposure to pesticides or herbicides, but the lack of appropriate case and control ascertainment and the fact that specific chemicals of interest were not asked about make this study difficult to interpret. Weisskopf et al. (2005) followed vital status of subjects in the American Cancer Society's cohort for the Cancer Prevention Study II and demonstrated an increased risk of ALS in those who served in any of the armed services during times of conflict. They adjusted for a variety of confounding variables in their model, including exposure to herbicides, and found that none of them significantly altered their conclusions. Thus, in an indirect way, this large study suggests the lack of a strong effect of herbicide exposure on ALS. Finally, a case–control study of Australian Vietnam veterans reported an association between deployment in Vietnam and ALS (ADVA, 2005c) but did not specifically study exposure to pesticides or herbicides.

No additional studies concerning exposure to the chemicals of interest and ALS were found for review in *Update 2008*.

Table 9-2 summarizes the results of the relevant studies.

Update of the Epidemiologic Literature

Since the last update, there has been one report evaluating the relationship between a variety of chemical exposures and death from ALS in more than 1 million participants of the American Cancer Prevention Study (Weiskopf et al., 2009). Among men, 617 deaths due to ALS were identified, and 539 deaths among women. Exposure to pesticides and herbicides were considered together, so the exposure characterization was not sufficiently specific to meet the committee's criteria. Nonetheless, no evidence of a significant relationship of exposure to death from ALS was found.

Biologic Plausibility

No toxicology studies concerning exposure to the chemicals of interest and ALS have been published since *Update 2008*. A general summary of the biologic plausibility of neurologic effects of exposure to the herbicides used in Vietnam is presented at the end of this chapter.

Synthesis

No well-designed studies have implicated a relationship between compounds of interest and the risk of developing ALS.

TABLE 9-2 Epidemiologic Studies of Pesticide[a] Exposure and Amyotrophic Lateral Sclerosis

Reference; Country	Study Group	Comparison Group	Exposure Assessment	Significant Association with Pesticides[a]	**Exposure of Interest**/ Estimated Risk (95% CI)	Neurologic Dysfunction
Morahan and Pamphlett, 2006; Australia	179	179	Questionnaire—exposure to environmental toxicants		**Herbicides, pesticides**/1.6 (1.0–2.4); industrial exposure: 5.6 (2.1–15.1)	Self-reported
ADVA, 2005c; Australia	nr	nr	Deployment to Vietnam		**All COIs**/4.7 (1.0–22.8)	
Weisskopf et al., 2005	nr	nr	Self-administered questionnaire		**Military Service**/1.5 (1.1–2.1); p = 0.007	Self-reported military services, death certificates
Burns et al., 2001; US	1,567	40,600	Industrial hygienist ranked jobs for exposure to 2,4-D to derive years of exposure and cumulative exposure	+	**2,4-D**/3.45 (1.1–11.1)	Death certificates
McGuire et al., 1997; US	174	348	Self-reported lifetime job history, workplace exposures reviewed by panel of four industrial hygienists	+	**Herbicides**/2.4 (1.2–4.8); significant trend analysis for dose–effect relationship with agricultural chemicals; p = 0.03	New diagnosis of ALS 1990–1994 in western Washington state
Chancellor et al., 1993; Scotland	103	103	Required regular occupational exposure to pesticides for 12 months or more		**Pesticides** 1.4 (0.6–3.1)	Scottish Motor Neuron Register
Savettieri et al., 1991; Italy	46	92	Continual exposure to agricultural chemicals		**Pesticides** 3.0 (0.4–20.3)	Cases reviewed by neurologists
Deapen and Henderson, 1986; US	518	518	Ever worked in presence of pesticides		**Pesticides** 2.0 (0.8–5.4)	ALS Society of America

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; ALS, amyotrophic lateral sclerosis; CI, confidence interval; COI, chemical of interest; nr, not reported; OR, odds ratio.

[a]For the objective of the VAO review series, only associations with herbicides are of possible relevance; only phenoxy herbicides, cacodylic acid, and picloram are of specific interest.

Conclusions

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that the evidence of an association between exposure to the chemicals of interest and ALS remains inadequate or insufficient.

CHRONIC PERIPHERAL SYSTEM DISORDERS

Peripheral neuropathies comprise a spectrum of disorders caused by damage to nerve fibers (axonal neuropathies) or to the myelin sheath that surrounds many fibers (demyelinating neuropathies). Manifestations of neuropathy can include a combination of sensory changes, motor weakness, and autonomic instability. Clinically, various forms of peripheral neuropathy can be characterized by the distribution of nerve abnormalities and their patterns of progression.

Peripheral neuropathy resulting from toxic exposure usually affects nerve fibers in a symmetric pattern, beginning distally in the longest fibers (in the toes) and moving proximally (toward the spine). This kind of neuropathy is called symmetric axonal sensorimotor polyneuropathy. Sensory deficits begin at the toes, progress above the ankles, and affect the hands only later. Motor symptoms show the same general pattern. Physiologically, various forms of peripheral neuropathy can be characterized by results of electrodiagnostic testing to indicate which neural structures are affected. Most toxicant-induced neuropathies involve injury to the nerve-cell bodies (neurons) or nerve fibers (axons) that produces changes in the amplitude of a nerve's response to an electric stimulus.

The clinical appearances of most symmetric axonal neuropathies are quite similar except for variation in rates of progression and in whether pain is a prominent symptom. There is no specific signature that distinguishes a toxicant-related neuropathy from one induced by other causes. As many as 30% of neuropathies are "idiopathic"; that is, no etiology is determined despite exhaustive clinical evaluation.

The most common toxicant-induced neuropathy occurs as a result of chronic alcohol exposure. Peripheral neuropathy also occurs commonly as a complication of diabetes; its reported prevalence in people who have chronic diabetes is up to 50%. It is important to include assessment of alcohol use and diabetes as covariates in epidemiologic studies, because the neuropathies that are related to these conditions are clinically and physiologically indistinguishable from other toxicant-induced neuropathies.

Toxicant exposure can result in an immediate response of peripheral neuropathy (early onset) or chronic peripheral neuropathy that occurs years after the external exposure has ended (delayed onset). The committee considers a neuropathy to be early onset if abnormalities appear within a year after external exposure ends or to be chronic if abnormalities appear more than a year after external exposure has ended. A review of the data supporting the association of

exposure with early-onset peripheral neuropathy is presented in Appendix B, and will not be recapitulated here. Because the exposures of interest for Vietnam veterans are long past, immediate effects of the chemicals of interest are no longer pertinent for this cohort. The focus of this section will be on data related to chronic peripheral neuropathy.

Summary from *VAO* and Previous Updates

VAO reviewed epidemiology studies of populations potentially exposed to TCDD in the environment. A series of studies in Italy evaluated peripheral neuropathy in the Seveso population. Barbieri et al. (1988) reported a higher rate of abnormalities on neurologic examination and electrodiagnostic testing in subjects who had a history of chloracne and were examined 6 years after the accident, but there was no significant increase in peripheral neuropathy as defined by the World Health Organization criteria. Assennato et al. (1989) studied 193 exposed residents of the area 9 years after the accident and did not demonstrate neurophysiological abnormalities. Other environmental studies reviewed in *VAO* were of Missouri residents potentially exposed to TCDD in the early 1970s when waste oil was sprayed to control dust (Hoffman et al., 1986; Stehr et al., 1986; Webb et al., 1987). Although more frequent sensory abnormalities were reported in potentially exposed subjects, the differences were not statistically significant, and the semiecologic study design was not suited to causal inference. Some of the data from epidemiologic studies of environmental exposures have suggested an increased risk of peripheral nerve abnormalities, but evidence of an association between exposure to the chemicals of interest and peripheral neuropathy is inconsistent.

Studies of Vietnam veterans were also reviewed in *VAO* (AFHS, 1984, 1987, 1991; CDC, 1988). A study by the Centers for Disease Control (now the Centers for Disease Control and Prevention) (CDC, 1988) focused on service in Vietnam, not on exposure to the chemicals of interest, and therefore provided no evidence of the possible effects of specific exposures. There was no indication of increased risk of peripheral neuropathy in the first reports on Ranch Hand veterans (AFHS, 1984, 1987, 1991). Studies reviewed in *VAO* did not indicate an association between exposure and peripheral neuropathy in Vietnam veterans.

Update 1996 reviewed two new epidemiologic studies. Using an administrative database, Zober et al. (1994) found no evidence of increased use of medical services for diagnosis of peripheral neuropathy in workers previously exposed to TCDD at a BASF plant. Decoufle et al. (1992) reported no association between self-reported exposure to herbicides in Vietnam and peripheral neuropathy. The limitations of those studies were such that they did not confirm or refute a possible relationship between exposure and neuropathy.

Update 2000 reviewed what was then the most recent report on Ranch Hand veterans (AFHS, 2000), which combined signs of peripheral neuropathy to pro-

duce increasingly specific, graded indexes of neuropathy—a common approach in epidemiologic studies. Ranch Hand veterans were significantly more likely than comparison subjects to have abnormalities in the indexes, and the prevalence of abnormalities increased with dioxin concentration. Although the clinical relevance of epidemiologic indexes of neuropathy is never certain, the strong associations described between the indexes and the conditions known to produce peripheral neuropathy, such as diabetes and alcohol use, supported their validity in this study. The AFHS investigators included those conditions as potential confounders in their statistical analysis. However, the effect of diabetes could not be eliminated in the most specific neuropathy index, because there were not enough nondiabetic subjects. It therefore was impossible, lacking any effect of diabetes, to estimate the association between dioxin exposure and neuropathy.

Update 2002 considered one peer-reviewed article that described the peripheral-neuropathy data on the AFHS cohort (Michalek et al., 2001). In a primary analysis, the investigators had included diabetes as a potential confounder in the statistical model. In a secondary analysis, subjects who had conditions that were known to be associated with neuropathy were excluded, and subjects who had diabetes were enumerated. In both analyses, there were strong and significant associations between dioxin concentrations and possible and probable neuropathy, and significant trends were found with increasing concentrations of dioxin. However, there were too few nondiabetic subjects to produce useful estimates of risk in the absence of the contribution of diabetes. Thus, questions remained about the specific association between exposure to the chemicals of interest and peripheral neuropathy in the absence of any effect of diabetes.

In summary, studies on Vietnam veterans originally did not demonstrate a relationship between service and symptoms of neuropathy; however, the more recent studies suggesting a relationship are not due to an increase in neuropathic symptoms but to a more sensitive measure of assaying symptom complexes (AFHS, 2000; Michalek et al., 2001). All of the large veteran studies are limited by the confounding nature of concurrent diabetes and alcohol exposure, both of which also are related to neuropathy.

Update of the Scientific Literature

Since the last update, there has been one study evaluating the association of exposure to a variety of toxicants to the presence of neuropathy in subjects with either frank diabetes or impaired glucose tolerance (Lee et al., 2008). Concentrations of dioxin-like polychlorinated biphenyls (PCBs) were ranked, and subjects with hemoglobin A1C levels of greater or less than 7 were compared separately. In neither group was there evidence of an increased incidence of neuropathy or of a dose response that suggested a concentration dependent risk of neuropathy. Given the underlying risk of neuropathy inherent in patients with diabetes, the

lack of information regarding duration of diabetes as well as small subject numbers renders this study difficult to evaluate.

Also, Pelclová et al. (2009) updated a study of Czech workers (aged 64.4 ± 1.5 years) exposed to TCDD between 1965–1968, while working in a plant producing 2,4,5-T. Eleven out of the original group of approximately 80 workers were reevaluated for this update. Seven exposed workers were found to have mild polyneuropathy, as well as diabetes. The usefulness of this study is limited because of the small sample size, the lack of a well-defined comparison population, the lack of comparison data between the exposed and non-exposed populations, and the absence of information about the relationship between diabetes and neuropathy in these workers.

Biologic Plausibility

No new studies directly pertinent to peripheral neuropathy were identified in the present update. However, it is worth reiterating findings from earlier updates. Neuronal cell cultures treated with 2,4-D showed decreased neurite extension associated with intracellular changes, including a decrease in microtubules, inhibition of the polymerization of tubulin, disorganization of the Golgi apparatus, and inhibition of ganglioside synthesis (Rosso et al., 2000a,b). Those mechanisms are important for maintaining synaptic connections between nerve cells and supporting the mechanisms involved in axon regeneration during recovery from peripheral neuropathy. Grahmann et al. (1993) and Grehl et al. (1993) reported the observations of electrophysiologic and pathologic abnormalities, respectively, in the peripheral nerves of rats treated with TCDD. When the animals were sacrificed 8 months after exposure, there was pathologic evidence of persistent axonal nerve damage and histologic findings typical of toxicant-induced injury. Those results constitute evidence of the biologic plausibility of an association between exposure to the chemicals of interest and peripheral neuropathy.

A summary of the biologic plausibility of neurologic effects arising from exposure to the chemicals of interest is presented at the end of this chapter.

Synthesis

The epidemiological studies relating industrial or individual exposure to acute neuropathy were judged by the committee for *Update 1996* and subsequent updates to constitute limited or suggestive evidence of an association between exposure to the chemicals of interest and early-onset transient peripheral neuropathy. As summarized above, further studies of the long-term sequelae of these exposures also suggest persistence of symptoms either permanently or over years.

There are, however, no data that suggest that exposure to compounds of interest can lead to the development of delayed-onset chronic neuropathy many

years after termination of exposure among those who did not originally complain of early onset neuropathy.

Conclusions

The committee concludes that, in addition to evidence for transient early-onset peripheral neuropathy, there is limited or suggestive evidence of an association between exposure to the chemicals of interest and early-onset peripheral neuropathy that may be persistent.

On the basis of the evidence reviewed here and by previous committees, however, this committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and delayed-onset chronic neuropathy.

HEARING LOSS

Hearing loss increases markedly with age, with about one in four people over 70 years of age being affected and the prevalence being somewhat higher in men than women (NCHS, 1994, 2010). The most common forms of hearing impairment developing adults are presbycusis and tinnitus. Heritable factors may be influenced susceptibility to hearing loss, but external agents can also contribute. Aspirin at high doses can cause reversible tinnitus, while permanent hearing loss may be induced by pharmaceuticals (particularly antibiotics and anti-neoplastic drugs) and by some environmental and industrial chemicals (primarily solvents and metals). In occupational medicine, hearing loss is most often considered as being noise-induced. Cochlear development has been found to be impaired by hypothyroidism induced by endocrine disruptors (Howdeshell, 2002), but such a gestational effects would not pertain to Vietnam veterans exposed to herbicides as adults.

Update of the Epidemiologic Literature

A cohort of Australian Vietnam veterans (O'Toole et al., 2009) was studied between 1990–1993 and reexamined in 2005–2006. In the original assessment, 641 Australian Vietnam veterans were randomly selected for participation from the list of Army veterans deemed eligible for previous studies of Agent Orange and 450 were included in the more recent assessment. Interviewers administered the Australian Bureau of Statistics National Health Survey that assessed physical health and associated risk factors, a 32-item combat index, an assessment for combat-related PTSD, and an assessment of general psychiatric status. The prevalences of a variety of self-reported health conditions were compared to the general population and standardized mortality ratios (SMRs) were calculated (standardized to the Australian male population in 5-year age groups). Compared

to the general population, Vietnam veterans had an increased prevalence of diseases of the ear and mastoid (SMR = 1.93, 95% CI 1.81–2.05; SMR = 5.96, 95% CI 5.36–6.57) for complete or partial deafness and tinnitus, respectively. The committee had serious concerns that the results reported in O'Toole et al. (2009) were compromised by recall bias and other methodologic problems.

Crawford et al. (2008) examined hearing loss among licensed pesticide applicators in the Agricultural Health Study (see Chapter 5). Self-reported hearing loss was reported in the AHS 5-year follow-up interview. In this nested case–control study of the 14,229 white male applicators, 4,926 reported hearing loss (35%) not resulting from a congenital condition or infection (as determined from additional survey questions). Several variables related to pesticide accidents or high-exposure events were related to self-reported hearing loss. For example, compared to those who had not received pesticide-related medical care or who did not experience a high pesticide exposure event, risk of self-reported hearing loss was increased (OR = 1.81, 95% CI 1.25–2.62; OR = 1.38, 95% CI 1.24–1.53), for having been treated for a pesticide-related medical condition or ever having a high pesticide exposure event, respectively. Similarly, ever having a diagnosis of pesticide poisoning was associated with hearing loss (OR = 1.75, 95% CI 1.36–2.26). Analyses by pesticide class did not show strong associations with hearing loss. Compared to no reported days of insecticide use, applicators in the exposure category (greater than 175 days of insecticide use) was associated with self-reported hearing loss (OR = 1.19, 95% CI 1.04–1.35). In contrast, applicators reporting more than 651 lifetime days of herbicide use did not have a higher risk of self-reported hearing loss (OR = 1.04, 95% CI 0.91–1.20).

Biologic Plausibility

Toxicologic studies of hearing impairment in conjunction with the chemicals of interest have not been found in the published literature.

Synthesis

While two studies observed increased risk of hearing loss among Vietnam veterans and among pesticide applicators, neither study was able to examine the specific chemicals of interest to the committee and neither was able to clinically confirm hearing loss. Further, the report from the AHS (Crawford et al., 2008) only observed an association among insecticide applicators and not herbicide applicators. While the O'Toole study evaluated Vietnam veterans, the comparison group was limited to the general population and not veterans from the same era not deployed to Vietnam and therefore could not distinguish between hearing loss that may be associated with noise-related to military service and hearing loss potentially associated with exposures to toxic chemicals.

Conclusion

On the basis of the evidence reviewed here, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and hearing loss.

SUMMARY

Biologic Plausibility

Experimental data continue to accrue regarding the biologic plausibility of a connection between exposure to the chemicals of interest and various neurologic disorders. This section summarizes in a general way some of the information reviewed in the current update and, to make the summary complete, includes information from prior updates.

Several studies have dealt with mechanisms of neurotoxicity that might be ascribed to the chemicals of concern, notably 2,4-D and TCDD. Molecular effects of the chemicals of concern are described in detail in Chapter 4. Some of the effects suggest possible pathways by which there could be effects on the neural systems. A number of the studies suggest that there are neurologic effects, both neurochemical and behavioral, of the chemicals of interest, primarily 2,4-D, in animal models if exposure occurs during development or in cultured nerve cells (Konjuh et al., 2008; Rosso et al., 2000a,b; Sturtz et al., 2008); older references described behavioral effects of developmental exposure of rodents to a 2,4-D–2,4,5-T mixture (Mohammad and St. Omer, 1986; St. Omer and Mohammad, 1987). TCDD has caused deficits in learning behavior in the rat after exposure during development (Hojo et al., 2008). However, caution against overinterpreting the significance of these studies is urged because the developing nervous system is different from the mature nervous system and may not be an appropriate model for the possible consequences of exposure of adults to the chemicals of interest.

Some studies further support suggestions that the level of reactive oxygen species could alter the functions of specific signaling cascades and may be involved in neurodegeneration (Drechsel and Patel, 2008). Such studies do not specifically concern the chemicals of interest but are potentially relevant to these chemicals inasmuch as TCDD and herbicides have been reported to elicit oxidative stress (Byers et al., 2006; Celik et al., 2006; Shen et al., 2005). In addition, TCDD has been shown to affect phosphokinase C biochemistry in nerve cells and therefore could affect the integrity and physiology of nerve cells (Kim et al., 2007; Lee et al., 2007). Cytochrome P450 1A1, the aryl hydrocarbon receptor (AHR), and the AHR nuclear transporter occur in the brain, so TCDD might be likely to exert effects in the brain (Huang et al., 2000). In addition, although they dealt with hepatocytes and not cells of the nervous system, earlier studies have

indicated that 2,4-D affected aspects of mitochondrial energetics and mitochondrial calcium flux (Palmeira et al., 1994a,b, 1995a,b); if these effects can also occur with nervous system cell mitochondria, which is feasible, then the energy balance and pathways of cells in the nervous system could be affected, with later damage to nervous system function. Those mechanistic studies, although they did not produce convincing evidence of specific effects of the chemicals of interest in the neurologic outcomes of concern, suggest possible avenues to pursue to determine linkages between the chemicals of interest and the neurologic outcomes that could occur in adult humans.

Basic scientific studies have emphasized the importance of alterations in neurotransmitter systems as potential mechanisms that underlie TCDD-induced neurobehavioral disorders. Neuronal cultures treated with 2,4-D exhibited decreased neurite extension associated with intracellular changes, including a decrease in microtubules, inhibition of the polymerization of tubulin, disorganization of the Golgi apparatus, and inhibition of ganglioside synthesis. Those mechanisms are important for maintaining the connections between nerve cells that are necessary for neuronal function and that are involved in axon regeneration and recovery from peripheral neuropathy. Animal experiments have demonstrated that TCDD treatments affect the fundamental molecular events that underlie neurotransmission initiated by calcium uptake. Mechanistic studies have demonstrated that 2,4,5-T can alter cellular metabolism and the cholinergic transmission necessary for neuromuscular transmission.

TCDD treatment of rats at doses that do not cause general systemic illness or wasting disease produces electrodiagnostic changes in peripheral nerve function and pathologic findings that are characteristic of toxicant-induced axonal peripheral neuropathy.

As discussed in Chapter 4, extrapolation of observations of cells in culture or animal models to humans is complicated by differences in sensitivity and susceptibility among animals, strains, and species; by the lack of strong evidence of organ-specific effects among species; and by differences in route, dose, duration, and timing of chemical exposures. Thus, although the observations themselves cannot support a conclusion that the chemicals of interest produced neurotoxic effects in humans, they do suggest the biologic plausibility of an association and describe potential mechanisms that might have come into play.

Conclusions

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence of an association between exposure to the chemicals of interest (2,4-D, 2,4,5-T, TCDD, picloram, and cacodylic acid) and neurobehavioral disorders (cognitive or neuropsychiatric) or ALS.

Previous VAO reports had concluded that there was inadequate or insufficient evidence of an association between exposure to the chemicals of interest and PD. The committee for *Update 2008* reviewed both new data published after *Update 2006* and older studies investigating the relationship between herbicide exposure and PD risk. Although a compelling biologic mechanism has not been identified, the bulk of evidence suggests a risk of PD is posed by herbicide exposure in general. That impression was strengthened by newer studies that reported a specific risk related to the chemicals of interest, so the committee for *Update 2008* concluded that there is limited or suggestive evidence of an association between exposure to the chemicals of interest and PD. The additional relevant information published since *Update 2008* is consistent with that finding.

The committee for *Update 2004* exhaustively reviewed the data on peripheral neuropathy and concluded that there was limited or suggestive evidence of an association between exposure and "early-onset, transient" peripheral neuropathy, but that the evidence was inadequate or insufficient to support an association between exposure to the chemicals of interest and "delayed or persistent" peripheral neuropathy. The committees responsible for *Update 2006* and *Update 2008* concurred with that conclusion. The current committee scrutinized the available follow-up findings on individuals experiencing peripheral neuropathy shortly after exposure and wishes to clarify that early-onset peripheral neuropathy is not necessarily transient. Consequently, the distinction to be made concerning the type of peripheral neuropathy for which there is limited or suggestive evidence of association with herbicide exposure is based on time of onset rather than chronicity.

In summary, aside from noting limited or suggestive evidence of an association for persistent, as well as transient, peripheral neuropathy, on the basis of its review of new data and a re-evaluation of older studies, the present committee concurs with the conclusions of previous committees concerning neurologic outcomes.

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[1]Throughout the report the same alphabetic indicator following year of publication is used consistently for the same article when there were multiple citations by the same first author in a given year. The convention of assigning the alphabetic indicator in order of citation in a given chapter is not followed.

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10

Cardiovascular and Metabolic Effects

In this report, for the first time in the *Veterans and Agent Orange* series, cardiovascular health outcomes and metabolic effects are being addressed independently of other health outcomes. In previous reports in the series—*Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*, hereafter referred to as *VAO* (IOM, 1994), *Veterans and Agent Orange: Update 1996* (hereafter referred to as *Update 1996*) (IOM, 1996), *Update 1998* (IOM, 1999), *Update 2000* (IOM, 2001), *Update 2002* (IOM, 2003), *Update 2004* (IOM, 2005), *Update 2006* (IOM, 2007), and *Update 2008* (IOM, 2009)—those health outcomes were included in the "Other Health Outcomes" chapter. The change reflects the growth of evidence pertaining to metabolic syndrome and its potential role in the development of cardiovascular disease.

Some controversy remains as to whether increases in waist circumference, triglycerides, blood pressure, and fasting glucose and a decrease in high-density lipoprotein cholesterol constitute a "syndrome." But there is little dispute that these physical effects, which are often related to obesity and regarded as indicators of the "metabolic syndrome," are commonly present as comorbidities with adverse conditions of which there is increasing evidence of an association with Agent Orange exposure, and this suggests a possible interrelationship. This chapter summarizes and presents conclusions about the strength of the evidence from epidemiologic studies regarding an association between exposure to the chemicals of interest—2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), picloram, and cacodylic acid—and type 2 diabetes, lipid and lipoprotein disorders, and circulatory disorders.The committee also considers studies of exposure to polychlorinated biphenyls (PCBs) and other dioxin-like

chemicals informative if their results were reported in terms of TCDD toxic equivalents (TEQs) or concentrations of specific congeners.

TYPE 2 DIABETES

Diabetes mellitus is a group of heterogeneous metabolic disorders characterized by hyperglycemia and quantitative or qualitative deficiency of insulin action (Orchard et al., 1992). Although all forms share hyperglycemia, the pathogenic processes involved in its development differ. Most cases of diabetes mellitus are in one of two categories: type 1 diabetes is characterized by a lack of insulin caused by the destruction of insulin-producing cells in the pancreas (b cells), and type 2 diabetes is characterized by a combination of resistance to the actions of insulin and inadequate secretion of insulin (called relative insulin deficiency). In old classification systems, type 1 diabetes was called insulin-dependent diabetes mellitus or juvenile-onset diabetes mellitus, and type 2 was called non–insulin-dependent diabetes mellitus or adult-onset diabetes mellitus. The modern classification system recognizes that type 2 diabetes can occur in children and can require insulin treatment. Long-term complications of both types can include cardiovascular disease (CVD), nephropathy, retinopathy, neuropathy, and increased vulnerability to infections. Keeping blood sugar concentrations within the normal range is crucial for preventing complications.

About 90% of all cases of diabetes mellitus are of type 2. Onset can occur before the age of 30 years, and incidence increases steadily with age. The main risk factors are age, obesity, abdominal fat deposition, a history of gestational diabetes (in women), physical inactivity, ethnicity (prevalence is greater in blacks and Hispanics than in whites), and—perhaps most important—family history. The relative contributions of those features are not known. Prevalence and mortality statistics in the US population for 2006 are presented in Table 10-1.

The etiology of type 2 diabetes is unknown, but three major components have been identified: peripheral insulin resistance (thought by many to be primary) in target tissues (muscle, adipose tissue, and liver), a defect in β-cell secretion of insulin, and overproduction of glucose by the liver. In states of insulin resistance, insulin secretion is initially higher for each concentration of glucose than in people who do not have diabetes. That hyperinsulinemic state is a compensation for peripheral resistance and in many cases maintains normal glucose concentrations for years. Eventually, β-cell compensation becomes inadequate, and there is progression to overt diabetes with concomitant hyperglycemia. Why the β cells cease to produce sufficient insulin is not known. The onset of type 2 diabetes can be preceded by a set of clinical findings that are collectively called metabolic syndrome. A number of definitions of the syndrome have been proposed, but it typically includes a combination of high waist circumference, low high-density lipoprotein cholesterol, high triglycerides, high blood pressure, and high fasting glucose.

TABLE 10-1 Prevalence of Mortality from Diabetes, Lipid Disorders, and Circulatory Disorders in United States, 2006

ICD-9 Range	Diseases of Circulatory System	Prevalence (% of Americans 20 years old and older)		Mortality (no. deaths, all ages)	
		Men	Women	Men	Women
250	Diabetes	nr	nr	36,000	36,400
	Physician-diagnosed	7.9[a]	7.9[a]	nr	nr
	Undiagnosed	3.8[a]	1.9[a]	nr	nr
	Prediabetes	35.9[a]	22.2[a]	nr	nr
	Lipid disorders				
	Total cholesterol ≥ 200 mg/dL	45.2	47.9	nr	nr
	Total cholesterol ≥ 240 mg/dL	15.0	17.2	nr	nr
	LDL cholesterol ≥ 130 mg/dL	33.1	32.0	nr	nr
	HDL cholesterol < 40 mg/dL	25.0	7.9	nr	nr
390–459	All circulatory disorders	37.9	35.7	398,600	432,700
390–398	Rheumatic fever and rheumatic heart disease	nr	nr	1,022	2,226
401–404[b]	Hypertensive disease			24,400	32,200
401	Essential hypertension	nr	nr	nr	nr
402	Hypertensive heart disease	nr	nr	nr	nr
403	Hypertensive renal disease	nr	nr	nr	nr
404	Hypertensive heart and renal disease	nr	nr	nr	nr
410–414, 429.2	Ischemic, coronary heart disease	9.1	7.0	224,500	200,900
410, 412	Acute, old myocardial infarction	4.7	2.6	76,100	65,400
411	Other acute, subacute forms of ischemic heart disease	nr	nr	nr	nr
413	Angina pectoris	4.6	4.6	nr	nr
414	Other forms of chronic ischemic heart disease	nr	nr	nr	nr
429.2	Cardiovascular disease, unspecified	nr	nr	nr	nr
415–417[b]	Diseases of pulmonary circulation	nr	nr	nr	nr
420-429	Other forms of heart disease (such as pericarditis, endocarditis, myocarditis, cardiomyopathy)	nr	nr	nr	nr
426–427	Arrhythmias	nr	nr	nr	nr
428	Heart failure	3.1	2.1	123,600	159,200

TABLE 10-1 Continued

ICD-9 Range	Diseases of Circulatory System	Prevalence (% of Americans 20 years old and older)		Mortality (no. deaths, all ages)	
		Men	Women	Men	Women
430–438[b]	Cerebrovascular disease (such as hemorrhage, occlusion, transient cerebral ischemia; includes mention of hypertension in ICD-401)	2.5	3.2	54,500	82,600
440–448[b]	Diseases of arteries, arterioles, capillaries	nr	nr	nr	nr
451–459	Diseases of veins, lymphatics, other diseases of circulatory system	nr	nr	nr	nr

ABBREVIATIONS: HDL, high-density lipoprotein; ICD, International Classification of Diseases; LDL, low-density lipoprotein; nr, not reported.
SOURCE: AHA, 2010 (pp. e209–e210).
[a]For ages 18 years and above.
[b]Gap in ICD-9 sequence follows.

Type 1 diabetes occurs as a result of immunologically mediated destruction of β cells in the pancreas, which often occurs during childhood but can occur at any age. As in many autoimmune diseases, genetic and environmental factors influence pathogenesis. Some viral infections are believed to be important environmental factors that can trigger the autoimmunity associated with type 1 diabetes.

Pathogenetic diversity and diagnostic uncertainty are among the important problems associated with epidemiologic study of diabetes mellitus. Given the multiple likely pathogenetic mechanisms that lead to diabetes mellitus—which include diverse genetic susceptibilities (as varied as autoimmunity and obesity) and all sorts of potential environmental and behavioral factors (such as viruses, nutrition, and activity)—many agents or behaviors can contribute to risk, especially in genetically susceptible people. The multiplicity of mechanisms also can lead to heterogeneous responses to various exposures. Because up to half the cases of diabetes are undiagnosed, the potential for ascertainment bias in population-based surveys is high (more intensively followed groups or those with more frequent health-care contact are more likely to get the diagnosis); this emphasizes the need for formal standardized testing (to detect undiagnosed cases) in epidemiologic studies.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the chemicals of interest and diabetes mellitus. Additional information available to the committees responsible for *Update 1996* and *Update 1998* did not change that conclusion.

In 1999, in response to a request from the Department of Veterans Affairs, the Institute of Medicine called together a committee to conduct an interim review of the scientific evidence regarding type 2 diabetes. That review focused on information published after the deliberations of the *Update 1998* committee and resulted in the report *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes*, hereafter referred to as *Type 2 Diabetes* (IOM, 2000). The committee responsible for that report determined that there was limited or suggestive evidence of an association between exposure to at least one chemical of interest and type 2 diabetes. The committees responsible for *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008* upheld that finding. Reviews of the pertinent studies are found in the earlier reports; Table 10-2 presents a summary.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

Cypel and Kang (2010) updated information on cause-specific mortality in the Army Chemical Corps (ACC) cohort. The update includes 14 additional years of follow-up of the report by Dalager and Kang (1997). ACC members who served in Vietnam had a 79% excess risk of diabetes mortality compared with ACC members who did not serve in Vietnam (relative risk [RR] = 1.79, 95% confidence interval [CI] 0.73–4.39) after adjustment for race, rank, duration of military service, and age at entry into follow-up. A subsample of those who served in Vietnam provided self-reported information on whether they were involved in herbicide spraying. There were only 11 diabetes deaths in this subsample. Those who reported spraying had a higher rate of diabetes death than those who did not (RR = 2.21, 95% CI 0.61–8.02). Because of the low frequency of diabetes death, the RR estimates are imprecise, and CIs around the estimates include the null value.

Australian Vietnam veterans were studied in 1990–1993 (O'Toole et al., 1996) and reexamined in 2005–2006 (O'Toole et al., 2009). In the original assessment, 641 Australian Vietnam veterans in a randomly selected sample of 1,000 from the list of Army veterans deemed eligible for previous studies of Agent Orange responded; 450 responded to the second interview and are the subjects of the recent report. Prevalences of a variety of self-reported health conditions were compared with those in the general population, and standardized mortality ratios

TABLE 10-2 Selected Epidemiologic Studies—Diabetes and Related Health Outcomes

Reference	Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Risk (95% CI)[a]
VIETNAM VETERANS			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans			**All COIs**
Michalek and Pavuk, 2008	AFHS—follow-up through 2004		
	Ranch Hand veterans vs SEA comparison group		
	Calendar period in Vietnam		
	During or before 1969	130	1.7 (p = 0.005)
	Background (serum TCDD ≤ 10 ppt)	39	1.3 (0.8–2.0)
	Low (10–91 ppt)	40	1.9 (1.2–2.9)
	High (> 91 ppt)	51	2.0 (1.3–3.1)
	After 1969	50	0.9 (p = 0.45)
	Spraying during tour		
	≥ 90 days	170	1.3 (p = 0.04)
	Background (serum TCDD ≤ 10 ppt)	42	1.0 (0.7–1.4)
	Low (10–91 ppt)	60	1.5 (1.0–2.0)
	High (> 91 ppt)	68	1.6 (1.1–2.2)
	< 90 days	10	0.6 (p = 0.12)
AFHS, 2005	AFHS—2002 examination cycle		
	Ranch Hand veterans—relative risk with 2-fold increase in 1987 TCDD		1.3 (1.1–1.5)
Kern et al., 2004	AFHS—Ranch Hand–comparison subject pairs—within-pair differences: lower Ranch Hand insulin sensitivity with greater TCDD levels		
	1997 examination (29 pairs)		(p = 0.01)
	2002 examination (71 pairs)		(p = 0.02)
Michalek et al., 2003	Air Force Ranch Hand veterans (n = 343)	92	ns
AFHS, 2000[b]	AFHS—1997 exam cycle	(Numerous analyses discussed in the text of *Type 2 Diabetes*)	
	Ranch Hand veterans and comparisons		
Longnecker and Michalek, 2000[b]	AFHS—comparison veterans only, OR by quartiles of serum dioxin concentration		
	Quartile 1: < 2.8 ng/kg	26	1.0
	Quartile 2: 2.8– < 4.0 ng/kg	25	0.9 (0.5–1.7)
	Quartile 3: 4.0– < 5.2 ng/kg	57	1.8 (1.0–3.0)
	Quartile 4: ≥ 5.2 ng/kg	61	1.6 (0.9–2.7)

continued

TABLE 10-2 Diabetes and Related Health Outcomes, continued

Reference	Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Risk (95% CI)[a]
Henriksen et al., 1997[b]	AFHS—through 1992 examination cycle Ranch Hand veterans—high-exposure group		
	Glucose abnormalities	60	1.4 (1.1–1.8)
	Diabetes prevalence	57	1.5 (1.2–2.0)
	Use of oral medications for diabetes	19	2.3 (1.3–3.9)
	Serum insulin abnormalities	18	3.4 (1.9–6.1)
AFHS, 1991b	AFHS—1987 examination cycle—elevation in blood glucose with serum TCDD		*Significance of slope*
	Ranch Hand veterans and comparisons	85	p = 0.001, p = 0.028
AFHS, 1984	AFHS—1982 examination cycle—elevation in blood glucose with serum TCDD		
	Ranch Hand veterans and comparisons	158	p = 0.234
US VA Cohort of Army Chemical Corps			**All COIs**
Cypel and Kang, 2010	US ACC personnel		
	Deployed vs nondeployed	27	1.79 (0.71–4.39)
	Sprayed herbicides in Vietnam vs never	ns	2.21 (0.62–8.02)
Kang et al., 2006	US ACC personnel		
	Deployed vs nondeployed	226	1.2 (0.9–1.5)
	Sprayed herbicides in Vietnam vs never	123	1.5 (1.1–2.0)
US CDC Vietnam Experience Study			**All COIs**
Boehmer et al., 2004	Follow-up of CDC Vietnam Experience Cohort	nr	nr
CDC, 1988	VES—deployed vs nondeployed		
	Interviewed—self-reported diabetes	155	1.2 (p > 0.05)
	Subset with physical examinations		
	Self-reported diabetes	42	1.1 (p > 0.05)
	Fasting serum glucose		geometric means 93.4 vs 92.4 mg/dL (p < 0.05)
Australian Vietnam Veterans vs Australian Population			**All COIs**
O'Toole et al., 2009	Survey of Australian Vietnam Veterans Compared to the Australian General Populations	55	1.0 (0.8–1.3)
ADVA, 2005b	Australian Vietnam veterans vs Australian population—mortality	55	0.5 (0.4–0.7)
	Navy	12	0.5 (0.3–0.9)
	Army	37	0.5 (0.4–0.7)
	Air Force	6	0.5 (0.2–1.0)
CDVA, 1998a[b]	Australian Vietnam veterans—male		*Cases expected (95% CI)*
	Self-report of doctor's diagnosis (proportion of respondents)	2,391 (6%)	1,780 (1,558–2,003)
CDVA, 1998b[b]	Australian Vietnam veterans—female		*Cases expected (95% CI)*
	Self-report of doctor's diagnosis (proportion of respondents)	5 (2%)	10 (9–11)
O'Toole et al., 1996	Australian Vietnam veterans		
	Self-report of doctor's diagnosis	12	1.6 (0.4–2.7)

TABLE 10-2 Diabetes and Related Health Outcomes, continued

Reference	Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Risk (95% CI)[a]
Australian Conscripted Army National Service (deployed vs nondeployed)			**All COIs**
ADVA, 2005c	Australian men conscripted into Army National Service—deployed vs nondeployed—mortality	6	0.3 (0.1–0.7)
Other Studies of Vietnam Veterans			**All COIs**
Kim et al., 2003	Korean veterans of Vietnam—Vietnam veterans	154	2.7 (1.1–6.7)
OCCUPATIONAL			
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)			**Dioxin/phenoxy herbicides**
Vena et al., 1998	Production workers and sprayers in 12 countries	33	2.3 (0.5–9.5)
NIOSH Mortality Cohort (12 US plants, production 1942–1984) (included in the IARC cohort)			**Dioxin/phenoxy herbicides**
Steenland et al., 1999[b]	US chemical production workers—Highly exposed industrial cohorts (n = 5,132)		
	Diabetes as underlying cause	26	1.2 (0.8–1.7)
	Diabetes among multiple causes	89	1.1 (0.9–1.3)
	Chloracne subcohort (n = 608)	4	1.1 (0.3–2.7)
Steenland et al., 1992[b]	NIOSH cohort of dioxin-exposed workers—mortality[c]		
	Diabetes as underlying cause	16	1.1 (0.6–1.8)
	Diabetes among multiple causes	58	1.1 (0.8–1.4)
Sweeney et al., 1992	NIOSH production workers	26	1.6 (0.9–3.0)
Preliminary NIOSH Cross-Sectional Medical Study			**Dioxin/phenoxy herbicides**
Sweeney et al., 1997/1998	Dioxin-exposed workers in two chemical plants		1.1, $p < 0.003$
NIOSH/Ranch Hand Comparison			
Steenland et al., 2001	Ranch Hand veterans, workers exposed to TCDD-contaminated products compared with nonexposed comparison cohorts		
	Ranch Hands	147	1.2 (0.9–1.5)
	Workers	28	1.2 (0.7–2.3)

continued

TABLE 10-2 Diabetes and Related Health Outcomes, continued

Reference	Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Risk (95% CI)[a]
Monsanto Plant—Nitro, WV (included in IARC and NIOSH cohort)			**Dioxin/phenoxy herbicides**
Moses et al., 1984	2,4,5-T, TCP production workers with chloracne	22	2.3 (1.1–4.8)
Dow Chemical Company—Midland, MI (included in IARC and NIOSH cohorts)			**Dioxin/phenoxy herbicides**
Collins et al., 2009a	TCP production workers, Midland, MI	16	1.1 (0.6–1.8)
Collins et al., 2009b	PCP production workers, Midland, MI	8	1.1 (0.5–2.2)
Ramlow et al., 1996	Subset of PCP production workers—mortality	4	1.2 (0.3–3.0)
Cook et al., 1987	Production workers—mortality	4	0.7 (0.2–1.9)
New Zealand Production Workers—Dow plant in New Plymouth, NZ (included in IARC cohort)			**Dioxin/phenoxy herbicides**
McBride et al., 2009a	TCP production workers	3	0.7 (0.2–2.2)
BASF Production Workers (included in the IARC cohort)			**Dioxin/phenoxy herbicides**
Ott et al., 1994	BASF production workers		p = 0.06
Zober et al., 1994	BASF production workers	10	0.5 (0.2–1.0)
German Production Workers			**Dioxin/phenoxy herbicides**
Von Benner et al., 1994	West German chemical production workers	nr	nr
United Kingdom Production Workers			**Dioxin/phenoxy herbicides**
May, 1982	TCP production workers	2	nr
United States Production Workers			**Dioxin/phenoxy herbicides**
Calvert et al., 1999[b]	Workers exposed to 2,4,5-T, derivatives	26	1.5 (0.8–2.9)
	Serum TCDD pg/g of lipid		
	< 20	7	2.1 (0.8–5.8)
	20–75	6	1.5 (0.5–4.3)
	75–238	3	0.7 (0.2–2.6)
	238–3,400	10	2.0 (0.8–4.9)
Other Production Workers			**Dioxin/phenoxy herbicides**
Pazderova-Vejlupkova et al., 1981	2,4,5-T, TCP production workers (admitted to hospital in Prague)	11	nr

TABLE 10-2 Diabetes and Related Health Outcomes, continued

Reference	Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Risk (95% CI)[a]
Waste-Incineration Worker Studies			**Dioxin/phenoxy herbicides**
Kitamura et al., 2000	Workers exposed to PCDD at municipal waste incinerator	8	nr, but ns
Agricultural Health Study			**Herbicides**
Montgomery et al., 2008	US AHS—self-reported incident diabetes (1999–2003) in licensed applicators		
	2,4-D	73	0.9 (0.8–1.1)
	2,4,5-T	28	1.0 (0.9–1.2)
Saldana et al., 2007	US AHS—self-reported gestational diabetes in wives of licensed applicators		
	Documented exposure during 1st trimester		*ORs read from graph*
	2,4-D	10	~1.0 (ns)
	2,4,5-T	3	~5 ($p < 0.05$)
	2,4,5-TP	2	~7 ($p < 0.05$)
	Dicamba	7	~3 ($p \sim 0.06$)
Blair et al., 2005	US AHS—mortality		
	Private applicators (male and female)	26	0.3 (0.2–0.5)
	Spouses of private applicators (> 99% female)	18	0.6 (0.4–1.0)
Paper and Pulp Workers			**Dioxin**
Henneberger et al., 1989	Paper and pulp workers	9	1.4 (0.7–2.7)
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Consonni et al., 2008	Seveso residents (men and women)—25-yr mortality follow-up		
	Zone A	3	1.0 (0.3–3.1)
	Zone B	26	1.3 (0.9–1.9)
	Zone R	192	1.3 (1.1–1.5)
Baccarelli et al., 2005b	Children residing in Seveso at time of incident—development of diabetes		
	101 with chloracne	1	nr
	211 without chloracne	2	nr
Bertazzi et al., 2001	Seveso residents—20-yr follow-up		
	Zones A, B—males	6	0.8 (0.3–1.7)
	females	20	1.7 (0.1–2.7)
Bertazzi et al., 1998[b]	Seveso residents—15-yr follow-up		
	Zone A—females	2	1.8 (0.4–7.0)
	Zone B—males	6	1.2 (0.5–2.7)
	females	13	1.8 (1.0–3.0)
Pesatori et al., 1998[b]	Zone R—males	37	1.1 (0.8–1.6)
	females	74	1.2 (1.0–1.6)

continued

TABLE 10-2 Diabetes and Related Health Outcomes, continued

Reference	Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Risk (95% CI)[a]
National Health and Nutrition Examination Survey			**Dioxin, dl PCBs**
Everett et al., 2007	Total diabetes (self-report or HbA1c > 6.1%)		
	NHANES 1999–2002 participants		
	HxCDD (TEF = 0.1)		
	> 42.0–99.1 pg/g		1.8 (1.1–2.8)
	> 99.1 pg/g		2.0 (0.9–4.4)
	PCB 126 (TEF = 0.1)		
	> 31.3–83.8 pg/g		1.7 (1.0.–2.7)
	> 83.8 pg/g		3.7 (2.1–6.5)
Lee et al., 2006	NHANES 1999–2002 participants		
	HpCDD > 90th percentile vs nondetectable	46	2.7 (1.3–5.5)
	OCDD > 90th percentile vs nondetectable	31	2.1 (0.9–5.2)
Other Environmental Studies			
Turyk et al., 2009	Great Lakes sport fish consumers—cross–sectional study		**dl PCBs**
	Sum of dioxin-like PCBs		Adjusted prevalence OR
	< Limit of detection		Reference
	0.2–0.3 ng/g lipid		1.2
	0.3–1.6 ng/g lipid		2.1 ($p < 0.05$)
			p = trend = 0.03
Jørgensen et al., 2008	Survey Greenland Inuit—cross-sectional study		**dl PCBs**
	Quartile of dl PCBs (compared to Q1)		Adjusted prevalence OR
	Quartile 2		1.6 (0.6–4.1)
	Quartile 3		1.9 (0.7–5.1)
	Quartile 4		1.2 (0.4–3.2)
Turunen et al., 2008	Finish fisherman and spouses (mortality compared to Finnish population)		**Dioxin**
	Men	5	0.67 (0.14–0.99)
	Women	5	0.83 (0.32–1.94)
Uemura et al., 2008	Survey of Japanese adults		**Dioxin**
	Total dioxins (pg TEQ/g lipid)		
	≥ 20.00–31.00	17	2.1 (0.9–5.4)
	≥ 31.00	39	3.8 (1.6–10.1)
Chen et al., 2006	Residents around 12 municipal waste incinerators in Taiwan—prevalence of physician-diagnosed diabetes with TEQs for serum PCDD/Fs in logistic model adjusted for age, sex, smoking, BMI	29	**Dioxins/phenoxy herbicides** 2.4 (0.2–31.9)
Fierens et al., 2003	Belgium residents (142 women, 115 men) exposed to dioxins, PCBs		**Dioxins, PCBs**
	Subjects in top decile for dioxins		5.1 (1.2–21.7)
Masley et al., 2000	Population-based survey in Saskatchewan	28	nr

TABLE 10-2 Diabetes and Related Health Outcomes, continued

Reference	Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Risk (95% CI)[a]
Cranmer et al., 2000[b]	Vertac/Hercules Superfund site residents (n = 62)—OR for high insulin in nondiabetic subjects at various times, levels for TCDD > 15 ppt compared with persons with TCDD < 15 ppt		**TCDD**
	Fasting (insulin > 4.5 µIU/mL)	3	8.5 (1.5–49.4)
	30-min (insulin > 177 µIU/mL)	3	7.0 (1.3–39.0)
	60-min (insulin > 228 µIU/mL)	4	12 (2.2–70.1)
	120-min (insulin > 97.7 µIU/mL)	6	56 (5.7–556)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TP, 2-(2,4,5-trichlorophenoxy) propionic acid; ACC, Army Chemical Corps; AFHS, Air Force Health Study; AHS, Agricultural Health Study; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; dl, dioxin-like; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HpCDD, 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin; HxCDD, 1,2,3,6,7,9-hexachlorodibenzo-*p*-dioxin; IARC, International Agency for Research on Cancer; IU, international unit; MI, Michigan; NHANES, National Health and Nutrition Examination Survey; NIOSH, National Institute for Occupation Safety and Health; nr, not reported; ns, not significant; NZ, New Zealand; OCDD, 1,2,3,4,6,7,8,9-octachlorodibenzo-*p*-dioxin; OR, odds ratio; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin; PCDD/Fs, chlorinated dioxins and furans combined; PCP, pentachlorophenol; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCDF, tetrachlorodibenzofuran; TCP, trichlorophenol; TEF, toxicity equivalency factor; TEQ, (total) toxic equivalent; VA, US Department of Veterans Affairs; VES, Vietnam Experience Study; WV, West Virginia.

[a]Given when available; results other than estimated risk explained individually.

[b]Study is discussed in greater detail in *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes* (IOM, 2000).

[c]Includes some subjects covered in other references cited in the category occupational cohorts.

(SMRs) were calculated (standardized to the Australian male population in 5-year age groups). The relative prevalence of diabetes was 1.01 (95% CI 0.76–1.27). There was no assessment of the likelihood of exposure to the chemicals of interest. Neither of the studies was able to exclude the role of chance as an explanation for the findings. The committee had serious concerns that the results reported by O'Toole et al. (2009) were compromised by recall bias and other methodologic problems.

Occupational Studies

Collins et al. (2009a) followed the mortality experience of 1,615 workers exposed to dioxins in trichlorophenol (TCP) production in Midland, Michigan.

Historical dioxin exposure was estimated by back-extrapolating from a serum survey of 17% of the eligible workers. The survey confirmed that TCDD exposure was higher in these workers than in nonexposed workers. There were 16 deaths from diabetes, and workers were not at higher risk for diabetes than the US population (SMR = 1.1, 95% CI 0.6–1.8). The analytic approach of Collins et al. (2009a) has been criticized (Villenueve and Steenland, 2010) on the grounds that it considered persons to be at risk for death from TCDD exposure after the first day of exposure. A statistical model without latency is implausible for chronic diseases that have long natural histories.

Collins et al. (2009b) also assessed mortality in 773 workers exposed to dioxins during pentachlorophenol production. Some of the workers were also included in the TCP-worker sample. Dioxin exposure in this group was high: 20% of workers developed chloracne, which is a hallmark of extreme dioxin exposure. Mortality was assessed over an average of 35 years of follow-up. Workers were categorized according to putative dioxin exposure based on work history, industrial-hygiene monitoring, and patterns of chloracne occurrence. There were only eight deaths from diabetes, and mortality was not statistically different from expected (SMR = 1.1, 95% CI 0.5–2.2). There were too few cases for reliable estimation of a dose–response pattern in mortality in the cohort itself.

McBride et al. (2009a) updated and expanded the analysis of the mortality experience through 2004 of 1,599 workers (247 deceased) employed at the Dow Chemical plants in New Plymouth, New Zealand, at which TCP was manufactured from 1969 to 1988, when 2,4,5-T production stopped. The mortality experience through 1987 of 1,038 workers in this group who had been employed by 1984 was included in the International Agency for Research on Cancer phenoxy herbicide cohort (Saracci et al., 1991). The report included additional workers, refined dose estimates based on serum dioxin evaluations, and additional follow-up. Of the identified workers, 21% were lost to follow-up. Inasmuch as only three workers who were ever exposed to TCDD died from diabetes—of five total deaths—the cohort provides little evidence for or against a dioxin–diabetes link (SMR = 0.7, 95% CI 0.2–2.2). McBride et al. (2009b) have also published mortality findings on the plant through 2004, including all 1,754 workers who were employed there from 1969 to 2003 (again, 247 deaths); however, it has not been included, because its results were diluted by inclusion of a set of workers who had no opportunity for TCDD exposure and no observed deaths.

Pelclová et al. (2009) updated a study of Czech workers (aged 64.4 ± 1.5 years) exposed to TCDD between 1965–1968, while working in a plant producing 2,4,5-T. Eleven out of the original group of approximately 80 workers were reevaluated for this update. Two additional workers were diagnosed with diabetes since the workers were last evaluated in 2007 (Pelclová et al., 2007; Urban et al., 2007), for a total of 6 out of 11 workers who received a diabetes diagnosis. The usefulness of this study is limited, however, because of the small sample size, the

lack of a well-defined comparison population, and the lack of comparison data between the exposed and non-exposed populations.

Environmental Studies

Turunen et al. (2008) reported on the mortality experience of 6,410 Finnish fishermen and 4,260 of their spouses over an average follow-up period of 12 years. Given the likelihood that fisherman are high fish consumers and therefore may have high ingestion of persistent organic pollutants that may accumulate in fish, this group was expected to have a higher exposure to dioxin and dioxin-like compounds. In a small substudy of 161 cohort members, dioxin total toxic equivalents (TEQs; pg/g lipid) were measured to be 94 in men and 59 in women—higher than those in a comparison group derived from another study, which found TEQs in adipose tissue to be 47 and 41 in men and women, respectively. The cause-specific death rates were compared with those in the Finnish general population. The fishermen themselves had significantly fewer deaths attributed to diabetes than expected (SMR = 0.43, 95% CI 0.14–0.99), whereas their wives' mortality experience did not differ significantly from that in the general population (SMR = 0.83, 95% CI 0.27–1.94).

Jørgensen et al. (2008) surveyed 692 adult Inuits living in Greenland. The survey included the collection of blood and a 75-g 2-hour oral glucose-tolerance test. The three dioxin-like polychlorinated biphenyls (PCB 105, 118, and 156) were among the 13 most prevalent PCB congeners in this population. Compared with those in the lowest quartile of exposure to these compounds, those in the second, third, and fourth exposure quartiles for the dioxin-like PCBs had a statistically nonsignificant increase in prevalence of diabetes (prevalence odds ratio [OR] = 1.6, 95% CI 0.6–4.1; OR = 1.9, 95% CI 0.7–5.1; and OR = 1.2, 95% CI 0.4–3.6, respectively). Those estimates adjusted for age, sex, ethnicity, waist circumference, physical activity, smoking, and educational level. There was no significant dose–response relationship across the quartiles. These relationships were somewhat stronger than those seen in connection with non–dioxin-like PCBs. In the 621 subjects who did not have diabetes, no association was seen between dioxin-like PCBs and impaired glucose tolerance, fasting glucose, or mean fasting insulin; there was a modest inverse relationship ($p = 0.04$) for 2-hour glucose, but the finding was similar for non–dioxin-like PCBs and the 11 organochlorine pesticides measured.

Turyk et al. (2009) recontacted participants in a cohort of Great Lakes sport fishermen. Of the original 4,200 cohort members, 1,788 participants provided additional health information. Of the 1,788, 515 provided blood samples and 503 provided all desired study data. Diabetes was defined on the basis of self-report or having hemoglobin A1c (HbA1c) values above 6.3% (n = 85). Hemoglobin A1c reflects long-term glycemic control; higher values indicate poorer control. A number of persistent organic pollutants were assessed. Lipid-adjusted con-

centrations of PCB 118 and PCB 167 were summed to provide an estimate of exposure to dioxin-like PCBs. Those in the highest category of these PCBs were 2.1 times ($p < 0.05$) more likely to have diabetes than those with no detectable PCBs after adjustment for age, body mass index (BMI, weight/height^2), sex, triglycerides, and cholesterol. There was a significant linear trend of increasing prevalence of diabetes with increasing concentrations of dioxin-like PCBs ($p = 0.03$). The concentration of those PCBs correlated strongly ($p < 0.0001$) with concentrations of *p*,*p*′-diphenyldichloroethene (DDE). After further adjustment for DDE, the associations between dioxin-like PCBs and diabetes were no longer statistically significant; it was not reported whether the association with DDE remained significant after adjustment for dioxin-like PCBs, but when adjusted for other factors, the DDE association was somewhat stronger ($p < 0.005$) than that for dioxin-like PCBs.

Other Reviewed Studies

Several studies did not characterize exposure with sufficient specificity or described outcomes that would be considered biomarkers rather than disease states, so their findings have not been entered in the results table, but the committee did consider them as supportive information.

Three cross-sectional studies have related exposure of the chemicals of interest to metabolic findings indicative of increased diabetes risk. Uemura et al. (2009) associated metabolic syndrome with a large number of persistent organic pollutants in a sample of 1,374 Japanese residents who had no history of occupational exposure to polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), or dioxin-like PCBs. Participants across Japan were sampled. They were required to have lived in the same area for at least 10 years. The definition of metabolic syndrome was not standard in that central obesity and fasting glucose were not measured. In their place, the authors used a BMI cutoff of 25 as the central-obesity measure and HbA1c over 5.6% in place of serum glucose. Concentrations of PCDDs, PCDFs, and dioxin-like PCBs were all associated with the presence of metabolic syndrome. The median TEQ for the cohort was 20 (pg TEQ/g lipid). The adjusted prevalence odds of having metabolic syndrome increased in a dose-dependent fashion. The adjusted odds of having metabolic syndrome for those in the highest quartile (31 TEQs or higher) vs those in the lowest (12 TEQ or lower) was 5.3 (95% CI 2.3–13.0). TEQs were significantly associated with each of the individual components of the syndrome. The strongest relationship was with HbA1c; the OR when the highest TEQ quartile was compared with the lowest was 8.6 (95% CI 2.1–28).

Chang et al. (2010) studied 1,234 nondiabetic persons who lived near a deserted PCP factory. Participants who had insulin resistance (determined by an index constructed from fasting glucose and insulin measures) had higher dioxin concentrations (24.3 vs 19.8 pg TEQ/g lipid). Those in the 90th percentile of

dioxin TEQs (54.1 or higher) had a likelihood of being insulin-resistant 5 times greater (95% CI 1.5–18) than did those in the 10th percentile after adjustment for age, sex, BMI, smoking, physical activity, and family history of diabetes. Fasting glucose, BMI, and waist circumference were all higher in those who had higher TEQs, and the index of β-cell function was not associated with TEQ.

Using data from the third National Health and Nutrition Examination Survey, Schreinemachers (2010) related urinary 2,4-D concentrations to fasting insulin, glucose, and C-peptide concentrations, a measure of endogenous insulin production. In a multivariate model, none of the three indices was significantly associated with urinary 2,4-D.

Biologic Plausibility

Several biologic mechanisms that have been studied in cell culture and animal models may explain the potential diabetogenic effects of TCDD in humans. TCDD is known to modify expression of genes related to insulin transport and signaling and to glucose metabolism (Fujiyoshi et al., 2006; Sato et al., 2008). The present committee's literature review included two new studies that increased mechanistic biologic plausibility. Kurita et al. (2009) found that exposure of mice to dioxin significantly reduced insulin secretion after a glucose challenge, although it did not alter plasma glucose clearance. In an in vitro study of differentiated adipocytes, TCDD significantly reduced insulin-stimulated glucose uptake (Hsu et al., 2010). Thus, mechanisms associated with insulin signaling and glucose uptake may contribute to the diabetogenic effects of TCDD observed in humans.

Synthesis

The new epidemiologic evidence reviewed in this update includes results of studies of Vietnam veterans and occupational cohorts and of population surveys. Several of the studies used death from diabetes as the endpoint of interest. That endpoint is problematic. In contrast with some diseases, such as rapidly fatal cancers, more people die *with* diabetes than *from* diabetes. That is, although diabetes contributes to mortality, it is infrequently listed as the underlying cause of death. Therefore, it is certain that deaths ascribed to diabetes substantially underestimate the disease's true burden. Furthermore, it is unclear whether the deaths that are ascribed to diabetes fairly represent the pattern of diabetes in the population as a whole. If they do not, then the reported associations may be distorted by this biased selection. In that light, studies reporting diabetes mortality should be interpreted cautiously.

The study of most direct relevance is the follow-up of the ACC cohort (Cypel and Kang, 2010). The strengths of that study include the likely exposure to the chemicals of interest among those deployed to Vietnam and the study's abil-

ity to compare the mortality experience of veterans deployed to Vietnam with that of those not deployed. The comparison is more relevant than the common comparisons with the general population because factors related to participation in military service are accounted for. The veterans who served in Vietnam had an 80% higher diabetes mortality than those not deployed to Vietnam. Among the veterans who served in Vietnam, those who sprayed herbicides had a 121% higher diabetes mortality than those who did not. Neither estimate is statistically significant, so the role of chance cannot be ruled out as an explanation, but the increase in RR with putative dose suggests a dose–response relationship, which is an important indicator of a causal association. Weaknesses of the study are its inability to control for important potential confounders, such as BMI, and its reliance on mortality in that many persons who develop diabetes die from other diseases that diabetes promotes, such as coronary heart disease and stroke.

The O'Toole (2009) study of Australian veterans and their health several decades after service showed no association with prevalent diabetes. Although the study subjects were Vietnam veterans, several important weaknesses render the result unreliable. Disease ascertainment was by self-report, which may be inaccurate. The survey design involved two stages of sampling, and it is not entirely clear that the resulting sample was representative of all returning Australian veterans. Finally, by definition, prevalent cases do not include cases that may have occurred in the past but are no longer in the population at the time of study; veterans who died with diabetes before the survey were not considered. If exposure to Agent Orange led to higher case fatality, the prevalence comparison would underestimate the effect of exposure on diabetes occurrence. That so-called prevalence–incidence bias has been shown to occur in studies of other chronic diseases.

The three occupational cohorts considered contribute little to our understanding, because so few diabetes deaths were considered. With such a small number of cases, the estimates are very imprecise and are consistent with a wide array of possible associations.

The environmental studies provide some additional insight. Least useful is the Finnish fishermen study (Turunen et al., 2008). That group had a lower expected mortality from diabetes, but with only five deaths in each sex, the estimate is very imprecise. The study provides data showing that the fishermen had higher dioxin TEQs than nonfishing populations, but taking fishermen as a group implies an assumption that all fishermen are exposed at the same mean concentration, which is unlikely to be the case. Furthermore, because fishing is a strenuous occupation, the higher physical activity would be expected to reduce diabetes occurrence. Control of confounding by physical activity or other factors is not possible in the standardized mortality analysis used.

The study by Jørgensen et al. (2008) of Inuit residents of Greenland had several strengths. The presence of diabetes was confirmed with the appropriate clinical laboratory measurements. The association persisted after adjustment for

a number of potential confounding variables. That the association was stronger for dioxin-like PCBs than for non–dioxin-like PCBs suggests a specific effect. However, the study was cross-sectional so, in addition to potential selection bias, it cannot be certain whether the PCBs concentrations were increased because they cause diabetes or whether some feature of the diabetic phenotype predisposes to the accumulation of dioxin-like PCBs.

The study of Great Lakes sport fishermen (Turyk et al., 2009) also found an association between concentrations of dioxin-like PCBs and diabetes. The presence of diabetes was based on either self-report or a high Hb A1c value. There was a significant dose–response relationship after adjusting for age, BMI, sex, triglycerides, and cholesterol concentration. The authors report that the associations were no longer significant after adjustment for concentrations of DDE. They note that DDE was highly correlated with dioxin-like PCBs. The loss of statistical significance after adjustment for a variable might reflect confounding by the variable or, in the case of highly correlated variables, loss of statistical significance because of inflation in the estimate of the statistical error. The authors did not provide data to distinguish between those alternatives.

The population surveys reported by Uemura et al. (2009) and Chang et al. (2010) both show strong associations between dioxin TEQs and indexes of diabetes risk in nondiabetic people after adjustment for relevant confounders. Those findings support dioxin's role in the natural history of diabetes, but as in the case of the Jørgensen et al. (2008), it cannot be certain whether some feature of the diabetic phenotype predisposes to the accumulation of dioxin-like PCBs. The data from Schreinemacher (2010) show no association between urinary 2,4-D (a measure of recent exposure) and diabetes.

In the aggregate, the newly added studies support prior VAO committees' inclusion of diabetes in the limited and suggestive category. The new studies that fail to support an effect are either underpowered or susceptible to substantial bias. The environmental surveys are supportive and generally include better measurements of both exposure and disease than the veterans or occupational-cohort studies; they support a physiologic connection between dioxin activity and diabetes, but, because of their study designs, it is not possible to prove that the exposure to the putative cause preceded the onset of the outcome.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is limited or suggestive evidence of an association between exposure to at least one chemical of interest and diabetes.

LIPID AND LIPOPROTEIN DISORDERS

Plasma concentrations of lipid—notably cholesterol—have been shown to predict cardiovascular disease and are considered fundamental to the underlying atherosclerotic process (Roberts et al., 2000). Cholesterol and triglycerides, the two major types of lipids, are carried in the blood attached to proteins to form lipoproteins, which are classified by density. Very-low-density lipoprotein (VLDL, the major triglyceride particle) is produced in the liver and is progressively catabolized (hydrolyzed), mainly by an insulin-stimulated enzyme (lipoprotein lipase), to form intermediate-density lipoprotein, or VLDL remnants. Most of the VLDL remnants are rapidly cleared by low-density lipoprotein (LDL) receptors (types B and E) in the liver, and the rest form LDL, the major "bad cholesterol." LDL is cleared by LDL receptors in the liver and other tissues. High-density lipoprotein (HDL), the "good cholesterol," is produced in the small intestine and liver. It also results from the catabolism of VLDL. LDL is involved in the delivery of cholesterol to the tissues, and HDL is involved in "reverse" transport and facilitates the return of cholesterol to the liver for biliary excretion (Vergès, 2005).

Beginning with this report, the VAO committees will no longer report on lipid and lipoprotein disorders as a separate category of adverse health outcomes. Because of logistical difficulties in obtaining the appropriate measures to identify persons who have lipid or lipoprotein disorders, the literature contains few relevant data. As a consequence, past VAO committees have had insufficient evidence to conclude whether there is an association between the chemicals of interest and lipid disorders. That situation is unlikely to change. Therefore, new information related to lipids will be included in the section on cardiovascular disease under the heading "Other Reviewed Studies."

CIRCULATORY DISORDERS

This section covers a variety of conditions encompassed by the 9th revision of the *International Classification of Diseases* (ICD-9), codes 390–459, such as acute and chronic rheumatic fever (ICD-9 390–398), hypertension (ICD-9 401–404), ischemic heart disease (ICD-9 410–414), heart failure (ICD-9 428), cerebrovascular disease (ICD-9 430–438), and peripheral vascular disease (ICD-9 443). *Coronary heart disease* is related specifically to atherosclerosis; *ischemic heart disease* is broader and typically includes atherosclerosis and its symptoms. The American Heart Association reports mortality related to coronary heart disease, not to its symptoms, which include angina and myocardial infarction. Table 10-1 contains estimates of prevalence of and mortality from individual disorders of the circulatory system in the US population in 2006.

The methods used in morbidity studies can involve the direct assessment of the circulatory system, including analysis of symptoms or history, physical examination of the heart and peripheral arteries, ultrasound measurements of the

heart and arteries, electrocardiography (ECG), chest radiography, cardiac computed tomography (CT), and more recently cardiac magnetic resonance imaging (MRI). Ultrasonography, CT, and MRI can be used to visualize the heart and related vasculature directly. ECG can be used to detect heart conditions and abnormalities, such as arrhythmias (abnormal heart rhythms), heart enlargement, and heart attacks (myocardial infarctions). Chest radiography can be used to assess the consequences of ischemic heart disease and hypertension, such as the enlargement of the heart seen in heart failure. It is sometimes difficult to determine the time of onset of clinical findings, so the temporal relationship between exposure and disease occurrence may be uncertain. Cardiovascular-disease epidemiologists prefer to observe cohorts over time for the incidence of discrete clinical events, such as acute myocardial infarction (ideally verified on the basis of changes in ECG readings and enzyme concentrations) and death due to heart disease. The onset of new angina symptoms or the performance of a revascularization procedure in a person who has no history of disease is also used as evidence of incident disease. In many occupational studies, only mortality information is available. The attribution of death to a vascular cause is often based on a death certificate, the accuracy of which can be uncertain.

Conclusions from *VAO* and Previous Updates

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the chemicals of interest and circulatory disorders. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, and *Update 2004* did not change that conclusion.

The committee responsible for *Update 2006* reviewed new studies and intensively revisited all the studies related to ischemic heart disease and hypertension that had been discussed in previous updates and concluded that there is limited or suggestive evidence to support an association between exposure to the herbicides used in Vietnam and hypertension. That committee was unable to reach a consensus as to whether that was also the case for ischemic heart disease, so that outcome remained in the category of inadequate evidence.

After consideration of the relative strengths and weaknesses of the evidence regarding the chemicals of interest and ischemic heart disease (ICD-9 410–414), and the relevant toxicologic literature, the committee responsible for *Update 2008* judged that the evidence was adequate to advance this health outcome from the "inadequate or insufficient" category into the "limited or suggestive" category, again acknowledging that bias and confounding could not be entirely ruled out. The *Update 2006* conclusion of limited or suggestive evidence of an association between herbicide exposure and hypertension was reaffirmed. For all other types of circulatory disease, the committee found that the evidence is inadequate or

insufficient to determine whether there is an association with exposure to the chemicals of interest.

The previous studies and studies published since *Update 2008* are all summarized in Table 10-3.

Update of the Epidemiologic Literature

The practice of evaluating the evidence on hypertension separately from that of other circulatory diseases, established in *Update 2008*, is continued in the present update.

Hypertension

Vietnam-Veteran Studies Hypertension was considered in two new publications on cohorts of Vietnam veterans. Cypel and Kang (2010) found that ACC veterans as a whole were more likely to die from hypertension than the general US male population, but ACC veterans who served in Vietnam were no more likely to die from hypertension than ACC veterans without Vietnam service after adjustment for race, rank, duration of military service, and age (RR = 0.85, 95% CI 0.19–3.86). The estimate was based on only eight deaths and so is unreliable.

A survey of Australian Vietnam veterans (O'Toole et al., 2009) found a 13% increase in prevalence of self-reported hypertension (OR = 1.13, 95% CI 1.01–1.25) as compared to the general public.

Occupational Studies Pelclová et al. (2009) updated a study of Czech workers (aged 64.4 ± 1.5 years) exposed to TCDD between 1965–1968, while working in a plant producing 2,4,5-T. Eleven out of the original group of approximately 80 workers were reevaluated for this update. One additional worker was being treated for hypertension since the workers were last evaluated in 2007 (Pelclová et al., 2007; Urban et al., 2007), for a total of 7 out of 11 workers who received a diagnosis of hypertension. The usefulness of this study is limited, however, because of the small sample size, the lack of a well-defined comparison population, and the lack of comparison data between the exposed and nonexposed populations.

Environmental Studies In their study of metabolic syndrome in the general population of Japan, Uemura et al. (2009) found that having blood concentrations of PCDDs, PCDFs, or dioxin-like PCBs in the highest quartile was associated with a significant increase in the prevalence of hypertension ($p < 0.05$). Participants with a dioxin TEQ in the highest quartile had 90% higher odds (OR = 1.9, 95% CI 1.1–3.1) of having hypertension, defined as blood pressure above 135/85 mm Hg or a history of physician-diagnosed hypertension, after adjustment for age, sex, smoking, drinking, regional block, residential area, and survey year.

TABLE 10-3 Selected Epidemiologic Studies—Circulatory Disorders

Reference[a]	Study Population[b]	Exposed Cases[c]	Exposure of Interest/ Estimated Risk (95% CI)[c]	Exposure/ Comments
VIETNAM VETERANS				
US Air Force Health Study—Ranch Hand veterans vs SEA veterans				**All COIs**
AFHS, 2005	AFHS, 2002 exam cycle (1,951 participants)—morbidity [results update those of 1982, 1985, 1987, 1997, and 1999 exams cycles]			
Number in analysis:	Model 1: RH subjects vs SEA comparisons (also available separately for officer, enlisted flyer, enlisted groundcrew)			All analyses adjusted for age, race, rank, smoking, alcohol history, HDL, cholesterol, cholesterol HDL ratio, uric acid, diabetes, BMI or percent body fat, waist–hip ratio, family history of heart disease.
1,885	Essential hypertension	412 of 759	0.92 (0.53–1.13)	
1,902	Heart disease (except essential hypertension)	644 of 767	1.20 (0.94–1.54)	
308	Enlisted flyer	120 of 131	2.46 (1.19–5.11)	
1,902	Myocardial infarction	77 of 767	0.81 (0.59–1.12)	
1,902	Stroke or transient ischemic attack	29 of 767	1.39 (0.82–2.34)	
	Model 2: RH subjects with extrapolated initial serum TCDD (> 10 ppt in 1987)		*Relative risk for 2-fold increase in serum TCDD*	
406	Essential hypertension	244	1.12 (0.91–1.37)	
411	Heart disease (except essential hypertension)	344	1.08 (0.85–1.38)	
411	Myocardial infarction	42	1.31 (0.97–1.77)	
411	Stroke or transient ischemic attack	17	1.26 (0.78–2.03)	
	Model 3: All subjects with serum TCDD readings (RH group vs comparisons)			
1,344	Essential hypertension			
	Comparison	644	1.0	
	RH background (< 10 ppt, 1987)	168	0.88 (0.67–1.16)	
	RH low (10–118 ppt, initial)	109	0.74 (0.53–1.04)	
	RH high (> 118 ppt, initial)	135	1.32 (0.94–1.87)	

continued

TABLE 10-3 Circulatory Disorders, continued

Reference[a]	Study Population[b]	Exposed Cases[c]	Exposure of Interest/ Estimated Risk (95% CI)[c]	Exposure/ Comments
1,355	Heart disease (except essential hypertension)			
	Comparison	937	1.0	
	RH background (< 10 ppt, 1987)	299	1.33 (0.94–1.89)	
	RH low (10–118 ppt, initial)	171	1.03 (0.68–1.54)	
	RH high (> 118 ppt, initial)	173	1.21 (0.81–1.82)	
1,355	Myocardial infarction			
	Comparison	132	1.0	
	RH background (< 10 ppt, 1987)	34	0.81 (0.53–1.25)	
	RH low (10–118 ppt, initial)	18	0.60 (0.34–1.04)	
	RH high (> 118 ppt, initial)	24	1.04 (0.63–1.74)	
1,355	Stroke or transient ischemic attack			
	Comparison	36	1.0	
	RH background (< 10 ppt, 1987)	12	1.21 (0.59–2.45)	
	RH low (10–118 ppt, initial)	7	1.10 (0.47–2.57)	
	RH high (> 118 ppt, initial)	10	2.16 (0.98–4.77)	
	Model 4: RH subjects with 1987 serum TCDD readings		*Relative risk for 2-fold increase in serum TCDD*	
748	Essential hypertension		1.11 (0.98–1.25)	
755	Heart disease (except essential hypertension)		0.90 (0.78–1.06)	
755	Myocardial infarction		1.03 (0.85–1.24)	
755	Stroke or transient ischemic attack		1.04 (0.76–1.44)	
Ketchum and Michalek, 2005	AFHS—circulatory disease—mortality			
	Ranch Hand subjects vs all SEA veterans	66	1.3 (1.0–1.6)	Not adjusted for known risk factors.
	Pilots and navigators	18	1.1 (0.7–1.8)	
	Administrative officers	2	1.8 (0.4–7.8)	
	Enlisted flight engineers	6	0.5 (0.2–1.1)	
	Ground crew	40	1.7 (1.2–2.4)	
	Atherosclerosis	28	1.7 (1.1–2.5)	

	Hypertensive disease	2	2.5 (0.6–10.8)	
	Stroke	5	2.3 (0.9–6.0)	
	Subjects with serum TCDD measures			
	SEA comparison group	31	1.0	Adjusted for smoking and family history of heart disease
	Background (0.6–10.0 ppt)	8	0.8 (0.4–1.8)	
	Low (10.0–29.2 ppt)	12	1.8 (0.9–3.5)	
	High (18.0–617.8 ppt)	9	1.5 (0.7–3.3)	
US VA Cohort of Army Chemical Corps				**All COIs**
Cypel and Kang, 2010	Vietnam veterans vs non-Vietnam veterans—mortality			Deaths and causes of deaths ascertained through national death registries Adjustment for race, rank duration of service, and age
	Circulatory system disease	184	1.21 (0.93–1.58)	
	Hypertension	5	0.85 (0.19–3.86)	
	Cerebrovascular disease	27	1.48 (0.67–3.27)	
	Sprayers vs nonsprayers (subset studied in Kang et al., 2006)			
	Circulatory system disease	ns	1.17 (0.60–2.28)	
	Hypertension	ns	2.35 (0.19-28.52)	
	Cerebrovascular disease	ns	2.12 (0.37–12.30)	
Kang et al., 2006 and supplemental data	ACC—morbidity			Diagnoses not confirmed by medical record review. Adjusted for age, race, rank, BMI, and smoking Serum TCDD levels measured in subset of subjects; self-reported sprayers did have significantly higher concentrations than others. Therefore, the sprayer category is regarded as a valid surrogate for elevated exposure
	Vietnam veterans vs non-Vietnam veterans			
	Hypertension requiring medication	496	1.06 (0.89–1.27)	
	Heart disease diagnosed by physician	243	1.09 (0.87–1.38)	
	Sprayers vs nonsprayers			
	All (diabetics, nondiabetics)			
	Hypertension requiring medication	247	1.26 (1.00–1.58)	
	Heart disease diagnosed by physician	129	1.41 (1.06–1.89)	
	All veterans, contribution of spraying to logistic regression model			
	All (diabetics, nondiabetics)			
	Hypertension requiring medication		1.32 (1.08–1.61)	
	Heart disease diagnosed by physician		1.52 (1.18–1.94)	
	Nondiabetics only			
	Hypertension requiring medication		1.23 (0.99–1.52)	
	Heart disease diagnosed by physician		1.52 (1.14–2.01)	

continued

TABLE 10-3 Circulatory Disorders, continued

Reference[a]	Study Population[b]	Exposed Cases[c]	Exposure of Interest/ Estimated Risk (95% CI)[c]	Exposure/ Comments
	Controlling for diabetic status			
	Hypertension requiring medication		1.27 (1.04–1.55)	
	Heart disease diagnosed by physician		1.45 (1.13–1.86)	
Thomas and Kang, 1990	ACC vs US male population—mortality			Not adjusted for known risk factors
	Circulatory diseases (ICD 390–458)	6	0.55	
US CDC Vietnam Experience Study				**All COIs**
Boehmer et al., 2004	CDC VES—mortality			
	Deployed vs nondeployed	185	1.01 (0.82–1.24)	
	Circulatory disease			
	Year of death			
	1970–1984	nr	0.56 (0.28–1.15)	Adjusted for age, race, military occupation
	1985–2000 (partition at 1970 arbitrary)	nr	1.06 (0.85–1.32)	
	Discharged before 1970	nr	0.83 (0.62–1.12)	
	Discharged after 1970	125	1.43 (1.02–1.99)	
	Ischemic heart diseases			
	0–15 yrs since discharge	8	0.77 (0.31–1.55)	
	> 15 yrs since discharge	117	1.14 (0.87–1.50)	
CDC, 1988	CDC VES—morbidity			
	Deployed vs nondeployed			
	Hypertension after discharge			Not adjusted for known risk factors
	Interviewed	2,013	1.3 ($p < 0.05$)	
	Examined	623	1.2 ($p < 0.05$)	
US VA Mortality Study of Army and Marine Veterans (ground troops serving July 4, 1965–March 1, 1973)				**All COIs**
Bullman and Kang, 1996	US wounded Vietnam veterans vs US men (through 1981, focus on suicide)			
	Circulatory disease	246	0.72 (0.55–0.91)	

Watanabe and Kang, 1996	US Army and Marine Corps Vietnam-era veterans—mortality (PMR, 1965–1988)			
	Served in Vietnam vs never deployed to SEA			
	Circulatory diseases (ICD-8 390–458)			
	Army	5,756	0.97 ($p > 0.05$)	Not adjusted for known
	Marine Corps	1,048	0.92 ($p < 0.05$)	risk factors
US VA Cohort of Female Vietnam Veterans				**All COIs**
Cypel and Kang, 2008	Female US Vietnam-era veterans—mortality (through 2004)			Adjusted for
	Circulatory system diseases			duration of service, year
	Vietnam vs non-SEA veterans	129	0.8 (0.6–1.0)	of birth, race
	Nurses only	102	0.8 (0.6–1.0)	
American Legion Cohort				**All COIs**
Stellman et al., 1988	American Legionnaires serving during Vietnam era—morbidity			
	Service in SEA vs not, with medically diagnosed			
	High blood pressure	592	1.12 ($p > 0.05$)	Not age adjusted.
	Heart disease	97	1.45 ($p < 0.05$)	Age adjusted
State Studies of US Vietnam Veterans				**All COIs**
Anderson et al., 1986	Wisconsin Vietnam veterans—all diseases of circulatory system—mortality			
	White male Vietnam veterans vs:	100		
	National population		0.69 ($p < 0.05$)	
	State population		0.62 ($p < 0.05$)	
	Nonveterans		0.58 ($p < 0.05$)	
	All veterans		0.86 ($p > 0.05$)	
	Vietnam-era veterans		0.99 (0.80–1.20)	
Kogan and Clapp, 1985	Massachusetts Vietnam-era veterans (1958–1973)—mortality (1972–1983)			
	Deployed vs nondeployed			Not adjusted for age;
	Deaths 1972–1983			Vietnam veterans thought
	Circulatory system (except cerebrovascular)	139	PMR = 0.88 ($p > 0.05$)	to be younger.
	Cerebrovascular	28	PMR = 1.11 ($p > 0.05$)	
	Deaths 1978–1983			Expected less "diluted"
	Circulatory system (except cerebrovascular)	85	PMR = 0.80 ($p < 0.05$)	effect for later time.
	Cerebrovascular	19	PMR = 1.64 ($p < 0.05$)	

continued

TABLE 10-3 Circulatory Disorders, continued

Reference[a]	Study Population[b]	Exposed Cases[c]	Exposure of Interest/ Estimated Risk (95% CI)[c]	Exposure/ Comments
Australian Male Army Vietnam Veterans (random sample) vs Australian Population				**All COIs**
O'Toole et al., 2009	Self-reported chronic disease prevalence			
	In 2005–2006			
	Hyertensive disease	192	1.13 (1.01–1.25)	Prevalence ratios calculated with age-adjustment
	Ischemic heart disease			
	Angina	44	2.34 (1.68–2.99)	
	Without angina	59	4.07 (3.11–5.04)	
	Cerebrovascular disease	12	2.39 (1.24–3.53)	
	Hemorrhoids	81	7.65 (6.13–9.17)	
O'Toole et al., 1996	In 1990–1993		99% CIs	
	Hypertension	nr	2.17 (1.71–2.62)	
	Heart disease	nr	1.98 (0.91–3.05)	
	Hemorrhoids	nr	7.43 (5.51-9.34)	
	Other circulatory diseases	nr	2.39 (1.61–3.17)	
Roster of Australian Vietnam Veterans vs Australian Population				**All COIs**
ADVA, 2005b	Mortality			
	Circulatory disease	1,767	0.88 (0.84–0.92)	Pattern of increasing risks with time could perhaps indicate dissipation of healthy warrior effect
	1963–1979	186	0.69 (0.59–0.79)	
	1980–1990	546	0.88 (0.80–0.95)	
	1991–2001	1,035	0.93 (0.87–0.99)	
	Ischemic heart disease	1,297	0.94 (0.89–0.99)	
	1963–1979	124	0.70 (0.58–0.82)	
	1980–1990	421	0.95 (0.86–1.04)	
	1991–2001	753	0.99 (0.92–1.06)	
	Stroke	223	0.80 (0.70–0.91)	
	1963–1979	35	0.81 (0.54–1.07)	
	1980–1990	59	0.73 (0.54–0.92)	
	1991–2001	129	0.83 (0.69–0.97)	

CDVA, 1997a	Australian Vietnam veterans—mortality (1980–1994)			
	Circulatory disease		0.96 (0.88–1.05)	Not adjusted for known
	Ischemic heart disease		1.04 (0.94–1.14)	risk factors
	Cerebral hemorrhage		0.80 (0.53–1.22)	
Australian Conscripted Army National Service (deployed vs nondeployed)				**All COIs**
ADVA, 2005c	Mortality			
	Circulatory disease	208	1.05 (0.87–1.27)	
	Ischemic heart disease	159	1.18 (0.94–1.47)	
	Stroke	15	0.61 (0.30–1.15)	
CDVA, 1997b	Mortality (1982–1994)			
	Deployed vs nondeployed			
	Circulatory disease	77	0.95 (0.70–1.28)	Not adjusted for known
	Ischemic heart disease	57	0.97 (0.68–1.39)	risk factors
	Cerebral hemorrhage	3	0.96 (0.14–5.66)	
	Other	17	0.88 (0.44–1.69)	
Other International Studies of Vietnam Veterans				**All COIs**
Kim et al., 2003	Korean veterans of Vietnam—morbidity			Concerns of selection
	Deployed vs nondeployed (unadjusted)			bias, quality of diagnosis,
	Valvular heart disease	8	p = 0.0019	low participation
	Congestive heart failure	5	p = 0.5018	Gross pooling of blood
	Ischemic heart disease	34	p = 0.0045	samples made TCDD
	Hypertension	383	p = 0.0143	concentrations useless
	Adjusted for age, smoking, alcohol, BMI, education, and marital status		2.29 (1.33–3.95)	

continued

TABLE 10-3 Circulatory Disorders, continued

Reference[a]	Study Population[b]	Exposed Cases[c]	Exposure of Interest/ Estimated Risk (95% CI)[c]	Exposure/ Comments
OCCUPATIONAL STUDIES				
IARC Phenoxy Herbicide Cohort (mortality vs national mortality rates)				**Dioxin, phenoxy herbicides**
Vena et al., 1998 (same dataset as *Kogevinas et al., 1997* [emphasis on cancer])	IARC cohort of phenoxy herbicide workers—mortality (1939–1992)			
	All male phenoxy herbicide workers			
	All circulatory disease (ICD 390–459)	1,738	0.91 (0.87–0.95)	Not adjusted for known risk factors
	Ischemic heart disease (ICD 410–414)	1,179	0.92 (0.87–0.98)	
	Cerebrovascular disease (ICD 430–438)	254	0.86 (0.76–0.97)	
	Other diseases of heart (ICD 415–429)	166	1.11 (0.95–1.29)	
	All female phenoxy herbicide workers			
	All circulatory disease (ICD 390–459)	48	1.00 (0.73–1.32)	
	Ischemic heart disease (ICD 410–414)	24	1.07 (0.68–1.59)	
	Cerebrovascular disease (ICD 430–438)	9	0.73 (0.33–1.38)	
	Other diseases of heart (ICD 415–429)	6	0.92 (0.34–2.00)	
	Workers with phenoxy herbicide exposure only			
	All circulatory disease (ICD 390–459)	588	0.86 (0.79–0.93)	
	Ischemic heart disease (ICD 410–414)	394	0.85 (0.77–0.94)	
	Cerebrovascular disease (ICD 430–438)	96	0.86 (0.70–1.05)	
	Other diseases of heart (ICD 415–429)	32	0.86 (0.79–0.93)	
	TCDD-exposed workers			
	All circulatory disease (ICD 390–459)	1,170	0.94 (0.88–0.99)	
	Ischemic heart disease (ICD 410–414)	789	0.97 (0.90–1.04)	
	Cerebrovascular disease (ICD 430–438)	162	0.84 (0.71–0.98)	
	Other diseases of heart (ICD 415–429)	138	1.20 (1.01–1.42)	
	Contribution of TCDD exposure to Poisson regression analysis			
	All circulatory disease (ICD 390–459)	1,151	1.51 (1.17–1.96)	Adjusted for age, timing of exposure
	Ischemic heart disease (ICD 410–414)	775	1.67 (1.23–2.26)	
	Cerebrovascular disease (ICD 430–438)	161	1.54 (0.83–2.88)	

NIOSH Mortality Cohort (12 US plants, production 1942–1984) (included in the IARC cohort)				**Dioxin, phenoxy herbicides**
Steenland et al., 1999	NIOSH cohort (subcohorts of IARC cohort at 12 US plants)—mortality (through 1993)			
	Total cohort (5,132) vs US population	69	0.96 (0.74–1.21)	Not adjusted for known
	Cerebrovascular disease (ICD 430–438)	456	1.09 (1.00–1.20)	risk factors
	Ischemic heart disease (ICD 410–414)	92	1.17 (0.94–1.44)	
	Chloracne subcohort (608) vs US population			
	Exposure subcohort (3,538)	nr	1.0	Adjusted for age
	< 19 cumulative TCDD	nr	1.23 (0.75–2.00)	
	19–138	nr	1.34 (0.83–2.18)	
	139–580	nr	1.30 (0.79–2.13)	No units given for
	581–1,649	nr	1.39 (0.86–2.24)	exposure derived from
	1,650–5,739	nr	1.57 (0.96–2.56)	job–exposure matrix
	5,740–20,199	nr	1.75 (1.07–2.87)	
	≥ 20,200		p-trend cumulative expo = 0.05	
			p-trend log[cumulative expo] < 0.001	
US Cohorts in NIOSH Cohort (also in IARC cohort)				**Dioxin, phenoxy herbicides**
Calvert et al., 1998	Two US chemical plants—morbidity			
	Verified conditions			
	TCDD-exposed (281) vs nonexposed (260)			
	Myocardial infarction	17	1.33 (0.62–2.84)	Not adjusted for known
	Current systolic hypertension	64	1.05 (0.70–1.58)	risk factors
	Current diastolic hypertension	77	1.23 (0.83–1.82)	
	TCDD effect vs nonexposed in logistic model. Self-reported and verified conditions combined.			
	Myocardial infarction			
	Serum TCDD < 238 pg/g of lipid	nr	1.14 (0.29–4.49)	
	Serum TCDD ≥ 238 pg/g of lipid	nr	1.09 (0.23–5.06)	

continued

TABLE 10-3 Circulatory Disorders, continued

Reference[a]	Study Population[b]	Exposed Cases[c]	Exposure of Interest/ Estimated Risk (95% CI)[c]	Exposure/ Comments
	Hypertension			Adjusted for age, sex, BMI, smoking, drinking, diabetes, triglycerides, total cholesterol, HDL, family history of heart disease, and chemical plant
	Serum TCDD < 238 pg/g of lipid	nr	1.34 (0.89–2.02)	
	Serum TCDD ≥ 238 pg/g of lipid	nr	1.05 (0.58–1.89)	
	Verified conditions			
	Current systolic hypertension			
	Serum TCDD < 238 pg/g of lipid	nr	1.09 (0.65–1.83)	
	Serum TCDD ≥ 238 pg/g of lipid	nr	1.20 (0.61–2.34)	
	Current diastolic hypertension			
	Serum TCDD < 238 pg/g of lipid	nr	1.35 (0.88–2.09)	
	Serum TCDD ≥ 238 pg/g of lipid	nr	0.97 (0.51–1.87)	
Monsanto Plant—Nitro, WV (included in IARC and NIOSH cohorts)				**Dioxin, phenoxy herbicides**
Suskind and Hertzberg, 1984	Workers exposed to 2,4,5-T production (204) vs nonexposed (163) (self-report)—morbidity			
	Hypertension	70	($p > 0.05$)	Adjusted for age
	Coronary artery disease	22	($p > 0.05$)	
Zack and Gaffey, 1983	Monsanto workers (884)—mortality (1955–1977)			
	Circulatory diseases (ICD 390–458)	92	1.11 ($p > 0.05$)	Not adjusted for known risk factors
	Atherosclerosis and CHD (ICD 410–413)	79	1.33 ($p < 0.05$)	
	All other	13	0.56 ($p < 0.05$)	
Zack and Suskind, 1980	Monsanto workers—mortality (1955–1978)			
	Workers with chloracne (121)			
	Circulatory diseases (ICD 390–458)	17	0.68 ($p > 0.05$)	Not adjusted for known risk factors
	Atherosclerosis and CHD (ICD 410–413)	13	0.73 ($p > 0.05$)	

Dow TCP Cohort—Trichlorophenol (1942–1979) or 2,4,5–T (1948–1982) workers (n = 1,615) in Midland, MI (included in IARC and NIOSH cohorts)				**Dioxin, phenoxy herbicides**
Collins et al., 2009a	Mortality (1942–2003)			No adjustment discussed
	Ischemic heart disease	218	1.1 (0.9–1.2)	
	Cerebrovascular disease	37	1.0 (0.7–1.4)	
Burns et al., 2001	2,4-D workers (1945–1994, n = 1,517 men)			
	Mortality (1945–1994)			
	Circulatory disease			
	0 yrs latency	158	0.95 (0.80–1.11)	Not adjusted for known risk factors
	≥ 20 yrs latency	130	1.05 (0.87–1.24)	
Dow PCP Cohort—Pentacholorphenol (1937–1980) workers (n = 577 with no exposure to TCP) in Midland, MI (little TCDD among dioxins in PCP, not part of IARC or NIOSH cohorts)				**Phenoxy herbicides**
Collins et al., 2009b	Mortality (1940–2003)			No adjustment discussed
	Ischemic heart disease	99	1.0 (0.8–1.3)	
	Cerebrovascular disease	17	0.9 (0.5–1.2)	
Ramlow et al., 1996	Dow PCP workers (1930–1980, n = 770)—mortality (1940–1989)			
	Circulatory diseases (ICD 390–458)	115	0.95 (0.79–1.14)	
	Arteriosclerotic heart disease (ICD 410–414)	86	1.02 (0.82–1.26)	
	Cerebrovascular disease (ICD 430–438)	15	1.02 (0.57–1.68)	
BASF Production Workers (included in IARC cohort)				**Dioxin, phenoxy herbicides**
Ott and Zober, 1996	Cleanup workers at German TCP reactor—mortality (1953–1992)			
	Circulatory diseases	37	0.8 (0.6–1.2)	Reliability of estimated body burden is questionable
	< 0.1 estimated TCDD µg/kg bw	13	0.8 (0.4–1.4)	
	0.1–0.99	11	1.0 (0.5–1.7)	
	≥ 1.0	13	0.8 (0.4–1.3)	
	Ischemic heart disease	16	0.7 (0.4–1.1)	
	< 0.1 estimated TCDD µg/kg bw	7	0.9 (0.3–1.8)	
	0.1–0.99	4	0.7 (0.2–1.7)	
	≥ 1.0	5	0.6 (0.2–1.3)	

continued

TABLE 10-3 Circulatory Disorders, continued

Reference[a]	Study Population[b]	Exposed Cases[c]	Exposure of Interest/ Estimated Risk (95% CI)[c]	Exposure/ Comments
Dutch Production Workers (included in IARC cohort)				**Dioxin, phenoxy herbicides**
Boers et al., 2010	Dutch herbicide factory workers (IARC subcohort)—mortality (1955–2006)			
	Ischemic heart disease			Hazard ratios adjusted for age and year of first employment. Referent group are unexposed workers
	Factory A	43	1.2 (0.7–2.0)	
	Accident 1963	17	1.6 (0.7–3.6)	
	Main production workers	9	1.0 (0.5–2.2)	
	Occasionally exposed	17	1.1 (0.6–2.1)	
	Factory B	18	1.6 (0.8–3.1)	
	Main production workers	5	1.7 (0.6–4.6)	
	Occasionally exposed	13	1.6 (0.7–3.3)	
	Cerebrovascular disease			
	Factory A	17	1.2 (0.4–3.6)	
	Accident 1963	2	0.3 (0.1–1.4)	
	Main production workers	5	1.3 (0.4–4.7)	
	Occasionally exposed	10	1.5 (0.5– 4.3)	
	Factory B	7	1.0 (0.4–2.8)	
	Main production workers	1	0.9 (0.1–7.1)	
	Occasionally exposed	6	1.1 (0.4-3.2)	
Hooiveld et al., 1998	Dutch herbicide factory workers (IARC subcohort)—mortality (1955–1991)			
	549 exposed vs 482 nonexposed male workers			
	All circulatory diseases (ICD 390–459)	45	1.4 (0.8–2.5)	Adjusted for age, timing of exposure
	TCDD > 124 ng/kg	nr	1.5 (0.8–2.9)	
	Ischemic heart diseases (ICD 410–414)	33	1.8 (0.9–3.6)	
	TCDD > 124 ng/kg	nr	2.3 (1.0–5.0)	
	Cerebrovascular diseases (ICD 430–438)	9	1.4 (0.4–5.1)	

	TCDD > 124 ng/kg	nr	0.8 (0.2–4.1)	
	Other heart disease (ICD 415–429)	3	0.7 (0.1–4.3)	
	TCDD > 124 ng/kg	nr	0.4 (0.0–4.9)	
German Production Workers (included in IARC cohort)				**Dioxin, phenoxy herbicides**
Flesch-Janys et al., 1995	Hamburg, Germany, herbicide production workers (IARC subcohort) vs gas workers—mortality (1952–1992; estimated blood PCDD, PCDF, TCDD from work history, measures on 190 of 1,189 men, divided into four lowest quintiles, top two deciles)			
	Estimated final PCDD, PCDF TEQs (ng/kg)			Gas workers provide a more appropriate comparison group for the data on production workers than the national population data used in the analysis in Flesch-Janys, 1997/1998; Flesch-Janys et al., 1998
	Circulatory disease (ICD 390–459)	156		
	1.0–12.2		0.93 (0.57–1.50)	
	12.3–39.5		0.92 (0.59–1.46)	
	39.6–98.9		1.48 (1.01–2.17)	
	99.0–278.5		1.55 (1.07–2.24)	
	278.6–545.0		1.63 (1.01–2.64)	
	545.1–4,361.9		2.06 (1.23–3.45)	
			p-trend < 0.01	
	Ischemic heart disease (ICD 410–414)	76		Not adjusted for known risk factors
	1.0–12.2		1.02 (0.54–1.95)	
	12.3–39.5		0.96 (0.51–1.82)	
	39.6–98.9		0.97 (0.52–1.81)	
	99.0–278.5		1.13 (0.64–2.00)	Potential for exposure misclassification
	278.6–545.0		1.73 (0.92–3.27)	
	545.1–4,361.9		2.72 (1.49–4.98)	
	Estimated final TCDD (ng/kg)		p-trend < 0.01	
	Circulatory disease (ICD 390–459)	156		
	0–2.8		1.22 (0.81–1.83)	
	2.81–14.4		0.88 (0.54–1.44)	
	14.5–49.2		1.35 (0.91–2.01)	
	49.3–156.7		1.64 (1.12–2.39)	
	156.8–344.6		1.53 (0.95–2.44)	
	344.7–3,890.2		1.96 (1.15–3.34)	
			p-trend = 0.01	

continued

TABLE 10-3 Circulatory Disorders, continued

Reference[a]	Study Population[b]	Exposed Cases[c]	Exposure of Interest/ Estimated Risk (95% CI)[c]	Exposure/ Comments
	Ischemic heart disease (ICD 410–414)	76		
	0–2.8		1.43 (0.83–2.44)	
	2.81–14.4		0.81 (0.41–1.61)	
	14.5–49.2		1.18 (0.65–2.16)	
	49.3–156.7		0.90 (0.47–1.75)	
	156.8–344.6		1.61 (0.85–3.04)	
	344.7–3,890.2		2.48 (1.32–4.66)	
			p-trend < 0.01	
Becher et al., 1996 (Mortality through 1992 for Hamburg plant reported above by Flesch-Janys)	Phenoxy herbicide workers at four German plants (four IARC subcohorts, including Hamburg)—mortality (through 1989)			
	Circulatory diseases (ICD 390–458)			
	Bayer Uerdingen	12	0.74 (0.38–1.30)	
	Bayer Dormagen	3	0.34 (0.07–0.99)	
	BASF Ludwigshafen	32	0.78 (0.53–1.10)	
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)				**Dioxin, phenoxy, herbicides**
McBride et al., 2009a	New Zealand phenoxy herbicide workers—ischemic heart disease mortality			
	Ever-exposed workers—stroke	15	1.1 (0.6–1.9)	
	Ever-exposed workers—ischemic heart disease	61	1.1 (0.9–1.5)	
	Ischemic heart disease:			
	TCDD exposure ppt-months			
	0–68.3	14	1.0 (reference group)	Adjusted for age, sex, hire yr, birth yr
	68.4–475.0	18	1.24 (0.58–2.64)	
	475.1–2,085.7	15	1.32 (0.60–2.90)	
	2,088.7+	14	0.93 (0.37–2.35)	

't Mannetje et al., 2005 (IARC subcohort)	New Zealand phenoxy herbicide workers—mortality			Not adjusted for known risk factors
	Producers (1969–2000)			
	Circulatory disease	51	1.0 (0.7–1.3)	All-causes SMR = 1.0 (0.8–1.2)
	Hypertensive disease	0	0.0 (0.0–3.5)	
	Ischemic heart disease	38	1.0 (0.7–1.4)	
	Sprayers (1973–2000)			
	Circulatory disease	33	0.5 (0.4–0.7)	All-causes SMR = 0.6 (0.5–0.8)
	Hypertensive disease	1	0.8 (0.0–4.5)	
	Ischemic heart disease	22	0.5 (0.3–0.8)	
United Kingdom Production Workers (included in IARC cohort)				**Dioxin, phenoxy, herbicides**
Coggon et al., 1991	British Chemical Manufacturers at four plants (four IARC subcohorts)—mortality			
	Circulatory disease	74	1.16 (0.91–1.46)	
	Plant A (1975–1987)	34	1.67 (adjusted = 1.39, $p \approx 0.05$)	
	Plant B (1969–1987)	5	0.95	
	Plant C (1963–1987)	12	0.84	
	Plant D (1969–1987)	23	0.97	
Coggon et al., 1986	British MCPA manufacturers (5th of seven UK IARC cohorts)—mortality			
	Hypertensive, ischemic heart disease (ICD 401–414, 428–429)	337		
	vs national rates		0.81 (0.73–0.90)	
	with rural adjustment		0.86 (0.77–0.96)	
Waste-Incinerator Workers				**Dioxin, phenoxy herbicides**
Kitamura et al., 2000	Municipal waste-incinerator workers—morbidity			Adjusted for age, BMI, and smoking
	Hypertension by PCDD, PCDF	14 of 94	No increases observed	

continued

TABLE 10-3 Circulatory Disorders, continued

Reference[a]	Study Population[b]	Exposed Cases[c]	Exposure of Interest/ Estimated Risk (95% CI)[c]	Exposure/ Comments
Agricultural Health Study				**Herbicides**
Mills et al., 2009	AHS—myocardial infarction			
	Mortality among 54,069 male applicators			Adjusted for age, state, smoking. Incidence analysis further adjusted for body mass index
	2,4-D	73	0.90 (0.72–1.11)	
	2,4,5-T	32	0.98 (0.79–1.23)	
	2,4,5-TP	14	1.06 (0.79–1.42)	
	Dicamba	42	0.94 (0.75–1.18)	
	Non-fatal incidence among 32,024 male applicators—year 5 survey			
	2,4-D	78	1.16 (0.97–1.38)	
	2,4,5-T	37	1.21 (1.03–1.43)	
	2,4,5-TP	14	1.08 (0.86–1.35)	
	Dicamba	47	1.13 (0.94–1.34)	
Blair et al., 2005	AHS—mortality			Adjusted for age, race, state, sex, and calendar yr of death
	Private applicators (farmers), spouses			
	Circulatory disease (1994–2000)	619	0.5 (0.5–0.6)	
Other Agricultural Studies				**Herbicides**
Gambini et al., 1997	Italian rice growers—mortality (1957–1992) (phenoxy herbicide use common 1960–1980)			
	Myocardial infarction	67	0.72 (0.56–0.92)	
	Other ischemic heart diseases	72	0.41 (0.32–0.52)	
	Stroke	155	0.96 (0.81–1.12)	
Other Studies of Herbicide and Pesticide Applicators				**Herbicides**
Swaen et al., 2004	Dutch licensed herbicide applicators—mortality (1980–2000)			
	Circulatory disease	70	0.68 (0.53–0.86)	
Blair et al., 1983	Florida, US licensed pesticide applicators—mortality			Not adjusted for known risk factors
	Circulatory diseases (ICD 390–458)	159	0.88 ($p > 0.05$)	

Forestry Workers				**Herbicides**
Alavanja et al., 1989	US forest and soil conservationists—mortality		PMRs	
	Ischemic heart disease (ICD 410–414)	543	1.0 (0.9–1.1)	Not adjusted for known risk factors
	Cerebrovascular disease (ICD 430–438)	99	0.9 (0.8–1.1)	
Paper and Pulp Workers				**Dioxins**
McLean et al., 2006	IARC cohort of pulp and paper workers—circulatory disease—mortality			
	Never exposed to nonvolatile organochlorines	2,727	0.92 (0.80–0.96)	Not adjusted for known risk factors
	Ever exposed to nonvolatile organochlorines	2,157	0.99 (0.95–1.04)	
Environmental Studies				
Seveso, Italy Residential Cohort				**TCDD**
Consonni et al., 2008	Seveso, Italy—mortality–25 yrs (1976–2001)			
	Zone A, sexes combined			Adjusted for gender, age, period
	All circulatory diseases (ICD 390–459)	45	1.1 (0.8–1.4)	
	Chronic rheumatic heart diseases (ICD 393–398)	3	5.7 (1.8–18.0)	
	Hypertension (ICD 400–405)	5	2.2 (0.9–5.3)	
	Ischemic heart diseases (ICD 410–414)	13	0.8 (0.5–1.4)	
	Acute myocardial infarction (ICD 410)	6	0.6 (0.3–1.4)	
	Chronic ischemic heart diseases (ICD 412, 414)	7	1.1 (0.5–2.3)	
	Cerebrovascular diseases (ICD 430–438)	11	0.9 (0.5–1.6)	
	Zone B, sexes combined			
	All circulatory diseases (ICD 390–459)	289	1.0 (0.9–1.1)	
	Chronic rheumatic heart diseases (ICD 393–398)	1	0.3 (0.0–2.2)	
	Hypertension (ICD 400–405)	11	0.7 (0.4–1.3)	
	Ischemic heart diseases (ICD 410–414)	102	1.0 (0.8–1.2)	
	Acute myocardial infarction (ICD 410)	54	0.9 (0.7–1.1)	
	Chronic ischemic heart diseases (ICD 412, 414)	47	1.1 (0.8–1.4)	
	Cerebrovascular diseases (ICD 430–438)	101	1.2 (1.0–1.5)	

continued

TABLE 10-3 Circulatory Disorders, continued

Reference[a]	Study Population[b]	Exposed Cases[c]	Exposure of Interest/ Estimated Risk (95% CI)[c]	Exposure/ Comments
	Zone R, sexes combined			
	All circulatory diseases (ICD 390–459)	2,357	1.1 (1.0–1.1)	
	Chronic rheumatic heart diseases (ICD 393–398)	24	1.0 (0.6–1.5)	
	Hypertension (ICD 400–405)	144	1.2 (1.0–1.4)	
	Ischemic heart diseases (ICD 410–414)	842	1.1 (1.0–1.1)	
	Acute myocardial infarction (ICD 410)	447	1.0 (0.9–1.1)	
	Chronic ischemic heart diseases (ICD 412, 414)	390	1.2 (1.0–1.3)	
	Cerebrovascular diseases (ICD 430–438)	695	1.1 (1.0–1.2)	
National Health and Nutrition Examination Survey				**Dioxin, phenoxy, herbicides**
Ha et al., 2009	NHANES, 1999–2002—newly diagnosed hypertension—524 adults (≥ 40 years old) excluding treated hypertensives		≥ 75th percentile vs < 25th percentile	Adjusted for age, race, income, BMI, cigarette-smoking, serum cotinine, alcohol, exercise
	Men			
	PCDDs	23	2.3 (0.7–7.8) p-trend = 0.15	
	PCDFs	21	1.9 (0.7–4.9) p-trend = 0.17	
	Dioxin-like PCBs	27	1.7 (0.8–6.6) p-trend = 0.11	
	Women			
	PCDDs	33	5.0 (1.2–21.5) p-trend = 0.08	
	PCDFs	30	4.2 (1.3–14.3) p-trend = 0.01	
	Dioxin-like PCBs	28	1.1 (0.3–3.5) p-trend = 0.93	
	26.1–59.1		1.1 (0.9–1.4)	
	> 59.1		1.8 (1.2–2.6)	

	PCB 156 (ng/g of lipid) (TEF = 0.0005)			
	≤ 12.5		1.0	
	12.6–15.4		1.3 (0.9–1.9)	
	> 15.4		1.2 (0.8–1.9)	
	PCB 169 (pg/g of lipid) (TEF = 0.01)			
	≤ 27.0		1.0	
	27.1–46.4		1.1 (0.9–1.5)	
	> 46.4		1.3 (0.9–1.9)	
Ha et al., 2007	NHANES, 1999–2002—self-reported cardiovascular disease (excluding hypertension)—889 nondiabetics ≥ 40 years old		≥ 75th percentile vs < 25th percentile	Adjusted for age, race, income, BMI, cigarette-smoking, serum cotinine, alcohol, exercise HDL, total cholesterol, triglycerides hypertension, C-reactive protein
	Men			
	HxCDD	18	2.5 (0.8–7.7)	
	HpCDD	18	2.4 (0.5–10.3)	
	OCDD	16	2.1 (0.6–7.7)	
	PCDDs	23	2.2 (0.8–6.1)	
	PCDFs	19	0.7 (0.3–1.7)	
	Dioxin-like PCBs	22	1.7 (0.6–5.5)	
	Women			
	HxCDD	21	2.8 (0.9–8.6)	
	HpCDD	14	1.9 (0.3–10.8)	
	OCDD	17	0.7 (0.2–2.8)	
	PCDDs	19	2.0 (0.7–6.4)	
	PCDFs	15	1.0 (0.3–2.8)	
	Dioxin-like PCBs	23	5.0 (1.2–20.4)	

continued

TABLE 10-3 Circulatory Disorders, continued

Reference[a]	Study Population[b]	Exposed Cases[c]	Exposure of Interest/ Estimated Risk (95% CI)[c]	Exposure/ Comments
Everett et al., 2008b	NHANES, 1999–2004—prevalent hypertension (self-report that told by doctor, ≥ 140/90 mmHg, or antihypertensive medications)—3,398–3,712 individuals depending on congener			
	PCB 118 (ng/g of lipid) (TEF = 0.0001)			Adjusted for age, sex, race, smoking status, BMI, exercise, total cholesterol, family history of myocardial infarction
	≤ 12.5		1.0	
	12.6–27.5		1.4 (1.1–1.8)	
	> 27.5		2.0 (1.3–3.0)	
	PCB 126 (pg/g of lipid) (TEF = 0.1)			
	≤ 26.1		1.0	
	26.2–59.1		1.1 (0.9–1.4)	
	> 59.1		1.8 (1.2–2.6)	
	PCB 156 (ng/g of lipid) (TEF = 0.0005)			
	≤ 12.5		1.0	
	12.6–15.4		1.3 (0.9–1.9)	
	> 15.4		1.2 (0.8–1.9)	
	PCB 169 (pg/g of lipid) (TEF = 0.01)			
	≤ 27.0		1.0	
	27.1–46.4		1.1 (0.9–1.5)	
	> 46.4		1.3 (0.9–1.9)	
Lee et al., 2007c	NHANES, 1999–2002—721 nondiabetics ≥ 20 yrs old with fasting blood samples and measured POPs high blood pressure (≥ 130/85 mmHg)	nr	≥ 75th percentile vs those with nondetectable levels	
	PCDDs		1.7 (1.0–3.1)	Adjusted for age, race, sex, income, cigarette-smoking, serum cotinine, alcohol consumption, exercise
	HxCDD		1.2 (0.7–2.2)	
	HpCDD		2.6 (1.3–5.0)	
	OCDD		1.1 (0.6–2.0)	

	PCDFs		1.9 (1.2–3.3)	
	PeCDF		1.3 (0.7–2.4)	
	HxCDF		2.3 (1.3–4.0)	
	HpCDF		1.4 (0.8–2.3)	
	Dioxin-like PCBs		1.4 (0.8–2.7)	
	PCB 74		1.2 (0.6–2.4)	
	PCB 118		1.8 (1.0–3.5)	
	PCB 126		2.1 (1.2–3.7)	
	PCB 169		0.6 (0.3–1.1)	
Other Environmental Studies				
Turunen et al., 2008	Finnish fishermen and spouses—mortality (1980–2005)			**TCDD, PCBs, TEQs**
	Ischemic heart disease			Standardized mortality analysis—age adjusted
	Men	269	0.73 (0.65–0.81)	
	Women	62	0.65 (0.50–0.83)	
	Cerebrovascular disease			
	Men	67	0.67 (0.52–0.85)	
	Women	46	0.95 (0.70–11.27)	
Karouna-Renier et al., 2007	Superfund site caused by wood-treatment facility in Pensacola, Florida—47 workers, residents—prevalence			**Dioxin/phenoxy herbicides**
	Hypertension defined by self-report, medication use, or two readings of systolic blood pressure greater than 140 mmHg or diastolic blood pressure greater than 90 mmHg		1.1 (1.1–1.2) [error likely; published OR and lower confidence limit identical to three decimal places]	Adjusted for age, race, sex, BMI, tobacco and alcohol use, worker status
	Serum PCDD/F (TEQs in logistic model)			

continued

TABLE 10-3 Circulatory Disorders, continued

Reference[a]	Study Population[b]	Exposed Cases[c]	Exposure of Interest/ Estimated Risk (95% CI)[c]	Exposure/ Comments
Chen et al., 2006	Residents around 12 municipal waste incinerators in Taiwan—prevalence			**Dioxin/phenoxy herbicides:**
	Hypertension diagnosed by a physician	118	5.6 (1.6–19.6)	Adjusted for age, sex, smoking, BMI
	Serum PCDD/F (TEQs in logistic model)		0.9 (0.2–3.7)	

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; ACC, Army Chemical Corps; AFHS, Air Force Health Study; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CHD, coronary heart disease; COI, chemical of interest; HDL, high-density lipoprotein; HpCDD, 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin; HpCDF, 1,2,3,4,6,7,8-heptachlorodibenzofuran; HxCDD, 1,2,3,6,7,8-hexachlorodibenzo-*p*-dixion; HxCDF, 1,2,3,4,7,8-hexachlorodibenzofuran; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; MCPA, 2-methyl-4-chlorophenoxyacetic acid; NHANES, National Health and Nutrition Examination Survey; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; MI, Michigan; NZ, New Zealand; OCDD, 1,2,3,4,6,7,8,9-octachlorodibenzo-*p*-dioxin; OR, odds ratio; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin; PCDD/F, dioxins and furans combined; PCDF, polychlorinated dibenzofuran; PCP, PeCDF, 2,3,4,7,8-pentachlorodibenzofuran; pentachlorophenol; PMR, proportional mortality ratio; POP, persistent organic pollutant; RH, Ranch Hand; SEA, Southeast Asia; SMR, standardized mortality ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dixoin; TCP, trichlorophenol; TEF, toxicity equivalency factor for individual congener; TEQ, (total) toxic equivalent; VA, US Department of Veterans Affairs; VES, Vietnam Experience Study; WV, West Virginia.

[a]New citations labeled as such and bolded; section shaded for citations with dose–response information on TCDD.

[b]Subjects male unless otherwise noted.

[c]Given when available; results other than estimated risk explained individually.

Ha et al. (2009) examined "newly diagnosed" hypertension and its relationship to persistent organic pollutants from data gathered in the National Health and Nutrition Examination Survey (NHANES) of 1999–2002. Persons with known diabetes or hypertension were excluded from the study because knowledge of these conditions might lead to lifestyle changes that would yield a risk-factor profile that did not exist when the conditions developed. Hypertension was defined as blood pressure above 140/90 mm Hg. Associations were adjusted for age, race, income, BMI, smoking, concentrations of cotinine (a nicotine metabolite), alcohol consumption, and leisure-time physical activity. The study examined pollutants that were measurable in at least 60% of the NHANES population and included three PCDDs, three PCDFs, and five dioxin-like PCBs. In the 524 adults (at least 40 years old) in the sample, 123 new cases of hypertension were identified. When people in the lowest quartile for the grouped classes of pollutants were used as the referent, the men had generally increased risks in association with PCDDs, PCDFs, and dioxin-like PCBs, but none of the risks in even the highest quartile was significant, and there were no indications of a trend with increasing concentrations of any of these substances. The risks associated with PCDD and PCDF concentrations were more extreme in women than in men—there were significant increases and significant trends for PCDDs and PCDFs, but this was not the case for dioxin-like PCBs.

Circulatory Diseases

Ideally, epidemiologic investigations of circulatory diseases would consider the conditions in this category separately rather than together because they have different patterns of occurrence and many have different etiologies. However, many mortality studies follow the ICD-9 rubric and report deaths from circulatory disease together. Deaths from coronary or ischemic heart disease, heart failure, and to a lesser extent stroke will predominate. Many of the reports also break out subcategories (such as cerebrovascular disease and hypertension). The dominance of heart failure would be determined by the age of the cohort. In younger cohorts, most of the deaths in this category would be expected to be from ischemic heart disease. Cerebrovascular deaths are deaths from strokes, which can be classified as either ischemic or hemorrhagic. In the US population, the great majority of strokes are of the ischemic type.

Vietnam-Veteran Studies In the most recent report on the ACC veterans, 272 deaths from circulatory systems diseases were ascertained (Cypel and Kang, 2010). Mortality in the deployed portion of the ACC cohort was significantly greater than that expected in the US male population (SMR = 1.16, 95% CI 1.00–1.34), and mortality in the nondeployed group was not (SMR = 0.87, 95% CI 0.69–1.07). ACC veterans who served in Vietnam had an estimated 21% higher risk of death from circulatory system diseases than those who did not (RR

= 1.21, 95% CI 0.93–1.58). In those who served in Vietnam, self-reported herbicide spraying was associated with a statistically nonsignificant increase in circulatory system deaths (RR = 1.17, 95% CI 0.60–2.28). There was a nonsignificant increase in mortality from cerebrovascular disease in the deployed ACC veterans (RR = 1.48, 95% CI 0.67–3.27) compared with the nondeployed. In the Vietnam cohort, self-reported spraying was associated with a statistically nonsignificant increase in cerebrovascular-disease deaths (RR = 2.12, 95% CI 0.37–12.30).

In comparison to the general public, the Australian Vietnam veterans studied by O'Toole et al. (2009) had a higher prevalence of self-reported angina (prevalence ratio [PR] = 2.34, 95% CI 1.68–2.99), of ischemic heart disease not including angina (PR = 4.07, 95% CI 3.11–2.99), of heart failure (PR = 1.76, 95% CI 1.01–2.52), and of cerebrovascular disease (PR = 2.39, 95% CI 1.24–3.53). The committee had serious concerns that the results reported in O'Toole et al. (2009) were compromised by recall bias and other methodologic problems.

Occupational Studies Boers et al. (2010) report on the updated mortality experience of employees at two Dutch factories involved in chlorophenoxy herbicide production. The experience of the workers at the plants has been included in IARC pooled analyses (through 1985 and 1986 in Saracci et al., 1991; through 1991 in Kogevinas et al., 1997). This study includes an additional 15 years of follow-up beyond that previously reported. In 1963, an accident at factory A, which primarily produced 2,4,5-T, led to the exposure of workers to many chemicals, including TCDD. Factory B primarily produced 2,4-D. Workers in both factories were considered to be exposed or not exposed to chlorophenoxy herbicides on the basis of job classifications; workers at factory A would have had more chance of TCDD exposure. Exposure assignment was validated against blood TCDD measured in samples drawn in 1993. In factory A (539 exposed and 482 unexposed), exposure to the chemical production was associated with a 15% higher age-adjusted rate of ischemic heart disease mortality (RR = 1.15, 95% CI 0.66–1.98) and a 23% higher rate of cerebrovascular disease mortality (RR = 1.23, 95% CI 0.42–3.56). Workers exposed in the 1963 accident were at an even higher risk of ischemic heart disease death (RR = 1.60, 95% CI 0.72–3.55) but not death from cerebrovascular disease (RR = 0.27, 95% CI 0.05–1.36). In factory B (411 exposed and 626 unexposed), exposure to chemical production was associated with higher mortality from ischemic heart disease (RR = 1.56, 95% CI 0.79–3.11), but not cerebrovascular disease (RR = 1.04, 95% CI 0.39–2.80).

In their studies of the mortality experience through 2003 of 1,615 workers exposed to dioxins in TCP production in Midland, Michigan, Collins et al. (2009a) did not find higher than expected mortality from either ischemic heart disease (SMR = 1.1, 95% CI 0.9–1.2) or cerebrovascular disease (SMR = 1.0, 95% CI 0.7–1.4) compared with the US population. Collins et al. (2009b) also assessed mortality for the same period in 773 workers involved in PCP production during 1937–1980; PCP contains some contamination with dioxin-like congeners but not specifically TCDD, as is found in TCP. With the US population again as

the referent group, the 577 workers who had not also experienced TCP exposure were found not to have increased mortality from either ischemic heart disease (SMR = 1.0, 95% CI 0.9–1.3) or cerebrovascular disease (SMR = 0.9, 95% CI 0.5–1.6).

McBride et al. (2009a) provide an updated and expanded analysis of the mortality experience of 1,599 workers employed at a New Zealand chemical plant at which TCP was manufactured;. the group was part of the IARC cohort (Saracci et al., 1991). This report includes additional workers, refined dose estimates based on serum dioxin evaluations, and additional follow-up. Some 21% of the identified workers were lost to follow-up. There were 75 deaths from ischemic heart disease and 17 deaths from stroke. Mortality from ischemic heart disease did not differ from that in the New Zealand population (SMR = 1.1, 95% CI 0.9–1.5), nor did mortality from stroke (SMR = 1.1, 95% CI 0.6–1.9). The authors were able to classify workers into four categories of TCDD exposure based on job histories; the classifications were validated by using serum dioxin concentrations. Workers in the two middle categories of dose had statistically nonsignificant increases in ischemic heart disease mortality (RR = 1.24, 95% CI 0.58–2.64 and RR = 1.32, 95% CI 0.60–2.90) compared with the low exposure category. The mortality experience of those in the highest exposure category was similar to that of the low-exposure group (RR = 0.93, 95% CI 0.37–2.35). McBride et al. (2009b) also published mortality findings from this plant that include all workers employed at the site during 1969–2003; because the results were diluted by the addition of younger workers who were not exposed to the chemicals of interest, they are not considered further.

Using data from the Agricultural Health Study (AHS), Mills et al. (2009) reported on a possible association between 48 chemicals used in agriculture and fatal and nonfatal heart attack (myocardial infarctions, MIs). They assessed exposure to 2,4-D, 2,4,5-T, 2-(2,4,5-trichlorophenoxy) propionic acid (2,4,5-TP, Silvex), and dicamba. The study examined MI mortality and incidence in separate subsets of the AHS study cohort. Mortality was assessed in 54,069 men enrolled in the study by ascertaining deaths through national mortality registries. Nonfatal cases were ascertained in 32,024 respondents to a 5-year post-baseline questionnaire (about 70% of original enrollees). Those reporting a physician diagnosis of MI since the baseline assessment were considered to have incident nonfatal cases. Those reporting a history of MI at or before the baseline assessment were excluded from analysis. Established heart-disease risk factors (such as age and smoking) were associated with both fatal and nonfatal MI in the expected direction. After adjustment for age, state, BMI, and smoking status, 2,4-D was not associated with MI mortality (RR = 0.90, 95% CI 0.72–1.11), and the increase in incidence was of borderline significance (RR = 1.16, 95% CI 0.97–1.38). 2,4,5-T was significantly associated with MI incidence (RR = 1.21, 95% CI 1.03–1.43) but not mortality (RR = 0.98, 95% CI 0.79–1.23). 2,4,5-TP was not associated with either mortality or incidence (RR = 1.06, 95% CI 0.79–1.42 and RR = 1.08, 95% CI 0.86–1.35, respectively), nor was dicamba (RR = 0.94, 95% CI 0.75–1.18

and RR = 1.13, 95% CI 0.94–1.34, respectively). Other chemicals associated with increased MI risk were DDT, aldrin, ethylene dibromide, and ziram.

Pelclová et al. (2009) updated a study of Czech workers (aged 64.4 ± 1.5 years) exposed to TCDD between 1965–1968 while working in a plant producing 2,4,5-T. Eleven out of the original group of approximately 80 workers were reevaluated for this update. Five out of the 11 workers were diagnosed with ischemic health disease. The usefulness of this study is limited, however, because of the small sample size, the lack of a well-defined comparison population, and the lack of comparison data between the exposed and nonexposed populations.

Environmental Studies Turunen et al. (2008) found that Finnish fishermen and their spouses had lower 12-year mortality from ischemic heart disease than expected (SMR = 0.73, 95% CI 0.65–0.81 and SMR = 0.65, 95% CI 0.50–0.83, respectively). The fishermen also had significantly fewer deaths attributed to cerebrovascular disease than expected (SMR = 0.67, 95% CI 0.52–0.85), whereas their wives' mortality experience did not differ significantly from that of the general population (SMR = 0.95, 95% CI 0.70–1.27).

Other Reviewed Studies Several studies did not characterize exposure with sufficient specificity or described outcomes that would be considered biomarkers rather than disease states, so their findings have not been entered into the results table, but the committee did consider them as supportive information.

In their study of metabolic syndrome, Uemura et al. (2009) found that participants who had dioxin TEQs in the highest quartile had 170% higher OR (2.7, 95% CI 1.3–5.9) of low HDL cholesterol (less than 40 mg/dL in men and less than 50 mg/dL in women) after adjustment for age, sex, smoking, drinking, regional block, residential area, and survey year. Among the classes of compounds contributing to the TEQ calculation, PCDDs had a particularly strong association (OR = 3.2, 95% CI 1.7–6.4).

Biologic Plausibility

It is well established that the vasculature, specifically endothelial cells, are a target of TCDD toxicity. TCDD exposure of vessels in vivo or of endothelial cells in vitro induces major changes in gene expression and leads to substantial increases in oxidative stress, inflammatory markers, structural remodeling, and functional reactivity (Ishimura et al., 2009; Kopf and Walker, 2010; Kopf et al., 2008; Majkova et al., 2009; Puga et al., 2004). There is also growing evidence from a variety of experimental models that TCDD induces hypertension and promotes the development of CVD in animal models. In a recent study, Kopf et al. (2010) demonstrated that chronic exposure of mice to TCDD induces hypertension associated with significant increases in vascular oxidative stress and decreases in vascular relaxation. Furthermore, induction of cytochrome

P4501A1 (CYP1A1) was required for those responses; none of them occurred in TCDD-exposed CYP1A1-null mice. Previous studies had shown that TCDD increases the incidence, severity, and progression of atherosclerotic plaques in ApoE-null mice (Dalton et al., 2001), and rats chronically exposed to TCDD exhibit significant arterial remodeling characterized by endothelial-cell hypertrophy, extensive smooth-muscle cell proliferation, and inflammation (Jokinen et al., 2003). In addition to the vasculature, studies have suggested that the heart is a target of TCDD. TCDD exposure increases hypertrophy of rat cardiac cells in culture (Zordoky and El-Kadi, 2010), increases myocardial fibrosis (Riecke et al., 2002), and leads to cardiac hypertrophy and alteration in control of heart rhythm in vivo (Kopf et al., 2008, 2010; Lin et al., 2001; Thackaberry et al., 2005a,b). Constitutive activation of the aryl hydrocarbon receptor (AHR) results in disruption of cardiovascular homeostasis, as shown in transgenic mice that have a constitutively active AHR and develop an age-progressive cardiac hypertrophy (Brunnberg et al., 2006). The data show that activation of the AHR, endogenously or by xenobiotics, induces cardiovascular injury and leads to CVD in animal models.

In addition to direct effects of TCDD on the vasculature and heart, there is considerable evidence that TCDD influences other CVD risk factors, including promotion of macrophage lipid accumulation, induction of lipid mobilization, and alteration of lipid metabolism. For example, Boverhof et al. (2005) found that exposure of mice to a single high dose of TCDD (30 µg/kg of body weight) increased serum triglycerides 1–7 days after exposure, and the increase was associated with changes in hepatic gene expression that were consistent with mobilization of peripheral fat. Similarly, Dalton et al. (2001) found that exposure of mice to a cumulative TCDD dose of 15 µg/kg over 3 days increased serum triglycerides and LDL that were measured 4 weeks after exposure. Increases in serum triglycerides have also been seen in TCDD-exposed rhesus monkeys (Rier et al., 2001). The mechanism underlying alteration of lipid metabolism has not been elucidated, but the animal studies provide some evidence of biologic plausibility that TCDD exposure can directly alter serum lipid and lipoprotein concentrations. Thus, on the basis of animal models, there appear to be several overlapping and potentially contributing pathways that may link TCDD exposure and increased CVD risk.

Synthesis

In this section, the committee synthesizes information on circulatory disorders from the new studies described above and reconsiders studies that were reviewed in previous updates. Because circulatory diseases constitute a broad group of diverse conditions, hypertension and ischemic heart disease are discussed separately from other circulatory diseases so that the new studies can be adequately synthesized and integrated with the earlier studies.

Hypertension

Hypertension, typically defined as blood pressure above 140/90 mmHg, affects more than 70 million adult Americans and is a major risk factor for coronary heart disease, myocardial infarction, stroke, and heart and renal failure. The major quantifiable risk factors for hypertension are well established and include age, race, BMI or percentage of body fat, and diabetes; the strongest conclusions regarding a potential increase in the incidence of hypertension come from studies that have controlled for these risk factors. The committee responsible for *Update 2006* concluded that the available evidence was consistent with the placement of hypertension in the limited or suggestive category. Additional evidence reviewed in *Update 2008* reaffirmed this conclusion.

With respect to the new evidence published since *Update 2008*, the two veteran studies are of limited utility in judging the association. Too few deaths were ascribed to hypertension in the ACC veterans study to allow any useful conclusions to be drawn. Furthermore, although very common, hypertension is rarely identified as an underlying cause of death. Most often, deaths associated with hypertension are ascribed to clinical conditions *caused by* hypertension, such as ischemic heart disease or stroke. Thus, the degree of correspondence between death from hypertension and the occurrence of hypertension in the exposed populations is unclear. The results of the Australian veterans survey are also unreliable; the occurrence of hypertension was based on self-reports, which can be unreliable, and the study did not assess potential chemical exposures, so its findings cannot separate potential Agent Orange–related effects from the general health consequences of Vietnam service.

The third NHANES analysis (Ha et al., 2009) complements other NHANES analyses that were featured in *Update 2008* (Everett et al., 2008a,b; Lee et al., 2007c). NHANES data on many important potential confounding variables permits adjustment for these factors, and hypertensive status was based on measured values and not self-reports. There was an association between the chemicals of interest and hypertension, which was particularly strong in women. The Japanese population survey (Uemura et al., 2009) shares the strengths of the NHANES studies. It also found dioxin and dioxin-like compounds to be associated with the prevalence of hypertension. Both are limited in being cross-sectional studies, whose weaknesses have been discussed above. Nevertheless, the surveys are consistent with a relationship between the compounds of interest and hypertension. The additional supporting evidence and the strong biologic rationale affirm the present committee's placement of hypertension in the limited and suggestive category.

Ischemic Heart Disease

Circulatory diseases comprise a group of diverse conditions, of which hypertension, coronary heart disease, and stroke are the most prevalent and account for

75% of deaths from circulatory diseases in the United States. The major quantifiable risk factors for circulatory diseases are similar to those for hypertension and include age, race, smoking, serum cholesterol, BMI or percentage of body fat, and diabetes.

The committee responsible for *Update 2008* revisited the entire body of evidence on TCDD exposure and heart disease and concluded that the evidence supported moving ischemic heart disease to the limited and suggestive category. That conclusion was based on evidence of a dose–response relationship in the occupational cohorts, evidence of increased risk of MI in Vietnam veterans, supporting cross-sectional survey data, and a strong biologic rationale.

With the exception of those by Mills et al. (2009) and Turunen et al. (2008), all the newly reviewed studies are updates or extensions of previous studies. It might be expected that additional follow-up would increase the strength of an association between exposures and outcomes because the number of outcomes assessed grows with additional follow-up. In the case of multifactorial chronic diseases, such as heart disease, that intuition does not necessarily hold. Exposure to a particular agent may lead to excess cases, but the strength of the association is also related to the number of cases that occur in the nonexposed. The excess risk associated with a particular exposure becomes less important as the risk of disease in the nonexposed goes up. That phenomenon has been observed in the relationship between cholesterol and heart disease. In middle-aged men, the association between cholesterol and heart disease is easily detected because the number of cases in men who have normal cholesterol is low. In older men, however, the relative risk falls considerably because the rate of heart disease in those who have normal cholesterol levels rises quickly with age. Consequently, it is possible that the association between exposure and disease as indexed by the RR would fall with additional follow-up time even if there is no change in the underlying causal relationship.

Cypel and Kang (2010) studied mortality from overall circulatory diseases in ACC veterans. They found a nonsignificant increase in circulatory-disease mortality in ACC veterans who served in Vietnam compared with those who did not. The mortality experience in the Vietnam veterans significantly exceeded that expected on the basis of the US male population. The analysis did not adjust for smoking or other common risk factors, so confounding could not be ruled out. In addition, Vietnam service itself may be associated with future health in a variety of ways that are unrelated to herbicide exposure. To address that concern, Cypel and Kang compared deployed veterans who were involved in spraying with those who were not. Their analysis showed a slight increase in mortality in sprayers, but this association was not statistically significant. The survey of Australian Vietnam veterans (O'Toole et al., 2009) showed heart disease and several other circulatory diseases were increased in comparison to the general public. The survey is unreliable for a variety of reasons mentioned earlier in this chapter and discussed in greater detail in Chapter 5.

The updated occupational studies included studies in New Zealand, the Netherlands, and Midland, Michigan. The New Zealand study (McBride et al., 2009a) did not show a dose–response relationship between TCDD exposure and mortality from ischemic heart disease. Workers involved in the production of herbicides in the Netherlands (Boers et al., 2010) had a higher than expected number of ischemic deaths, but the difference was not statistically significant. The data for that report were drawn from two factories, in one of which there had been a significant accidental release of dioxin and other related compounds. Those who had experienced the accident had a larger increase in mortality risk than the group in the factory that had less intense exposures.

The studies from Midland report on the experiences of TCP and PCP production workers (Collins et al., 2009a,b). The workers had documented exposure to TCDD and other dioxins, and in this group the workers who had higher exposure had a greater RR of death from ischemic heart disease than less exposed workers. The difference was not statistically significant, and common potential confounders were not accounted for.

The AHS report provides new data on the occurrence of MI according to herbicide and pesticide exposures. The study was large: more than 54,000 men were included in the mortality analysis and 32,000 in the incidence population. Mills et al. (2009) ascertained 476 MI deaths and 839 new nonfatal cases in these groups. The study found statistical significance for an association between 2,4,5-T exposure and new nonfatal MI, although the association was not seen for MI death. The study is strong because of its longitudinal design, its consideration of both fatal and nonfatal cases, and the availability of important confounding variables, including smoking, BMI, and heart disease–related comorbidities, such as diabetes. The incidence study is of special interest because so much of the literature in this field reports only mortality data, but it does have some weaknesses. First, the analytic sample was assembled on the basis of completion of a 5-year follow-up survey. Bias could be introduced if the exposure–outcome relationship in the 40% who did not participate differed systematically from that in the participants. Furthermore, the design meant that only nonfatal cases could be studied. However, many new-onset cases would be expected to lead to death within the observation period and so would not be included in the incidence analysis, and this could lead to bias if exposure status was associated with case fatality.

Finnish fishermen and their spouses were at decreased risk for mortality from ischemic heart disease. However, because of the design issues discussed previously in this chapter, the data are of little help in evaluating the relationship between the chemicals of interest and ischemic heart disease.

The new epidemiologic evidence, although imperfect, generally supports the continued placement of ischemic heart disease in the ”limited and suggestive” category. The most relevant studies show an excess of ischemic heart disease associated with exposure to the chemicals of interest, although the role of chance could be ruled out in only one case. The best new evidence from the AHS study also shows the strongest association even after adjustment for common confound-

ing variables. The present committee therefore decided to retain ischemic heart disease in the "limited and suggestive" category.

Other Circulatory Disease

Several of the studies reviewed for the present update provided data on cerebrovascular disease (Boers et al., 2010; Collins et al., 2009a,b; Cypel and Kang, 2010; McBride et al., 2009a; O'Toole et al., 2009; Turunen et al., 2008). Cypel and Kang (2010) reported a 48% excess of cerebrovascular-disease deaths in the ACC veterans who served in Vietnam compared with those who did not. The association is not statistically significant, and important potential confounders were not measured. None of the occupationally exposed populations showed an increase in cerebrovascular-disease mortality.

The Cypel and Kang data are interesting but on the whole fragmentary and inconsistent. There is insufficient evidence to conclude that exposure to the chemical of interest is associated with the occurrence of stroke.

Conclusion

After carefully examining the new evidence, the present committee deemed that the new information justified the continued placement of both hypertension (ICD-9 401–405) and ischemic heart disease (ICD-9 410–414) in the limited and suggestive category but that other forms of circulatory disease should remain in the inadequate or insufficient category.

SUMMARY

On the basis of the occupational, environmental, and veterans studies reviewed and in light of information concerning biologic plausibility, the committee reached one of four conclusions about the strength of the evidence regarding an association between exposure to the chemicals of interest and each of the health outcomes discussed in this chapter. In categorizing diseases according to the strength of the evidence, the committee applied the same criteria (discussed in Chapter 2) that were used in *VAO*, *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008*. To be consistent with the charge to the committee by the Secretary of Veterans Affairs in Public Law 102-4 and with accepted standards of scientific review, the distinctions between conclusions are based on statistical association.

Health Outcomes with Sufficient Evidence of an Association

For this category, a positive association between exposure and outcome must be observed in studies in which chance, bias, and confounding can be ruled out with reasonable confidence. On the basis of the literature, none of the health ef-

fects discussed in this chapter satisfies the criteria necessary for inclusion in this category.

Health Outcomes with Limited or Suggestive Evidence of an Association

For this category, the evidence must suggest an association between exposure and outcome, although it can be limited because chance, bias, or confounding could not be ruled out with confidence.

On the basis of its evaluation of available scientific evidence, the committee responsible for *Type 2 Diabetes* concluded that there was limited or suggestive evidence of an association between exposure to at least one chemical of interest and type 2 diabetes; the committees responsible for *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008* reached the same conclusion. New evidence reviewed by the present committee supports that conclusion.

The committee for *Update 2006* added the cardiovascular condition hypertension to the list of health outcomes in the category of limited or suggestive evidence. The committee for *Update 2008* confirmed the finding of limited or suggestive evidence of an association between the exposures of interest and hypertension and reached consensus that another cardiovascular outcome, ischemic heart disease, belonged in this category. New evidence reviewed by the present committee supports those conclusions.

Health Outcomes with Inadequate or Insufficient Evidence to Determine Whether There Is an Association

The scientific data on many of the health outcomes reviewed by the present committee were inadequate or insufficient to determine whether there is an association between exposure to the chemicals of interest and the outcomes. For the health outcomes in this category, the available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association. Some studies failed to control for confounding or used inadequate exposure assessment. This category includes circulatory disorders (except as qualified above). The present committee decided that any perturbations concerning lipids and lipoproteins serve more as indications of biologic plausibility of cardiovascular disease than as adverse health outcomes themselves.

Health Outcomes with Limited or Suggestive Evidence of *No* Association

To classify outcomes in this category, several adequate studies covering the full range of known human exposure must be consistent in not showing a positive association between exposure and outcome at any magnitude of exposure. The studies also must have relatively narrow confidence intervals. A conclusion of *no* association is inevitably limited to the conditions, magnitudes of exposure, and

periods of observation covered by the available studies. The possibility of a very small increase in risk at the exposure studied can never be excluded.

The committees responsible for *VAO*, *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008* concluded that none of the health outcomes discussed in this chapter had limited or suggestive evidence of *no* association with exposure to the chemicals of interest. The most recent scientific evidence supports that conclusion.

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11

Other Health Effects

This chapter discusses data on the possible association between exposure to the herbicides used in Vietnam—2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), picloram, and cacodylic acid—and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a contaminant of 2,4,5-T, and several noncancer health outcomes: respiratory disorders, immune-system disorders, diabetes, lipid and lipoprotein disorders, gastrointestinal and digestive disease (including liver toxicity), circulatory disorders, and adverse effects on thyroid homeostasis. The committee also considers studies of exposure to polychlorinated biphenyls (PCBs) and other dioxin-like chemicals informative if their results were reported in terms of TCDD toxic equivalents (TEQs) or concentrations of specific congeners.

In previous updates, chloracne and porphyria cutanea tarda (PCT) were considered along with these chronic noncancer conditions. These are conditions that are quite well accepted to be associated with dioxin exposure, but when they occur this happens within a matter of months of the exposure. In this update these two health outcomes have been moved to an appendix on short-term effects along with transient early-onset peripheral neuropathy, which had previously been discussed in the chapter on neurologic disorder.

For each type of health outcome, background information is followed by a brief summary of the findings described in earlier reports by the Institute of Medicine (IOM) Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. In the discussion of the most recent scientific literature, studies are grouped by exposure type (Vietnam veteran, occupational, or environmental). For articles that report on only a single health outcome and that are not revisiting a previously studied population, design information is summarized

with the results; design information on other studies can be found in Chapter 5. A synopsis of toxicologic and clinical information related to the biologic plausibility that the chemicals of interest can influence the occurrence of a health outcome is presented next and followed by a synthesis of all the material reviewed. Each health-outcome section ends with the present committee's conclusions regarding the strength of the evidence that supports an association with the chemicals of interest. The categories of association and the committee's approach to categorizing the health outcomes are discussed in Chapters 1 and 2.

RESPIRATORY DISORDERS

For the purposes of this report, noncancerous respiratory disorders comprise acute and chronic lung diseases other than cancer. Acute noncancerous respiratory disorders include pneumonia and other respiratory infections; they can increase in frequency and severity when the normal defense mechanisms of the lower respiratory tract are compromised. Chronic noncancerous respiratory disorders generally take two forms: airways disease and parenchymal disease. Airways disease encompasses disorders, among them asthma and chronic obstructive pulmonary disease (COPD), characterized by obstruction of the flow of air out of the lungs. COPD is also known as chronic obstructive airways disease and includes emphysema and chronic bronchitis. Parenchymal disease, or interstitial disease, generally includes disorders that cause inflammation and scarring of the deep lung tissue, including the air sacs and supporting structures; parenchymal disease is less common than airways disease and is characterized by reductions in lung capacity, although it can include a component of airway obstruction. Some severe chronic lung disorders, such as cystic fibrosis, are hereditary. Because Vietnam veterans received health screenings before entering military service, few severe hereditary chronic lung disorders are expected in that population.

The most important risk factor for many noncancerous respiratory disorders is inhalation of cigarette smoke. Although exposure to cigarette smoke is not associated with all diseases of the lungs, it is the major cause of many airways disorders, especially COPD; it contributes to some interstitial disease; and it compromises host defenses in such a way that people who smoke are generally more susceptible to some types of pneumonia. Cigarette-smoking also makes almost every respiratory disorder more severe and symptomatic than it would otherwise be. The frequency of habitual cigarette-smoking varies with occupation, socioeconomic status, and generation. For those reasons, cigarette-smoking can be a major confounding factor in interpreting the literature on risk factors for respiratory disease. Vietnam veterans are reported to smoke more heavily than are non-Vietnam veterans (Kang et al., 2006; McKinney et al., 1997).

It is well known that causes of death from respiratory diseases, especially chronic diseases, are frequently misclassified on death certificates. Grouping various respiratory diseases for analysis, unless they all are associated with a given

exposure, will lead to attenuation of the estimates of relative risk (RR) and to a diminution of statistical power. Moreover, diagnosis of the primary cause of death from respiratory and cardiovascular diseases (CVDs) is often inconsistent. In particular, when persons have both conditions concurrently and both contributed to death, there may be some uncertainty about which cause should be selected as the primary underlying cause. In other instances, errors may arise in selecting one underlying cause in a complex chain of health events (for example, if COPD leads to congestive heart failure and then to respiratory failure).

Many study populations are small, so investigators group deaths from all noncancerous respiratory diseases into one category that combined pneumonia, influenza, and other diseases with COPD and asthma. The committee notes that an association for the grouping of all noncancerous respiratory diseases with any of the chemicals of interest would be too nonspecific to be clinically meaningful; at most, such a pattern would be an indication that within this broad classification some particular disease entity might be impacted by an exposure of interest.

Conclusions from *VAO* and Previous Updates

The committee responsible for *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*, hereafter referred to as *VAO* (IOM, 1994) concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the chemicals of interest and the respiratory disorders specified above. Additional information available to the committees responsible for *Veterans and Agent Orange: Update 1996* (IOM, 1996) and *Update 1998* (IOM, 1999) did not change that finding.

Veterans and Agent Orange: Update 2000 (IOM, 2001) drew attention to findings on the Seveso cohort that suggested a higher mortality from noncancerous respiratory disorders in study subjects, particularly males, who were more heavily exposed to TCDD. Those findings were not replicated in several other relevant studies, although one showed an increase that did not attain statistical significance. The committee responsible for *Update 2000* concluded that although new evidence suggested an increased risk of noncancerous respiratory disorders, particularly COPD, in people exposed to TCDD, the observation was tentative and the information insufficient to determine whether there is an association between exposures to the chemicals of interest and respiratory disorders. Additional information available to the committee responsible for *Veterans and Agent Orange: Update 2002* (IOM, 2003) did not change that finding.

Veterans and Agent Orange: Update 2004 (IOM, 2005) included a new cross-sectional study of residents near a wood-treatment plant (Dahlgren et al., 2003). Soil and sediment samples from a ditch in the neighborhood contained dioxins and furans. Although exposed residents reported a greater frequency of chronic bronchitis by history (17.8% vs 5.7%; $p < 0.0001$) and asthma by history (40.5% vs 11.0%; $p < 0.0001$) than a "nonexposed" control group, the committee

concluded that selection bias and recall bias limited the utility of the results and that there was a possibility of confounding in that history of tobacco use was not accounted for adequately.

Veterans and Agent Orange: Update 2006 (IOM, 2007) reviewed a number of studies of veterans of the Vietnam War. Mortality from respiratory diseases was not found to be higher than expected in the Centers for Disease Control and Prevention Vietnam Experience Study (Boehmer et al., 2004), in the Air Force Health Study (Ketchum and Michalek, 2005), and in two Australian studies of Vietnam veterans (ADVA, 2005b,c). In contrast, in the US Army Chemical Corps cohort of Vietnam veterans, Kang et al. (2006) found that the prevalence of self-reported noncancerous respiratory problems diagnosed by a doctor was significantly increased by about 40–60%, although no differences in the prevalence of respiratory problems was found in the subset of veterans whose serum TCDD was above 2.5 ppt.

In addition, *Update 2006* addressed new studies of potentially exposed occupational cohorts. No associations with respiratory mortality were found in a small subcohort of New Zealand phenoxy-herbicide sprayers included in the International Agency for Research on Cancer (IARC) cohort ('t Mannetje et al., 2005). In the Agricultural Health Study (AHS), no associations between the herbicide and mortality from COPD were found in private applicators or their spouses (Blair et al., 2005). There was also an AHS analysis (Hoppin et al., 2006a) of specific pesticide exposures and the self-reported prevalence of wheeze that showed an association with "current" exposure to 2,4-D.

Several additional new AHS publications were reviewed in *Veterans and Agent Orange: Update 2008* (IOM, 2009) concerning morbidity from particular self-reported respiratory health problems: another analysis concerning wheeze (Hoppin et al., 2006b), asthma (Hoppin et al., 2008), "farmer's lung" or hypersensitivity pneumonitis (Hoppin et al., 2007a), and chronic bronchitis (Hoppin et al., 2007b; Valcin et al., 2007). The 25-year follow-up of the mortality of the Seveso population through 2001 (Consonni et al., 2008) was also considered in *Update 2008*; again there was some elevation in mortality from COPD as had been seen in the earlier mortality follow-up reviewed in *Update 2000*.

Table 11-1 summarizes the results of the relevant studies.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

The Army Chemical Corps (ACC) cohort is of particular interest because the members deployed to Vietnam had potential exposure to the chemicals of interest second only to that of the Ranch Hand veterans. Cypel and Kang (2010) reported the cause-specific mortality through 2005 in ACC veterans who served in Vietnam between July 1, 1965–March 28, 1973 (n = 2,872) and ACC veterans

TABLE 11-1 Selected Epidemiologic Studies—Noncancerous Respiratory Disease

Reference	Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Risk (95% CI)[a]
VIETNAM VETERANS			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans			**All COIs**
Ketchum and Michalek, 2005	Rand Hand personnel (n = 1,262) vs SEA veterans (19,078)—respiratory disease (ICD-9 460–519)		
	Mortality through 1999	8	1.2 (0.6–2.5)
AFHS, 1996	Mortality through 1993	2	0.5 (0.1–1.6)
US VA Cohort of Army Chemical Corps			**All COIs**
Cypel and Kang, 2010	Deployed veterans (2,872) vs nondeployed (2,737)—mortality through 2005		
	Respiratory system disease	32 vs 8	2.2 (1.0–4.9)
	Pneumonia and influenza	12 vs 6	1.3 (0.5–3.6)
	COPD	20 vs 2	4.8 (1.1–21.2)
	ACC deployed men in Kang et al. (2006) reported sprayed herbicide vs did not spray		
	Respiratory system disease	8	2.2 (0.4–11.8)
	Pulmonary disease (COPD)	6	3.6 (0.4–32.1)
Kang et al., 2006	Self-reported morbidity 1999—noncancerous respiratory problems diagnosed by doctor		
	Deployed (n = 1,499) vs nondeployed (n = 1,428)	267	1.4 (1.1–1.8)
	Sprayed herbicides in Vietnam vs never	140	1.6 (1.2–2.1)
Dalager and Kang, 1997	Mortality through 1991		
	Respiratory system disease	11 vs 2	2.6 (0.5–12.2)
US CDC Vietnam Experience Study			**All COIs**
Boehmer et al., 2004	Vietnam Experience Cohort		
	Noncancerous respiratory mortality (ICD-9 460–519)	20	0.8 (0.5–1.5)
CDC, 1988	Cross-sectional study, with medical examinations, of US Army Vietnam veterans vs nondeployed US Army veterans		
	Odds ratios from pulmonary-function tests (case definition: ≥ 80% predicted value)		
	FEV_1	254	0.9 (0.7–1.1)
	FVC	177	1.0 (0.8–1.3)
	FEV_1/FVC	152	1.0 (0.8–1.3)
US VA Mortality Study of Army and Marine Veterans (ground troops serving July 4, 1965–March 1, 1973)			**All COIs**
Watanabe and Kang, 1996	Mortality of US Vietnam veterans who died during 1965–1988, PMR analysis of noncancerous respiratory mortality (ICD-8 460–519)		
	Army	648	0.8 ($p < 0.05$)
	Marine Corps	111	0.7 ($p < 0.05$)

TABLE 11-1 Noncancerous Respiratory Disease, continued

Reference	Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Risk (95% CI)[a]
US VA Cohort of Monozygotic Twins			**All COIs**
Eisen et al., 1991	Incidence in deployed vs nondeployed monozygotic twins who served in US military during Vietnam era		
	Respiratory conditions		
	Present at time of survey	nr	1.4 (0.8–2.4)
	At any time since service	nr	1.4 (0.9–2.0)
	Required hospitalization	nr	1.8 (0.7–4.2)
Other US VA Vietnam Veteran Studies			**All COIs**
Bullman and Kang, 1996	Male Vietnam veterans who were wounded in combat vs US population		
	Noncancerous respiratory mortality (ICD 9 460–519)	43	0.9 (0.7–1.2)
State Studies of US Vietnam Veterans			**All COIs**
Anderson et al., 1986	White males with Wisconsin death certificate (1968–1978), mortality from noncancerous respiratory disease (ICD-8 460–519)		
	Vietnam veterans vs expected deaths calculated from proportions for:	10	
	Nonveterans		0.5 (0.3–0.8)
	All veterans		0.8 (0.4–1.5)
	Vietnam-era veterans		1.0 (0.5–1.8)
Australian Vietnam Veterans vs Australian Population			**All COIs**
ADVA, 2005b	Third Australian Vietnam Veterans Mortality Study		
	Deployed veterans vs Australian population		
	All branches		
	Respiratory system diseases	239	0.8 (0.7–0.9)
	COPD	128	0.9 (0.7–1.0)
	Navy		
	Respiratory system diseases	50	0.8 (0.6–1.0)
	COPD	28	0.9 (0.6–1.3)
	Army		
	Respiratory system diseases	162	0.8 (0.7–0.9)
	COPD	81	0.9 (0.7–1.0)
	Air Force		
	Respiratory system diseases	28	0.6 (0.4–0.9)
	COPD	18	0.8 (0.4–1.2)
CDVA, 1997a	Mortality of male Australian Vietnam veterans vs Australian population		
	Noncancerous respiratory mortality (ICD-9 460–519)		
	1964–1979	3	0.1 (0.0–0.3)
	1980–1994	92	0.9 (0.7–1.1)
	Chronic obstructive airways disease (ICD-9 490–496)	47	0.9 (0.7–1.2)

continued

TABLE 11-1 Noncancerous Respiratory Disease, continued

Reference	Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Risk (95% CI)[a]
Australian Conscripted Army National Service (deployed vs nondeployed)			**All COIs**
ADVA, 2005c	Mortality 1966–2001		
	Respiratory diseases	18	1.1 (0.6–2.2)
	COPD	8	1.0 (0.3–2.8)
CDVA, 1997b	Mortality from noncancer respiratory disease		
	1965–1982	2	2.6 (0.2–30.0)
	1982–1994	6	0.9 (0.3–2.7)
Australian Army Vietnam Veterans—sample of 1,000 vs Australian National Health Survey—self-reported chronic conditions			**All COIs** Relative Prevalence
O'Toole et al., 2009	Veterans interviewed 2005–2006 (n = 450) vs 2004–2005 National Survey results		
	Chronic lower respiratory disease	nr	
	Bronchitis	nr	2.9 (2.2–3.6)
	Emphysema	nr	2.0 (1.3–2.7)
	Asthma	nr	1.3 (1.0–1.6)
	Hay fever and allergic rhinitis	nr	1.2 (0.96–1.4)
	Chronic sinusitis	nr	1.7 (1.5–2.0)
	Other diseases of the respiratory system	nr	15.4 (11.7–19.1)
O'Toole et al., 1996	Veterans interviewed 1990–1993 (n = 641) vs 1989–1990 National Survey results		
	Asthma	nr	0.9 (0.5–1.4)
	Bronchitis, emphysema	nr	4.1 (2.8–5.5)
	Other	nr	4.0 (2.2–5.9)
OCCUPATIONAL			
IARC Phenoxy Herbicides Cohort (mortality vs national mortality rates)			**Dioxin, phenoxy herbicides**
Kogevinas et al., 1997	Mortality in international workers producing or applying phenoxy herbicides, noncancerous respiratory mortality (ICD-9 460–519), 1939–1992		
	Men	252	0.8 (0.7–0.9)
	Women	7	1.1 (0.4–2.2)
NIOSH Mortality Cohort (12 US plants, production 1942–1984) (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Steenland et al., 1999	NIOSH mortality study of chemical workers at 12 plants in US exposed to TCDD		
	Noncancerous respiratory mortality (ICD-9 460–519)	86	0.9 (0.7–1.1)
Preliminary NIOSH Cross-Sectional Medical Study—workers in production of sodium trichlorophenol, 2,4,5-T ester contaminated with TCDD—morbidity			**Dioxin, phenoxy herbicides**
Sweeney et al., 1997/98	Chronic bronchitis and COPD	2	nr

TABLE 11-1 Noncancerous Respiratory Disease, continued

Reference	Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Risk (95% CI)[a]
Calvert et al., 1991	Odds ratios for increase in 1 ppt of serum TCDD compared to unexposed workers		
	Chronic bronchitis	nr	0.5 (0.1–2.6)
	COPD	nr	1.2 (0.5–2.8)
Monsanto Production Workers—Nitro, WV, 2,4,5-T plant			**Dioxin, phenoxy herbicides**
Suskind and Hertzberg, 1984	Cross-sectional study, 1979, comparing exposed with nonexposed workers for "abnormal" outcome on pulmonary-functions tests:		
	FEV_1 (< 80% predicted)		2.81 (p = 0.02)
	FVC (< 80% predicted)		2.25 (p = 0.03)
	FEV_1/FVC (< 70%)		2.97 (p = 0.01)
	FEF_{25-75} (< 80% predicted)		1.86 (p = 0.05)
Dow Chemical Company—Midland, MI (included in IARC and NIOSH cohorts)			**Dioxin, phenoxy herbicides**
Collins et al., 2009a	Mortality 1942–2003—noncancerous respiratory disease (ICD-10 J00–J99)		
	TCP workers	44	0.8 (0.6–1.0)
Collins et al., 2009b	Mortality 1942–2003—noncancerous respiratory disease (ICD-10 J00–J99)		
	PCP workers without TCP exposure	19	0.7 (0.4–1.2)
Burns et al., 2001	Mortality of 2,4-D workers, 1945–1994		
	Noncancerous respiratory (ICD-8 460–519)	8	0.4 (0.2–0.7)
	Pneumonia	4	0.6 (0.2–1.4)
Ramlow et al., 1996	Mortality of PCP workers, 1940–1989		
	Noncancerous respiratory mortality (ICD-8 460–519)	14	0.9 (0.5–1.5)
	Cumulative PCP exposure		
	< 1 unit	3	0.6 (0.2–1.9)
	≥ 1 unit	11	1.4 (0.8–2.5)
	Pneumonia (ICD-8 480–486)	6	1.1 (0.4–2.4)
	Emphysema (ICD-8 492)	4	1.3 (0.4–3.3)
BASF Production Workers—German workers exposed to trichlorophenol contaminated with TCDD from 1953 accident (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Ott and Zober, 1996	Noncancerous respiratory mortality through 1993 vs West German rates (n = 243 men)	1	0.1 (0.0–0.8)
Zober et al., 1994	Prevalence—cohort (n = 158), reference (n = 161) (illness episodes per 100 person–years, 1953–1989)		
	All noncancerous respiratory diseases (ICD-9 460–519)	nr	33.7/31.0 (p = 0.22)
	Upper respiratory tract infections (ICD-9 460–478)	nr	12.0/9.0 (p = 0.00)
	Pneumonia or influenza (ICD-9 480–487)	nr	17.4/18.8 (p = 0.08)
	COPD (ICD-9 490–496)	nr	8.0/7.5 (p = 0.31)

continued

TABLE 11-1 Noncancerous Respiratory Disease, continued

Reference	Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Risk (95% CI)[a]
Dutch Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Boers et al., 2010	Dutch chlorophenoxy workers		
	Diseases of the respiratory system		
	Factory A (HR for exposed vs unexposed)	19 vs 12	1.0 (0.4–2.3)
	Factory B (HR for exposed vs unexposed)	6 vs 15	0.5 (0.2–1.2)
German Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Becher et al., 1996	Four German facilites for production of phenoxy herbicides, chlorophenols, noncancerous respiratory mortality (ICD-9 460–519)		
	Boehringer Ingelheim	10	0.5 (0.3–1.0)
	Bayer Uerdingen	2	0.9 (0.1–3.1)
	Bayer Dormagen	0	0.0
	BASF Ludwigshafen	4	0.6 (0.2–1.6)
New Zealand Production Workers—Dow plant in Plymouth, NZ (included in IARC cohort)			**Dioxin, phenoxy herbicides**
McBride et al., 2009a	Dow trichlorophenol workers in Plymouth, NZ		
	Ever-exposed workers	12	0.8 (0.4–1.4)
't Mannetje et al., 2005	New Zealand phenoxy herbicide workers, noncancerous respiratory mortality (ICD-9 480–519)		
	Producers	9	0.9 (0.4–1.8)
	Sprayers	6	0.7 (0.2–1.2)
United Kingdom Production Workers (included in IARC cohort)			**Dioxin, phenoxy herbicides**
Coggon et al., 1991	Production of phenoxy herbicides, chlorophenols in four British plants, mortality from noncancerous respiratory diseases, 1963–1985	8	0.7 (0.3–1.3)
Coggon et al., 1986	British plant manufacturing MCPA, mortality from noncancerous respiratory diseases (ICD-9 460–519), 1947–1983	93	0.6 (0.5–0.8)
Agricultural Health Study			**Herbicides**
Hoppin et al., 2009	US AHS—prevalence at enrollment among male agricultural workers of:		
	Allergic asthma		
	2,4,5-T	38	1.4 (1.0–2.2)
	2,4-D	110	1.6 (0.9–2.7)
	Nonallergic asthma		
	2,4,5-T	88	1.2 (0.9–1.6)
	2,4-D	264	1.2 (0.9–1.6)
Slager et al., 2009	US AHS—commercial pesticide applicators	1,664	
	Current rhinitis and exposure to:		
	2,4-D	750	1.3 (1.1–1.6)

TABLE 11-1 Noncancerous Respiratory Disease, continued

Reference	Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Risk (95% CI)[a]
Hoppin et al., 2008	US AHS—prevalence at enrollment among farm women of:		
	Atopic asthma having exposure to:		
	2,4-D	52	1.5 (1.1–2.1)
	Dicamba	11	1.1 (0.6–2.1)
	Nonatopic asthma having exposure to:		
	2,4-D	66	1.1 (0.8–1.4)
	Dicamba	13	0.7 (0.4–1.3)
Hoppin et al., 2007a	US AHS—prevalence at enrollment of self-reported farmer's lung (hypersensitivity pneumonitis)		
	Private applicators exposed to phenoxy herbicides	392	1.2 (0.8–1.7)
	Spouses exposed to phenoxy herbicides	16	1.4 (0.7–2.7)
Hoppin et al., 2007b	US AHS—prevalence at enrollment of chronic bronchitis in private applicators exposed to:		
	2,4-D	78	1.1 (0.9–1.4)
	2,4,5-T (lifetime days)	28	1.5 (1.3–1.8)
	None	74	1.0
	1–14	16	1.4 (1.1–1.8)
	15–55	6	1.3 (0.9–1.8)
	> 55	4	1.0 (0.6–1.5)
	2,4,5-TP (lifetime days)	9	1.7 (1.3–1.3)
	None	92	1.0
	1–14	3	1.1 (0.7–1.8)
	15–55	3	1.6 (1.0–2.8)
	> 55	2	1.4 (0.8–2.5)
	Dicamba	48	1.0 (0.8–1.2)
Valcin et al., 2007	US AHS—prevalence at enrollment of chronic bronchitis in nonsmoking farm women exposed to:		0.9 (0.7–1.1)
	2,4-D	16	1.2 (0.9–1.6)
	2,4,5-T	1	1.0 (0.4–2.5)
	Dicamba	5	1.1 (0.6–2.0)
Hoppin et al., 2006a	US AHS—cross-sectional study of wheeze in commercial applicators with current use of:		
	2,4-D	225	1.3 (1.0–1.7)
	Dicamba	167	1.1 (0.9–1.4)

continued

TABLE 11-1 Noncancerous Respiratory Disease, continued

Reference	Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Risk (95% CI)[a]
Hoppin et al., 2006b	US AHS—prevalence at enrollment of wheeze (added adjustment for exposure to herbicide chlorimuron-ethyl)		
	Private applicators with current use of:		
	2,4-D	nr	1.0 (0.9–1.1)
	Dicamba	nr	1.1 (0.9–1.2)
	Commercial applicators with current use of:		
	2,4-D	nr	1.0 (0.7–1.3)
	Dicamba	nr	0.8 (0.6–1.1)
Blair et al., 2005	US AHS—COPD mortality		
	Private applicators	50	0.2 (0.2–0.3)
	Spouses	15	0.3 (0.2–0.7)
Other Agricultural Studies			**Herbicides**
Senthilselvan et al., 1992	Cross-sectional study of self-reported prevalence of self-reported asthma (n = 83) in male farmers (n = 1,939) in Saskatchewan (1982–1983)		Asthmatics vs nonasthmatics
	Phenoxyacetic herbicide use	71	85.5% vs 88.5%
Herbicide and Pesticide Applicators			**Herbicides**
Blair et al., 1983	Licensed pesticide applicators, Florida, noncancerous respiratory diseases, (ICD-8 460–519)	2	0.9 (nr)
	Analyses by length of licensure		
	≥ 10 yrs	8	0.6 (nr)
	10–19 yrs	8	1.5 (nr)
	≥ 20 yrs	4	1.7 (nr)
Forestry Workers			**Herbicides**
Alavanja et al., 1989	PMR study of US Department of Agriculture soil, forest conservationists, mortality 1970–1979 from noncancerous respiratory diseases (ICD-9 460–519)	80	0.8 (0.6–1.0)
ENVIRONMENTAL			
Seveso, Italy Residential Cohort			**TCDD**
Consonni et al., 2008	25-yr follow-up of Seveso residents—mortality		
	Respiratory disease (ICD-9 460–519)		
	Zone A	9	1.4 (0.7–2.7)
	Zone B	48	1.0 (0.8–1.4)
	Zone R	341	1.0 (0.9–1.1)
	COPD (ICD-9 490–493)		
	Zone A	7	2.5 (1.2–5.3)
	Zone B	26	1.3 (0.9–1.9)
	Zone R	175	1.2 (1.0–1.4)

TABLE 11-1 Noncancerous Respiratory Disease, continued

Reference	Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Risk (95% CI)[a]
Bertazzi et al., 2001	20-yr follow-up of Seveso residents—mortality		
	Respiratory disease (ICD-9 460–519)	44	1.0 (0.8–1.4)
	Zone A	9	1.9 (1.0–3.6)
	Zone B	35	1.3 (0.9–2.0)
	COPD (ICD-9 490–493)	29	1.5 (1.1–2.2)
	Zone A	7	3.3 (1.6–6.9)
	Zone B	22	1.3 (0.9–2.0)
Bertazzi et al., 1998; Pesatori et al., 1998	15-yr follow-up of Seveso residents—mortality		
	Respiratory disease (ICD-9 460–519)		
	Zone A		
	Men	5	2.4 (1.0–5.7)
	Women	2	1.3 (0.3–5.3)
	Zone B		
	Men	13	0.7 (0.4–1.2)
	Women	10	1.0 (0.5–1.9)
	Zone R		
	Men	133	1.1 (0.9–1.3)
	Women	84	1.0 (0.8–1.2)
	COPD (ICD-9 490–493)		
	Zone A		
	Men	4	3.7 (1.4–9.8)
	Women	1	2.1 (0.3–14.9)
	Zone B		
	Men	9	1.0 (0.5–1.9)
	Women	8	2.5 (1.2–5.0)
	Zone R		
	Men	74	1.2 (0.9–1.5)
	Women	37	1.3 (0.9–1.9)
Bertazzi et al., 1989a,b (results from Bertazzi et al., 1989a)	10-yr follow-up on Seveso residents—mortality in Zones A, B, and R		
	Respiratory disease (ICD-9 460–519)		
	Men	55	1.0 (0.7–1.3)
	Women	24	1.0 (0.7–1.6)
	Pneumonia (ICD-9 480–486)		
	Men	14	0.9 (0.5–1.5)
	Women	9	0.8 (0.4–1.6)
	COPD (ICD-9 490–493)		
	Men	31	1.1 (0.8–1.7)
	Women	8	1.0 (0.5–2.2)

continued

TABLE 11-1 Noncancerous Respiratory Disease, continued

Reference	Study Population	Exposed Cases[a]	**Exposure of Interest/** Estimated Risk (95% CI)[a]
Other Environmental Studies			
Dahlgren et al., 2003	Cross-sectional study of residents near wood-treatment plant (creosote, PCP) in Mississippi, who were plaintiffs (n = 199) in lawsuit vs subjects in comparable area (n = 115) without known exposures		**Dioxins, furans** Prevalence in exposed vs nonexposed
	Chronic bronchitis		
	By history		21.7% vs 4.3% ($p < 0.0001$)
	Diagnosed by physician		17.8% vs 5.8% ($p < 0.0001$)
	Asthma		
	By history of wheeze		40.5% vs 11.0% ($p < 0.0001$)
	Diagnosed by physician		13.1% vs 12.0% ns
Svensson et al., 1995	Swedish fishermen exposed to TCDD, mortality from bronchitis or emphysema (ICD-7 490–493)		**TCDD**
	East coast	4	0.5 (0.2–1.2)
	West coast	43	0.8 (0.6–1.1)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TP, 2-(2,4,5-trichlorophenoxy) propionic acid; ACC, Army Chemical Corps; AHS, Agricultural Health Study; CI, confidence interval; COI, chemical of interest; COPD, chronic obstructive pulmonary disease; FEF_{25-75}, forced midexpiratory flow; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD-8, *International Classification of Diseases, 8th revision*; ICD-9, *International Classification of Diseases, 9th revision*; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MI, Michigan; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; ns, not significant; NZ, New Zealand; PCP, pentachlorophenol; PMR, proportionate mortality ratio; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs; WV, West Virginia.

[a]Given when available; results other than estimated risk explained individually.

who did not serve in Vietnam (n = 2,737). Observed deaths for the ACC Vietnam veteran cohort were compared with expected deaths for US men, as well as being contrasted between the deployed and nondeployed veterans. In addition, mortality was also examined in a subset of the original Vietnam cohort who either reported spraying herbicide (n = 662) or not spraying herbicide (n = 811); the morbidity of this subset was analyzed by Kang et al. (2006). Cypel and Kang (2010) reported a statistically significant excess mortality (adjusted RR = 4.82, 95% confidence interval [CI] 1.10–21.18) when 20 deaths from COPD among ACC Vietnam vet-

erans were compared to 2 COPD deaths among ACC veterans who did not serve in Vietnam. A similar pattern of elevated excess COPD mortality among the ACC Vietnam veterans was observed when comparisons were made with the US male population (standardized mortality ratio [SMR] = 1.62, 95% CI 0.99–2.51), not quite reaching the traditional 0.05 level of statistical significance. When the subgroup of ACC Vietnam veterans who reported spaying herbicides was compared to the ACC Vietnam veterans who did not report spraying herbicides, a nonsignificantly elevated risk for death due to the less specific category of noncancerous respiratory system disease was reported (adjusted RR = 2.24, 95% CI 0.42–11.83). Although this comparison did not report mortality due specifically to COPD, it is important to note that this is the only comparison that controlled not only for self-reported herbicide exposure and body mass index (BMI), but also for smoking status, a major risk factor for COPD. Comparisons with the large cohort of ACC veterans who served in Vietnam benefit from a larger sample size (n = 2,737), but are limited due to lack of information on confounding factors, including smoking, alcohol use, dietary habits, and post-service occupational exposure. In Kang et al. (2006), 71% of ACC Vietnam veterans were regular smokers, while 60% of ACC non-Vietnam veterans were regular smokers, which is about twice the rate of smoking in US males. The high self-reported rate of current smoking in the ACC Vietnam veterans could have directly contributed to elevated COPD in this group when compared to the general US male population. In addition to not controlling for smoking and other risk factors for COPD, another limitation of the mortality study of Cypel and Kang (2010) is the reliance on death certificates for information on causes of death. Disease diagnosis at time of death and International Classification of Diseases (ICD) classification are factors that may impact the quality of cause of death statistics from death certificates. Detection bias and potential lack of uniformity of access to the health-care system in the ACC cohort are other concerns. COPD is commonly associated with other comorbidities that could have been included on death certificates, including angina, myocardial infarction, respiratory infection, pneumonia, and cardiac disorders (Soriano et al., 2005). Lung function tests are necessary for an accurate diagnosis of COPD but are rarely done. Another factor that may contribute to the observed increase in COPD mortality in the ACC Vietnam veterans, relative to the ACC non-Vietnam veterans, is the low number of only two deaths due to COPD in the cohort of 2,737 ACC non-Vietnam veterans. Deaths due to COPD were lower in ACC non-Vietnam veterans relative to males in the US population (SMR = 0.3, 95% CI 0.04–1.07), which is noteworthy because the prevalence of smoking in the ACC non-Vietnam veterans was about twice that of the comparison group of males in the US population. In summary, although Cypel and Kang (2010) reported an increase in mortality due to COPD in ACC Vietnam veterans, the relative strength of this study is limited by a number of factors, including reliance on death certificates, known limitations in the accuracy and consistency with which COPD is reported as a cause of death, and not controlling for smoking, which is a major risk factor for COPD.

The self-reported physical and mental health of Australian Vietnam veterans, from the 2004–2005 National Health Survey Interview, was compared with age- and gender-matched data from the Australian general population (O'Toole et al., 2009). The relative prevalences (RPs) of several chronic lower respiratory diseases were significantly elevated in the Australian Vietnam Veterans (n = 450) for bronchitis (RP = 2.90, 95% CI 2.18–3.63), emphysema (RP = 2.03, 95% CI 1.32–2.74), and asthma (RP = 1.33, 95% CI 1.01–1.64). For the condition, "other diseases of the respiratory system," the relative prevalence was markedly elevated (RP = 15.41, 95% CI 11.71–19.11), but there was no further description of this category. The relative prevalence of chronic sinusitis was also significantly elevated (RP = 1.73, 95% CI 1.45–2.01), while hay fever and allergic rhinitis was not significantly elevated (RP = 1.16, 95% CI 0.96–1.36). It is noteworthy that, with the exception of hay fever and allergic rhinitis, the relative prevalences of all noncancerous diseases of the respiratory system were elevated in this cohort of Australian Vietnam veterans, but it is not possible to draw any sound conclusions from this study, which relied solely on self-reported health data. The committee had serious concerns that the results reported in O'Toole et al. (2009) were compromised by recall bias and other methodologic problems.

Occupational Studies

A third follow-up in Dutch chlorophenoxy herbicide manufacturing workers (n = 2,106) investigated the cause specific mortality as of the end of 2006 (Boers et al., 2010). No increase in the hazard ratio (HR) for death due to diseases of the respiratory system was found in exposed relative to nonexposed workers in factories A (HR = 1.00, 95% CI 0.43–2.29) and B (HR = 0.46, 95% CI 0.18–1.15).

Mortality rates in trichlorophenol workers in Midland, Michigan, with exposure to TCDD were assessed for the period 1942–2003 (Collins et al., 2009a). The standardized mortality ratio of the workers (n = 1,615) compared with the US population were not increased for death due to noncancerous respiratory disease (SMR = 0.8, 95% CI 0.6–1.0). In a related study, the mortality rates were assessed in 773 workers exposed to dioxins in the manufacture of pentachlorophenol at a plant in Midland, Michigan (Collins et al., 2009b). The standardized mortality ratio for the workers compared with the US and Michigan population were not increased for death due to noncancerous respiratory disease (SMR = 0.8, 95% CI 0.5–1.1).

Mortality was also assessed at the end of 2004 in 1,599 workers exposed to TCDD at a trichlorophenol plant in New Zealand (McBride et al., 2009a). SMRs for death due to noncancerous respiratory disease were not increased in ever-exposed workers (SMR = 0.8, 95% CI 0.4–1.4) or in never-exposed workers (SMR = 0.4, 95% CI 0.0–1.5) compared with the New Zealand population. McBride et al. (2009b) have also published mortality findings through 2004 from this plant that include all workers employed at the site from 1969 to 2003

(n = 1,754, also 247 deaths). The results of McBride et al. (2009b) have not been included because they were diluted by inclusion of a set of workers with no possible opportunity for TCDD exposure and no observed deaths.

Hoppin et al. (2009) assessed pesticide use and adult-onset asthma, defined as doctor-diagnosed asthma after the age of 20 years, in a cohort of 19,704 male farmers in the AHS. For ever-use of 2,4,5-T, there were elevated but not significant risks for allergic asthma (odds ratio [OR] = 1.44, 95% CI 0.96–2.14) and nonallergic asthma (OR = 1.20, 95% CI 0.93–1.56). For ever-use of 2,4-D, there were elevated, but not significant risks for allergic asthma (OR = 1.56, 95% CI 0.91–2.69) and nonallergic asthma (OR = 1.19, 95% CI 0.86–1.64). This analysis was adjusted for age, US state, smoking, high pesticide exposure events, and BMI. In another AHS report, Slager et al. (2009) investigated the association between current rhinitis and pesticide use in 2,245 Iowa commercial pesticide applicators. Current use of 2,4-D was associated with a significant increase in current rhinitis (OR = 1.34, 95% CI 1.09–1.64, adjusted for age, education status, and growing up on a farm) relative to those who had not used it in the past year.

Environmental Studies

Mortality in Finnish fisherman (n = 6,410) and their wives (n = 4,260) as of 2005 was assessed relative to the general Finnish population (Turunen et al., 2008). The average fish consumption and serum concentrations of fish-derived fatty acids and environmental contaminants (TEQs from dioxins and PCBs) were higher among the fishermen and their wives than among the general population from the same region. However, the fishermen and their wives had lower mortality for diseases of the respiratory system, pneumonia, bronchitis, and emphysema.

Biologic Plausibility

Evaluation of the biological plausibility of chemicals of interest inducing or contributing to the development of lung diseases is hampered by the lack of animal models to study endpoints such as COPD or asthma, because these diseases usually develop in humans in response to additional co-factors (i.e., smoking/air pollution). Activation of AH receptor (AHR) by TCDD, however, has been shown to modify expression of genes in the lung that code for inflammatory cytokines, matrix metalloproteases (MMPs), and mucin production (Wong et al., 2010). These results are consistent with changes associated with a variety of lung diseases, such as bronchitis, asthma, small airway disease, and lung remodeling (fibrosis), and support the role of AHR activation in the development of lung injury. AHR activation in vitro in NCI H441 in the Clara cells also activates an IL-1b–to–COX-2–mediated process, which leads to increased mucin production. This process might be facilitated via differentiation of the Clara cell to a mucin producing, goblet-like cell phenotype. One of the major clinical characteristics

of COPD is mucous/goblet cell hyperplasia in the airways. In a related study, Lee et al. (2010) reported that TCDD induced a time-dependent elevation of MUC5AC mRNA and protein synthesis in primary normal human bronchial epithelial cells and in an immortalized normal human bronchial epithelial cell line (HBE1). MUC5AC is a major gel-forming mucin that is frequently elevated in various airway diseases (Rose and Voynow, 2006; Voynow et al., 2006).

Acute noncancerous respiratory disorders, including pneumonia and other respiratory infections, also can be increased in frequency and severity when the normal defense mechanisms of the lower respiratory tract are compromised. Thus exposure to chemicals that affect those mechanisms could exacerbate respiratory disorders. There is no evidence that the herbicides used in Vietnam alter such defense mechanisms. However, several laboratory studies have shown that treatment of mice with TCDD increases their mortality after infection with influenza virus (Burleson et al., 1996; Warren et al., 2000). Treatment with TCDD also suppressed the animals' ability to generate an immune response to the virus (Mitchell and Lawrence, 2003). The mechanism underlying increased influenza mortality was not related to the suppression of the immune response to influenza by TCDD but appeared to involve an increase in the inflammatory response associated with an increased flow of neutrophils into the lung (Mitchell and Lawrence, 2003). Neutrophils produce several toxic products (which kill pathogens), so it is possible that excess numbers of neutrophils in the lung produce excess collateral damage and pathologic changes that increase mortality.

Although AHR expression was shown to be required for TCDD to increase neutrophils in the lungs, the cells expressing AHR were not the neutrophils themselves or other immune cells, and this suggests that lung parenchyma was being directly affected by TCDD (Teske et al., 2008). However, the concentration of Clara cell secretory protein, an inflammatory mediator produced by lung-associated Clara cells, was not altered by TCDD in mouse lung. Thus, the mechanisms underlying the increase in mortality after influenza infection remain to be determined. On the basis of those findings, it is biologically plausible that exposure to TCDD results in exacerbation of acute lung disease that is associated with reduced immune responses or of chronic lung diseases including COPD, that is associated with increased inflammatory responses. It is also plausible that the induction of CYP1A1 and CYP1B1 enzymes in the lung by TCDD result in the metabolism of several chemicals found in tobacco smoke to more toxic intermediates. Exposure to TCDD would thus increase the toxic effects of tobacco smoke and increase respiratory disease.

Synthesis

Noncancerous Respiratory Disease (without further specification) Results of the studies of mortality from noncancerous respiratory diseases reported in *Update 2008* and earlier VAO reports (ADVA, 2005b,c; Anderson et al., 1986;

Becher et al., 1996; Blair et al., 1983, 2005; Boehmer et al., 2004; Bullman and Kang, 1996; Burns et al., 2001; Coggon et al., 1986, 1991; Consonni et al., 2008; Crane et al., 1997a; Ketchum and Michalek, 2005; Kogevinas et al., 1997; Ott and Zober, 1996; Ramlow et al., 1996; Steenland et al., 1999; Svensson et al., 1995; 't Mannetje et al., 2005; Zober et al., 1994) do not support the hypothesis that exposures to herbicides or TCDD are associated with the general category of noncancerous respiratory diseases.

A study of the prevalence of self-reported physician-confirmed respiratory problems in a subset of US Army Chemical Corps personnel (Kang et al., 2006) was reviewed in *Update 2006*. Comparison of deployed to nondeployed veterans indicated an association (OR = 1.41, 95% CI 1.13–1.76), as did comparison of those who reported spraying herbicides in Vietnam to those who did not (OR = 1.62, 95% CI 1.26–2.05). In the subset of subjects for whom serum TCDD concentrations had been determined, however, individuals with respiratory problems were evenly distributed above and below the median, which argues against the association arising from herbicide exposure.

In the current update, another study of ACC Vietnam veterans (Cypel and Kang, 2010), this time on the mortality experience of the entire cohort, was considered. Elevation in mortality due to respiratory system disease was statistically significant when the deployed veterans were compared to males in the US population (SMR = 1.58, 95% CI 1.08–2.23). This observation is in contrast to four new occupational studies, which did not report an association of death due to noncancerous respiratory disease with exposures to herbicides and/or TCDD (Boers et al., 2010; Collins et al., 2009a,b; McBride et al., 2009a). Similarly, a study in Finnish fisherman found that elevation of serum dioxin TEQs was not associated with noncancerous respiratory mortality (Turunen et al., 2008).

The committee does not believe that scientific conclusions can be based on health outcomes that are defined vaguely, for example, by combining a wide array of disparate respiratory health outcomes into one large category of noncancerous respiratory disease. The nonspecificity of the types of respiratory conditions reported in these studies makes it exceedingly difficult to draw any conclusions regarding specific respiratory conditions.

COPD In an earlier study of mortality, as of 1991, the ACC Vietnam veteran cohort had a nonsignificant adjusted RR of 2.59 for death due to noncancerous respiratory system diseases when compared with their non-Vietnam peers (Dalager and Kang, 1997). The study by Cypel and Kang (2010) added 14 years of observation and found an increased risk of death from noncancerous respiratory diseases on the cusp of statistical significance (adjusted RR = 2.20, 95% CI 0.99–4.91). For COPD in particular, they reported a statistically significant excess mortality in ACC Vietnam veterans (adjusted RR = 4.82, 95% CI 1.10–21.18), when compared to ACC veterans who did not serve in Vietnam. A similar pattern of excess COPD mortality among the ACC Vietnam veterans per-

sisted when comparisons were made with the US male population (SMR = 1.58, 95% CI 1.08–2.23). In accord with these mortality data, a morbidity survey of 2,927 of these ACC veterans (deployed and nondeployed) conducted in 1999–2000 (Kang et al., 2006) had found a significant increase in the broader category of self-reported noncancerous respiratory conditions in ACC Vietnam veterans (adjusted OR = 1.41, 95% CI 1.13–1.76), which was also significantly related to reported use of herbicides in Vietnam (adjusted OR = 1.62, 95% CI 1.28–2.05), using a multiple logistic regression model with adjustments for age, race, BMI, rank, and smoking. Among the deployed ACC veterans who had particated in the morbidity study, only 120 deaths had occurred by the end of 2005, so when Cypel and Kang (2010) assessed mortality risk among them for self-reported herbicide use, adjusted for smoking status, the estimated increase for COPD (3.55) had a 95% CI spanning two orders of magnitude (0.39–32). Other studies of American Vietnam veterans, including the Ranch Hand cohort, have found no significant increase in mortality due to the broader classification of noncancerous respiratory mortality (Anderson et al., 1986; Boehmer et al., 2004; Ketchum and Michalek, 2005) but have not addressed causes of death as specific as COPD. The Vietnam Experience Study (CDC, 1988) did not find evidence of compromised lung function; as yet, there have been no integrated publications on specific aspects of respiratory morbidity in the Ranch Hand cohort.

The self-reported physical and mental health of Australian Vietnam veterans in 2005–2006 was compared with age- and gender-matched data gathered in the 2004–2005 national survey of the Australian general population (O'Toole et al., 2009). While COPD was not specified as a condition in this study, the relative prevalences of bronchitis (RP = 2.90, 95% CI 2.18–3.63) and emphysema (RP = 2.03, 95% CI 1.32–2.74) were significantly elevated in the Australian Vietnam veterans (n = 450); these conditions are clinical conditions consistent with COPD. In an earlier iteration of this study for health status of Australian army Vietnam veterans in 1990–1993, O'Toole et al. (1996) had reported a four-fold excess prevalence in chronic bronchitis and emphysema over the results of the 1989–1990 national survey. The committee did have concerns, however, that the results of the studies conducted by O'Toole et al. were compromised by recall bias and other methodologic problems. Studies of the full cohort of male Australian Vietnam veterans vs the general population (ADVA, 2005b; CDVA, 1997a) and of deployed vs nondeployed Australian Army National Service (conscripted) veterans (ADVA, 2005c; CDVA, 1997b) showed no suggestion of increased mortality from COPD or noncancerous respiratory deaths.

Almost all the studies of mortality in industrial cohorts considered in the VAO updates assessed only the nonspecific category of mortality due to noncancerous respiratory disease, and no significant excesses were reported (Becher et al., 1996; Burns et al., 2001; Kogevinas et al., 1997; Ott and Zober, 1996; Steenland et al., 1999; 't Mannetjie et al., 2005). Only an earlier mortality study of Dow TCP workers (Ramlow et al., 1996) reported on a more specific type of

respiratory death, emphysema, which was not significantly increased. Only three studies of morbidity related to COPD in industrial populations have been considered in the VAO updates. Increases in the odds ratios for measures of abnormal pulmonary function were reported in workers at a 2,4,5-T plant in Nitro, West Virginia (Suskind and Hertzberg, 1984), but the other two cross-sectional studies of COPD prevalence had negative findings. Zober et al. (1994) found episodes of COPD among workers at a BASF plant in Germany were not associated with TCDD exposure. The NIOSH cross-sectional study of production workers exposed to TCDD (Calvert et al., 1991) did not show an increase in COPD or chronic bronchitis, or altered pulmonary function measures associated with elevated serum TCDD concentration in workers compared to a community-based referent population.

An early agricultural study (Senthilselvan et al., 1992) found no relationship between self-reported asthma and the use of phenoxy herbicides. Recently, the Agricultural Health Study has generated a number of publications with COPD-related findings. First, Blair et al. (2005) found significant *decreases* in mortality due to COPD in both private applicators and their spouses in comparison to state rates, which may be due to the healthy worker effect and the inability to adjust for low tobacco use. Analyses with adjustment for smoking of self-reported prevelance at enrollment (1993–1997) and prior exposure to phenoxy herbicides found indications of associations for chronic bronchitis in farmers (mostly men) significant for 2,4,5-T and 2,4,5-TP (Hoppin et al., 2007b), but only a 20% nonsignificant increase among nonsmoking farm women (Valcin et al., 2007); some association with phenoxy herbicide exposure was evident for allergic asthma (significant for 2,4-D in women and 2,4,5-T in men), but not so clear for nonallergic asthma in men (Hoppin et al., 2009) or women (Hoppin et al., 2008).

Mortality studies of the Seveso incident have reported an emerging picture of increased risks of death from COPD (Bertazzi et al., 1998, 2001; Consonni et al., 2008; Pesatori et al., 1998), with higher and significant RRs found in the zone (A) closest to the accident and somewhat lower RRs for the outlying zones. Adjustment for smoking has not been possible for the Seveso cohort. In the only other relevant environmental study, Svensson et al. (1995) assumed TCDD exposure was elevated from fish consumption among Swedish fishermen but found no increase in mortality from bronchitis or emphysema. Dahlgren et al. (2003) reported that the prevelance of chronic bronchitis was positively associated with environmental exposure to creosote and pentachlorophenol emissions from a wood processing plant, but strong concerns about bias are raised by the fact that the study sample was composed of plaintiffs in a law suit. There have been no other studies of environmental exposure to the chemicals of interest and COPD-related morbidity.

As discussed in more detail in Chapter 5, the committee had reservations about the validity of the multitude of significant findings reported by O'Toole et al. (2009), including those for increased prevalence of two respiratory condi-

tions consistent with COPD (bronchitis and emphysema) among the Australian Vietnam Veterans. It was the large increase in relative risk of mortality from COPD in the ACC cohort that served in Vietnam (Cypel and Kang, 2010) that motivated the committee to go beyond its comprehensive review of all studies reporting morbidity or mortality associated with COPD and exposure to the chemicals of interest. In addition to its standard review process, the committee consulted in open session with Paul Enright of the University of Arizona, a medical expert on COPD, who has investigated occupational lung diseases for the Centers for Disease Control and Prevention (CDC) and has been responsible for the development of national and international clinical practice guidelines for pulmonary function testing.

From the March 3, 2011, reply of Drs. Cypel and Kang (available upon request from the VAO public access file) to several questions, the committee learned that the six deaths from "pulmonary disease" among deployed ACC veterans from the morbidity study (Table 5 in the 2010 paper) were indeed COPD cases; among the nondeployed ACC veterans from the morbidity study there had only been one death from respiratory system disease, and it had not been from COPD; and all the respiratory deaths had been smokers. Conclusions from analysis of COPD mortality in the ACC morbidity-study subset are limited by the very small number of deaths that had occurred by the end of 2005 and by the fact that this subset cannot be considered representative of the entire ACC cohort in that they were all alive in 1999. In response to the committee's inquiry as to whether they could adjust the full set of ACC mortality for smoking status, Cypel and Kang replied that a greater percentage of ACC veterans who served in Vietnam smoked, compared to the non-Vietnam cohort (71.5% vs 60.1%). This information, however, was only available for the individuals participating in the 1999–2000 morbidity survey (n = 2,927), so they lacked the ability to adjust the relative risk of COPD mortality in the entire ACC cohort (n = 5,609). Because cigarette-smoking is the major cause of COPD, the committee viewed this as strongly constraining the conclusions that could be drawn from the ACC data overall.

The committee's consultation with Dr. Enright increased its concern (as delineated at the beginning of this section on respiratory diseases) that causes of death from COPD are frequently misclassified on death certificates. The common presence of comorbid conditions in individuals with COPD makes it difficult to deduce a single contributing cause of death. Furthermore, it was emphasized that COPD is often incorrectly diagnosed in prevalance investigations, and there is currently considerable debate about the appropriate diagnosic criteria for COPD, particularly in relation to factoring normal decreased capacity with age (Celli and Halbert, 2010a,b; Enright and Brusasco et al., 2010a,b).

Thus, the committee concluded that it could not base a conclusion about association for COPD on mortality data given the very questionable nature of death certificate information on COPD and the routine inability to adjust for

smoking. The committee believes morbidity data for COPD would be much more informative than mortality findings. Additional studies of the incidence of COPD, using rigorous criteria for its diagnosis and with adjustment for smoking would be particularly valuable in resolving whether there is evidence to support anssociation with exposure to the chemicals of interest.

Other Specific Respiratory Diseases Adding to the AHS papers on wheeze and farmer's lung reviewed in *Update 2008*, the literature for this update contained two more AHS reports addressing the prevalance of respiratory problems in relation to exposure to specific pesticides. The findings presented on asthma in male and female farmers did not constitute evidence of an association with the herbicides of interest.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence of an association between exposure to the chemicals of interest and mortality from all noncancerous respiratory diseases or from COPD specifically. There is also inadequate or insufficient evidence of an association between exposure to the chemicals of interest and the prevalence of respiratory diseases, such as wheeze or asthma, COPD, and farmer's lung.

GASTROINTESTINAL AND DIGESTIVE DISEASE, INCLUDING LIVER TOXICITY

This section discusses a variety of conditions encompassed by ICD-9 520–579: diseases of the esophagus, stomach, intestines, rectum, liver, and pancreas. Details on peptic ulcer and liver disease, the two conditions most often discussed in the literature reviewed, are provided below. The symptoms and signs of gastrointestinal disease and liver toxicity are highly varied and often vague.

The essential functions of the gastrointestinal tract are to absorb nutrients and eliminate waste. Those complex tasks involve numerous chemical and molecular interactions on the mucosal surface and complex local and distant neural and endocrine activity. One common condition of the gastrointestinal tract is motility disorder, which might be present in 15% of adults. The most convenient way to categorize diseases that affect the gastrointestinal system is according to the effected anatomic segment. Esophageal disorders predominantly affect swallowing; gastric disorders are related to acid secretion; and conditions that affect the small and large intestines are reflected in alterations in nutrition, mucosal integrity, and motility. Some systemic disorders (inflammatory, vascular, infectious, and neoplastic conditions) also affect the gastrointestinal system.

Peptic-Ulcer Disease

Peptic-ulcer disease refers to ulcerative disorders of the gastrointestinal tract that are caused by the action of acid and pepsin on the stomach or duodenal mucosa. Peptic-ulcer disease is characterized as gastric or duodenal ulcer, depending on the site of origin. Peptic-ulcer disease occurs when the corrosive action of gastric acid and pepsin overcomes the normal mucosal defense mechanisms that protect against ulceration. About 10% of the population has clinical evidence of duodenal ulcer at some period in life; a similar percentage is affected by gastric ulcer. The incidence of duodenal ulcer peaks in the fifth decade and the incidence of gastric ulcer about 10 years later.

Evidence increasingly indicates that the bacterium *Helicobacter pylori* is linked to peptic-ulcer disease (both duodenal and gastric). *H. pylori* colonizes the gastric mucosa in 95–100% of patients with duodenal ulcer and in 75–80% of patients with gastric ulcer. Healthy subjects in the United States under 30 years old have gastric colonization rates of about 10%. Over the age of 60 years, colonization rates exceed 60%. Colonization alone, however, is not sufficient for the development of ulcer disease; only 15–20% of subjects with *H. pylori* colonization will develop ulcers in their lifetimes. Other risk factors include genetic predisposition (such as some blood and human leukocyte antigen [HLA] types), cigarette-smoking, and psychologic factors (chronic anxiety and stress).

Liver Disease

Blood tests that reflect liver function are the mainstay of diagnosis of liver disease. Increases in serum bilirubin and in the serum concentrations of some hepatic enzymes—aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and γ-glutamyltransferase (GGT)—are commonly noted in liver disorders. The relative sensitivity and specificity of those enzymes for diagnosing liver disease vary, and diagnosis can require several tests. The only regularly reported abnormality in liver function associated with TCDD exposure in humans is an increase in GGT. Estimated serum activity of that enzyme is a sensitive indicator of a variety of conditions, including alcohol and drug hepatotoxicity, infiltrative lesions of the liver, parenchymal liver disease, and biliary tract obstruction. Increases are noted after many chemical and drug exposures that are not followed by evidence of liver injury. The confounding effects of alcohol use (often associated with increased GGT) make interpretation of changes in GGT in exposed people difficult (Calvert et al., 1992). An increase in GGT can be considered a normal biologic adaptation to chemical, drug, or hormone exposure.

Cirrhosis is the most commonly reported liver disease in epidemiologic studies of herbicide or TCDD exposure. Cirrhosis is irreversible chronic injury of the liver with extensive scarring and resulting loss of liver function. Clinical symptoms and signs include jaundice, edema, abnormalities in blood clotting, and metabolic disturbances. Cirrhosis can lead to portal hypertension with associ-

ated gastroesophageal varices, enlarged spleen, abdominal swelling attributable to ascites, and ultimately hepatic encephalopathy that can progress to coma. It generally is impossible to distinguish the various causes of cirrhosis by using clinical signs and symptoms or pathologic characteristics. The most common cause of cirrhosis in North America and many parts of western Europe and South America is excessive alcohol consumption. Other causes are chronic viral infection (hepatitis B or hepatitis C), the poorly understood condition primary biliary cirrhosis, chronic right-sided heart failure, and a variety of less common metabolic and drug-related conditions.

Conclusions from *VAO* and Previous Updates

Studies that have been reviewed by previous committees have consisted of some focusing on liver enzymes and others that have reported specific liver diseases. Evaluation of the effect of herbicide and TCDD exposure on noncancer gastrointestinal ailments is challenging in that clinical experience suggests that medical history and physical examination are undependable diagnostic tools for some ailments, so incidence data are sometimes problematic. The strong interdependence among the characteristics of a given person (such as weight and laboratory indexes of hepatic function and health) and TCDD body burden complicates the already difficult task of assessing association.

Most of the analyses of occupational or environmental cohorts have had insufficient numbers of cases to support confident conclusions. The IARC cohort of phenoxy herbicide and chlorophenol production workers and sprayers (Vena et al., 1998), the only study with a relatively large number of observations, found less digestive system disease and cirrhosis mortality in exposed workers than in nonexposed controls. A study comparing Australian veterans to the general population (O'Toole et al., 1996) suggested a higher incidence of stomach and duodenal ulcers in both men and women, but the information was self-reported and the analyses were not controlled for confounding influences.

A report from the AFHS (2000) found a significantly higher percentage of other liver disorders in the Ranch Hand veterans in the high-dioxin category than in the SEA comparison subjects. The excesses were primarily of transaminase and other nonspecific liver abnormalities. Data were consistent with an interpretation of a dose–response relationship, but other explanations were also plausible. There have been subsequent reports (AFHS, 2005) of some abnormalities in liver enzymes in the Ranch Hand cohort, including decreasing C4 complement as dioxin increased; abnormal triglyceride concentrations also increased as the 1987 dioxin concentration increased. Mortality studies of the Ranch Hand cohort, however, have not found increased mortality related to gastrointestinal or liver disease (Ketchum and Michalek, 2005).

A study of Army Chemical Corps Vietnam veterans reported in *Update 2006* found an increased rate of hepatitis associated with Vietnam service but

not with a history of spraying herbicide (Kang et al., 2006). Likewise, the Australian Vietnam-veterans study (ADVA, 2005b) did not find an increase in liver disease in military personnel who served in Vietnam compared with the general population of Australia.

Update 2008 reviewed the mortality results through 2001 for the Seveso cohort in Italy (Consonni et al., 2008) and found no excess in deaths related to digestive diseases or in the subset of deaths specifically related to cirrhosis.

The reports to date have been inconsistent, and interpretation of individual studies is difficult because of a lack of information on alcohol consumption and other risk factors. In the studies that showed the strongest association between potential exposure and gastrointestinal disease (specifically cirrhosis), there was strong evidence that excess alcohol consumption was the cause of the cirrhosis.

The committee responsible for *VAO* concluded that there was inadequate or insufficient information to determine whether there is an association between exposure to the chemicals of interest and gastrointestinal and digestive disease, including liver toxicity. Additional information available to the committees responsible for *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008* has not changed that conclusion.

Update of the Epidemiologic Literature

Vietnam-Veteran Studies

Cypel and Kang (2010) examined the risk of disease-related mortality of the Army Chemical Corps veterans who handled or sprayed herbicides in Vietnam in comparison with their non-Vietnam veteran peers or US men. Thirty digestive system deaths were observed, 21 in the Vietnam cohort and 9 in the non-Vietnam cohort. The adjusted relative risk was 1.80 (95% CI 0.80–4.03). All but two of the cases were cirrhosis of the liver (adjusted RR = 1.74, 95% CI 0.77–3.94).

O'Toole et al. (2009) published a follow-up study of a random sample of Australian veteran National Servicemen who had been deployed to Vietnam and completed the Australian Bureau of Statistics Health Interview Survey along with several other measures of psychiatric health and combat experience when contacted by mail in 2005–2006. Self-reported health status was compared to the results for the general Australian population on this survey instrument; the comparability of the circumstances of administration of the survey is not clear. Approximately 50,000 Australians were deployed during the Vietnam War, and using military databases the investigators randomly selected 1,000 veterans for follow-up. In the second wave of interviews with this sample, only 450 of the original sample responded (51% of those not known to have died). Of 67 long-term conditions with reported results, the prevalences of 47 were said to be significantly higher than in the general population experience and 4 more to be significantly lower. The prevalence of diseases of the esophagus was 4.5% (RP = 1.89, 95% CI 1.08–2.69). The prevalence of stomach/duodenal/gastrointestinal

ulcer was 11% (RP = 2.11, 95% CI 1.65–2.57). Irritable bowel was reported by 2.2% of the responders (RP = 4.19, 95% CI 1.62–6.76). The reported prevalence of gallstones (2.2%) was not elevated (RP = 1.19, 95% CI 0.66–4.31). The committee had serious concerns that the results reported in O'Toole et al. (2009) were compromised by recall bias and other methodologic problems.

Occupational Studies

Boers et al. (2010) examined digestive system (noncancer) deaths in the third follow-up results of a retrospective cohort study of two Dutch chlorophenoxy herbicide manufacturing factories, producing mainly 2,4,5-T (Factory A) and 4-chloro-2-methylphenoxyacetic acid, 4-chloro-2-methylphenoxy propanoic acid, and 2,4-D (Factory B). The cohort consists of all persons working in one of the two factories during 1955–1985 (Factory A) or 1965–1986 (Factory B). Six cases of deaths due to digestive causes were observed in Factory A (HR = 0.60, 95% CI 0.18–2.01). No digestive system deaths were observed in Factory B.

A pair of papers reported on the mortality experience of workers employed by Dow Chemical Company in Midland, Michigan, in the production of trichlorophenol (TCP) (Collins et al., 2010a) or pentachlorophenol (PCP) (Collins et al., 2010b) from 1937 to 1980. Collins et al. (2009a) examined the mortality experience of the 1,615 workers in this cohort who had been involved in TCP production. The mean duration of follow-up was 36.4 years. Two cases of death from stomach or duodenal ulcers were observed (SMR = 0.8, 95% CI 0.1–2.9). Six cases of death by cirrhosis were observed (SMR = 0.4, 95% CI 0.1–0.8).

In the companion paper, Collins et al. (2009b) described the mortality experience of 773 workers who were exposed to chlorinated dioxins other than TCDD in the production of PCP. Seventy-five percent of the cohort has been followed for more than 27 years. SMRs were calculated comparing the PCP workers with the general US population and the population of the state of Michigan. The authors examined exposure response using both internal and external comparisons. There were five observed deaths from ulcers of the stomach and duodenum (SMR = 3.0, 95% CI 1.0–7.1). When one case was removed because of concurrent TCP and associated TCDD exposure, the SMR remained 3.0, but the 95% CI widened to 0.8–7.6. There was no trend for increasing risk of death from ulcers with increasing TEQs. With eight observed deaths from cirrhosis, the risk for the workers was at expected levels (SMR = 1.0, 95% CI 0.4–2.0), but a proportional hazards model based on this small number of cases showed some increase in risk of death from cirrhosis with increasing TEQs (SMR = 2.0, 95% CI 0.5–5.2). In a previous study of these workers, Ramlow et al. (1996) had reported increased risks of death from stomach ulcers and from cirrhosis, but the SMRs for both these conditions were lower in this follow-up study.

The fourth occupational mortality study was of workers in the Dow AgroSciences plant in New Plymouth, New Zealand, who were potentially exposed to 2,3,7,8-TCDD (McBride et al., 2009a). Workers who had been employed

between January 1969 and October 2003 were followed to the end of 2004, and SMRs were calculated using national mortality rates. A total of 1,754 workers were included in the study, but 22% were lost to follow-up. No cases of death due to stomach or duodenal ulcer were observed. The four cases of cirrhosis deaths among exposed workers were more than expected on the basis of the national population (SMR = 2.5, 95% CI 0.7–6.5), while no deaths from cirrhosis were observed among the never-exposed workers. McBride et al. (2009b) have also published mortality findings through 2004 from this plant that include all workers employed at the site from 1969–2003 (n = 1,754, also 247 deaths). The results of McBride et al. (2009b) have not been included because they were diluted by inclusion of a set of workers with no possible opportunity for TCDD exposure and no observed deaths.

Environmental Studies

No environmental studies of gastrointestinal diseases have been published since the 2008 review.

Biologic Plausibility

The liver is a primary target for the toxicity of many chemicals. It is the first organ that encounters chemicals absorbed from the gastrointestinal tract and is responsible for metabolizing them to water-soluble chemicals that can be excreted in the urine. Because the liver has many detoxifying enzymes that efficiently metabolize many chemicals, liver toxicity is usually associated only with high-dose acute exposure or chronic exposure to lower doses. The liver can be damaged if metabolism of a chemical results in the production of a reactive intermediate that is more toxic than the parent chemical. Changes in serum concentrations of liver enzymes are biomarkers for liver toxicity, and their magnitude correlates with the degree of liver damage. Exposure of laboratory animals to high doses of 2,4-D, 2,4,5-T, and TCDD is known to cause liver damage. The mechanisms by which the phenoxy herbicides damage the liver is based on inhibition of mitochondrial function by blocking of oxidative phosphorylation; this leads to loss of generation of adenosine triphosphate, death of cells, and hepatic necrosis and fibrosis. TCDD-induced hepatotoxicity is mediated by activation of the AHR, which leads to changes in gene transcription and associated changes in cell function. Changes in gene expression are associated with several physiologic processes, oxidative stress, and apoptosis (Boverhof et al., 2005, 2006). TCDD-mediated hepatic steatosis is characterized by the accumulation of triglyceride due to the combined up-regulation of CD36/fatty acid translocase and fatty acid transport proteins, suppression of fatty acid oxidation, inhibition of hepatic export of triglycerides, increase in peripheral fat mobilization, and increased hepatic oxidative stress (Lee et al., 2010). Exposure of rats to TCDD over a 2-year period (NTP, 2004)

also produced several changes in the liver, including hepatocyte hypertrophy, multinucleated hepatocytes, inflammation, pigmentation, diffuse fatty change, necrosis, bile duct hyperplasia, bile duct cyst, nodular hyperplasia, portal fibrosis, and cholangiofibrosis.

The AHR displays interspecies differences; for example the human and mouse AHR C-terminal region sequences share only 58% amino acid sequence identity. Compared with the mouse AHR (mAHR), the human AHR (hAHR) has approximately 10-fold lower relative affinity for TCDD, which has been attributed to the amino acid residue valine 381 in the ligand-binding domain of the hAHR (Flaveny et al., 2009; Ramadoss and Perdew, 2004). Species differences associated with AHR activation are supported by the divergence in the transcriptomic responses to TCDD in mouse, rat, and human liver (Boutros et al., 2008, 2009; Carlson et al., 2009; Kim et al., 2009), but it should be noted that these in vitro human hepatocyte studies may not reflect the in vivo response of human liver to TCDD. In vitro studies with transformed cell lines and primary hepatocytes cannot replicate the complexity of a tissue response that is important in eliciting the toxic responses observed in vivo (Dere et al., 2006).

Few health-relevant effects of phenoxy herbicides or TCDD on the gastrointestinal tract, even after high levels of exposure, have been reported. Thus, the animal data do not support a plausible link between herbicide exposure and gastrointestinal toxicity in Vietnam veterans.

Synthesis

Reports of increased risk of abnormal liver-function tests have been mixed, but evidence is lacking that Vietnam veterans are at greatly increased risk for serious liver disease, peptic ulcers, or other specific gastrointestinal diseases. The possibility of a relationship between dioxin exposure and subtle alterations in the liver and in lipid metabolism cannot be ruled out, but effects on the GI system of clinical importance have not been demonstrated.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and gastrointestinal and digestive diseases.

THYROID HOMEOSTASIS

Clinical disruptions of thyroid function include various disorders grouped in ICD-9 242.8 and 246.8. The thyroid gland secretes the hormones thyroxine (T4) and triiodothyronine (T3), which stimulate and help to regulate metabolism

throughout the body. The thyroid also secretes calcitonin, a hormone that controls calcium concentration in the blood and storage of calcium in bones. Secretion of T4 and T3 is under the control of thyroid-stimulating hormone (TSH), which is secreted by the anterior pituitary gland. Iodine operates in thyroid physiology both as a constituent of thyroid hormones and as a regulator of glandular function. Concentrations of those circulating hormones are regulated primarily by a negative-feedback pathway that involves three organs: the thyroid, the pituitary, and the hypothalamus. In the hypothalamus–pituitary–thyroid feedback scheme, the hypothalamus releases thyrotropin-releasing hormone (TRH), which stimulates the pituitary to produce TSH, which triggers the thyroid to produce T4 and T3. Cells in the hypothalamus and pituitary respond to concentrations of circulating T4 and T3. When T4 and T3 are low, the pituitary is stimulated to deliver more TSH to the thyroid, which increases T4 and T3 output. When circulating T4 and T3 are high, they signal to reduce the output of TRH and TSH. This negative-feedback loop maintains hormone homeostasis.

Disruption of thyroid homeostasis can be stimulatory (hyperthyroidism) or suppressive (hypothyroidism). Both conditions are diagnosed on the basis of blood concentrations of thyroid hormones, TSH, and other proteins (antithyroid antibodies). The prevalence of thyroid dysfunction in adults in the general population ranges from 1% to 10%, depending on the group, the testing setting, sex, age, method of assessment, and the presence of conditions that affect thyroid function. People with subclinical (biochemical) conditions may or may not show other evidence (signs or symptoms) of thyroid dysfunction.

In *hypothyroidism*, the body lacks sufficient thyroid hormone. Overt hypothyroidism is seen as a high serum concentration of TSH and a low serum concentration of free T4. Subclinical hypothyroidism is defined as a high serum concentration of TSH and a normal serum concentration of free T4. People who have hypothyroidism typically have symptoms of low metabolism. Studies consistently show that subclinical hypothyroidism is common and occurs more frequently in women than in men (Canaris et al., 2000; Hollowell et al., 2002; Sawin et al., 1985). In the Framingham study, for example, among 2,139 people 60 years old or older, 14% of women and 6% of men had subclinical hypothyroidism (Sawin et al., 1985). Subclinical hypothyroidism is a risk factor for overt hypothyroidism. Studies have reported association of hypothyroidism with a wide variety of other conditions.

The term *hyperthyroidism* may involve any disease that results in overabundance of thyroid hormone. Clinical or overt hyperthyroidism is characterized as a low serum concentration of TSH and high serum concentration of free T4. Subclinical hyperthyroidism is defined as a low serum concentration of TSH and a normal serum concentration of free T4. The prevalence of subclinical hyperthyroidism was estimated at about 1% in men and 1.5% in women over 60 years old (Helfand and Redfern, 1998). Conditions associated with hyperthyroidism include Graves disease and diffuse toxic goiter. Like hypothyroidism, hyper-

thyroidism is more common in women than in men, and, although it occurs at all ages, it is most likely to occur in people more than 15 years old. A form of hyperthyroidism called neonatal Graves disease occurs in infants born to mothers who have Graves disease. Occult hyperthyroidism may occur in patients more than 65 years old and is characterized by a distinct lack of typical symptoms.

It is important to distinguish between potential effects on adults and effects that may occur during development. In adults, the thyroid is able, within reason, to compensate for mild or moderate disruption (such as that caused by hyperplasia or goiter). In contrast, the fetus is highly sensitive to alterations in thyroid hormones, and alterations in thyroid homeostasis can hamper the development of many organ systems, including the nervous and reproductive systems; such findings are discussed in Chapter 8, which addresses potential consequences of Vietnam veterans' exposure to herbicides on their offspring. Only observations on adults are considered here.

Summary of Previous Updates

Koopman-Esseboom et al. (1994) found an association between dioxin-like congeners and markers of disrupted thyroid homeostasis, this report focused on TCDD and maternal thyroid function during pregnancy and therefore is less relevant to the experience of the predominantly male Vietnam veterans.

Extensive assessment of endocrine function including a series of thyroid function tests was carried out in connection with the Ranch Hand study (AFHS, 1991b). These studies failed to show any difference in thyroid function between exposed and control veterans. When individual TCDD readings had been obtained for subjects in the AFHS, however, Pavuk et al. (2003) found statistically significantly increased TSH measures from the 1985 and 1987 examinations in the high-exposure category and a significant increasing trend across the three TCDD categories in data gathered during the 1982, 1985, 1987, and 1992 examinations. Other studies of veterans of the Vietnam War have not documented an increased risk of thyroid disease.

Calvert et al. (1999) provided evidence of higher adjusted mean free T4 levels in TCDD-exposed workers, but there was no dose–response with serum TCDD levels. Bloom et al. (2006) found indications of an inverse relationship between the sum of dioxin-like compounds and the concentration of free T4 in anglers in New York State, but no association between the sum of dioxin-like compounds and TSH or T3. Abdelouahab et al. (2008) described thyroid function in adult freshwater-fish consumers in Canada; dioxin-like congeners were associated with an increase in TSH and a decrease in T4, but below the threshold at which clinical symptoms would be present. An analysis of 1999–2002 NHANES data (Turyk et al., 2007) found total T4 to have a weak inverse relationship with serum TEQs with effects somewhat stronger in individuals over 60 years of age and women more than men.

The committee for *Update 2008* concurred with previous committees that there was inadequate or insufficient evidence of an association between exposure to the chemicals of interest and clinical or overt adverse effects on thyroid homeostasis. Prior committees have also noted increasing evidence of an association between exposure to certain chemicals of interest and changes in markers of thyroid function below the threshold of clinical symptoms, perhaps because of the adaptive capacity of the adult system to accommodate such variation.

The Table 11-2 summarizes findings from studies that have examined the association between dioxin-like congeners and markers of thyroid function.

Update of the Scientific Literature

Vietnam-Veteran Studies

O'Toole et al. (2009) published a follow-up study on the 641 veterans from a random sample of 1,000 drawn from the Australian roster of Army veterans (both regular enlistment and National Service conscription) deployed to Vietnam who had been interviewed in 1990–1993. In 2005–2006, 450 veterans in the original sample were interviewed, with 391 individuals participating in both phases of this study. Self-reported health status of these Vietnam veterans was compared to that of the general Australian population based on responses gathered in the Australian 2004–2005 National Health Survey. Of 67 long-term conditions with reported results, the prevalences of 47 were found to be significantly higher among the veterans than in the general population experience. The prevalence of diseases of the thyroid was 2.2% (RP = 1.39, 95% CI 0.54–2.24). The committee had serious concerns that the results reported in O'Toole et al. (2009) were compromised by recall bias and other methodologic problems.

Occupational Studies

Goldner et al. (2010) published a study of pesticide use and self-reported history of physician-diagnosed thyroid disease among women in the Agricultural Health Study. No significant associations were observed between thyroid disease and ever having used 2,4-D, 2,4,5-T, or dicamba. Among individuals with 2,4-D exposure, there were 46 cases of hyperthyroidism (OR = 0.93, 95% CI 0.68–1.3), 147 cases of hypothyroidism (OR = 0. 96, 95% CI 0.8–1.1), and 87 other thyroid conditions (OR = 1.2, 95% CI 0.95–1.5). Among individuals exposed to 2,4,5-T, there were 7 cases of hypothyroidism (OR = 1.01, 95% CI 0.46–2.2). Among individuals exposed to dicamba there were 17 cases of hyperthyroidism (OR = 1.3, 95% CI 0.79–2.1), 27 cases of hypothyroidism (OR = 0.66, 95% CI 0.45–0.98), and 19 other thyroid conditions (OR = 0.96, 95% CI 0.60–1.5).

TABLE 11-2 Selected Epidemiologic Studies—Thyroid Homeostasis

Reference	Study Population	Exposed Cases	**Exposure of Interest/** Reported Results
VIETNAM VETERANS			
Air Force Health Study			**All COIs**
Pavuk et al., 2003	Ranch Hands (RH) in AFHS cohort—1987 findings		
	THS uptake by TCDD category		Normal = 0–3 µIU/ml
	Comparisons (SEA veterans—no TCDD spraying)	1,247	0.83
	RH background (TCDD ≤ 10 ppt)	409	0.84 (p = 0.88)
	RH low (TCDD > 10 ppt, ≤ 94 ppt)	273	0.87 (p = 0.16)
	RH high (TCDD > 94 ppt)	275	0.90 (p = 0.04)
	T4 (thyroxine) means by TCDD category		Normal = 4.5–11.5 µg/dl
	Comparisons (SEA veterans—no TCDD spraying)	1,247	7.47
	RH background (TCDD ≤ 10 ppt)	409	7.56 (p = 0.19)
	RH low (TCDD > 10 ppt, ≤ 94 ppt)	273	7.54 (p = 0.38)
	RH high (TCDD > 94 ppt)	275	7.56 (p = 0.28)
	T3% (triiodothyronin) uptake means by TCDD category		Normal = 25%–35%
	Comparisons (SEA veterans—no TCDD spraying)	1,247	30.7
	RH background (TCDD ≤ 10 ppt)	409	30.7 (p = 0.19)
	RH low (TCDD > 10 ppt, ≤ 94 ppt)	273	30.7 (p = 0.98)
	RH high (TCDD > 94 ppt)	275	30.5 (p = 0.24)
Australian Deployed Army Vietnam Veterans vs General Population			**All COIs**
O'Toole et al., 2009	Australian Vietnam veterans vs age- and sex-matched data from general population—prevalence		
	Disorders of the thyroid gland	450	1.4 (95% CI 0.5–2.2)
OCCUPATIONAL			
National Institute for Occupational Safety and Health			**Dioxin, phenoxy herbicides**
Calvert et al., 1999	TCDD-exposed workers employed > 15 yrs earlier in 1 of 2 US 2,4,5-T plants vs matched controls		
	TSH mU/l		Adjusted mean (SE)
	All workers	278	2.0 (0.1) p = 0.66
	TCDD < 20	75	2.2 (0.3) p = 0.28
	20 ≤ TCDD < 75	66	2.0 (0.3) p = 0.88
	75 ≤ TCDD < 238	66	1.9 (0.3) p = 0.94
	228 ≤ TCDD < 3,400	64	1.8 (0.3) p = 0.65
	Referents (< 20)	257	1.9 (0.1)

continued

TABLE 11-2 Thyroid Homeostasis, continued

Reference	Study Population	Exposed Cases	**Exposure of Interest/** Reported Results
	T4 nmol/l		
	All workers	278	101.4 (1.0) p = 0.07
	TCDD < 20	75	102.7 (2.0) p = 0.08
	20 ≤ TCDD < 75	66	99.4 (2.1) p = 0.79
	75 ≤ TCDD < 238	66	102.7 (2.1) p = 0.09
	228 ≤ TCDD < 3,400	64	100.1 (2.2) p = 0.58
	Referents (< 20)	257	98.8 (1.1)
	Free T4 index umol/l		
	All workers	278	27.8 (0.3) p = 0.02
	TCDD < 20	75	27.7 (0.5) p = 0.15
	20 ≤ TCDD < 75	66	27.4 (0.6) p = 0.36
	75 ≤ TCDD < 238	66	28.2 (0.6) p = 0.03
	228 ≤ TCDD < 3,400	64	27.7 (0.6) p = 0.19
	Referents (< 20)	257	26.8 (0.3)
Agricultural Health Study			**Herbicides**
Goldner et al., 2010	Thyroid disease among female spouses in Iowa and North Carolina (1993–2003)		**2,4-D, 2,4,5-T, dicamba**
	Hyperthyroid		
	Self-reported 2,4-D exposure	46	0.9 (95% CI 0.7–1.3)
	Self-reported 2,4,5-T exposure	3	NA
	Self-reported dicamba exposure	17	0.8 (95% CI 0.8–2.1)
	Hypothyroid		
	Self-reported 2,4-D exposure	147	0.96 (95% CI 0.8–1.1)
	Self-reported 2,4,5-T exposure	7	1.0 (95% CI 0.5–2.2)
	Self-reported dicamba exposure	27	0.7 (95% CI 0.5–0.98)
	Other thyroid conditions		
	Self-reported 2,4-D exposure	87	1.2 (95% CI 0.95–1.5)
	Self-reported 2,4,5-T exposure		
	Self-reported dicamba exposure	19	0.96 (95% CI 0.6–1.5)
Other Occupational Studies			
Johnson et al., 2001	Sprayers in Victoria, Australia		**2,4,5-T, 2,4-D**
	TSH vs estimated serum TCDD level	32	Normal = 0.3–5.0μIU/ml
	Based on local levels		0.2
	Based on individual sampling LDs		–.03
	Based on back extrapolation		–0.4 (p < 0.05)
	T4 vs estimated serum TCDD level	32	Normal = 0.045–2.125 μg/ml
	Based on local levels		0.1
	Based on individual sampling LDs		–0.0
	Based on back extrapolation		–0.0
	T3 vs estimated serum TCDD level	32	Normal = 0.9–1.9 μg/ml
	Based on local levels		–0.1
	Based on individual sampling LDs		–0.4 (p < 0.05)
	Based on back extrapolation		–0.5 (p < 0.01)

TABLE 11-2 Thyroid Homeostasis, continued

Reference	Study Population	Exposed Cases	**Exposure of Interest/** Reported Results
ENVIRONMENTAL			
National Health and Nutrition Examination Survey			**2,4-D**
Schreine-machers, 2010	NHANES III—analysis of data from subjects with detectable limits of urinary 2,4-D		
	TSH		
	Detectable 2,4-D	102	1.6 mU/L
	Non-detectable 2,4-D	625	1.7 mU/L
	T4		
	Detectable 2,4-D	102	8.5 µg/dl
	Non-detectable 2,4-D	625	8.6 µg/ml
Turyk et al., 2007	NHANES (1999–2002, 2001–2002)—Association with TEQs in individuals without thyroid disease		**dl TEQs, dl PCBs**
	Men (1999–2000)		
	T4	402	–0.12 (–0.61 to 0.37)
	TSH	402	–0.09 (–0.38 to 0.20)
	Men (2000–2001)		
	T4	497	–0.47 (–0.97 to 0.04)
	TSH	497	–0.02 (–0.20 to 0.16)
	Women (1999–2000)		
	T4	310	–0.19 (–0.70 to 0.33)
	TSH	309	0.15 (–0.14 to 0.44)
	Women (2000–2001)		
	T4	386	–0.58 (–1.26 to 0.10)
	TSH	385	0.06 (–0.15 to 0.35)
Other Environmental Studies			
Dallaire et al., 2009	Cross-sectional study of Inuit residents of Nunavik (Québec, Canada)	607	**dl PCBs/** correlation of dl-congeners (adjusted)
	TSH		0.02
	fT4		–0.01
	fT3		–0.03 ($p < 0.05$)
Abdelouahab et al., 2008	Cross-sectional study of freshwater fish consumers from two Canadian communities		**dl PCBs/** dl PCB congeners β estimates
	Men	124	
	TSH		0.55 ($p < 0.001$)
	T4		–2.19 ($p < 0.05$)
	T3		–0.01
	Women	87	
	TSH		0.04
	T4		0.04
	T3		–0.01

continued

TABLE 11-2 Thyroid Homeostasis, continued

Reference	Study Population	Exposed Cases	**Exposure of Interest/** Reported Results
Meeker et al., 2007	Adult men recruited from Massachusetts infertility clinic (2000–2003)	341	**dl PCBs**
	T3		0.02 (95% CI 0.05–0.01)[a]
	fT4		0.01 (95% CI 0.01–0.05)[a]
	TSH		0.93 (95% CI 0.84–1.03)[a]
Bloom et al., 2006	Sportfish anglers from New York exposed to dioxin-like compounds in diet	38	**PCDDs, PCDFs, dl PCBs** mean/median (range)
	TSH µUL/mL		2.0/1.4 (0.2–15.7)
	T4 µg/dL		6.3/6.4 (3.2–10.0)
	Free T4 ng/mL		1.1/1.1 (0.9–1.6)
	T3 ng/dL		92.6/87.5 (56.0–181.0)
Nagayama et al., 2001	Japanese patients exposed in 1968 during the Yusho incident; blood collected from participants 1996 and 1997	16	**PCDDs, PCDFs, dl PCBs**
	TSH correlation coefficient		0.01 (p = 0.97)
	T4 correlation coefficient		0.03 (p = 0.9)
	T3 correlation coefficient		–0.09 (p = 0.74)
Environmental Studies of Pregnant Women			
Zhang et al., 2010	Cross-sectional study of a Chinese community in the vicinity of an electronic-waste recycling plant—maternal serum T4 levels at 16 weeks gestation (correlations with contaminant levels in cord blood)	50	**PCDDs, PCDFs, dl PCBs**
	dl PCBs		r = –0.413 (p = 0.01)
	PCDD/Fs		r = –0.198 (p = 0.21)
Chevrier et al., 2008	CHAMACOS study—334 pregnant women from Salinas Valley, CA, providing blood at 26 wk gestation		**dl PCBs** β (95% CI)
	Free T4 vs		
	PCB TEQs (pg/g)		–0.05 (–0.16 to 0.06)
	Mono-ortho PCBs (ng/g)		–0.09 (–0.19 to 0.01)
	PCB 118 (ng/g)		–0.05 (–0.15 to 0.06)
	PCB 156 (ng/g)		–0.06 (–0.13 to 0.01)
	Total T4 vs		
	PCB TEQs (pg/g)		0.26 (–0.45 to 0.96)
	Mono-ortho PCBs (ng/g)		–0.13 (–0.78 to 0.53)
	PCB 118 (ng/g)		0.26 (–0.43 to 0.95)
	PCB 156 (ng/g)		–0.05 (–0.52 to 0.42)
Foster et al., 2005	Cross-sectional examination of serum from pregnant women attending Canadian prenatal diagnosis clinic	150	**dl compounds**
	TSH correlation coefficient		ns (value nr)
	T4 correlation coefficient		ns (value nr)

TABLE 11-2 Thyroid Homeostasis, continued

Reference	Study Population	Exposed Cases	**Exposure of Interest/** Reported Results
Koopman-Esseboom et al., 1994	Part of the prospective longitudinal Dutch PCB/Dioxin study; 105 healthy mother-infant pairs living in or around Rotterdam, recruited June 1990–February 1992		**Dioxins and PCBs**
	Maternal serum correlations with dioxin TEQs	78	
	T4		–0.4 ($p \leq .001$)
	T3		–0.5 ($p \leq .001$)

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenol; AFHS, Air Force Health Study; CA, California; CI, confidence interval; COI, chemical of interest; dl, dioxin-like; LD, level of detection; NA, not available; NHANES, National Health and Nutrition Examination Survey; nr, no relationship; ns, nonsignificant; PCB, polychlorinated biphenyls; PCDD, polychlorinated dibenzo-*p*-dioxins; PCDF, polychlorinated dibenzofurans; ppt, parts per trillion; SE, standard error; SEA, Southeast Asia; RH, Ranch Hand; T3, triiodothyronine; T4, tetraiodothyronine; TCDD, tetrachlorodibenzo-*p*-dioxin; TEQ, (total) toxic equivalent; TSH, thyroid stimulating hormone.
[a]Adjusted coefficients for change in thyroid hormone level associated with an interquartile range increase in serum dioxin-like congeners.

Environmental Studies

Dallaire et al. (2009) studied thyroid function and plasma concentrations of polyhalogenated compounds in Inuit adults, including measurement of a number of dioxin-like compounds. Dioxin-like compounds were detected in 72.6% of the samples (n = 607). The positive correlation for TSH and the negative one for free T4 with concentrations of dioxin-like compounds were no longer significant when adjusted for sex, age, BMI, plasma lipids, smoking, education, and consumption of fish and alcohol. A similar unadjusted correlation was found with free T4. The negative correlation with free T3 levels remained significant with adjustment ($p < 0.05$). This population is exposed to a complex mixture of organochlorine compounds, making it difficult to isolate the effects of dioxin-like compounds.

Zhang et al. (2010) published a cross-sectional study of a Chinese community exposed to an electronic-waste recycling plant. Maternal serum and cord whole blood collected from 25 pregnant women in Zone A (exposed) and 25 pregnant women in Zone B (nonexposed) was analyzed to determine the association between thyroid hormone levels in their serum at 16 weeks gestation and polybrominated dibenzofuran, PCDD/F, and PCB exposures. Body burdens of the

three contaminants in cord blood were significantly higher in Zone A. Levels of T4 and TSH in serum in Zone A were significantly lower than those in Zone B ($p < 0.05$). An inverse trend was reported between the major groupings of persistent organic pollutants and T4. However there was no statistically significant association between ∑TEQ-PCDD/Fs, ∑PBDE, and T4. A significant negative correlation was found between ∑TEQ PCB and T4 ($p < 0.0091$). No correlations were observed between the PBDE, PCDD/F, and PCB exposures and the thyroid hormones T3 and TSH.

The CHAMACOS project has studied the cohort of births between October 1999 and October 2000 to women enrolled at the Center for the Health Assessment of Mothers and Children of Salinas in California. Chevrier et al. (2008) measured TSH, free T4, and total T4 levels in 334 women who had provided blood samples at 26 weeks gestation (or before delivery in 14 cases). Changes in free T4 and total T4 (adjusted for age and BMI) per 10-fold increase in exposure expressed in terms of PCB TEQs, mono-ortho PCB TEQs were presented. Such results were also reported for PCBs 118 and 156, the only two dioxin-like PCBs among the 19 PCBs (of 34 congeners measured) that were detected in at least 75% of the subjects. None of the associations for these particular measures were significant. It was stated without presenting data that TSH was not associated with these PCBs or any other of the persistent organic pollutants measured. Results on thyroid functions in the infants from these pregnancies (Chevrier et al., 2007) were discussed in Chapter 8.

Schreinemachers (2010) examined the association of recent exposure to 2,4-D with T4 and TSH in conjunction with indicators of lipid and glucose metabolism in 737 healthy subjects examined in NHANES III (1988–1994). Because only 14% of the values of urinary 2,4-D were above the limit of detection (LOD), it was decided to use urinary 2,4-D as a binary variable, above versus below the LOD, in linear regression analyses with adjustment for sex, age, BMI, ethnicity, smoking, urinary creatinine, alcohol consumption, education, income, and number of hours fasting before blood draw. No significant association was found between having detectable levels of 2,4-D or not and TSH levels (1.57 with 0.05 standard error [SE] vs 1.67 with 0.13 SE mg/L, respectively). Those having T4 below the median (8.5 µg/dl), who were hypothesized to be more sensitive, were analyzed separately, and a negative association was found for 2,4-D exposure with high density lipoprotein (HDL) levels ($\beta = -0.09$, 95% CI –0.16 to –0.02), but not with triglyceride levels ($\beta = 1.79$, 95% CI –0.18 to 3.76) or non-HDL levels ($\beta = -0.27$, 95% CI –1.30 to 0.76).

There has been considerable study of maternal exposure and perinatal effects on thyroid function, which is not directly applicable to the adult exposure of the Vietnam veterans whose own health is the primary concern of these updates. A discussion of these materials can be found in Chapter 8 on possible adverse effects on the offspring of Vietnam veterans.

Biologic Plausibility

The influence of TCDD on thyroid hormone homeostasis has been measured in numerous animal studies, with exposure associated with changes in serum concentrations of T4, T3, and TSH. In most studies, TCDD exposure is associated with a hypothyroid state, including reduced circulating T3 and T4 and increased TSH, especially after chronic exposure. Reduction in circulating T4 levels is robust and has recently been proposed as a biomarker of effect of dioxin-like compounds (Yang et al., 2010). Female rats exposed chronically to TCDD showed follicular-cell hyperplasia and hypertrophy of thyroid follicles, consistent with overstimulation of the thyroid gland by TSH (TSH increases as a homeostatic response to low T4 levels). TCDD enhances the metabolism of thyroid hormones primarily through an AHR-dependent induction of glucuronyl transferase activity (Kato et al., 2010; Nishimura et al., 2005). Enhanced accumulation of T4 in hepatic tissue of TCDD-treated mice may also contribute to the reduced circulating T4 (Kato et al., 2010).

Synthesis

Numerous animal experiments and several epidemiologic studies have shown that TCDD and dioxin-like compounds appear to exert some influence on thyroid homeostasis. The effects of these substances on thyroid hormone and TSH level in humans still remain to be definitely elucidated (Langer, 2008). Most of the literature to date has focused on the correlations between exposure to dioxin-like PCB congeners in environmentally exposed populations, with many of these studies limited to women and infants. Few studies of thyroid metabolism in the primarily male Vietnam veterans have been published. In the AFHS study considered in *Update 2004*, Pavuk et al. (2003) reported a trend toward an increasing concentration of TSH that was not accompanied by changes in circulating T4 or T3 in Vietnam veterans. In comparison, T4 has been shown to be susceptible to influence from dioxin-like compounds in epidemiological studies. Notably, in Vietnam veteran studies, there has been no evidence of changes in clinical thyroid disease. Although the overall assessment of the studies to date suggests some variation in thyroid hormone concentrations in relation to TCDD exposure, the functional importance of those changes remains unclear because adaptive capacity should be adequate to accommodate them. It should be noted, however, that although biomarkers of perturbation may be subclinical in most individuals, they may be associated with clear adversity in others.

Conclusions

There is inadequate or insufficient evidence of an association between exposure to the chemicals of interest and clinical or overt adverse effects on thyroid

homeostasis. Some effects have been observed in humans, but the functional importance of the changes reported in the studies reviewed remains unclear because adaptive capacity could be adequate to accommodate them.

EYE PROBLEMS

With advancing age, loss of vision becomes increasingly common, with about one in six people over 70 years of age having substantial impairment and men and women being similarly affected (NCHS, 2010). The most prevalent ocular problems in current age range of Vietnam veterans are age-related macular degeneration, cataracts, glaucoma, and diabetic retinopathy. Ocular problems involving chemical agents most often arise from acute, direct contact with caustic or corrosive substances that may have permanent consequences. Ocular impairment arising from systemic exposure to toxic agents may be mediated by nerve damage. Cataracts can be induced by chronic internal exposure of the lens to chemicals such as 2,4-dinitrophenol, corticosteroids, and thallium, while glaucoma may arise secondary to any toxic inflammation and also from topical or systemic treatment with anti-inflammatory corticosteroids (Casarett and Doull, 1995).

Update of Epidemiologic Evidence

A cohort of Australian Vietnam veterans (O'Toole et al., 2009) was studied between 1990–1993 and reexamined in 2005–2006. In the original assessment, 641 Australian Vietnam veterans responded from a random sample of 1,000 selected from the list of Army Veterans deemed eligible for previous studies of Agent Orange; 450 from the original sample responded in this most recent assessment. Interviewers administered the Australian Bureau of Statistics National Health Survey that assessed physical health and associated risk factors, a 32-item combat index, an assessment for combat-related PTSD, and an assessment of general psychiatric status. Self-reported health status and conditions were asked. The prevalences of these conditions were compared to those reported by the general population in response to the National Health Survey from 2004–2005. Relative prevalences were calculated standardized to the Australian male population in 5-year age groups. Compared to the general population, the Vietnam veterans had elevated prevalence of all the eye conditions assessed: cataracts (RP = 1.84, 95% CI 1.2–2.47), presbyopia (RP = 3.05, 95% CI 2.73–3.36), color blindness (RP = 1.06, 95% CI 0.71–1.41), and other diseases of the eye (RP = 2.17, 95% CI 1.01–3.34). The committee had serious concerns that the results reported in O'Toole et al. (2009) were compromised by recall bias and other methodologic problems.

Biologic Plausibility

There have been several recent reports of ocular activity associated with AHR-induction or TCDD exposure in rats (Sugamo et al., 2009), mice (Takeuchi et al., 2009), and human nonpigmented ciliary epithelial cells (Volotinen et al., 2009).

Synthesis

O'Toole et al. (2009) observed increased risks for several eye conditions among the Australian Vietnam veterans, but the study is limited by the lack of information on exposure to the chemicals of interest to the committee, lack of clinical confirmation of the eye conditions, and considerable likelihood of recall bias.

Conclusion

On the basis of the evidence reviewed here, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the chemicals of interest and eye conditions.

BONE CONDITIONS

This section discusses conditions encompassed by ICD-9 733: osteoporosis or decreased bone density. Osteoporosis is a skeletal disorder characterized by a decrease in bone mineral density (BMD) and loss of structural and biomechanical properties of the skeleton, leading to an increased risk of fractures. Although there currently are no practical methods to assess overall bone strength, BMD correlates closely with skeletal load-bearing capacity and fracture risk (Lash, 2009). The World Health Organization (WHO) has developed definitions for osteoporosis based on BMD measurements. The DEXA T-score is the number of the standard deviations from the mean BMD in young adult women, for whom osteoporosis is defined as T-score at any site of –5 or lower, whereas osteopenia is defined as a T-score between –1 and –2.5. Although there are no standardized diagnostic criteria for osteoporosis in men, most authorities use the WHO criteria of a T-score less than –2.5 relative to normal young women. Although men have much higher baseline BMD than women, they seem to have a similar fracture risk for a given BMD (Lash, 2009).

Gender is an important risk factor for osteoporosis with approximately 56% of postmenopausal women having decreased bone mineral density and 6% having osteoporosis (CDC, 2002). While data on the effects of aging on bone loss in women are well known, many health-care providers and patients are less familiar with the prevalence and impact of bone changes in older males (Orwoll et al., 2010). Individual patients have genetic and acquired risks for osteoporosis, and

the osteoporosis disease process can be without symptoms for decades. It is well known that hormones, vitamins, and pharmaceuticals can have adverse effects on bone. Drug-induced osteoporosis occurs primarily in postmenopausal women, but premenopausal women and men are also significantly affected. Glucocorticoids are the most common cause of drug-induced osteoporosis (Mazziotti et al., 2010). Other risk factors for loss of bone density include long-acting benzodiazepine or anticonvulsant drug use, previous hyperthyroidism, excessive caffeine intake, and standing 4 or fewer hours per day (Lash, 2009).

Several studies have described a link between organochlorine exposure and effects on bone growth, most notably reports of infants exposed *in utero* to high concentration of PCBs and polychlorinated dibenzofurans developing irregular calcifications of their skull bones (Miller, 1985) and reports of accidental organochlorine poisonings resulting in osteoporosis (Cripps et al., 1984; Gocmen et al., 1989). However; the epidemiological studies of the association between bone disorders and environmental exposures to organochlorine compounds have been inconsistent.

Summary of Previous Updates

Previous VAO updates have not examined bone density or osteoporosis as a health outcome. This is the first VAO update in which studies examining the association between exposures to the chemicals of interest and decrease in bone density are reviewed.

Update of the Scientific Literature

No Vietnam-veteran or occupational studies concerning the chemicals of interest and bone density or osteoporosis have been published.

Environmental Studies

Hodgson et al. (2008) studied the relationship between organochlorine exposure and BMD in a subset of 325 members of the Osteoporosis Cadmium as a Risk Factor (OSCAR) cohort who were at least 60 years old. Many of the cohort members lived close to the Baltic coast and may have had PCB exposure from fish consumption and potentially from exposure from a PCB-contaminated river. The cohort contains 1,021 individuals who provided information on employment, residence, smoking, diet, and medical history. Forearm BMD was measured on the distal site of the nondominant forearm with an osteometer using dual energy x-ray absorptiometry. Blood samples were analyzed for total TEQs for five mono-ortho chlorine substituted congeners (PCB 105, 118, 156, 157, and 167) and for the concentration of PCB 118 alone. TEQs for the mono-*ortho* PCBs ranged from 0.002 to 0.067 pg/mL in men and from 0.003 to 0.053 pg/mL in women. In males,

stepwise multivariate analyses adjusted for age, BMI, and milk consumption found PCB 118 to have a marginally significant negative association with BMD ($\beta = -0.00011$, $p = 0.079$), but TEQ for all five dioxin-like PCBs did not show an association ($\beta = 0.225$, $p = 0.846$). In females, stepwise multivariate analyses adjusted for age, BMI, age at menstruation, and ever-pregnant found PCB 118 alone and TEQ for all five dioxin-like PCBs were positively associated with BMD ($\beta = 0.00008$, $p = 0.045$; $\beta = 1.652$, $p = 0.057$, respectively). When the risk of low BMD (more than 1 standard deviation below the mean value) was treated as a binary variable in a similarly adjusted logistic model, there was a significant association with PCB 118 in men (OR = 1.06, 95% CI 1.01–1.12, $p = 0.027$), but none of the measured organochlorine compounds (also including non-dioxin-like PCB 138, 153, and 180) were predictive for the women.

Biological Plausibility

Animal studies suggest that TCDD may have some influence on bone formation and maintenance. For instance, TCDD exposure via the dam's milk impaired bone mineralization during postnatal development in mice due to a reduction of the osteoblastic activity, which is caused by TCDD-induced up-regulation in the active form of vitamin D in serum (Nishimura et al., 2009). TCDD altered osteogenesis (bone formation) in an in vitro osteoblast model, producing alterations in proteins associated with cytoskeleton organization and biogenesis and a decrease in the expression of calcium-binding proteins, which decreases osteoblast calcium deposition (Carpi et al., 2009).

Synthesis

The small amount of epidemiologic information available concerning possible adverse effects on bone structure in association with exposure to the chemicals of interest is based almost entirely on a single dioxin-like PCB. The findings of Hodgson et al. (2008) do not constitute a strong or consistent pattern.

Conclusion

There is inadequate or insufficient evidence of an association between exposure to the chemicals of interest and clinical or overt adverse effects of osteoporosis or loss of bone mineral density.

SUMMARY

On the basis of the occupational, environmental, and veterans studies reviewed and in light of information concerning biologic plausibility, the committee reached one of four conclusions about the strength of the evidence regarding

an association between exposure to the chemicals of interest and each of the health outcomes discussed in this chapter. In categorizing diseases according to the strength of the evidence, the committee applied the same criteria (discussed in Chapter 2) that were used in *VAO*, *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, *Update 2006*, and *Update 2008*. To be consistent with the charge to the committee by the Secretary of Veterans Affairs in Public Law 102-4 and with accepted standards of scientific reviews, the distinctions between conclusions are based on statistical association.

Health Outcomes with Sufficient Evidence of an Association

For diseases in this category, a positive association between exposure and outcome must be observed in studies in which chance, bias, and confounding can be ruled out with reasonable confidence. On the basis of the literature, none of the health effects discussed in this chapter satisfy the criteria necessary for inclusion in this category.

Health Outcomes with Limited or Suggestive Evidence of an Association

For this category, the evidence must suggest an association between exposure and outcome, although it can be limited because chance, bias, or confounding could not be ruled out with confidence. On the basis of the literature, none of the health effects discussed in this chapter satisfy the criteria necessary for inclusion in this category.

Health Outcomes with Inadequate or Insufficient Evidence to Determine Whether There Is an Association

The scientific data on many of the health outcomes reviewed by the present committee were inadequate or insufficient to determine whether there is an association between exposure to the chemicals of interest and the outcomes. For the health outcomes in this category, the available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association. Some studies failed to control for confounding or used inadequate exposure assessment. This category includes noncancerous respiratory disorders, such as COPD, asthma in isolation, pleurisy, pneumonia, and tuberculosis; gastrointestinal diseases; digestive diseases; liver toxicity; disorders of thyroid homeostasis; and disorders of the eyes and bones.

Health Outcomes with Limited or Suggestive Evidence of *No* Association

To classify outcomes in this category, several adequate studies covering the full range of known human exposure must be consistent in not showing a positive

association between exposure and outcome at any magnitude of exposure. The studies also must have relatively narrow confidence intervals. A conclusion of "no association" is inevitably limited to the conditions, magnitudes of exposure, and periods of observation covered by the available studies. The possibility of a very small increase in risk at the exposure studied can never be excluded.

The committees responsible for *VAO*, *Update 1996*, *Update 1998*, *Update 2000*, *Update 2002*, *Update 2004*, and *Update 2006* concluded that none of the health outcomes discussed in this chapter had limited or suggestive evidence of *no* association with exposure to the chemicals of interest. The most recent scientific evidence continues to support that conclusion.

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[1]Throughout the report the same alphabetic indicator following year of publication is used consistently for the same article when there were multiple citations by the same first author in a given year. The convention of assigning the alphabetic indicator in order of citation in a given chapter is not followed.

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12

Conclusions and Recommendations

SYNOPSIS OF COMMITTEE CONCLUSIONS

The committee weighed the strengths and limitations of the epidemiologic evidence reviewed in this report and in previous *Veterans and Agent Orange* (VAO) reports. Although the studies published since *Update 2008* are the subject of detailed evaluation here, the committee drew its conclusions in the context of the entire body of literature. The contribution of recent publications to the evidence database was considerable, but the committee did not weigh them more heavily merely because they were new. Epidemiologic methods and analytic capabilities have improved, but many of the recent studies were also particularly useful for the committee's purpose because they produced results in terms of serum 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) concentrations or total toxic equivalents (TEQs), which take into account exposure to all dioxin-like chemicals (DLCs), or because their findings consisted of observations on the aging population of primary concern, Vietnam veterans. The committee also notes that experimental data related to biologic plausibility of health conditions statistically associated with exposure to the components of Agent Orange have gradually emerged since the beginning of this series of VAO reports. These findings now better inform decisions about how to categorize the degree of association for individual conditions, so a footnote to this effect was added to Tables 1-1 and 12-1 by the committee for *Update 2008*. The current committee has added an additional notation to Table 12-1 indicating the correspondence of the lymphohematopoietic cancers (LHCs) that have been found to have evidence of an association with herbicide exposure and the biologic understanding of the clonal derivation of

LHCs that is the basis of the World Health Organization's classification system for these neoplasms.

On the basis of its evaluation of veterans, occupational, and environmental studies, the committee assigned each health outcome to one of four categories of relative certainty of association with exposure to the herbicides that were used in Vietnam or to any of their components or contaminants (with no intention of specifying particular chemicals). Changes made by the current committee to the categorizations determined by the committee for *Update 2008* (as presented in Table 1-1) are noted in boldface in Table 12-1.

The terminology of "early-onset transient peripheral neuropathy" was adopted in *Update 2004* as a replacement for the terminology of "acute and subacute peripheral neuropathy" used in *Update 1996*. *Update 1996*, the first VAO report to find "limited or suggestive evidence of association" with exposure to the chemicals of interest for this health outcome, also noted in the body of the report that this was a "transient" effect. When US Department of Veterans Affairs (VA) declared this outcome to be presumptively associated with service in Vietnam, its definition included the temporal constraints that symptoms develop within weeks or months of exposure to an herbicide and resolve within 2 years of the date of onset (VA, 1996; see Note 2 at end of Final Rule). Thus, currently qualifying cases are contingent upon when symptoms arise relative to when exposure occurred and that the symptoms are transitory in nature, with recent claims being extremely unlikely. A thorough review of the existing literature in populations with members experiencing early-onset peripheral neuropathy, however, indicates that some individuals continue to manifest neuropathy symptoms long after external exposure has ceased, demonstrating that early-onset peripheral neuropathy is not necessarily a transient condition. Based on this literature, the committee elected to delete the word *transient* to recognize that symptoms of early-onset peripheral neuropathy may be protracted and recovery from those symptoms may be incomplete. The changes to the classifications made since the previous update are bolded here in Table 12-1 and in Table S-1 in the Summary.

Although VA did not find hypertension to be presumptively related to service in Vietnam (VA, 2010), on the basis of the total weight of available evidence, the current committee reaffirmed the conclusion of the committees for *Update 2006* and for *Update 2008* to categorize hypertension as having limited/suggestive evidence of association.

As mandated by Public Law (PL) 102-4, the distinctions among categories are based on statistical association, not on strict causality. The committee was directed to review the scientific data, not to recommend VA policy; therefore, conclusions reported in Table 12-1 are not intended to imply or suggest policy decisions. The conclusions are related to associations between exposure and outcomes in human populations, not to the likelihood that any individual's health problem is associated with or caused by the chemicals in question.

TABLE 12-1 Summary from *Eighth Biennial Update* of Findings in Occupational, Environmental, and Veterans Studies Regarding the Association Between Specific Health Outcomes and Exposure to Herbicides[a]

Sufficient Evidence of Association

Epidemiologic evidence is sufficient to conclude that there is a positive association. That is, a positive association has been observed between exposure to herbicides and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence.[b] For example, if several small studies that are free of bias and confounding show an association that is consistent in magnitude and direction, there could be sufficient evidence of an association. There is sufficient evidence of an association between exposure to the chemicals of interest and the following health outcomes:

Soft-tissue sarcoma (including heart)
* Non-Hodgkin's lymphoma
* Chronic lymphocytic leukemia (CLL) (including hairy cell leukemia and other chronic B-cell leukemias)
* Hodgkin's disease
Chloracne

Limited or Suggestive Evidence of Association

Epidemiologic evidence suggests an association between exposure to herbicides and the outcome, but a firm conclusion is limited because chance, bias, and confounding could not be ruled out with confidence.[b] For example, a well-conducted study with strong findings in accord with less compelling results from studies of populations with similar exposures could constitute such evidence. There is limited or suggestive evidence of an association between exposure to the chemicals of interest and the following health outcomes:

Laryngeal cancer
Cancer of the lung, bronchus, or trachea
Prostate cancer
* Multiple myeloma
* AL amyloidosis
Early-onset peripheral neuropathy (category clarification from *Update 2008*)
Porphyria cutanea tarda
Parkinson's disease
Hypertension
Ischemic heart disease
Type 2 diabetes (mellitus)
Spina bifida in offspring of exposed people

Inadequate or Insufficient Evidence to Determine Association

The available epidemiologic studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association. For example, studies fail to control for confounding, have inadequate exposure assessment, or fail to address latency. There is inadequate or insufficient evidence to determine association between exposure to the chemicals of interest and the following health outcomes *that were explicitly reviewed*:

Cancers of the oral cavity (including lips and tongue), pharynx (including tonsils), or nasal cavity (including ears and sinuses)
Cancers of the pleura, mediastinum, and other unspecified sites within the respiratory system and intrathoracic organs
Esophageal cancer
Stomach cancer

continued

TABLE 12-1 Continued

Colorectal cancer (including small intestine and anus)
Hepatobiliary cancers (liver, gallbladder, and bile ducts)
Pancreatic cancer
Bone and joint cancer
Melanoma
Non-melanoma skin cancer (basal cell and squamous cell)
Breast cancer
Cancers of reproductive organs (cervix, uterus, ovary, testes, and penis; excluding prostate)
Urinary bladder cancer
Renal cancer (kidney and renal pelvis)
Cancers of brain and nervous system (including eye)
Endocrine cancers (thyroid, thymus, and other endocrine)
Leukemia (other than all chronic B-cell leukemias, including CLL and hairy cell leukemia)
Cancers at other and unspecified sites
Infertility
Spontaneous abortion (other than for paternal exposure to TCDD, which appears *not* to be associated)[b]
Neonatal or infant death and stillbirth in offspring of exposed people
Low birth weight in offspring of exposed people
Birth defects (other than spina bifida) in offspring of exposed people
Childhood cancer (including acute myeloid leukemia) in offspring of exposed people
Neurobehavioral disorders (cognitive and neuropsychiatric)
Neurodegenerative diseases, excluding Parkinson's disease
Chronic peripheral nervous system disorders
Hearing loss (newly addressed health outcome)
Respiratory disorders (wheeze or asthma, chronic obstructive pulmonary disease, and farmer's lung)
Gastrointestinal, metabolic, and digestive disorders (changes in liver enzymes, lipid abnormalities, and ulcers)
Immune system disorders (immune suppression, allergy, and autoimmunity)
Circulatory disorders (other than hypertension and ischemic heart disease)
Endometriosis
Effects on thyroid homeostasis
Eye problems (newly addressed health outcome)
Bone conditions (newly addressed health outcome)

This committee used a classification that spans the full array of cancers. However, reviews for nonmalignant conditions were conducted only if they were found to have been the subjects of epidemiologic investigation or at the request of the Department of Veterans Affairs. *By default, any health outcome on which no epidemiologic information has been found falls into this category.*

TABLE 12-1 Continued

Limited or Suggestive Evidence of *No* Association
Several adequate studies, which cover the full range of human exposure, are consistent in not showing a positive association between any magnitude of exposure to a component of the herbicides of interest and the outcome. A conclusion of "no association" is inevitably limited to the conditions, exposures, and length of observation covered by the available studies. *In addition, the possibility of a very small increase in risk at the exposure studied can never be excluded.* There is limited or suggestive evidence of *no* association between exposure to the herbicide component of interest and the following health outcomes:
Spontaneous abortion and paternal exposure to TCDD

[a]*Herbicides* indicates the following chemicals of interest: 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, or dioxin), cacodylic acid, and picloram. The evidence regarding association was drawn from occupational, environmental, and veteran studies in which people were exposed to the herbicides used in Vietnam, to their components, or to their contaminants.

[b]Evidence for an association can be strengthened by experimental data supporting biologic plausibility, but its absence would not detract from the epidemiologic evidence.

*The committee notes the consistency of these findings with the biologic understanding of the clonal derivation of hymphohematopoietic cancers that is the basis of the World Health Organization classification system (WHO, 2008).

COMMITTEE RECOMMENDATIONS

As part of its charge, the committee was asked to make recommendations concerning the need, if any, for additional scientific studies to resolve uncertainties concerning the health effects of the chemicals of interest sprayed in Vietnam: 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its contaminant TCDD, picloram, and cacodylic acid. This chapter summarizes the committee's recommendations.

Although progress continues to be made in understanding the health effects of exposure to the chemicals of interest and in elucidating the mechanisms underlying them, gaps in our knowledge remain. The scope of potential research on the chemicals is far reaching, and what follows here is not an exhaustive list of future research that might have value. There are many additional opportunities for progress in such areas as toxicology, exposure assessment, the conduct of continuing or additional epidemiologic studies, and systematic and comprehensive integration of existing data that have not been explicitly noted here. It is the committee's conviction, however, that work needs to be undertaken without delay, particularly to address questions regarding chronic obstructive pulmonary disease (COPD); the potential for paternally mediated, clinically defined health outcomes in offspring; and the effective utilization of VA's medical database.

- **VA should evaluate possibilities for studying health outcomes in Vietnam-era veterans by using the existing administrative and health-services databases.**

  The original *VAO* committee recommended that the Department of Defense (DOD) and VA identify Vietnam service in the computerized index of records. Linking that information with the VA electronic medical-record and associated administrative databases, such as discharge-diagnosis and pharmacy-use records, should make it possible to assemble epidemiologic information on common health conditions for evaluation of possible associations with military service in Vietnam. Particular attention should be paid to the feasibility of conducting epidemiologic studies of conditions that have been noted to be of special interest but on which the current evidence is inadequate or insufficient to determine whether there is an association with herbicide exposure (such as COPD, brain cancer, tonsil cancer, melanoma, and Alzheimer disease). For very uncommon health outcomes, a case–control design would probably be most appropriate.

  VA could possibly more effectively utilize its medical database, particularly if there is concern regarding a perceived conflict of interest in surveying its own databases, by involving external analysts. For example, an independent panel could be commissioned to identify and prioritize database information that would aid the VAO committee in fulfilling its charge to Congress. Alternatively or in addition, VA could establish an external advisory group that could recommend the most efficient mechanisms for mining the medical database information, which could include, but not be limited to, issuing requests for proposals (RFPs) for the conduct of analytic studies related to specific health outcomes of interest.

  Finally, as noted in *Update 2008*, data related to the distribution of claims that have been filed by Vietnam veterans could be very informative. Although applications for compensation and appeals constitute a nonrepresentative, self-selected sample that is influenced by which conditions are already judged to be service-related, an effort to use existing VA information should include a more systematic review of the distribution of health outcomes in the database. The information that had accumulated in VA's records clearly generated a signal that motivated VA to ask prior VAO committees to make special evaluations of whether several quite specific malignancies were associated with herbicide exposure; ancillary information was adequate to enable the committees to conclude that CLL and hairy-cell leukemia belong in the category of sufficient evidence of an association, but perhaps an answer for Vietnam veterans concerning tonsil cancer will only be found by a case–control study addressing deployment status and other emerging risk factors such as viral infection.

  In general, it is the committee's conviction that improved data linkage and sharing between DOD and VA would greatly enhance the conduct of

military epidemiology and the meaningfulness of its results. The committee does endorse the efforts DOD is making to improve collection of exposure data during current deployments, so the impasses associated with missing exposure information will not impede investigations of health consequences in future veterans, as has been the case for Vietnam veterans. For optimal use, however, such DOD information on a veteran's combat experience needs to be readily connected with future medical events, much of which resides with VA.

- **Available information should be gleaned from existing cohort studies.**

In 2006, the Committee on the Disposition of the Air Force Health Study (AFHS) (IOM, 2006) recommended that all data from the AFHS be retained and suggested mechanisms by which those data could be made available to researchers. Since that time, the Institute of Medicine (IOM) Medical Follow-up Agency (MFUA) became custodian of the data and biologic specimens (PL 109-364; 120 Stat. 2290); the specimens are now in storage at the Wright-Patterson Air Force Base under the MFUA's aegis and funding has been provided for IOM to maintain and manage the materials and to make them available as a resource for research. What is required is a strong commitment by the federal government to provide sufficient funds to develop the infrastructure necessary to meet the goals of further research using this invaluable database. Moreover, dedicated funding is required so that focused analyses can be carried out by independent investigators, especially as related to the research questions that concern the present committee. The investment would be a small fraction of the $143 million invested to date in the AFHS. Such research could clarify the various issues and would reap substantial benefits in the understanding of health issues of Vietnam veterans exposed to herbicides. Comprehensive longitudinal analyses of the data collected in the various medical-cycle examinations, data on medical interventions (such as hospitalizations and emergency-department visits), data on cancer incidence, data on mortality, and other data on exposure should be conducted to investigate further some of or all of the health outcomes that may be associated with the exposures under consideration in this report; conclusions about melanoma in particular remain in limbo. Of course, distillation of existing data could be further enhanced by incorporation of new results derived by assays of the biologic samples.

Members of the Army Chemical Corps (ACC) constitute the largest cohort of Vietnam veterans exposed directly to herbicides and TCDD. They were involved in the handling and distribution of the chemicals in Vietnam. ACC veterans who reported spraying herbicides as part of their duties have been shown to have increased serum TCDD concentrations; this highly exposed population has also been shown to be at increased risk for several diseases. The population should be the focus of additional study, with new re-

sources devoted to it, because it represents our best opportunity to understand the health effects of exposure to TCDD and the herbicides used in Vietnam. The new report (Cypel and Kang, 2010) revisiting the mortality experience of this group through 2005 was valuable input to this update; similar follow-up of their morbidity profile would be extremely useful, as in resolving some of the issues concerning COPD raised by the recent publication.

Few data on the women who served in Vietnam are available. The cohort of nurses studied by Kang et al. (2000) largely exhausted the source population. The mortality study of the population (Cypel and Kang, 2008) was helpful, but additional follow-up of the health status of the group and determination of their TCDD concentrations would be worthwhile.

At the direction of Congress, the National Vietnam Veterans Readjustment Study (1986–1988) investigated primarily psychiatric sequelae in a representative cohort of about 1,600 men and women. In 2000, Congress mandated (PL 106-419) that VA assess the current physical and mental well-being of the members of that cohort. In 2001, VA contracted for the work, named the National Vietnam Veterans Longitudinal Study (NVVLS), but progress ceased within 2 years. The VA Office of Inspector General (VAOIG, 2005) ruled that "the Study was not properly, planned, procured, or managed" but directed that it be completed and that provisions be made to avoid the previous problems. Because baseline information is available on symptoms and chronic health problems in the original cohort, the committee thinks that completion of the NVVLS could generate useful information for future updates and concurs that serious consideration should be given to restarting the study. On May 5, 2011, at a hearing of the House Veterans' Affairs Committee, the chair of the VAO committee for *Update 2008* had the privilege of testifying in support of reviving the NVVLS. The committee was pleased to learn that VA has reinitiated this study.

Starting in 1978, the National Institute for Occupational Safety and Health (NIOSH) began to study US workers potentially exposed to TCDD. A total of 5,132 workers in 12 large manufacturing companies were included in the NIOSH cohort. The cohort has been a source of data extremely valuable in assessing the health effects associated with TCDD exposure. The studies have included high-quality exposure assessment, and evaluations of a wide array of health outcomes have been published. Given its value as an important source of epidemiologic data, the committee recommends that studies of the NIOSH cohort be extended.

The committee also notes that future analyses of health outcomes in those and other important study populations should be as specific as possible because generic findings, such as those for "all respiratory outcomes," are not useful in addressing the committee's charge of determining associations of herbicide exposures with specific health conditions.

- **Possible health effects in offspring following paternal exposure merit further investigation.**

  The rapidly expanding field of epigenetics is revealing the molecular basis by which environmental agents can modify gene expression without changing DNA sequence long after exposure occurs, even in subsequent generations—at least in the case of maternal exposure to certain chemicals. There is a growing body of evidence that TCDD can induce epigenetic changes in animal models, but there remains extremely limited data on the risk of paternal exposure to xenobiotics in general, and the VAO chemicals of interest in particular, resulting in adverse effects on their offspring.

  VAO committees have been monitoring studies of morphological birth defects and cancer in the offspring of exposed parents, but this committee identified two major information gaps to assessing the link between exposure of Vietnam veterans to the chemicals of interest and the development of disease in their offspring: (1) a paucity of studies of the endpoints that VAO committees have been monitoring related to paternal exposure in the absence of maternal exposure, and (2) a failure to systematically review defined clinical health conditions that are manifested later in life by the offspring. While it now appears more physiologically possible for paternal exposure to cause changes in the offspring, the last of the few publications on birth defects among the offspring of male Vietnam veterans was published before the report on the children of female Vietnam veterans (Kang et al., 2000), and none of the epidemiology studies recently reviewed by this committee assessed the role of paternal exposure in the occurrence of such effects. Thus, most of the available epidemiology studies are not relevant to the primary exposure group of concern: male Vietnam veterans. In addition, the epidemiology studies of maternal exposure and adverse effects in offspring other than morphological birth defects and cancer reviewed by this committee did not assess specific diseases in the offspring, but rather they measured physiological biomarkers that might or might not predict the potential for disease development later in life.

  Based on these information gaps, the present committee recommends renewed effort to conduct epidemiology studies on all the developmental effects in offspring that may be associated with **paternal exposure.** In addition, new studies should evaluate offspring for **defined clinical health conditions that develop later in life,** focusing on those organ systems that have shown the greatest impact following maternal exposure, including neurologic, immune, and endocrine. Lastly, while the committee recognizes that there is evidence that environmental exposures can affect subsequent generations through fetal and germ-line modifications, epidemiologic investigation designed to associate toxicant exposures to health effects manifested in **later generations** will be even more challenging to conduct than research on adverse effects on the first generation. Thus, the committee recommends

development of epidemiologic protocols to address the logistical challenge of determining whether adverse effects are being manifested in later generations as a result of paternal exposure: consideration must be given to (a) the minimum sample size needed to detect changes if present; (b) the most sensitive and reliable outcome measures that should be included; and (c) the need for animal studies to provide mechanistic insight into documented epidemiological associations. The best cohorts for revealing potential associations would be those with known, well-characterized exposure information. Another approach could be adopting a case–control approach and exploring whether information about Vietnam exposure or specific herbicide exposure could be ascertained in any of the many birth cohorts that have been established in the past several decades. To hone in on a paternal effect, however, it will be necessary to establish that the mothers did not have the opportunity for other than background exposure to the chemicals of interest.

- **Potential emergence of metabolic syndrome should be analyzed.**

  Within the study populations reviewed, the committee recognized a possible interrelationship among the reported associations of serum concentrations of DLCs with certain health outcomes, including obesity, hypertriglyceridemia, type 2 diabetes, hypertension, and ischemic heart disease. The first four of those outcomes are key criteria for the diagnosis of metabolic syndrome, and the fifth is a major consequence of it. Thus, the committee recommends that, in addition to analysis of the association of exposure to the chemicals of interest with individual health outcomes, the incidence of multiple health outcomes that define metabolic syndrome should be analyzed as a group. One cross-sectional study reviewed for this update was highly informative in that regard (Uemura et al., 2009), and use of the Ranch Hand and Army Chemical Corps cohorts for these types of analyses are recommended.

- **There is a need for epidemiology studies on the incidence of COPD and measuring immune/inflammation biomarkers of disease.**

  The committee recommends two key areas that require additional study in humans: the relationship of exposure to the chemicals of interest with (1) the incidence of COPD and (2) meaningful biomarkers of immune/inflammatory diseases.

  A recent study on Army Chemical Corps personnel reviewed by this committee reported a high risk of mortality resulting from COPD (Cypel and Kang, 2010); however, numerous factors made it difficult to interpret the strength of this association, including the lack of adjustment for smoking status, the inconsistency inherent in the diagnosis of COPD, and the likelihood of comorbidities that could contribute to death from COPD. Nonetheless, the committee was greatly concerned about the level of risk reported in this study and urges that studies be conducted to evaluate the incidence of COPD in

exposed populations, emphasizing the importance of adjusting for smoking and establishing the appropriate functional diagnosis of COPD.

In addition, the present committee recognizes that great strides have been made in recent years to elucidate the mechanisms underlying TCDD-induced changes in the immune system; specifically acknowledging that new biomarkers of immune/inflammatory disease have been identified from laboratory-based animal studies. Although various immune system biomarkers have been measured in human epidemiology studies, it is critical in the future that these biomarkers be the most predictive for risk of disease and not just those that are most readily measured. Thus, the committee urges the measurement in human studies of meaningful biomarkers of immune/inflammatory disease, such as Fox p3+ T regulatory cells, Th17 cells, and dendritic cells; interleukin 6 elevations; frequency and duration of specific types of infections; and inflammatory cytokines under resting and challenged conditions.

- **There is a need for new animal models to elucidate mechanisms of diseases and disease progression.**

  The committee believes that experimental research in the mechanisms that underlie human health outcomes (particularly cardiovascular disease, B-cell cancers, and paternally mediated effects in offspring) could provide valuable information related to the risk of disease in Vietnam veterans and their children. The development of animal models of various chronic health conditions and their progression would be useful for understanding the possible contributions of the chemicals of interest to compromise the health of aging Vietnam veterans. Specifically, determining the mechanism by which dioxin-like chemicals induce B-cell cancers and how exposure to dioxin-like chemicals alters the susceptibility to developing obesity and components of metabolic syndrome would fill important knowledge gaps. Furthermore, animal models elucidating the impact of paternal exposure on the development of disease in offspring would be very informative, particularly in identifying the timing and duration of exposure that is most critical and the susceptibility of specific organ systems to disease development in offspring later in life.

The predecessors of this committee have made similar recommendations concerning the need for additional research to resolve outstanding questions. This committee remains particularly concerned about COPD, hypertension, melanoma, tonsil cancer, Alzheimer disease, and paternally transmitted effects to offspring. In closing, the current committee notes that there has been little or no action toward implementing such investigations that would address veterans' concerns and scientific insights needed to inform decision-making by future VAO committees. Table 12-2 provides a terse summary of the committee's current priorities for future research.

TABLE 12-2 Research Needs

Relevant Chapter	Committee Research Recommendation
Chapter 4 Biologic Plausibility	• Develop new animal models to elucidate mechanisms of diseases and disease progression (particularly for cardiovascular disease, B-cell cancers, obesity and the components of metabolic syndrome, and paternally mediated effects in offspring). • Conduct toxicologic investigation of the potential for the chemicals of interest (particularly TCDD) to induce epigenetic modifications, with special attention to the capacity for paternal transmission of such effects. • Conduct more research to identify a biologic mechanism by which the chemicals of interest may cause Parkinson disease.
Chapter 5 Epidemiologic Study Populations	• Glean available information from existing cohort studies, particularly those of Vietnam veterans (Air Force Health Study, Army Chemical Corps cohort, female Vietnam veterans, National Vietnam Veterans Longitudinal Study), the National Institutes of Safety and Health and International Agency for Research on Cancer cohorts of dioxin workers, the Agricultural Health Study, and the Seveso cohort. • Link information in its electronic medical-record system, in its claims files, and in other associated administrative databases to assemble epidemiologic information on common health conditions for evaluation of possible associations with military service in Vietnam.
Chapter 6 Immune Outcomes	• Include immunologic biomarkers in future studies of other health outcomes that may involve compromised immune function as an intermediate step in the development of overt pathology.
Chapter 7 Cancer Outcomes	• Evaluate the occurrence of several neoplastic conditions (brain cancer, tonsil cancer, melanoma, and myelodysplastic syndrome) in Vietnam-era veterans by using existing VA administrative and health-services databases. • Perform a comprehensive analysis of melanoma in the entire AFHS data set to resolve ambiguity remaining in currently published results.
Chapter 8 Reproductive or Developmental Outcomes	• Conduct studies of defined clinical health conditions in mature offspring following exposure of either parent, rather than more investigations of physiological biomarkers that may merely be predictive of disease development later in life. • Develop epidemiologic protocols to address the logistical challenge of determining whether adverse effects are being manifested in later generations as a result of paternal exposure (in the absence of maternal exposure).
Chapter 9 Neurologic Outcomes	• Evaluate possibilities for studying neurodegenerative outcomes (such as amyotrophic lateral sclerosis and Alzheimer disease) in Vietnam-era veterans by using the existing VA administrative and health-services databases. • Conduct investigation relating PD incidence to exposure in the Vietnam-veteran population, including studies of biologic plausibility.
Chapter 10 Cardiovascular Outcomes	• Analyze the emergence of the individual health outcomes constituting metabolic syndrome in association with exposure to the chemicals of interest. • Analyze the incidence of the multiple health outcomes that define metabolic syndrome as a group.
Chapter 11 Other Health Outcomes	• Conduct epidemiology studies on the incidence of COPD and measure meaningful immune/inflammation biomarkers of disease. • Study the incidence of COPD among Vietnam-era veterans by using the existing VA administrative and health-services databases.

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[1]Throughout the report the same alphabetic indicator following year of publication is used consistently for the same article when there were multiple citations by the same first author in a given year. The convention of assigning the alphabetic indicator in order of citation in a given chapter is not followed.

Appendix A

Agendas of Public Meetings Held by the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Eighth Biennial Update)

FIRST PUBLIC MEETING

Monday, September 27, 2010
Keck Center, Room 105
500 Fifth Street, NW
Washington, DC 20001

Presentations

- **Welcome; Goals and Conduct of the Public Meeting; Introduction of Committee**
  Mary Walker, Committee Chair

- **Charge to the Committee**
  Victoria Cassano, MD, US Department of Veterans Affairs

- **IOM Veterans and Agent Orange Reports: A Brief History**
  David Butler, PhD, Institute of Medicine

- **Clinical Observations Concerning Autoimmune Conditions in Veterans**
  Margaret Kruckemeyer, RN/ARNP-C, Rehab Nurse Practitioner, Dayton VA Medical Center

- **Autoimmune Mixed Connective Tissue Disease (MCTD) following Extensive Exposure to Agent Orange during Service on Guam**
  MSgt LeRoy G. Foster, Ret USAF

- **Activities Involving the Vietnamese Population**
  Vaughan C. Turekian, PhD, Chief International Officer, AAAS and representative to US–Vietnam Dialogue Group on Agent Orange/Dioxin

- **Speaking on Behalf of Vietnam Veterans**
  Rick Weidman, Executive Director for Policy and Government Affairs, Vietnam Veterans of America

SECOND PUBLIC MEETING

Thursday, November 4, 2010
Hotel Allegro
171 West Randolph Street
Chicago, IL 60601

Presentations

- **Welcome; Goals and Conduct of the Public Meeting; Introduction of Committee**
  Mary Walker, Committee Chair

- **Parkinson Disease**
  Steve Fiscus
  Mike Trok

- **Oxidative Stress: Parkinson Disease and Birth Defects**
  Alan Oates, US Military Veterans with Parkinson Disease

- **Birth Defects in Offspring of a Father Who Served in the Republic of Vietnam (besides Spina Bifida)**
  John Michel, Military Order of the Purple Heart

- **Problems Faced by Grandchildren of Vietnam Veterans**
  Ray Parrish

- **Myelodysplastic Syndromes (MDS)**
  Robert Macfarlane

- **My Husband's Story**
  Presented by Bob Macfarlane on behalf of Lillian Mooradian

- **MDS and Agent Orange**
  Presented by Bob Macfarlane on behalf of Douglas Nelson

- **My MDS and VA**
  Larry Sauger

- **Classification of MDS as a Cancer in Vietnam-Era Veterans**
  John Herbert

- **Thyroid Risk and Agent Orange**
  Roger McGill, Vietnam Veteran

- **Personal Health**
  Lupe Alviar, Jr., Vietnam Veterans of America

- **Experience with Inter-Related Health Issues Due to Dioxin Exposure**
  Kurtis Borre

- **What Are the Effects of Agent Orange on a Three-Tour Veteran?**
  Ronald Mattox

THIRD PUBLIC MEETING

Thursday, December 16, 2010
Hotel Andaluz
125 2nd Street, NW
Albuquerque, NM 87102

Presentations

- **Welcome; Goals and Conduct of the Public Meeting; Introduction of Committee**
  Mary Walker, Committee Chair

- **Research Activities Concerning Herbicide Contamination in Vietnam and Health of the Vietnamese Population**
  Arnie Schecter

- **Glioblastomas and Herbicide Exposure**
  Eileen Whitacre Perkins

FOURTH PUBLIC MEETING

Wednesday, February 23, 2011
Wyndham Phoenix
50 East Adams Street
Phoenix, AZ 85004

Presentations

- **Welcome; Goals and Conduct of the Public Meeting; Introduction of Committee**
  Mary Walker, Committee Chair

- **My Husband's Alzheimer's**
  Jan Hughes

- **Questions and Discussion with Paul Enright**
  Paul Enright, University of Arizona–Mel and Enid Zuckerman College of Public Health

Appendix B

Short-Term Adverse Health Responses

As was indicated to be the intention of the committee responsible for *Update 2008*, the committee for *Update 2010* has removed chloracne, porphyria cutanea tarda (PCT), and early-onset peripheral neuropathy from the body of these Veterans and Agent Orange (VAO) reports. The three conditions that occur in temporal proximity to exposure have little relevance for new claims from Vietnam veterans, and there has been minimal new evidence since they were classified as having evidence of an association with herbicide exposure

The three conditions have long been recognized by the Department of Veterans Affairs as presumptively related to service in Vietnam. Consequently, the committee wants to provide easy access to the body of biomedical evidence on which these decisions were made by retaining the information distilled in this appendix and in the corresponding appendixes in future volumes in the VAO series.

CHLORACNE

Chloracne is a skin disease that is characteristic of exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and other diaromatic organochlorine chemicals. It shares some pathologic processes (such as the occlusion of the orifice of the sebaceous follicle) with more common forms of acne (such as acne vulgaris), but it can be differentiated by the presence of epidermoid inclusion cysts, which are caused by proliferation and hyperkeratinization (horn-like cornification) of the epidermis and sebaceous gland epithelium. Although chloracne is typically distributed over the eyes, ears, and neck, it can also occur on the trunk, genitalia, and buttocks of chemical-industry workers exposed to TCDD (Neuberger et al., 1998). It is resistant to acne treatments, but it usually regresses.

Chloracne has been used as a marker of exposure in epidemiologic studies of populations exposed to TCDD and related chemicals. It is one of the few findings in humans that are consistently associated with such exposure, and it is a well-validated indicator of high-dose exposure to TCDD and related chemicals (Sweeney et al., 1997/98). If chloracne occurs, it appears shortly after the chemical exposure, not after a long latent period; therefore, new cases of chloracne among Vietnam veterans would not be the result of exposure during the Vietnam War. It should be noted that absence of chloracne does not necessarily indicate absence of substantial exposure to TCDD, as is apparent from studies of people who had documented exposure to TCDD after the Seveso incident (Baccarelli et al., 2005a), nor is there necessarily a correlation between serum TCDD concentration and the occurrence or severity of chloracne. Susceptibility to the development of chloracne varies among individuals.

Conclusions from *VAO* and Previous Updates

The committee responsible for *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* (referred to as *VAO*; IOM, 1994) determined that there was sufficient evidence of an association between exposure to at least one chemical of interest (TCDD) and chloracne. Additional information available to the committees responsible for *Veterans and Agent Orange: Update 1996* (IOM, 1996), *Update 1998* (IOM, 1999), *Update 2000* (IOM, 2001), *Update 2002* (IOM, 2003), *Update 2004* (IOM, 2005), and *Update 2006* (IOM, 2007) has not modified that conclusion.

Even in the absence of full understanding of the cellular and molecular mechanisms that lead to the disease, several notable reviews (Panteleyev and Bickers, 2006; Sweeney and Mocarelli, 2000) have deemed the clinical and epidemiologic evidence of dioxin-induced chloracne to be strong. The occupational epidemiologic literature has many examples of chloracne in workers after reported industrial exposures (Beck et al., 1989; Bond et al., 1987, 1989a,b; Cook et al., 1980; Goldman, 1972; May, 1973, 1982; Oliver, 1975; Pazderova-Vejlupkova et al., 1981; Poland et al., 1971; Suskind and Hertzberg, 1984; Suskind et al., 1953; Zober et al., 1990). With relative-risk estimates as high as 5.5 in exposed workers compared with referent nonexposed workers, Bond et al. (1989a) identified a dose–response relationship between probable exposure to TCDD and chloracne. Not everyone exposed to relatively high doses develops chloracne, and some with lower exposure may acquire it (Beck et al., 1989).

Almost 200 cases of chloracne were recorded in those residing in the vicinity of the accidental industrial release of dioxin in Seveso, Italy. Most cases occurred in children, particularly in people who lived in the highest-exposure zone, and most cases resolved within 7 years (Assennato et al., 1989a,b; Caramaschi et al., 1981; Mocarelli et al., 1991). No cases of chloracne were identified in conjunc-

tion with the nonextreme environmental dioxin contamination at Times Beach, Missouri (Webb et al., 1987).

Exposures of Vietnam veterans were substantially lower than those observed in occupational studies and in environmental disasters, such as the one in Seveso. The long period since the putative exposure has imposed methodologic limitations on studies of Vietnam cohorts for chloracne. Nonetheless, the Vietnam Experience Study (CDC, 1988) found that chloracne was self-reported more often by Vietnam veterans than by Vietnam-era veterans (odds ratio [OR] = 3.9). An excess incidence was also found in Vietnam vs era veterans among subjects who were physically examined (OR = 7.3). In comparison with a nonexposed group, Air Force Ranch Hand personnel potentially exposed to Agent Orange reported a significant excess of acne (OR = 1.6) (Wolfe et al., 1990), but no cases of chloracne or postinflammatory scars were found on physical examination 20 years after possible herbicide exposure (AFHS, 1991b).

Biologic Plausibility

Previous updates have reported that chloracne-like skin lesions have been observed in several animal species in response to exposure to TCDD but not to purified phenoxy herbicides. Data accruing over the past several decades demonstrated that TCDD alters differentiation of human keratinocytes, and more recent studies have illuminated how. Geusau et al. (2005) found that TCDD accelerates the events associated with early differentiation but also obstructs completion of differentiation. Panteleyev and Bickers (2006) proposed that the major mechanism of TCDD induction of chloracne is activation of the stem cells in the basal layer of the skin to differentiate and inhibition of their ability to commit fully to a differentiated status. Ikuta et al. (2010) have investigated the expression of B-lymphocyte maturation protein 1 (Blimp1) in epidermal keratinocytes and sebocytes in mice after induction of the aryl hydrocarbon receptor (AHR). Recent work with a constitutively activated form of the AHR implicated additional inflammation-related mechanisms by which TCDD exposure may lead to chloracne (Tauchi et al., 2005). The data provide a biologically plausible mechanism for the induction of chloracne by TCDD.

Synthesis

No epidemiologic data in the past decade have refuted the conclusion of prior VAO committees that the evidence of an association between exposure to dioxin and chloracne is sufficient. The 2004 poisoning case of Ukrainian politician Victor Yuschenko has provided a high-profile instance that supports this condition as a response to high-level exposure to TCDD, and the careful monitoring of his case has demonstrated the course of chloracne's resolution in conjunction with subsiding serum concentrations (Sorg et al., 2009). The formation of chlor-

acne lesions after administration of TCDD has been observed in some species of laboratory animals.

Conclusion

On the basis of numerous epidemiologic studies of occupationally and environmentally exposed populations and supportive toxicologic information, previous VAO committees have consistently concluded that there is sufficient evidence of an association between exposure to at least one chemical of interest and chloracne. Because TCDD-associated chloracne becomes evident shortly after exposure, there is no risk of new cases long after service in Vietnam. Given the established relationship of an association between TCDD and chloracne and the long period that has elapsed since service in Vietnam, the present committee concludes that the emergence of additional biologic or epidemiologic evidence that would merit review and deliberation by later VAO committees is unlikely.

PORPHYRIA CUTANEA TARDA

Porphyrias are uncommon disorders caused by deficiencies of enzymes involved in the pathway of biosynthesis of heme, the iron-containing nonprotein portion of the hemoglobin molecule. PCT, the most common of the porphyrias, is a heterogeneous group of disorders caused by a deficiency of a specific enzyme, uroporphyrinogen decarboxylase. It, can be inherited but usually is acquired. Type I PCT, which accounts for 80–90% of all cases, is an acquired disease that typically becomes evident in adulthood. It can occur spontaneously but usually occurs in conjunction with environmental factors, such as alcohol consumption, exposure to estrogens, or use of some medications.

The most important clinical finding in PCT is cutaneous photosensitivity. Sensitivity to sunlight is thought to result from the excitation of excess porphyrins in the skin by long-wave ultraviolet radiation, which leads to cell damage. Fluid-filled vesicles and bullae develop on sun-exposed areas of the face and on the dorsal surfaces of the hands, feet, forearms, and legs. Other features include hypertrichosis (excess hair) and hyperpigmentation (increased pigment), especially on the face. People with PCT have increased porphyrins in the liver, plasma, urine, and stools. Iron, estrogens, alcohol, viral hepatitis, and chlorinated hydrocarbons can aggravate the disorder. Iron overload is almost always present in people who have PCT.

Conclusions from *VAO* and Previous Updates

On the basis of strong animal studies and case reports demonstrating TCDD-induced PCT and resolution after cessation of exposure, the committee respon-

sible for *VAO* determined that there was sufficient evidence of an association between exposure to TCDD and PCT in genetically susceptible people.

Epidemiologic studies of occupational populations have indicated inconsistent associations between the chemicals of interest and increased urinary uroporphyrin. Bleiberg et al. (1964) reported increased urinary uroporphyrin in 11 of 29 workers in a factory that manufactured 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and the manifestation of some clinical evidence of PCT in three of them. In a follow-up study of the same facility 6 years later, no abnormalities in urinary porphyrins were observed (Poland et al., 1971). Calvert et al. (1992) reported no difference in porphyrinuria or the occurrence of PCT between 281 workers in the National Institute for Occupational Safety and Health (NIOSH) cohort who were involved in the production of trichlorophenol and were exposed to TCDD and 260 nonexposed workers. Serum TCDD concentration was not associated with uroporphyrin or coproporphyrin concentrations.

Among people who were exposed to TCDD as a result of the 1976 chemical-plant explosion in Seveso, Italy, clinical PCT was observed only in a brother and a sister who had a mutant enzyme that confers susceptibility in the heterozygous state. In 1977, 60 Seveso residents were tested for increased porphyrins, and 13 had secondary coproporphyrinuria; increased concentrations persisted in only three cases that were thought to be due to liver damage and alcohol consumption (Doss et al., 1984). In the Quail Run mobile-home park in Missouri, residents exposed to dioxin as a result of the spraying of waste oil contaminated with TCDD were found to have higher urinary uroporphyrins than controls, but no cases of clinical PCT were diagnosed (Hoffman et al., 1986; Stehr-Green et al., 1987).

The baseline study of the US Air Force Ranch Hands (AFHS, 1984) showed no difference in uroporphyrin or coproporphyrin concentrations in urine between Ranch Hands and controls. There were no indications of the clinical appearance of PCT in Ranch Hands. Followup studies of the Ranch Hand cohort revealed that mean uroporphyrin was greater in the comparison group than in the Ranch Hands, whereas mean coproporphyrin was higher in Ranch Hands. The clinical significance of the small differences between the Ranch Hands and the comparison groups was uncertain.

The committee responsible for *Update 1996* considered three additional nonpositive citations of populations that had substantial exposure to TCDD. Jung et al. (1994) presented porphyrin data on former workers in a German pesticide plant that had manufactured 2,4-D and 2,4,5-T. Of 170 men tested, 27 had present or past chloracne. The study found no difference in porphyrin concentrations between subjects with and without chloracne. There was also no relationship between abnormal results of liver-function tests or porphyrin concentrations and the presence of chloracne. Additionally, there was no relationship between porphyrin concentrations in urine, red blood cells, or plasma and TCDD concentrations in adipose tissue. Three cases of chronic hepatic porphyria (none with overt PCT

and none with chloracne) were identified—a number that did not exceed the expected prevalence in this population. Von Benner et al. (1994) found no indication of clinical porphyria in self-referred workers at six other German chemical plants. Another report on the NIOSH cohort (Calvert et al., 1994) was negative. On the basis of the cumulative findings, the committee responsible for *Update 1996* concluded that there was only limited or suggestive evidence of an association. The committees for later updates have not changed the revised conclusion.

Because PCT is manifested shortly after exposure to TCDD, new cases of PCT attributable to exposure during the Vietnam War are not expected to occur.

Biologic Plausibility

PCT has not been exactly replicated in animal studies on the effects of TCDD although other porphyrin abnormalities have been reported. Administration of TCDD to mice results in an accumulation of uroporphyrin that occurs in a manner that requires the AHR, cytochrome P450 1A1 (CYP1A1), and CYP1A2 (Robinson et al., 2002; Smith et al., 2001; Uno et al., 2004), but the underlying mechanism of action has not been fully illuminated (Smith and Chernova, 2009; Smith and Elder, 2010).

Synthesis

No epidemiologic data have emerged in the last decade that refute the conclusion of previous VAO committees that there is limited or suggestive evidence of an association between the chemicals of interest and PCT.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is limited or suggestive evidence of an association between exposure to at least one chemical of interest and PCT. The occurrence of PCT is rare and may be influenced by genetic predisposition in people who have low concentrations of protoporphyrinogen decarboxylase. Because TCDD-associated changes in porphyrin excretion become evident shortly after exposure, there is no risk that new cases will occur long after service in Vietnam. Given the recognized association between TCDD and porphyrin excretion and the long period that has elapsed since service in Vietnam, the committee concludes that the emergence of additional biologic and epidemiologic evidence that would merit review and deliberation by later VAO committees is unlikely.

EARLY-ONSET PERIPHERAL NEUROPATHY

Since *Update 1996*, VAO committees have partitioned their consideration of peripheral neuropathy into two categories: early-onset (implicitly transient)

peripheral neuropathy and chronic peripheral neuropathy. Primarily on the basis of reports of short-term health effects after industrial accidents, the committee concluded in 1996 that there was limited or suggestive evidence of an association between exposure to the chemicals of interest and "acute and subacute" neuropathy, which was redesignated early-onset transient peripheral neuropathy by the committee responsible for *Update 2004*. The present committee recognized the imprecision in the nomenclature that has been used to characterize the type of peripheral neuropathy that is regarded as service-connected. The diagnosis in question is, in fact, contingent on the *proximity of its occurrence to the time of exposure*, rather than on the transitory nature of the adverse outcome. Clinically, in cases of an immediate response of peripheral neuropathy after toxicant exposure, stabilization or improvement is the rule after exposure ends. However, recovery may not be complete; the degree of recovery can depend on the severity of the initial deficits and the particular exposure. Furthermore, there is a possibility of "subclinical" effects, and a person might be unaware of symptoms although evidence of nerve dysfunction can be found through detailed neurologic examination or electrodiagnostic testing. Thus, the committee chose to delete the word *transient* to recognize that symptoms of early-onset peripheral neuropathy may be protracted and that recovery from these symptoms may be incomplete.

The information about peripheral neuropathy presented in this appendix demonstrates that this outcome may occur soon after exposure to extremely high concentrations of dioxin. In addition, this appendix addresses the evidence that, in populations with members who experience early-onset peripheral neuropathy (that is, during or shortly after dioxin exposure), some may continue to manifest the problem long after exposure has ceased, and this would show that early-onset peripheral neuropathy is not necessarily transient.

Conclusions from *VAO* and Previous Updates

Several occupational studies have evaluated whether herbicide exposure or production may lead to early-onset neuropathy. In March 1949, an explosion occurred in a reactor vessel at a chemical plant in Nitro, West Virginia, where 2,4,5-T was being produced. Many workers reported health effects (toxic hepatitis, increased serum lipids, and central nervous system involvement), including a severe acute neuropathy in four workers with chloracne (Ashe et al., 1949, 1950). Thirty years later, an attempt was made to identify workers who had been exposed during that accident and workers who may have been chronically exposed from 1948 through 1969 (Suskind and Hertzberg, 1984). Neurologic examination and nerve-conduction studies did not demonstrate abnormalities compared with a cohort of unexposed controls; however, the procedure for obtaining controls did not ensure equivalence. It is unclear whether the four subjects who had acute neuropathy were included in this effort.

In April 1979, chlorinated dibenzo-*p*-dioxin contamination was found in a community in Arkansas that was close to a plant where 2,4,5-T and 2,4-D had

been produced since 1957. Fifty-five workers of that plant who had no history of diabetes or alcohol abuse were identified from the total workforce; these subjects underwent neurologic examination and nerve-conduction studies (Singer et al., 1982). Both median motor and sural sensory nerve-conduction studies showed significantly lower conduction velocity in the workers from the plant than in control subjects.

Other industrial accidents have also suggested a link between compounds of interest and early-onset neuropathic symptoms, which persisted in some people. Jirasek et al. (1974) studied 55 of 80 workers who complained of a variety of symptoms after chronic exposure to 2,4,5-T at a manufacturing facility in the Czech Republic; of the 55 workers, 17 had physical examinations suggestive of neuropathy that was said to have been confirmed with electromyographic abnormalities. Follow-up of 44 of the 55 poisoned workers was conducted 10 years after exposure had ceased; about 30% of them were reported to have continued neuropathic symptoms (Pazderova-Vejlupkova et al., 1981). More recently, Urban et al. (2007) evaluated the long-term sequelae of subjects who developed neuropathy after the original exposure. Subjects had increased serum TCDD concentrations more than 30 years after exposure, and evidence of continued neuropathy was noted in 9 of 15 subjects who were available for study.

Acute neuropathic symptoms were reported after the Seveso accident, and persistent signs were noted. Gilioli et al. (1979) evaluated 35 subjects who had been exposed during the accident and noted abnormalities in a variety of neurophysiologic measures compared with age-matched controls 2 years after the exposure. However, it is unclear how the exposed subjects were selected for study. In a more complete survey, Boeri et al. (1978) studied 470 subjects from two exposure zones about a year after the accident and found a higher incidence of neurophysiologic abnormalities than in unexposed controls; the residents of the zone of greater exposure were more severely affected than those of the less exposed zone. The same group (Filippini et al., 1981) found increased prevalence of peripheral neuropathy in residents who had indicators of exposure compared with those who did not (RR = 2.6, 95% CI 1.0–7.2, for those with choracne; RR = 3.6, 95% CI 1.3–10.2, for those with increased hepatic enzymes) when they were evaluated 21 months after the accident. Improvement may have occurred since the accident. Assennato et al. (1989a,b) studied 193 exposed residents of the area 9 years after the accident and did not find neurophysiologic abnormalities. However, the number of residents in the group who originally complained of neuropathic symptoms was not discussed. Similiarly, 6 years after the accident, Barbieri et al. (1988) examined 153 residents who had developed chloracne. World Health Organization critieria for neuropathy were not fulfilled for any subjects, but there was a statistically significant increase in neurophysiologic abnormalities compared with those in unexposed age-matched controls.

There have been a number of case reports of exposure-associated early-onset neuropathy. Goldstein et al. (1959) reported the cases of three patients seen at the Mayo Clinic who had acute weakness and sensory loss demonstrated to be due to

peripheral neuropathy; symptoms occurred within hours of an exposure to 2,4-D that included sufficient skin contact for clothes and skin to be wet. All three patients recovered incompletely: in one of the patients, a cerebrospinal fluid (CSF) examination was normal except for minimally increased protein. Todd (1962) reported another case of neuropathy that occurred about 4 days after 2,4-D exposure, again in sufficient quantities to cause large areas of skin to be wet from the herbicide. Clinical examination demonstrated a sensory motor polyneuropathy; CSF examination showed slightly increased protein but was otherwise normal. The patient recovered substantially but not completely over 2 years. Finally, Berkley and Magee (1963) reported a case of a 39-year-old man who had symptoms of acute neuropathy that progressed to inability to walk starting 4 days after 2,4-D exposure; CSF analysis was completely normal, including normal protein concentrations, and he recovered nearly completely over the course of 8 months.

Case reports do not provide conclusive evidence of causal relationships, but the cases discussed above showed a close temporal relationship between high exposure to 2,4-D and neuropathy. The most likely non–toxicant-related acute neuropathy is Guillain-Barré syndrome; however, this syndrome is associated with characteristic findings on clinical neurophysiologic examination and highly increased protein in CSF. In the three cases above that had CSF evaluation, protein concentrations were either normal or increased to a minimal extent not consistent with Guillain-Barré syndrome. In addition, patients who had clinical neurophysiologic studies also showed abnormalities not consistent with Guillain-Barré. Thus, it seems likely that the cases represent the results of 2,4-D exposure.

Biologic Plausibility

Neuronal cell cultures treated with 2,4-D showed decreased neurite extension associated with intracellular changes, including a decrease in microtubules, inhibition of the polymerization of tubulin, disorganization of the Golgi apparatus, and inhibition of ganglioside synthesis (Rosso et al., 2000a,b). Those mechanisms are important for maintaining synaptic connections between nerve cells and supporting the mechanisms involved in axon regeneration during recovery from peripheral neuropathy. Grahmann et al. (1993) and Grehl et al. (1993) reported observations of electrophysiologic and pathologic abnormalities, respectively, in the peripheral nerves of rats treated with TCDD. When the animals were sacrificed 8 months after exposure, there were pathologic evidence of axonal nerve damage and histologic findings typical of toxicant-induced injury. Those results constitute evidence of the biologic plausibility of an association between exposure to the chemicals of interest and peripheral neuropathy.

Conclusions

On the basis of studies of health effects after industrial accidents and the well-documented cases reported above, VAO committees since that responsible

for *Update 1996* have concluded that there is limited or suggestive evidence of an association between exposure to the chemicals of interest and early-onset peripheral neuropathy. Inasmuch as new data on this subject, especially with regard to Vietnam veterans, are unlikely to emerge, the present committee reaffirms that finding.

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Appendix C

Clarification of Cancer Groupings Used in Reporting Results, with Correspondence to NIOSH Cause-of-Death Codes and ICD Codes for Cancers

In response to a request from the Department of Veterans Affairs, the committee responsible for *Update 2006* prepared Table C-1 to demonstrate how conclusions provided for the full range of cancer types and to clarify into which groupings any specific cancer diagnosis falls. The committee for *Update 2010* notes that it reframed its overview of lymphohematopoietic neoplasms according to the World Health Organization classification system (WHO, 2008), which partitions these disorders first according to the lymphoid or myeloid lineage of the transformed cells rather than as lymphomas or leukemias; this emphasizes the close etiologic relationship of chronic lymphocytic leukemia and hairy-cell leukemia with Hodgkin and non-Hodgkin lymphomas and with the neoplasm multiple myeloma and its related condition AL amyloidosis.

The major portion of evidence compiled for review in the *Veterans and Agent Orange* (*VAO*) series comes from cohort studies, primarily of mortality but some of incidence. Other data have been generated by case–control studies, which follow the only design amenable to studying very infrequent or very specific health outcomes. How researchers are able to group, analyze, and report their findings is influenced by the distribution of cases that they observe, so the data that VAO committees have had available for review reflect mortality experience at a level of specificity concordant with statistical analysis.

The *International Classification of Diseases* (ICD) system is used by physicians and researchers around the world to group related diseases and procedures so that morbidity and mortality information can be classified for statistical purposes in a standard form amenable to data storage and retrieval. It is a comprehensive hierarchic system that permits great detail but can be collapsed into broad categories. Codes mentioned in VAO reports are stated in terms of ICD,

TABLE C-1 Mapping of Groupings of Malignant Neoplasms That Are the Subjects of Conclusions in the *Veterans and Agent Orange* Series with ICD-9 Codes

NIOSH Category for Cause of Death			"VAO Characterization of Grouping"[a]	
Major	**Minor**	**NIOSH Groupings of Cancer Sites**	**Subsites**	**ICD-9 Codes**
02		Buccal cavity and pharynx	"Oral, nasal, and pharyngeal"	
	004	Lip		140
	005	Tongue		141
	006	Other parts of buccal cavity		
			Salivary glands	142
			Floor of mouth	144
			Gum and other mouth	143, 145
	007	Pharynx		
			Oropharynx	146
			Tonsil	146.0–146.2
			Nasopharynx	147
			Hypopharynx	148
			Other buccal cavity and pharynx	149
				(160 = nasal below)
03		Digestive organs and peritoneum		
	008	Esophagus	**"Esophagus"**	150
	009	Stomach	**"Stomach"**	151
	010	Intestine except rectum	**"Colorectal"**	
			Small intestine	152
			Colon (large intestine)	153
	011	Rectum		154
	012	Biliary passages, liver, and gall bladder	**"Hepatobiliary"**	
			Liver and intrahepatic bile ducts	155
			Gallbladder and extrahepatic bile ducts	156
	013	Pancreas		157

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TABLE C-1 Continued

NIOSH Category for Cause of Death			"VAO Characterization of Grouping"[a]	
Major	**Minor**	**NIOSH Groupings of Cancer Sites**	**Subsites**	**ICD-9 Codes**
	014	Retroperitoneum and other and unspecified digestive organs		158–159
04		Respiratory system	**"Respiratory"**	
	015	Larynx	**"Larynx"**	161
	016	Trachea, bronchus, and lung	**"Lung"**	162
			Trachea	162.0 (there is no ICD 162.1)
			Lung and bronchus	162.2–162.9
	017	Pleura		163
	018	Other respiratory		
			Nasal cavity, middle ear, and accessory sinuses	(160, above with oral and pharyngeal)
			Thymus, heart, and mediastinum	164 (164.0, below with endocrine; 164.1, below with soft tissue sarcoma)
			Other respiratory, unspecified	165 (discontinuity with ICD codes)
05	019	Breast (male and female)	**"Breast"**	174, 175
06		Female genital organs	**"Female reproductive"**	
	020	Cervix uteri		180
	021	Other unspecified parts of uterus		179, 181, 182
			Uterus, parts unspecified	179
			Placenta	181
			Body of uterus	182
	022	Ovary, fallopian tube, and broad ligament		183
			Ovary	183.0 (there is no ICD 183.1)
			Fallopian tube and other uterine adnexa	183.2–183.9

	023	Other female genital organs		184
07		Male genital system		185, 186
	024	Prostate	**"Prostate"**	185
	025	Testis	**"Testicular"**	186
		Penis and other male genital organs	[for NIOSH in minor group 036]	187
08		Urinary system		
	026	Kidney (including renal pelvis and ureter)	**"Renal"**	189.0–189.2
	027	Bladder and other urinary organs	**"Urinary bladder"**	188, 189.3–189.9
			Bladder	188
			Urethra, paraurethral glands, other and unspecified urinary	189.3–189.9
				(discontinuity with ICD codes)
09		Other and unspecified sites		
	028	Bone ("and articular cartilage" in ICD nomenclature)	**"Bone and joint"**	170
	029	Melanoma	**"Melanoma"**	172
	030	Other malignant skin neoplasm	**"Non-melanoma skin"**	173
	031	Mesothelioma		No codes (new minor code, above with lung)
	032	Connective ("and other soft" in ICD nomenclature) tissue	**"Soft-tissue sarcoma"**	171
			(heart)	(164.1)
	033	Brain and other parts of nervous system (ICD "soft tissue" includes peripheral nerves and autonomic nervous system)	**"Brain"**	191–192
	034	Eye		190
	035	Thyroid		193
			(thymus)	164.0
	036	Other and unspecified sites	Other endocrine cancers	194
			Other and ill-defined sites	195
			Stated or assumed to be secondary of specified sites	196–198

cointinued

TABLE C-1 Continued

NIOSH Category for Cause of Death			"VAO Characterization of Grouping"[a]	
Major	**Minor**	**NIOSH Groupings of Cancer Sites**	**Subsites**	**ICD-9 Codes**
			Site unspecified	199
10		Lymphatic and hematopoietic tissue		
		Lymphoma		
	037	**Hodgkin disease**		201
	038	**Non-Hodgkin lymphoma**		200, 202 (excluding 202.4), 273.3
	039	**Multiple myeloma**		203 (excluding 203.1)
	040	Leukemia and aleukemia	**"Leukemia (other than chronic B-cell leukemias)"**	204–208
		Lymphocytic	(primary grouping now with other neoplasms of lymphocytic origin, lymphomas and multiple myeloma)	
			Acute lymphocytic	204.0
			"Chronic lymphocytic (including hairy cell leukemia)"	204.1
			Other lymphocytic	202.4; 204.2–204.9
		Myeloid (granulocytic)		
			Acute myeloid	
			Acute	205.0
			Acute erythremia and erythroleukemia	207.0
			Megakaryocytic leukemia	207.2
			Chronic myeloid	205.1
			Other myeloid	205.2–205.3, 205.8–205.9
		Monocytic		
			Acute monocytic	206.0
			Chronic monocytic	206.1
			Other monocytic	206.2–206.9

Other leukemia		
	Other acute	208.0
	Other chronic	207.1, 208.1
	Aleukemic, subleukemia and "not otherwise specified"	203.1, 207.2, 207.8, 208.2–208.9

[a]**Boldface cancer (sub)site:** most comprehensive grouping for which a conclusion has been drawn.

Version 9 (ICD-9). ICD-7, ICD-8, and ICD-9 were in effect for deaths that occurred in 1960–1967, 1968–1978, and 1979–1998, respectively; the differences among them are fairly subtle. Although ICD-10, which went into effect for coding causes of deaths that occurred from 1999 on, appears radically different from the earlier versions, it corresponds in large part to basically the same disease entities (see Table C-2). To date, most published epidemiologic studies considered in the VAO series have been related to health outcomes that occurred and were encoded before ICD-10 went into effect.

Since 1983, the National Institute for Occupational Safety and Health (NIOSH) has maintained software for generating standardized expectations, as derived from US mortality data assembled by the National Center for Health Statistics, for ICD-encoded mortality datasets. An article by Robinson et al. (2006) discusses revisions to that standard software to incorporate deaths coded according to ICD-10 and includes conversions and equivalencies between ICD-7, -8, -9, and -10 for 119 exhaustive categories for cause of death. Codes for malignant neoplasms span the ICD-9 range 140.0–208.9, NIOSH's major categories 02–10, or NIOSH's more specific minor categories 004–040.

The NIOSH death codes for neoplasms provide comprehensive scaffolding for organizing the committee's reviews and conclusions by cancer type that is somewhat simpler than ICD classifications, but maps completely to the ICD system as it has evolved. Because the NIOSH system has been used to mediate analysis of many sets of cohort data, its groupings correspond quite closely with the published research findings available for review by VAO committees. In general cohort studies, one is unlikely to encounter results on more specific groupings than NIOSH's minor categories.

As discussed in Chapter 2, this committee has not framed its conclusions strictly in terms of ICD codes, but the ICD system has been a valuable tool for the work of VAO committees. There can be coding errors on hospital records or death certificates, but when researchers present their results labeled with ICD codes, there can be little ambiguity about what they intended. When their most definitive indication is something like "respiratory cancers," however, there can be uncertainty about where the evidence should be considered. In such cases, the committee has done its best to follow the hierarchy laid out in Table C-1.

As indicated above, many of the studies reviewed by the committee use or were written at a time when ICD-9 was in place. Accordingly, ICD references in this report use that scheme. ICD-10 began to be implemented in the United States in 1999. It differs from ICD-9 in level of detail (about 8,000 categories vs about 5,000 in ICD-9) and nomenclature (alphanumeric vs the numeric codes of ICD-9); additions and modifications were also made with regard to some coding rules and the rules for selecting an underlying cause of death (Anderson et al., 2001). Table C-2 lists the ICD-9 and ICD-10 codes for the various forms of malignant neoplasm addressed in this report. In situ neoplasms, benign neoplasms,

TABLE C-2 Surveillance, Epidemiology, and End Results (SEER) Program Malignant Neoplasm Site Groupings for ICD-9 and ICD-10

Cancer Site	ICD-9 Codes	ICD-10 Codes
Buccal cavity and pharynx		
Lip	140.0–140.9	C00.0–C00.9
Tongue	141.0–141.9	C01, C02.1–C02.9
Salivary glands	142.0–142.9	C07, C08.0–C08.9
Floor of mouth	144.0–144.9	C04.0–C04.9
Gum and other mouth	143.0–143.9, 145.0–145.6, 145.8–145.9	C03.0–C03.9, C05.0–C05.9, C06.0–C06.9
Nasopharynx	147.0–147.9	C11.1–C11.9
Tonsil	146.0–146.2	C09.0–C09.9
Oropharynx	146.3–146.9	C10.1–C10.9
Hypopharynx	148.0–148.9	C12, C13.0–C13.9
Other buccal cavity and pharynx	149.0–149.9	C14.0–C14.9
Digestive system		
Esophagus	150.0–150.9	C15.0–C15.9
Stomach	151.0–151.9	C16.0–C16.9
Small intestine	152.0–152.9	C17.0–C17.9
Colon excluding rectum	153.0–153.9, 159.0	C18.0–C18.9, C26.0
Rectum and rectosigmoid junction	154.0–154.1	C19, C20
Anus, anal canal, and anorectum	154.2–154.3, 154.8	C21.0–C21.9
Liver and intrahepatic bile duct		
Liver	155.0,155.2	C22.0, C22.2–C22.4, C22.7–C22.9
Intrahepatic bile duct	155.1	C22.1
Gallbladder	156.0	C23
Other biliary	156.1–156.9	C24.0–C24.9
Pancreas	157.0–157.9	C25.0–C25.9
Retroperitoneum	158.0	C48.0
Peritoneum, omentum, and mesentery	158.8–158.9	C48.1–C48.2
Other digestive organs	159.8–159.9	C26.8–26.9, C48.8
Respiratory system		
Nasal cavity, middle ear, and accessory sinuses	160.0–160.9	C30.0, C30.1, C31.0–C31.9
Larynx	161.0–161.9	C32.0–C32.9
Lung and bronchus	162.2–162.9	C34.0–C34.9
Pleura	163.0–163.9	C38.4
Trachea, mediastinum, and other respiratory organs	162.0, 164.2–165.9	C33, C38.1–C38.3, C38.8, C39
Bones and joints	170.0–170.9	C40.0–C40.9, C41.0–C41.9
Soft tissue (including heart)	171.0–171.9, 164.1	C38.0, C47.0–C47.9, C49.0–C49.9

continued

TABLE C-2 Continued

Cancer Site	ICD-9 Codes	ICD-10 Codes
Skin		
Malignant melanomas	172.0–172.9	C43.0–C43.9
Other malignant skin neoplasms	173.0–173.9	C44.0–C44.9
Breast (male and female)	174.0–174.9, 175	C50.0–C50.9
Female genital system		
Cervix	180.0–180.9	C53.0–C53.9
Corpus	182.0–182.1, 182.8	C54.0–C54.9
Uterus, not otherwise specified	179	C55
Ovary	183.0	C56.0–C56.9
Vagina	184.0	C52
Vulva	184.1–184.4	C51.0–C51.9
Other female genital organs	181, 183.2–183.9, 184.8, 184.9	C57.0–C57.9, C58
Male genital system		
Prostate	185	C61
Testis	186.0–186.9	C62.0–C62.9
Penis	187.1–187.4	C60.0–C60.9
Other male genital organs	187.5–187.9	C63.0–C63.9
Urinary system		
Urinary bladder	188.0–188.9	C67.0–C67.9
Kidney and renal pelvis	189.0, 189.1	C64.0–C64.9, C65.0–C65.9
Ureter	189.2	C66.0–C66.9
Other urinary organs	189.3–189.4, 189.8–189.9	C68.0–C68.9
Eye and orbit	190.0–190.9	C69.0–C69.9
Brain and other nervous system		
Brain	191.0–191.9	C71.0–C71.9
Meninges	192.1	C70.0–C70.9
Other nervous system[a]	192.0, 192.2–192.9	C72.0–C72.9
Endocrine system		
Thyroid	193	C73
Other endocrine (including thymus)	164.0, 194.0–194.9	C37, C74.00–C74.92, C75.0–C75.9
Lymphomas		
Hodgkin's disease	201.0–201.9	C81.0–81.9
Non-Hodgkin's lymphomas	200.0–200.8, 202.0–202.2, 202.8–202.9	C82.0–C82.9, C83.0–C83.9, C84.0–C84.5, C85.0–C85.9, C96.3
Multiple myeloma	203.0, 238.6	C90.0, C90.2

TABLE C-2 Continued

Cancer Site	ICD-9 Codes	ICD-10 Codes
Leukemias		
Lymphocytic		
Acute lymphocytic	204.0	C91.0
Chronic lymphocytic	204.1	C91.1
Other lymphocytic	202.4, 204.2–204.9	C91.2-C91.4, C91.7, C91.9
Myeloid (granulocytic)		
Acute myeloid	205.0, 207.0, 207.2	C92.0, C92.4–C92.5, C94.0, C94.2
Chronic myeloid	205.1	C92.1
Other myeloid	205.2–205.3, 205.8–205.9	C92.2–C92.3, C92.7, C92.9
Monocytic		
Acute monocytic	206.0	C93.0
Chronic monocytic	206.1	C93.1
Other monocytic	206.2–206.9	C93.2, C93.7, C93.9
Other leukemia		
Other acute	208.0	C94.4, C94.5, C95.0
Other chronic	207.1, 208.1	C94.1, C95.1
Aleukemic, subleukemic and "not otherwise specified"	203.1, 207.2, 207.8, 208.2–208.9	C90.1, C91.5, C94.3, C94.7, C95.2, C95.7, C95.9
Miscellaneous malignant neoplasms	159.1, 195.0–195.8, 196.0–196.9, 199.0–199.1, 202.3, 202.5–202.6, 203.8	C26.1, C76.0–C76.8, C77.0–C77.9, C78.0–C78.8, C79.0–C79.8, C80, C88.0–C88.9, C96.0–C96.2, C96.7, C96.9, C97

[a]Cancers of the peripheral nerves and the autonomic nervous system are classified as "soft tissue" in ICD.

SOURCE: Adapted from Ries et al. (2003), Table A-4.

neoplasms of uncertain behavior, and neoplasms of unspecified behavior have separate codes in both schemes.

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Appendix D

Biographies of Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Eighth Biennial Update) and Staff

Mary K. Walker, PhD (*Chair*), is Regents' Professor of Pharmacology/Toxicology in the University of New Mexico College of Pharmacy. Her research interests focus on the mechanisms by which various ligands (including dioxin) for the aryl hydrocarbon receptor (AHR) induce excessive or insufficient activation and thereby produce subtle changes in gene expression that lead to an increased risk of cardiovascular disease in adulthood and on the structural, functional, and molecular changes in adult cardiovascular physiology in a genetic mouse model that lacks the AhR gene. Dr. Walker has written numerous peer-reviewed articles and several book chapters. She is a fellow of the American Heart Association, a member of the Society of Toxicology, a panelist on the Environmental Protection Agency's Science Advisory Board, and a reviewer for several journals and study sections. She served on the committee for *Veterans and Agent Orange: Update 2006*.

Erin M. Bell, PhD, is Associate Professor in the Department of Epidemiology and Biostatistics and the Department of Environmental Health Sciences of the State University of New York's School of Public Health in Albany. She received her undergraduate degree in biology with honors from Hartwick College and her MS and PhD degrees in epidemiology from the University of Massachusetts–Amherst and the University of North Carolina at Chapel Hill, respectively. Between her master's and doctoral studies, she was a Research Associate in the Institute of Medicine (IOM) Medical Follow-up Agency. Her epidemiology research focuses on environmental exposures, particularly to pesticides, as they are related to reproductive, immune, and cancer outcomes. She previously served on the IOM committee for *Veterans and Agent Orange: Update 2008*.

Scott W. Burchiel, PhD, holds the Nunzio and Sherolyn DeSantis Endowed Chair in Pharmaco-genomics and is Associate Dean for Research at the University of New Mexico (UNM) College of Pharmacy in Albuquerque. He has served at UNM in numerous capacities since receiving his PhD in pharmacology in 1977 from the University of California, San Francisco School of Medicine. His con-

tinuing research interests include the development of monoclonal antibodies for nuclear imaging, nanotoxicology, lymphocyte activation and signal transduction, and development of biomarkers for immunotoxicity. He has previously served on National Academies committees that produced *Beryllium Alloy Exposures*, *Human Health Risks of Trichloroethylene*, *Jet Propulsion Fuel 8*, and *Veterans and Agent Orange: Update 2008*.

Rodney R. Dietert, PhD, is a Professor in the Department of Microbiology and Immunology at Cornell University College of Veterinary Medicine, with which he has been associated since 1991. He received his BS in zoology from Duke University in 1974 and his PhD from the University of Texas at Austin in 1977. Dr. Dietert has been director of graduate studies in immunology, a Senior Fellow in the Center for the Environment, Director of the Institute for Comparative and Environmental Toxicology, and Director of the program on breast cancer and environmental risk factors at Cornell's Sprecher Institute for Comparative Cancer Research. His research on immunotoxicology has been supported by the National Science Foundation, the US Department of Agriculture, the National Institutes of Health, and industry.

Naihua Duan, PhD, MA, is Professor of Biostatistics at Columbia University and Director of the Division of Biostatistics of the New York State Psychiatric Institute in New York City. He received a BS in mathematics from National Taiwan University, an MA in mathematical statistics from Columbia University, and a PhD in statistics from Stanford University. His research interests include health-services research, prevention research, sample design and experimental design, model robustness, transformation models, multilevel modeling, nonparametric and semi-parametric regression methods, and environmental exposure assessment. He previously served on the National Academies committees that authored *Human Exposure Assessment to Airborne Pollutants: Advances and Opportunities*; *Organ Procurement and Transplantation: Assessing Current Policies and the Potential Impact of the DHHS Final Rule*; *Carbon Monoxide Episodes in Meteorological and Topographical Problem Areas*; *Assessing the Medical Risks of Human Oocyte Donation for Stem Cell Research*; and *Veterans and Agent Orange: Update 2008*.

Russ B. Hauser, ScD, MD, MPH, is the Frederick Lee Hisaw Professor of Reproductive Physiology and Professor of Environmental and Occupational Epidemiology in the Department of Environmental Health and Department of Epidemiology, respectively, of the Harvard School of Public Health. Dr. Hauser received his MD from Albert Einstein College of Medicine and his ScD and MPH from the Harvard School of Public Health. His research focuses on the effects of environmental chemicals on male and female reproductive functioning, pregnancy outcomes, and children's health. Dr. Hauser is interested primarily in

endocrine disruptors, and his current studies include investigations of possible adverse reproductive effects of exposures to pesticides or dioxins, phthalates, and bisphenol. He served as a member of the Institute of Medicine Committee on Gulf War and Health: Literature Review of Pesticides and Solvents.

Karl Kelsey, MD, MOH, is Professor of Community Health and Pathology and of Laboratory Medicine at Brown University. He received his MD from the University of Minnesota and a master's degree in occupational health from Harvard University. Until 2007, he was on the faculty of the Harvard School of Public Health and Harvard Medical School. He is interested in the application of laboratory-based biomarkers in chronic-disease epidemiology and tumor biology and in characterizing individual susceptibility to cancer. He is an author of more than 200 publications and has served on the National Academies Committees on Toxicity Testing and Assessment of Environmental Agents, on Copper in Drinking Water, on the Evaluation of the Department of Veterans Affairs Uniform Case Assessment Protocol, to Review the Health Consequences of Service During the Persian Gulf War, to Conduct a Study on Curriculum Development in Environmental Medicine, and on the Health Effects of Mustard Gas and Lewisite.

Nancy I. Kerkvliet, PhD, is Professor of Environmental and Molecular Toxicology at Oregon State University in Corvallis, Oregon. Dr. Kerkvliet's research is focused on using animal models to understand how chemicals of environmental concern alter immune function, primarily on understanding how activation of the AHR by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and other ligands suppresses immune responses. In 2007, Dr. Kerkvliet was the recipient of the Society of Toxicology's Career Achievement Award in Immunotoxicology. She previously served on the Committee on Toxicology, its Subcommittee on Jet Propulsion Fuel 8, and the committees for the fifth, sixth, and seventh updates of *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*.

Stephen B. Kritchevsky, PhD, MSPH, is Professor of Internal Medicine in the Section on Gerontology and Geriatric Medicine and Director of the J. Paul Sticht Center on Aging of Wake Forest School of Medicine in Winston-Salem, North Carolina. After receiving both his M.S.P.H. and his Ph.D. degrees in epidemiology from the University at North Carolina, Chapel Hill, he joined the Department of Biostatistics and Epidemiology and later the Department of Preventive Medicine of the University of Tennessee Health Science Center. Dr. Kritchevsky's research interests are related to nutritional factors affecting the health and function of older adults including inflammation, obesity, metabolic syndrome, and cardiovascular disease.

Peter S. J. Lees, PhD, CIH, is a professor and director of the Division of Environmental Health Engineering at the Johns Hopkins University's Bloomberg

School of Public Health. After receiving a BS in biology from the College of William and Mary, he worked as an environmental-assessment project manager and obtained his certification as an industrial hygienist. On completing his doctorate in environmental health engineering and industrial hygiene at Johns Hopkins University, he joined the faculty. He also serves as Deputy Director of the school's National Institute for Occupational Safety and Health Education and Research Center. He has been a member of numerous advisory panels, including the Department of Veterans Affairs Advisory Committee for War-Related Illness and Injury Study Center, an Institue of Medicine Advisory Committee on a Medical Follow-up Agency study of exposure to warfare agents, and the National Research Council Committee to Review and Assess Industrial Hygiene Standards and Practices.

Linda A. McCauley, PhD, FAAN, RN, is Professor and Dean of Emory University's Nell Hodgson Woodruff School of Nursing in Atlanta. Dr. McCauley has expertise in the design of epidemiologic investigations of environmental hazards and in occupational and environmental health nursing. Her work aims to identify culturally appropriate interventions to decrease the effects of environmental and occupational health hazards in vulnerable populations, including workers and young children. Dr. McCauley was previously the Associate Dean for Research and the Nightingale Professor in Nursing of the University of Pennsylvania School of Nursing. She received a bachelor of nursing degree from the University of North Carolina, a master's degree in nursing from Emory, and a doctorate in environmental health and epidemiology from the University of Cincinnati. She became a member of the Institute of Medicine (IOM) in 2008. She has previously served on IOM's Committee to Review the Federal Response to the Health Effects Associated with the Gulf of Mexico Oil Spill and Committee on the Effect of Climate Change on Indoor Air Quality and Public Health, in addition to the Veterans and Agent Orange committees responsible for *Update 2006* and *Update 2008*.

James R. Olson, MS, PhD, is Professor of Pharmacology and Toxicology and Research Professor of Social and Preventive Medicine, and Director of the Division of Environmental Health Sciences of the University at Buffalo–the State University of New York. Dr. Olson received both his master's degree in pharmacology and his doctorate in pharmacology and toxicology from the Medical College of Wisconsin and was an National Institute of Environmental Health Sciences postdoctoral trainee and fellow at the Center in Environmental Toxicology at Vanderbilt University. His research focuses on the toxicity and mechanism of action of polychlorinated dibenzo-*p*-dioxin, polychlorinated dibenzofurans, and polychlorinated biphenyls in laboratory animals and humans. Dr. Olson has been a reviewer for numerous journals, a member of many advisory and grant panels, and a contributor to several Environmental Protection Agency and Agency for Toxic Substances and Disease Registry summary documents.

Jeremy Shefner, MD, PhD, is Professor and Chair of Neurology and Associate Vice President for Clinical and Translational Research at Upstate Medical University–State University of New York, Director of the Clinical Neurophysiology Laboratory, and Director of the MDA/ALS Research and Treatment Center at University Hospital in Syracuse, New York. He is also cochair of the Northwest ALS Clinical Trials Consortium. He received a PhD in experimental psychology from the University of Illinois in 1976 and was a National Research Service Awards research fellow from 1976 to 1979. Dr. Shefner earned his MD at Northwestern University Medical School in 1983. He completed a fellowship in clinical neurophysiology and neuromuscular disease with the Brigham and Women's Hospital in Boston, where he participated in ALS clinical trials. In Syracuse, he established the multidisciplinary ALS clinic, which conducts both industry-initiated and investigator-initiated clinical trials. Dr. Shefner is the recipient of numerous research grants from National Institutes of Health and industry sponsors and the author of more than 100 original research articles and book chapters on neurophysiology. Dr. Shefner previously served on the Institute of Medicine committees that prepared *Amyotrophic Lateral Sclerosis in Veterans* and *Veterans and Agent Orange: Update 2008*.

Michael K. Skinner, PhD, is a Professor in the School of Molecular Biosciences at Washington State University. He received his BS in chemistry from Reed College in Portland, Oregon, and his PhD in biochemistry from Washington State University, and he had a postdoctoral fellowship at the C.H. Best Institute at the University of Toronto. He has been on the faculty of Vanderbilt University and the University of California, San Francisco. Dr. Skinner's research is focused on how different cell types in a tissue interact and communicate to regulate gonadal growth and differentiation. His current research has demonstrated the ability of endocrine disruptors to promote transgenerational epigenetic disease phenotypes through abnormal germ-line programming in gonadal development. Dr. Skinner established and served as the Director of both the Washington State University and University of Idaho Center for Reproductive Biology and the Center for Integrated Biotechnology. In 2008, he stepped down from those directorships to focus on his research. His research has been highlighted in BBC and PBS documentaries and selected as among the top 100 discoveries in 2005 and 2007 by Discover. Dr. Skinner has served on numerous journal editorial boards and has more than 200 peer-reviewed publications.

Luoping Zhang, PhD, is currently an Associate Adjunct Professor in the Division of Environmental Health Sciences in the School of Public Health of the University of California, Berkeley. She is Associate Director of the Genes and Environment Laboratory and the Benzene Health Effects Program. Dr. Zhang is also coleader and coinvestigator in the university's Superfund Basic Research Program. She received her BS in physical chemistry from Wuhan University

and her MS in biochemistry from Huazhong University of Science and Technology, both in Wuhan, China. She completed her PhD in biochemical toxicology at Simon Fraser University, British Columbia, Canada, in 1993. Dr. Zhang is recognized as a leading authority on fluorescence in situ hybridization (FISH) methods and is an innovator in developing new FISH assays. Dr. Zhang has collaborated with the US National Cancer Institute, the Chinese Center for Disease and Prevention, and other academic institutions in several large-scale molecular epidemiologic studies. Dr. Zhang's major research focus is on applying biomarkers, molecular cytogenetics, and new genomic technologies to further the understanding of the causes and mechanisms of leukemia and lymphoma caused by environmental pollutants, and she has a developing interest in human stem-cell toxicology. She recently served on the National Research Council Committee on Tetrachloroethylene.

STAFF BIOGRAPHIES

Mary Burr Paxton, PhD, is a Senior Program Officer in the Institute of Medicine (IOM) Board on the Health of Select Populations. Before joining IOM, she worked as a consultant on the regulation of toxic substances and managed the conduct and analysis of several epidemiologic studies on veterans' health. She received an MS in biostatistics from the Johns Hopkins School of Hygiene and Public Health and a doctorate in genetics from the George Washington University. She is a diplomate of the American Board of Toxicology. Dr. Paxton has worked on several National Academies reports, including *Issues in Risk Assessment*; *Environmental Neurotoxicology*; *Gulf War and Health: Insecticides and Solvents*; *Gulf War and Health: Fuels, Combustion Products, and Propellants*; *Asbestos: Selected Cancers*; *Veterans and Agent Orange: Update 2004; Veterans and Agent Orange: Update 2006*; and *Veterans and Agent Orange: Update 2008*.

Jennifer A. Cohen, MPH, is a Program Officer in the Institute of Medicine (IOM) Board on the Health of Select Populations. She received her undergraduate degree and her MPH from the University of Maryland. She has been involved with the IOM committees that produced *Organ Procurement and Transplantation*; *Clearing the Air: Asthma and Indoor Air Exposures*; *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes*; *Veterans and Agent Orange: Update 2000*; *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Acute Myelogenous Leukemia in the Children of Vietnam Veterans*; *Veterans and Agent Orange: Update 2004*; *Veterans and Agent Orange: Update 2006*; and *Veterans and Agent Orange: Update 2008*. She was also rapporteur for the IOM report *Challenges and Successes in Reducing Health Disparities*.

Tia S. Carter, MS, is a Senior Program Assistant in the Institute of Medicine Board on the Health of Select Populations. She earned her master's in health-

care administration from the University of Maryland University College. She received her undergraduate degree in community health from the University of Maryland, College Park. Before going to IOM, she worked at the Greater Washington Urban League in the Division of Aging and Health Services as the health-promotions coordinator, where she was responsible for health-promotion and disease-prevention education services and activities among the elderly. She has been involved with the IOM committees that produced *Asbestos: Selected Cancers*; *Provision of Mental Health Counseling Services Under TRICARE*; *Climate Change, the Indoor Environment, and Health*; *Veterans and Agent Orange: Update 2004*; *Veterans and Agent Orange: Update 2006*; and *Veterans and Agent Orange: Update 2008*.

Frederick (Rick) Erdtmann, MD, MPH, is Director of the Board on the Health of Select Populations and of the Medical Follow-up Agency of the Institute of Medicine. He earned his MD from Temple University School of Medicine, and he holds an MPH from the University of California, Berkeley. He completed a residency program in general preventive medicine at Walter Reed Army Institute of Research in 1975 and is board-certified in that specialty. Dr. Erdtmann's assignments with the Army Medical Department included being chief of preventive-medicine services at Fitzsimons Army Medical Center, at Frankfurt Army Medical Center in Germany, and at Madigan Army Medical Center. He also served as division surgeon for the Second Infantry Division in Tongduchon, Korea. He later served as Deputy Chief of Staff for Clinical Operations in the Department of Defense's TRICARE Region 1 before assuming hospital command at Walter Reed Army Medical Center in March 1998. After that, he was assigned to the Office of the Surgeon General as the Deputy Assistant Surgeon General for Force Development. In 2001, after 30 years of commissioned military service, Dr. Erdtmann joined the National Academies and assumed his present responsibilities.

Norman Grossblatt, ELS(D), is a senior editor at the National Academies. Before joining the National Research Council Division of Medical Sciences in 1963, he worked as an analyst in information storage and retrieval at Documentation Incorporated and as a technical editor at the Allis-Chalmers Manufacturing Co., Nuclear Power Department, in Washington, DC. He received a BA in English from Haverford College. Mr. Grossblatt is a diplomate editor in the life sciences and was the founding president of the Board of Editors in the Life Sciences. He is a fellow of the American Medical Writers Association and a recipient of its President's Award; a member of the Council of Science Editors and since 1997 the manuscript editor of its journal, Science Editor; and a member of the European Association of Science Editors. At the National Academies, he has edited more than 300 reports.