Review of Acute Human-Toxicity Estimates for Selected Chemical-Warfare Agents

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Review of Acute Human-Toxicity Estimates for Selected Chemical-Warfare Agents

Subcommittee on Toxicity Values for Selected Nerve and Vesicant Agents
Committee on Toxicology
Board on Environmental Studies and Toxicology
Commission on Life Sciences
National Research Council

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Preface

Due to the Existence of large stocks of chemical-warfare (CW) agents, their easy producibility from ordinary industrial chemicals, and their potential lethal effects, there is a critical need to determine as precisely as possible the exposure levels at which CW agents cause toxic effects. This information could aid in protecting soldiers in the event of a CW attack.

This report, by the Subcommittee on Toxicity Values for Selected Nerve and Vesicant Agents of the National Research Council's Committee on Toxicology, is intended to assist the U.S. Army by assessing the scientific validity of existing human-toxicity estimates for several CW agents. The estimates considered in this report were proposed recently in the Army's Chemical Defense Equipment Process Action Team (CDEPAT) report entitled *Review of Existing Toxicity Data and Human Estimates for Selected Chemical Agents and Recommended Human Toxicity Estimates Appropriate for Defending the Soldier* (1994). The report was authored by S.A. Reutter, Ph.D., and W.A. Wade, D.V.M.; it is classified "secret" and can be obtained only with permission from the director of the U.S. Army Edgewood Research, Engineering and Development Center, Edgewood, Md.

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We are grateful for the assistance of the National Research Council staff in preparing this report. Staff members who contributed to this effort are Paul Gilman, executive director of the Commission on Life Sciences; James J. Reisa, director of the Board on Environmental Studies and Toxicology; Carol A. Maczka, program director for toxicology and risk assessment; Ruth E. Crossgrove, editor; Lucy V. Fusco, project assistant, and Catherine M. Kubik, senior program assistant. We especially wish to recognize the major contributions of the project director, Kulbir S. Bakshi, who directed the preparation of the subcommittee's report. His knowledge of the scientific and technical literature and his tireless efforts to obtain information and to organize the study plan, the subcommittee meetings, and the subcommittee's report aided in the successful completion of the project.

Finally, we would like to thank all the members of the subcommittee for their dedicated efforts throughout the development of this report.

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Summary

No reliable acute-exposure[1] standards have been established for the particular purpose of protecting soldiers from toxic exposures to chemical-warfare (CW) agents. Some human-toxicity estimates are available for the most common CW agents—organophosphorus nerve agents and vesicants; however, most of those estimates were developed for offensive purposes (that is, to kill or incapacitate the enemy) and were intended to be interim values only.

The U.S. Army's original purpose for developing human-toxicity estimates for CW agents was to enable it to predict the number of casualties that would occur during an offensive action in which the goal was to kill or incapacitate a certain fraction of the enemy forces (for example, killing or incapacitating a minimum of 50% of the least-sensitive (most-resistant) individuals). Such an approach would actually result in more than half of the exposed individuals dying (the "bonus effect"), because a certain percentage of those exposed would be expected to be more susceptible than the least-sensitive individual. Thus, exposure under the Army's original estimates would result in substantial "over-kill." These estimates understate the toxicity of the agents and therefore are inappropriate for protecting soldiers.

[1] A one-time, short-term exposure; for example, < 1 hr.

Because of the possibility of a chemical attack by a foreign power, the Army's Office of the Surgeon General asked the Army's Chemical Defense Equipment Process Action Team (CDEPAT) to review the toxicity data for the nerve agents GA (tabun), GB (sarin), GD (soman), GF, and VX, and the vesicant agent sulfur mustard (HD) and to establish a set of exposure limits that would be useful in protecting soldiers from toxic exposures to those agents. In the 1994 report entitled *Review of Existing Toxicity Data and Human Estimates for Selected Chemical Agents and Recommended Human Toxicity Estimates Appropriate for Defending the Soldier*, the team concluded that some of the existing human-toxicity estimates are too high and are inappropriate for use in protecting soldiers. In those cases, CDEPAT proposed new estimates for various routes of exposure—percutaneous vapor, vapor inhalation, and percutaneous liquid exposures. The proposed human-toxicity estimates are only for healthy male military personnel. They must not be used for civilians.

Before making a decision on acceptance of the human-toxicity estimates proposed by CDEPAT, the Department of the Army requested that the National Research Council (NRC) independently review the CDEPAT report to determine the scientific validity of the proposed estimates. The NRC assigned this project to the Committee on Toxicology (COT) of the Board on Environmental Studies and Toxicology. The COT convened the Subcommittee on Toxicity Values for Selected Nerve and Vesicant Agents, which prepared this report. Members of the subcommittee were selected for their recognized expertise in the fields of toxicology, medicine, pathology, biostatistics, and risk assessment. The subcommittee was charged to review the Army's proposed human-toxicity estimates for GA, GB, GD, GF, VX, and HD. Specifically, the subcommittee was charged with the following tasks:

1. Review the scientific protocols and quality of the toxicity data used in revising the human-toxicity estimates for acute exposures.
2. Review the toxicity estimates for mild and nonsevere effects and for severe and lethal effects.
3. Review the methods used in deriving the human-toxicity estimates for acute exposures.
4. Determine the appropriateness of the assumptions made in deriving the human-toxicity estimates for acute exposures.

The subcommittee was not asked to recommend new toxicity estimates

or to address the policy or operational consequences of lowering the proposed human-toxicity estimates. The subcommittee's evaluations of CDEPAT's proposed estimates for GA, GB, GD, GF, VX, and HD are summarized in Tables I through 6.

The subcommittee's conclusions concerning the scientific validity of the proposed CDEPAT estimates are grouped in four categories: (1) some estimates were judged to be scientifically valid; (2) other estimates were judged adequate to serve as interim estimates until further research is conducted; (3) some estimates need to be lowered; and (4) a few estimates need to be raised.

The toxicity data that CDEPAT used to derive its proposed estimates were generated primarily from a data base developed from the 1930s to the 1960s. The existing human-toxicity estimates were based on experiments performed 30–40 years ago using various animal species in often poorly controlled studies with vastly different protocols. In reviewing the available toxicity data for the six CW agents, the subcommittee recognized that the quality of the relevant toxicity data is marginal, but it also recognized that the Army needs "best estimates" to protect its troops from exposure. For each chemical agent, data were available for only a few adverse health effects, such as death, incapacitation, cholinesterase (ChE) inhibition, miosis (a decrease in pupil size), and rhinorrhea (running nose), vesication, and erythema. Thus, even though the subcommittee concluded that some of CDEPAT's proposed estimates are scientifically valid, those conclusions are based on a limited toxicity data base. By current standards of toxicology, the toxicity data base for the agents is inadequate, and such inadequacy is a major obstacle to the Army in developing human-toxicity estimates with statistical confidence and in developing risk-management strategies.

The subcommittee recommends that the Army convene an expert panel to develop a research strategy for deriving more scientifically sound toxicity values for the agents of concern. The panel should first consider the use of such techniques as structure-activity relationships, the uncertainty factors, and in vitro systems for estimating human-toxicity values for CW agents.

If these approaches do not appear to be useful, animal and human experimentation may be recommended. Although additional research is clearly desirable to provide improved confidence in existing data, such research should not be performed on laboratory animals until expert judgment documents the need on a case-by-case basis. It must be documented that the data to be obtained from laboratory animals is needed to make a significant improvement in the protection of human health.

TABLE 1 Evaluation of Human-Toxicity for GA

		Human-Toxicity Estimates for GA			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
LCt_{50}[a]	Percutaneous, vapor	20,000 mg-min/m^3	15,000 mg-min/m^3	Proposed estimate is scientifically valid	Proposed estimate supported by human data
	Inhalation, vapor	135 mg-min/m^3	70 mg-min/m^3	Proposed estimate should be lowered	Because of inadequate data on GA for this route, CDEPAT derived the estimate by assuming that GA is 0.5 times as toxic as GB; approach reasonable but estimate should be lowered because of recommended lowering of LCt_{50} for GB for this route; further research recommended
ECt_{50}[b]					
Threshold effects	Percutaneous, vapor	None	2,000 mg-min/m^3	Proposed estimate is scientifically valid	ChE inhibition data used for proposing new recommendation
Severe effects	Inhalation, vapor	None	50 mg-min/m^3	Proposed estimate should be lowered	CDEPAT's proposed estimate based on a study that indicated the ratio of ICt_{50}[e]/LC_{50} is 0.75; that assumption used to establish ECt_{50}. for severe effects; the subcommittee recommends that the ECt_{50} estimate be lowered to correspond to the lowered estimate for LCt_{50}; further research recommended
Mild effects	Inhalation, vapor	0.9 mg-min/m^3	0.5 mg-min/m^3	Proposed estimate should be raised	Human data show that humans can tolerate higher exposures; further research recommended

		Human-Toxicity Estimates for GA			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
LD_{50}[c]	Percutaneous, liquid	1,500 mg for 70-kg man	1,500 mg for 70-kg man	Proposed estimate should be lowered	No uncertainty factors used in lieu of limited animal data for proposed estimate; further research recommended
ED_{50}[d]	Percutaneous, liquid	None	880 mg for 70-kg man	Proposed estimate should be lowered	In the absence of adequate human or animal data for this effect, CDEPAT established the estimate by assuming ID_{50}[f]/LD_{50} ratio of 0.6 to estimate ED50; the subcommittee recommends that the ED_{50} estimate be lowered to correspond to the lowered estimate for LD_{50}; further research recommended

[a] LCt_{50}: Vapor exposure that produces lethality in 50% of the exposed animals. Ct refers to the product of concentration (c) and exposure time (t). Note that Ct is not necessarily a constant.
[b] ECt_{50}: Percutaneous vapor exposure or inhalation vapor exposure causing a defined effect (e.g., incapacitation, severe effects, mild effects, threshold effects).
[c] LD_{50}: Liquid dose causing lethality in 50% of the exposed animals.
[d] ED_{50}: Liquid dose causing a defined effect in 50% of the exposed animals.
[e] ICt_{50}: Vapor exposure that produces incapacitation in 50% of the exposed population.
[f] ID_{50}: Liquid dose causing incapacitation in 50% of the exposed population.

TABLE 2 Evaluation of Human-Toxicity Estimates for GB

		Human-Toxicity Estimates for GB			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
LCt_{50}[a]	Percutaneous, vapor	15,000 mg-min/m^3	10,000 mg-min/m^3	Proposed estimate is scientifically valid	Proposed estimate supported by studies in monkeys and humans
	Inhalation, vapor	70 mg-min/m^3	35 mg-min/m^3	Proposed estimate should be lowered	Estimate too high because human studies show 100% lethality at 40 mg-min/m^3
ECt_{50}[b]					
Threshold effects	Percutaneous, vapor	None	1,200 mg-min/m^3	Proposed estimate is scientifically valid	Estimate supported by studies of ChE inhibition in humans; further research recommended
Severe effects	Inhaiation, vapor	35 mg-min/m^3	25 mg-min/m^3	Proposed estimate should be lowered	ECt_{50}/LCt_{50} ratio of 0.7 used to develop estimate; LCt_{50} for this route of exposure was lowered; therefore, ECt_{50} should be lowered correspondingly; further research recommended
Mild effects	Inhalation, vapor	2 mg-min/m^3	0.5 mg-min/m^3	Proposed estimate should be raised	No effects in humans at 0.5 mg-min/m^3; effects begin to appear at ≈ 2 mg-min/m^3; further research recommended
LD_{50}[c]	Percutaneous, liquid	1,700 mg for 70-kg man	1,700 mg for 70-kg man	Low confidence in proposed estimate; proposed estimate should serve as interim value	Estimate based on a ratio of ChE inhibition in rabbits and humans; however, human data concerning the relation between ChE inhibition and adverse effects are inconsistent; further research recommended

		Human-Toxicity Estimates for GB			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
ED_{50}[d]					
Severe effects	Percutaneous, liquid	None	1,000 mg for 70-kg man	Proposed estimate should serve as interim value	In the absence of adequate data on GB for this effect, CDEPAT assumed that the ratio of lD_{50}[c]/LD_{50} is 0.6 and used that to estimate the ED_{50} values; further research recommended

[a] LCt_{50}: Vapor exposure that produces lethality in 50% of the exposed animals. Ct refers to the product of concentration (c) and exposure time (t). Note that Ct is not necessarily a constant.
[b] ECt_{50}: Percutaneous vapor exposure or inhalation vapor exposure causing a defined effect (e.g., incapacitation, severe effects, mild effects, threshold effects).
[c] LD_{50}: Liquid dose causing lethality in 50% of the exposed animals.
[d] ED_{50}: Liquid dose causing a defined effect in 50% of the exposed animals.
[c] ID_{50}: Liquid dose causing incapacitation in 50% of the exposed population.

TABLE 3 Evaluation of Human-Toxicity Estimates for GD

		Human-Toxicity Estimates for GD			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
LCt_{50}[a]	Percutaneous, vapor	None	2,500 mg-min/m^3	Proposed estimate is scientifically valid	Proposed estimate based on assumption that GD is 4 times more toxic than GB for percutaneous exposure
	Inhalation, vapor	70 mg-min/m^3	35 mg-min/m^3	Proposed estimate should be lowered	Proposed estimate based on the assumption that GD and GB are equipotent via this route; subcommittee recommends that LCt_{50} estimate for GD be lowered to correspond to lowered estimate for GB; further research recommended
ECt_{50}[b]					
Threshold effects	Percutaneous, vapor	None	300 mg-min/m^3	Proposed estimate should serve as an interim value	In the absence of adequate human or animal data, proposed estimate based on assumption that GD is 4 times more toxic than GB for percutaneous exposure; further research recommended
Severe effects	Inhalation, vapor	35 mg-min/m^3	25 mg-min/m^3	Proposed estimate should be lowered	In the absence of adequate human or animal data, proposed estimate based on assumption that potencies of GD and GB are comparable; ECt_{50} estimate for GD should be lowered to correspond to the lowered estimate for GB; further research recommended

		Human-Toxicity Estimates for GD			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
Mild effects	Inhalation, vapor	None	0.2 mg-min/m^3	Proposed estimate should be raised	In the absence of adequate human or animal data, proposed estimate based on assumption that GD is 2.5 times more potent than GB for miotic effects; subcommittee recommends that the LCt_{50} estimate for GD be raised to correspond to the recommended raised estimate for GB; further research recommended
LD_{50}[c]	Percutaneous, liquid	350 mg for 70-kg man	350 mg for 70-kg man	Proposed estimate should serve as an interim value	Because of wide range of LD50 values in animals, subcommittee's confidence in the proposed estimate is low; CDEPAT's proposed estimate of 350 mg for 70-kg man should serve as an interim value; further research recommended
ED_{50}[d]					
Severe effects	Percutaneous, liquid	None	200 mg for 70-kg man	Proposed estimate should serve as an interim value	In the absence of adequate human or animal data, proposed estimate was derived using the ID_{50}[e]/LD_{50} ratio of 0.6; the subcommittee recommends that CDEPAT's proposed estimate serve as an interim value; further research recommended

[a] LCt_{50}: Vapor exposure that produces lethality in 50% of the exposed animals. Ct refers to the product of concentration (c) and exposure time (t). Note that Ct is not necessarily a constant.
[b] ECt_{50}: Percutaneous vapor exposure or inhalation vapor exposure causing a defined effect (e.g., incapacitation, severe effects, mild effects, threshold effects).
[c] LD_{50}: Liquid dose causing lethality in 50% of the exposed animals.
[d] ED_{50}: Liquid dose causing a defined effect in 50% of the exposed animals.
[c] ID_{50}: Liquid dose causing incapacitation in 50% of the exposed population.

TABLE 4 Evaluation of Human-Toxicity Estimates for GF

		Human-Toxicity Estimates for GF			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
LCt_{50}[a]	Percutaneous, vapor	15,000 mg-min/m^3	2,500 mg-min/m^3	Proposed estimate should serve as an interim value	Rationale for the CDEPAT estimate not supported by data; further research recommended
	Inhalation, vapor	None	35 mg-min/m^3	Proposed estimate should be lowered	In the absence of adequate data, proposed estimate based on assumption that GF, GD, and GB are equipotent; approach is reasonable; because LCt_{50} for GB was recommended to be lowered, proposed value for GF should be lowered correspondingly; further research recommended
ECt_{50}[b]					
Threshold effects	Percutaneous, vapor	None	300 mg-min/m^3	Proposed estimate should serve as an interim value	Proposed estimate based on assumption that GF and GD are equipotent; approach is reasonable; further research recommended
Severe effects	Inhalation, vapor	None	25 mg-min/m^3	Proposed estimate should be lowered	In the absence of adequate data, proposed estimate based on assumption that GF, GD, and GB are equipotent; approach is reasonable; because ECt_{50}[s] for severe effects for GB and GD were recommended to be lowered, proposed value for GF should be lowered correspondingly; further research recommended

Toxicity Type	Route and Form of Exposure	Human-Toxicity Estimates for GF: Existing Estimates	Human-Toxicity Estimates for GF: CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
Mild effects	Inhalation, vapor	None	0.2 mg-min/m^3	Proposed estimate should be raised	In the absence of adequate human or animal data, the proposed estimate based on assumption that GF and GD are equipotent; approach is reasonable; because ECt_{50} for mild effects for GD was recommended to be raised, proposed value for GF should be raised correspondingly; further research recommended
LD_{50}[c]	Percutaneous, liquid	None	350 mg for 70-kg man	Proposed estimate should serve as an interim value	In the absence of adequate human or animal data, proposed estimate based on assumption that GF and GD are equipotent; approach is reasonable; further research recommended
ED_{50}[d]					
Severe effects	Percutaneous, liquid	None	200 mg for 70-kg man	Proposed value should serve as an interim value	In the absence of adequate human or animal data, the proposed estimate based on assumption that GF and GD are equipotent; approach is reasonable; further research recommended

[a] LCt_{50}: Vapor exposure that produces lethality in 50% of the exposed animals. Ct refers to the product of concentration (c) and exposure time (t). Note that Ct is not necessarily a constant.
[b] ECt_{50}: Percutaneous vapor exposure or inhalation vapor exposure causing a defined effect (e.g., incapacitation, severe effects, mild effects, threshold effects).
[c] LD_{50}: Liquid dose causing lethality in 50% of the exposed animals.
[d] ED_{50}: Liquid dose causing a defined effect in 50% of the exposed animals.

TABLE 5 Evaluation of Human-Toxicity Estimates for VX

		Human-Toxicity Estimates for VX			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
LCt_{50}[a]	Percutaneous, vapor	None	150 mg-min/m^3	Proposed estimate should be considered an interim value	Degree of confidence in data is low to moderate; further research recommended
	Inhalation, vapor	30 mg-min/m^3	15 mg-min/m^3	Proposed estimate should be lowered	Degree of confidence in data is low to moderate; further research recommended
ECt_{50}[b]					
Threshold effects	Percutaneous, vapor	None	10 mg-min/m^3	Proposed estimate should be considered an interim value	Degree of confidence in data is low; a no-observed-adverse-effect level (NOAEL) was not defined; further research recommended
Severe effects	Percutaneous, vapor	None	25 mg-mill/m^3	Proposed estimate should be considered an interim value	Degree of confidence low to moderate; further research recommended
	Inhalation, vapor	25 mg-min/m3	10 mg-min/m3	Proposed estimate should be considered an interim value	Insufficient data; further research recommended
Mild effects	Inhalation, vapor	0.09 mg-min/m^3	0.09 mg-min/m^3	Proposed estimate is scientifically valid	Available human data support the proposed estimate
LD_{50}[c]	Percutaneous, liquid	10 mg/70-kg man	5 mg/70-kg man	Proposed estimate should be lowered	Animal data indicate that the proposed estimate is too high; furthermore, no uncertainty factor used in lieu of variability associated with dermal penetration of various regions of body; further research recommended

		Human-Toxicity Estimates for VX			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
ED_{50}[d]					
Severe effects	Percutaneous, liquid	5 mg/70-kg man	2.5 mg/70kg man	Proposed estimate should be lowered	The ED_{50} is based on the ID_{50}[e]/LD_{50} ratio; the subcommittee recommends that the LD_{50} be lowered, therefore, the ED_{50} should be lowered correspondingly; further research recommended

[a] LCt_{50}: Vapor exposure that produces lethality in 50% of the exposed animals. Ct refers to the product of concentration (c) and exposure time (t). Note that Ct is not necessarily a constant.
[b] ECt_{50}: Percutaneous vapor exposure or inhalation vapor exposure causing a defined effect (e.g., incapacitation, severe effects, mild effects, threshold effects).
[c] LD_{50}: Liquid dose causing lethality in 50% of the exposed animals.
[d] ED_{50}: Liquid dose causing a defined effect in 50% of the exposed animals.
[e] ID_{50}: Liquid dose causing incapacitation in 50% of the exposed population.

TABLE 6 Evaluation of Human-Toxicity Estimates for HD

		Human-Toxicity Estimates for HD			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
LCt_{50}[a]	Percutaneous, vapor	10,000 mg min/m^3	5,000 mg-min/m^3	Proposed estimate should be lowered	Estimate might be too high because data from the most-sensitive species (rats and mice) not used; further research recommended
	Inhalation, vapor	1,500 mg min/m^3	900 mg-min/ m^3	Proposed estimate is scientifically valid	CDEPAT averaged LCt^{50} data in several animal species; in the absence of data on humans, that approach is reasonable
ECt_{50}[b]					
Threshold effects	Percutaneous, vapor	None	50 mg-min/ m^3 (moderate temperature); 25 mg-min/ m^3 (hot temperature)	Proposed estimates should serve as interim values	In the absence of details on studies on which estimates were based, proposed estimate should be considered interim value; further research recommended
Severe effects	Percutaneous, vapor	2,000 mg-min/ m^3 (moderate temperature) 1,000 mg min/ m^3 (hot temperature)	500 mg-min/ m^3 (moderate temperature); <200 mg-min/m^3 (hot temperature)	Proposed estimates are scientifically valid	Estimates based on human studies

		Human-Toxicity Estimates for HD			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
	Inhalation, vapor	200 mg-min/ m^3 (moderate temperature)	100 Mg-Min/ m^3 moderate temperature)	Proposed estimate is scientifically valid	Proposed estimate supported by human data
Mild effects	Inhalation, vapor	>50 mg min/ m^3	25 mg-min/ m^3	Proposed estimate is scientifically valid	Proposed estimate supported by human data
LD_{50}[c]	Percutaneous, liquid	7,000 mg for 70-kg man	1,400 mg for 70kg man	Proposed estimate is scientifically valid	Proposed estimate supported by a study in dogs
ED_{50}[d]					
Severe effects	Percutaneous, liquid	None	610 mg for 70-kg man	Proposed estimate is scientifically valid; however, it should be rounded to 600 mg for a 70-kg man to avoid appearance of precision that is not there	Proposed estimate supported by human data

[a] LCt_{50}: Vapor exposure that produces lethality in 50% of the exposed animals. Ct refers to the product of concentration (c) and exposure time (t). Note that Ct is not necessarily a constant.
[b] ECt_{50} Percutaneous vapor exposure or inhalation vapor exposure causing a defined effect (e.g., incapacitation, severe effects, mild effects, threshold effects).
[c] LD_{50}: Liquid dose causing lethality in 50% of the exposed animals.
[d] ED_{50}: Liquid dose causing a defined effect in 50% of the exposed animals.

The experimental designs should include the following:

- Define if and when experiments with humans are appropriate.
- In the absence of human experimentation, define the most appropriate animal model for each specific toxicity value and agent, including the end points to be observed.
- Define the adequacy of the design in determining the toxicity values for healthy female as well as healthy male military personnel.
- Define the requirements for observation of reversibility of adverse health effects.
- Identify adverse health effects at the low end of the dose-response curve to determine threshold exposure levels.
- Identify confidence limits for the proposed estimates as a measure of the uncertainty of the estimated incidence of toxic effects.
- Identify potentiation or antagonistic effects from exposures to mixtures of chemical agents.
- Identify more-sensitive biological markers of exposure and effects for CW agents.

1—

Introduction and Background

The U.S. Army's Chemical Defense Equipment Process Action Team (CDEPAT) recently conducted an extensive review of the scientific basis for toxicity estimates in use by the Army for several chemical-warfare (CW) agents: GA, GB, GD, GF, VX, and HD. Following a detailed analysis of the toxicity of these agents and using contemporary methods of analysis, CDEPAT concluded that many of the human-toxicity estimates in use would not protect the soldier adequately (CDEPAT 1994). Recalculations of the potencies of several of the CW agents indicate that their potencies are greater than previously determined. As a result, lower exposure levels of CW agents are expected to elicit adverse effects.

Before deciding whether to implement CDEPAT's recommendations, the U.S. Department of the Army requested that the National Research Council (NRC) independently review the CDEPAT report entitled *Review of Existing Toxicity Data and Human Estimates for Selected Chemical Agents and Recommended Human Toxicity Estimates for Defending the Soldier*. The NRC assigned the project to the Committee on Toxicology (COT) of the Board on Environmental Studies and Toxicology. The COT convened the Subcommittee on Toxicity Values for Selected Nerve and Vesicant Agents, which conducted the study and prepared this report. Subcommittee members were chosen for their expertise in several specialties, including

toxicology, medicine, pathology, biostatistics, and risk assessment. The subcommittee was charged with determining the scientific validity of CDEPAT's proposed human-toxicity estimates for CW agents for various routes of exposure (that is, percutaneous vapor exposures, vapor inhalation exposures, and percutaneous liquid exposures). The report considers only acute[1] exposures and acute effects. It should be noted that the human-toxicity estimates for the CW agents were proposed for healthy adult male soldiers only. They must *not* be used for the general population. Specifically, the subcommittee was charged with the following tasks:

1. Review the scientific protocols and the quality of the toxicity data used in revising the human-toxicity estimates for acute exposures.
2. Review the toxicity estimates for mild and nonsevere effects and for severe and lethal effects.
3. Review the procedures used in deriving the human-toxicity estimates for acute exposures.
4. Determine the appropriateness of the assumptions made in deriving the human-toxicity estimates for acute exposures.

In reviewing the toxicity data and the proposed human-toxicity estimates for acute exposures, the subcommittee evaluated the quality of the data, the appropriateness of the procedures used in obtaining the estimates, and the assumptions made in deriving them. The subcommittee also determined whether the supporting documentation justified the proposed recommendations and whether the studies and toxicity end points were appropriate for deriving the toxicity estimates. In reviewing the proposed human-toxicity estimates, the subcommittee reviewed only the toxicity information presented in the CDEPAT report. It did not perform an independent literature search, nor did it review any data other than those presented in the report. In addition, the subcommittee was not asked to recommend new estimates or to address the policy or operational consequences of the proposed lower human-toxicity estimates.

The exposures used in the estimates are defined as follows:

- LCt_{50} is the exposure to a vapor causing lethality in 50% of a given population and is expressed as the product of air concentration (c), in

[1] A one-time, short-term exposure; for example, < 1 hr.

milligrams per cubic meter, and exposure duration (t), usually in minutes.[2] Ct refers to the product of concentration and exposure time. LCt_{50}s were derived for either inhalation or percutaneous vapor exposures. It is important to note that the product of concentration and exposure duration (c × t) is not necessarily a constant.

- ECt_{50} is the exposure to a vapor causing a defined effect in 50% of a given population and is expressed as the product of c × t in mg-min/m^3, where c × t is not necessarily a constant. The effects include those classified as threshold (minimal), mild (miosis and/or rhinorrhea), or severe (incapacitation, prostration, collapse, and convulsions). ECt_{50}s were derived for either inhalation or percutaneous vapor exposures.
- ICt_{50} is the exposure to a vapor causing incapacitation in 50% of a given population and is expressed as the product of c × t in mg-min/m^3, where c × t is not necessarily a constant.
- LD_{50} is the acute dose of a liquid agent causing lethality in 50% of a given population and is expressed in milligrams per kilogram of body weight (mg/kg). In this report, all LD_{50}s are for percutaneous liquid exposure of bare skin.
- ID_{50} is the acute dose of a liquid agent causing incapacitation in 50% of a given population and is expressed in mg/kg. In this report, all ID_{50}s are for percutaneous liquid exposure of bare skin.
- ED_{50} is the acute dose of a liquid agent causing a defined effect in 50% of a given population and is expressed in mg/kg. In this report, all ED_{50}s are for percutaneous liquid exposure of bare skin. Effects include those in the threshold, mild, or severe (including incapacitation) categories.

The results of the subcommittee's deliberations are presented in Chapters 2 through 8 of this report. Chapters 2 through 7 review CDEPAT's proposed human-toxicity estimates for agents GA, GB, GD, GF, VX, and HD, respectively. Those chapters provide conclusions on the scientific validity of the proposed acute human-toxicity estimates and recommendations for research efforts. Chapter 8 evaluates the risk-estimation procedures used in the CDEPAT report. The Appendix discusses the offensive versus the defensive use of human-toxicity estimates for CW agents.

[2] The LCt_{50} units are abbreviated mg-min/m^3.

2—

Review of Acute Human-Toxicity Estimates for GA (Tabun)

GA (Tabun or ethyl *n*-dimethylphosphoramidocyanidate) is an organophosphate nerve agent and is a colorless, volatile liquid. The physical and chemical properties, toxicokinetics, and toxicity of GA are discussed in detail by CDEPAT (1994), Marrs et al. (1996), and Somani (1994). Human-toxicity estimates have been derived for percutaneous vapor exposures, vapor inhalation, and percutaneous liquid exposures. Only four toxicity end points were considered—lethality in animals, incapacitation, changes in cholinesterase (ChE) activity, and ocular changes in men and monkeys. The subcommittee's assessment of the scientific validity of CDEPAT's proposed human-toxicity estimates for GA is discussed below.

PERCUTANEOUS VAPOR EXPOSURE

Lethal Effects (LCt_{50})

CDEPAT's proposed LCt_{50} estimate for percutaneous exposure to GA vapor is 15,000 mg-min/m^3, assuming that soldiers are wearing light clothing

and are exposed for 30 to 50 min. The existing LCt_{50} is 20,000 mg-min/m ^{3} (Wood 1949).

The original human vapor exposure estimate corresponding to an LCt_{50} was 20,000 mg-min/m^3 but appears to have been established without supporting data or scientific rationale. LCt_{50} data from animal studies varies with species (CDEPAT 1994). For example, exposure of dogs and guinea pigs to GA vapor for 10 min resulted in a higher LCt_{50} value (approximately > 6,100 mg-min/m^3) than exposure of mice for the same time (2,500 mg-min/m^3). The LCt_{50} for the monkey was estimated to be 5,000 to 9,000 mg-min/m^3 for exposure durations of 132 to 305 min (Krackow and Fuhr 1949). The LCt_{50} in rabbits for exposure durations of 120 to 282 min was estimated to be > 20,000 mg-min/m^3 (Marquand and Kethley 1946). The rabbit LCt_{50} was > 20,000 mg-min/m^3 (Marquand and Kethley 1946). However, the mouse, guinea pig, and dog studies involving exposure durations of 10 min and the monkey and rabbit studies involving exposure durations of > 120 min (120 to 305 min) are not applicable in deriving LCt_{50} values for humans. Krackow and Fuhr (1949) exposed 16 men at Cts (concentration × time) of 520 to 2,000 mg-min/m^3 for 10 to 40 min. The men used gas masks and wore only shorts, socks, and shoes. The exposure caused a slight decrease in ChE activity. The authors concluded that such exposure was safe at Cts as high as 2,000 mg-min/m^3. Those human data provide support for CDEPAT's proposed LCt_{50} estimate of 15,000 mg-min/m^3. The subcommittee concludes that the proposed estimate is scientifically valid.

ECt_{50} for Threshold Effects

ECt_{50} for threshold (minimal) effects is the vapor exposure that would result in a significant ChE inhibition (< 15%) but without any identifiable adverse biological consequences.

CDEPAT's proposed ECt_{50} estimate for threshold effects of percutaneous exposure to GA is 2,000 mg-min/m^3 for exposure durations of 30 to 50 min in moderate temperatures. CDEPAT's confidence in this estimate is relatively high and is based on significant ChE inhibition (CDEPAT 1994). There is no existing ECt_{50} estimate for threshold effects (CDEPAT 1994).

Changes in ChE activity have been reported in men and monkeys after percutaneous vapor exposure. The human data indicate that a slight but

significant reduction in ChE activity occurs after percutaneous vapor exposures above 1,000 mg-min/m^3 (Krackow and Fuhr 1949). Data are also available that indicate that men wearing only shorts, socks, and shoes and using gas masks could be safely exposed (that is, without degradation in performance) to vapor doses as high as 2,000 mg-min/m^3 (Krackow and Fuhr 1949). Masks were used to avoid exposures via inhalation and to protect against ocular effects. On the basis of the human data, the subcommittee concludes that CDEPAT's proposed ECt_{50} estimate of 2,000 mg-min/m^3 is scientifically valid.

INHALATION VAPOR EXPOSURE

Lethal Effects (LCt_{50})

CDEPAT's proposed LCt_{50} estimate for inhalation exposure to GA vapor is 70 mg-min/m^3, assuming exposure durations of 2 to 10 min and minute volumes of 15 liters. The existing LCt_{50} value is 135 mg-min/m^3 (CDEPAT 1994).

The LCt_{50}s estimates for GA vary with time. In one study, they were 4 mg-min/m^3, 8 mg-min/m^3, and 16 mg-min/m^3 for exposure durations of 48, 40, and 19 min, respectively (Wills and DeArmon 1954). Questions about the accuracy of those data and the longer exposure time make those data inappropriate for calculating human-toxicity estimates for a 2- to 10-min exposure. Other estimates of the LCt_{50} for humans ranged from 400 to 500 mg-min/m^3 (Welchman 1946). However, the rationale and justification for making such estimates are obscure.

A number of animal studies using a variety of species have been conducted to establish LCt_{50} values following inhalation exposure to GA vapor. Unfortunately, most of those studies were conducted over 50 years ago, and few details concerning the exposure and monitoring aspects of the study were recorded. In general, the LCt_{50} values for GA ranged from 135 to 500 mg-min/m^3 for exposures of 10 min or less. CDEPAT's estimates were largely based on studies using rhesus monkeys in which the LCt_{50}s were 135 and 187 mg-min/m^3 for 2-min and 10-min exposures, respectively (Cresthull et al. 1957).

The poor quality of the animal data used in estimating the LCt_{50} provides little confidence in the ability to predict the human LCt_{50}. Existing human data are also inadequate for estimating LCt_{50} values. Thus,

CDEPAT based its proposed LCt_{50} estimate for humans primarily on the assumption that GA is probably about 0.5 times as potent as GB (HEC 1960).

The subcommittee accepts CDEPAT's approach of assuming that GA is 0.5 times as toxic as GB in deriving its LCt_{50} estimate for this route. The subcommittee recommends that the LCt_{50} estimate for GA be lowered, as was done for GB by the subcommittee. The subcommittee also recommends that further research be conducted to establish the LCt_{50} estimate with a greater degree of confidence.

ECt_{50} for Severe Effects

CDEPAT's proposed ECt_{50} estimate for severe effects following inhalation exposure to GA is 50 mg-min/m^3, assuming exposure durations of 2 to 10 min and minute volumes of 15 liters. CDEPAT's degree of confidence in this estimate is moderate. There is no existing toxicity estimate for ECt_{50} for severe effects following inhalation of GA vapors (CDEPAT 1994).

CDEPAT's proposed ECt_{50} estimate of 50 mg-min/m^3 was derived on the basis of the study by Cresthull et al. (1957), which indicated that the ratio of the incapacitation vapor dose (ICt_{50}) to the LCt_{50} is about 0.75. The reported ICt_{50}s for 2-min and 10-min exposures were 102 and < 180 mg-min/m^3, respectively.

The subcommittee believes that CDEPAT's approach of estimating the ECt_{50} for severe effects is reasonable in its assumption that the ratio of ICt_{50} to LCt_{50} is 0.75. The subcommittee recommends that CDEPAT's estimate of 50 mg-min/m^3 be lowered to correspond to the lowered estimate for LCt_{50} until further research is conducted to establish the ECt_{50} for severe effects with a greater degree of confidence.

ECt_{50} for Mild Effects

CDEPAT's proposed ECt_{50} estimate for mild effects (miosis or rhinorrhea) following exposure to GA vapor is 0.5 mg-min/m^3, assuming a 2-min to 10-min exposure period. The Army's existing ECt_{50} estimate for mild effects is 0.9 mg-min/m^3; the duration of exposure was 5 min (Mumford 1950).

Human data are available that indicate that the proposed ECt_{50} esti

mate could be greater than 0.5 mg-min/m^3. At concentrations of 0.7 mg-min/m^3 and exposure periods ranging from 2 to 10 min, GA could be detected by smell (Udhe and Moore 1945). However, the number of volunteers detecting the odor was not specified. Tightness of the chest was also observed at exposures of 0.7 mg-min/m^3 (Udhe and Moore 1945). In the same study, tightness of the chest and miosis, with impaired vision, occurred at doses ranging from 3.2 to 30 mg-min/m^3 (Udhe and Moore 1945). At higher vapor doses, those effects were accompanied by severe eye pain, headaches, nausea, and vomiting. On the basis of the review of the available data, the subcommittee concludes that CDEPAT's proposed estimate of 0.5 mg-min/m^3 can be raised. The subcommittee recommends that further research be conducted to establish the ECt_{50} estimate with a greater degree of confidence.

PERCUTANEOUS LIQUID EXPOSURE

Lethal Effects (LD_{50})

CDEPAT's proposed LD_{50} for percutaneous exposure to GA liquid on bare skin is 1,500 mg for a 70-kg man. The proposed LD_{50} estimate does not differ from the existing estimate (CDEPAT 1994).

LD_{50} values reported for animals ranged from 1 mg/kg for mice to 30 to 50 mg/kg for dogs. However, it is difficult to use those data for predicting the human LD_{50} estimate because many of the animal studies involved the use of depilated animals (animals whose hair was removed chemically, thus making them more susceptible to toxic effects of chemicals) and others tested only crude material. The proposed LD_{50} estimate for men was based on animal data without the use of uncertainty factors to account for inter-species variability. Thus, the subcommittee concludes that the proposed LD_{50} value for humans is not scientifically defensible because it is based on the use of limited animal data without the use of uncertainty factors. The subcommittee recommends that the proposed estimate be lowered until further research is conducted on GA to establish an LD_{50} estimate With a greater degree of confidence.

ED_{50} for Severe Effects

CDEPAT's proposed estimate for the ED_{50} for severe effects (that is,

incapacitation in 50% of animals, or ID_{50}) following acute percutaneous exposure to GA liquid on bare skin is 880 mg for a 70-kg man. There is no existing ED_{50} estimate (CDEPAT 1994).

Because of the lack of human or animal data on GA for severe effects, the ED_{50} was derived by assuming that the ratio of ID_{50} to LD_{50} is 0.6 (CDEPAT 1994). The assumption that the ratio is 0.6 is based on a study using weanling pigs in which the ratio of ID_{50} to LD_{50} for GB was 0.6 (Silver 1953). CDEPAT assumed the same ratio for GA because GA and GB belong to the same class of compounds. The subcommittee believes that the CDEPAT approach is reasonable. The subcommittee recommends that CDEPAT's estimate of 880 mg for a 70-kg man, based on the ID_{50}-to-LD_{50} ratio of 0.6, be lowered to correspond to the lowered estimate for LD_{50} until further research is done to establish the ED_{50} estimate with a greater degree of confidence.

CONCLUSIONS AND RECOMMENDATIONS

The subcommittee's conclusions concerning CDEPAT's proposed human-toxicity estimates for GA are summarized in Table 2-1.

Of the seven human-toxicity estimates for GA proposed by CDEPAT, the subcommittee agrees that two estimates are scientifically valid for protecting the soldier and recommends that four be lowered and one raised. The subcommittee also recommends the need for additional research to establish human-toxicity estimates with a greater degree of confidence.

TABLE 2-1 Evaluation of Human-Toxicity Estimates for GA

		Human-Toxicity Estimates for GA			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
LCt_{50}[a]	Percutaneous, vapor	20,000 mg-min/m^3	15,000 mg-min/m^3	Proposed estimate is scientifically valid	Proposed estimate supported by human data
	Inhalation, vapor	135 mg-min/m^3	70 mg-min/m^3	Proposed estimate should be lowered	Because of inadequate data on GA for this route, CDEPAT derived the estimate by assuming that GA is 0.5 times as toxic as GB; approach reasonable but estimate should be lowered because of recommended lowering of LCt_{50} for GB for this route; further research recommended
ECt_{50}[b]					
Threshold effects	Percutaneous, vapor	None	2,000 mg-min/m^3	Proposed estimate is scientifically valid	ChE inhibition data used for proposing new recommendation
Severe effects	Inhalation, vapor	None	50 mg-min/m^3	Proposed estimate should be lowered	CDEPAT's proposed estimate based on a study that indicated the ratio of ICt_{50}[e]/LCt_{50} is 0.75; that assumption used to establish ECt_{50} for severe effects; the subcommittee recommends that the ECt_{50} estimate be lowered to correspond to the lowered estimate for LCt_{50}; further research recommended
Mild effects	Inhalation, vapor	0.9 mg-min/m^3	0.5 mg-min/m^3	Proposed estimate should be raised	Human data show that humans can tolerate higher exposures; further research recommended

		Human-Toxicity Estimates for GA			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
LD_{50}[c]	Percutaneous, liquid	1,500 mg for 70-kg man	1,500 mg for 70-kg man	Proposed estimate should be lowered	No uncertainty factors used in lieu of limited animal data for proposed estimate; further research recommended
ED_{50}[d]	Percutaneous, liquid	None	880 mg for 70-kg man	Proposed estimate should be lowered	In the absence of adequate human or animal data for this effect, CDEPAT established the estimate by assuming ID_{50}[f]/LD_{50} ratio of 0.6 to estimate ED_{50}; the subcommittee recommends that the ED_{50} estimate be lowered to correspond to the lowered estimate for LD_{50}; further research recommended

[a] LCt_{50}: Vapor exposure that produces lethality in 50% of the exposed animals. Ct refers to the product of concentration (c) and exposure time (t). Note that Ct is not necessarily a constant.
[b] ECt_{50}: Percutaneous vapor exposure or inhalation vapor exposure causing a defined effect (e.g., incapacitation, severe effects, mild effects, threshold effects).
[c] LD_{50}: Liquid dose causing lethality in 50% of the exposed animals.
[d] ED_{50}: Liquid dose causing a defined effect in 50% of the exposed animals.
[e] ICt_{50}: Vapor exposure that produces incapacitation in 50% of the exposed population.
[f] ID_{50}: Liquid dose causing incapacitation in 50% of the exposed population.

3—

Review of Acute Human-Toxicity Estimates for GB (Sarin)

GB (Sarin or isopropyl methylphosphonofluoridate) is an organophosphate nerve agent. The physical and chemical properties, toxico-kinetics, and toxicity of GB are discussed in detail by CDEPAT (1994), Marrs et al. (1996), and Somani (1994). Only a few toxicity end points were considered (for example, lethality in animals, incapacitation, changes in cholinesterase (ChE) activity, and ocular effects). The subcommittee's assessment of the scientific validity of CDEPAT's proposed human-toxicity estimates for GB is discussed below.

PERCUTANEOUS VAPOR EXPOSURE

Lethal Effects (LCt_{50})

After reviewing the available animal lethality data, CDEPAT proposed a human LCt_{50} estimate of 10,000 mg-min/m^3 following percutaneous exposure to GB vapor, assuming light clothing and exposure durations of 30 to 50 min for the soldiers. The existing LCt_{50} estimate is 15,000 mg-min/m^3 (CDEPAT 1994).

The Army's proposed estimate is supported by an LCt_{50} of 9,700 mg

min/m^3 in monkeys exposed to hot temperatures (80–95°F) and moderate relative humidity (35% to 55%) (Oberst et al. 1952). On the basis of the monkey and human studies, a lethal Ct (concentration × time) for humans was estimated to be slightly higher than 12,800 mg-min/m^3 (McGrath et al. 1951). Silver (1953) estimated the LCt_{50} to be about 15,000 mg-min/m^3; the estimate was based on studies of McGrath et al. (1951) who investigated the inhibition of cholinesterase (ChE) in monkeys and men exposed to GB. The subcommittee believes that, on the basis of available data, 10,000 mg-min/m^3 is a conservative estimate of the human LCt_{50}.

The preliminary studies involved exposure to the right forearm, and data from these studies were used to determine the whole-body exposures. Therefore, the subcommittee concludes that CDEPAT's LCt_{50} estimate of 10,000 mg-min/m^3 for GB is scientifically valid.

ECt_{50} for Threshold Effects

CDEPAT's proposed ECt_{50} estimate for threshold (minimal) effects following percutaneous exposure to GB vapor is 1,200 mg-min/m^3, assuming light clothing and exposure durations of 30 to 50 min. There is no existing ECt_{50} estimate for threshold effects (CDEPAT 1994).

The Army's proposed estimate of 1,200 mg-min/m^3 is based on human data using the most appropriate study (McGrath et al. 1951). Exposures of 190 to 1,010 mg-min/m^3 (concentrations of 21 to 92 mg/m^3; durations of 9 to 11 min) resulted in ChE levels of 95% to 108% of baseline; all subjects were asymptomatic, supporting a no-effect level of < 1,000 mg-min/m^3 (McGrath et al. 1951). Humans exposed at 1,255 to 1,850 mg-min/m^3 (concentrations of 81 to 109 mg/m^3; exposure durations of 11.5 to 20 min) had ChE activities ranging from 31% to 90%. Two of nine individuals were asymptomatic, and the other seven experienced sweating that persisted for a minimum of 24 hr and a maximum of 30 days (McGrath et al. 1951). Therefore, the subcommittee concludes that CDEPAT's proposed ECt_{50} estimate for threshold effects is scientifically valid.

INHALATION VAPOR EXPOSURE

Lethal Effects (LCt_{50})

CDEPAT's proposed LCt_{50} estimate following inhalation exposure to GB vapor is 35 mg-min/m^3, assuming minute volumes of 15 liters and exposure

durations of 2 to 10 min. The existing LCt_{50} estimate is 70 mg-min/m ^{3} (CDEPAT 1994).

The LCt_{50} data for inhalation exposure for several animal species (mouse, rat, primate, dog, rabbit, cat, and pig) provide an LCt_{50} estimate for humans of 60 mg-min/m^3 for 10-min exposures. The average ratio (of LCt_{50} for GA, GB, and GF) for 10-min and 2-min exposures was calculated to be 0.6 (CDEPAT 1994) and that ratio was also supported by a classified study. Using a factor of 0.6 to estimate the 2-min LCt_{50} from the 10-min LCt_{50}, CDEPAT obtained a value of 35 mg-min/m ^{3} ($60 \times 0.5 \approx 35$).

Human data from the Adamek Report (as cited in Wills and DeArmon 1954) showed deaths in four of four subjects exposed at 4 mg/m^3 for 10 min (a Ct (concentration × time) of 40 mg-min/m^3). Data were available for 48 other subjects, all of whom received some type of post-exposure therapy. Using data from exposed and unexposed individuals, the authors calculated an LCt_{50} of 24 mg-min/m^3 (Wills and DeArmon 1954). However, on the basis of the 100% lethality observed in humans exposed at 40 mg-min/m^3, the subcommittee recommends that the CDEPAT's proposed LCt_{50} estimate of 35 mg-min/m^3 be lowered. The subcommittee also recommends that further research be conducted to establish the LCt_{50} estimate for inhalation with a greater degree of confidence.

ECt_{50} for Severe Effects

CDEPAT's proposed ECt_{50} estimate for severe effects following inhalation exposure to GB vapor is 25 mg-min/m^3, assuming minute volumes of 15 liters and exposure durations of 2 to 10 min. The existing ECt_{50} estimate is 35 mg-min/m^3 (CDEPAT 1994).

In the absence of adequate data on GB for this effect, CDEPAT's proposed estimate is based on the assumption that the ratio of ICt_{50} (incapacitation dose for 50% of a given population) and LCt_{50} is about 0.7. The ratio is supported by a study conducted in monkeys (Cresthull et al. 1957). The proposed ECt_{50} estimate of 25 mg-min/m^3 was calculated by multiplying the LCt_{50} of 35 mg-min/m^3 by 0.7, which equals 25 mg-min/m^3. The subcommittee believes this approach is reasonable. However, the subcommittee recommended that the LCt_{50} for inhalation exposure be lowered; therefore, the ECt_{50} should be lowered correspondingly. The subcommittee recommends that further research be conducted to establish the ECt_{50} for severe effects with a greater degree of confidence.

ECt_{50} for Mild Effects

CDEPAT's recommended ECt_{50} estimate for mild effects (miosis or rhinorrhea) after exposure to GB vapor is 0.5 mg-min/m^3, assuming exposure durations of 2 to 10 min. That estimate is independent of minute volume. The existing ECt_{50} estimate is 2 mg-min/m^3 (CDEPAT 1994). A question that needs to be addressed is the degree of miosis and rhinorrhea that should be used to estimate the ECt_{50} for mild effects. The data listed in the CDEPAT report do not support CDEPAT's (1994) conclusion that "Review of other human data indicated that miosis and rhinorrhea probably occur in at least 50% of the population at GB doses of • 1.0 mg-min/m^3." Further, some reports suggest that neither miosis nor rhinorrhea occurred at 0.5 mg-min/m^3. The threshold symptoms appear to occur at exposures of approximately 2 mg-min/m^3. Thus, the ECt_{50} value could be slightly higher (because of a steep dose-response curve) for the nerve agents.

The subcommittee concludes that CDEPAT's estimate of 0.5 mg-min/m^3 is not supported by the available data, which indicate that the value is higher; therefore, the subcommittee recommends that the proposed estimate be raised. The subcommittee also recommends that further research be conducted to establish the ECt_{50} for mild effects with a greater degree of confidence.

PERCUTANEOUS LIQUID EXPOSURE

Lethal Effects (LD_{50})

CDEPAT's proposed LD_{50} estimate for percutaneous exposure to GB liquid on bare skin is 1,700 mg for a 70-kg man. That estimate is the same as the existing estimate (CDEPAT 1994). The proposed value was calculated using a ratio of ChE_{50} inhibition levels in rabbits (whole blood) to ChE_{50} inhibition levels in humans (red blood cells) (CDEPAT 1994). In rabbits, a reduction of 88.8% ChE resulted in 53% deaths. In humans, ChE_{50} inhibition was based on exposure of bare skin and was estimated to be between 350 and 400 mg for a 70-kg man. One of three subjects who died was exposed to a concentration of 20 mg of GB liquid under one layer of serge plus one layer of flannel and showed a 96% inhibition of ChE. The two other subjects showed 82% and 87% ChE inhibition but had no clinical symptoms. On the basis of the limited and inconsistent data in humans, the

subcommittee concludes that the degree of confidence in CDEPAT's estimate is low. The subcommittee recommends that the proposed LD_{50} estimate of 1,700 mg for a 70-kg man be considered an interim value until further research is done. The subcommittee also recommends that further research be conducted to establish the LD_{50} estimate with a greater degree of confidence.

ED_{50} for Severe Effects

CDEPAT's proposed ED_{50} for severe effects after percutaneous exposure to GB liquid on bare skin is 1,000 mg for a 70-kg man. There is no existing toxicity estimate for GB via this route (CDEPAT 1994).

Data are not sufficient to estimate the human ED_{50} for severe effects after percutaneous exposure to liquid GB, and there are few estimates. The proposed estimate of 1,000 mg per a 70-kg man is based on data assuming that the ID_{50}-to-LD_{50} ratio of 0.6 is valid. The data were extrapolated from relative similarities in ChE inhibition in pigs and humans; the human LD_{50} was estimated to be 2,500 mg for a 70-kg man, and the ID_{50} was estimated to be 1,500 mg for a 70-kg man (Silver 1953). Thus, the ratio of 0.6 (1,500 mg for a 70-kg man to 2,500 mg for a 70-kg man = 0.6) was used to estimate the ED_{50} for severe effects from percutaneous liquid exposure to GB (Reutter et al. 1992). The subcommittee supports CDEPAT's proposed ED_{50} estimate of 1,000 mg for a 70-kg man ($0.6 \times 1{,}700 \approx 1{,}000$) as an interim value. The subcommittee recommends that further research be conducted to establish the ED_{50} estimate for severe effects with a greater degree of confidence.

CONCLUSIONS AND RECOMMENDATIONS

The subcommittee's conclusions concerning CDEPAT's proposed estimates for GB are summarized in Table 3-1.

Of the seven human-toxicity estimates for GB proposed by CDEPAT, the subcommittee agrees that two estimates are scientifically valid for protecting soldiers. The subcommittee recommends that two serve as interim estimates, two be lowered, and one raised. The subcommittee recommends further research for most of the adverse health effects to establish the estimates with a greater degree of confidence.

TABLE 3-1 Evaluation of Human-Toxicity Estimates for GB

		Human-Toxicity Estimates for GB			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GB	Rationale for Subcommittee's Evaluation
LCt_{50}[a]	Percutaneous, vapor	15,000 mg-min/m^3	10,000 mg-min/m^3	Proposed estimate is scientifically valid	Proposed estimate supported by studies in monkeys and humans
	Inhalation, vapor	70 mg-min/m^3	35 mg-min/m^3	Proposed estimate should be lowered	Estimate too high because human studies show 100% lethality at 40 mg-min/m^3
ECt_{50}[b]					
Threshold effects	Percutaneous, vapor	None	1,200 mg-min/m^3	Proposed estimate is scientifically valid	Estimate supported by studies of ChE inhibition in humans; further research recommended
Severe effects	Inhalation, vapor	35 mg-min/m^3	25 mg-min/m^3	Proposed estimate should be lowered	ECt_{50}/LCt_{50} ratio of 0.7 used to develop estimate; LCt_{50} for this route of exposure was lowered; therefore, ECt_{50} should be lowered correspondingly; further research recommended
Mild effects	Inhalation, vapor	2 mg-min/m^3	0.5 mg-min/m^3	Proposed estimate should be raised	No effects in humans at 0.5 mg-min/m^3; effects begin to appear at ≈ 2 mg-min/m^3; further research recommended
LD_{50}[c]	Percutaneous, liquid	1,700 mg for 70-kg man	1,700 mg for 70-kg man	Low confidence in proposed estimate; proposed estimate should serve as interim value	Estimate based on a ratio of ChE inhibition in rabbits and humans; however, human data concerning the relation between ChE inhibition and adverse effects are inconsistent; further research recommended

		Human-Toxicity Estimates for GB			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GB	Rationale for Subcommittee's Evaluation
ED_{50}[d]					
Severe effects	Percutaneous, liquid	None	1,000 mg for 70-kg man	Proposed estimate should serve as interim value	In the absence of adequate data on GB for this effect, CDEPAT assumed that the ratio of ID_{50}[e]/LD_{50} is 0.6 and used that to estimate the ED_{50} values; further research recommended

[a] LCt_{50}: Vapor exposure that produces lethality in 50% of the exposed animals. Ct refers to the product of concentration (c) and exposure time (t). Note that Ct is not necessarily a constant.
[b] ECt_{50}: Percutaneous vapor exposure or inhalation vapor exposure causing a defined effect (e.g., incapacitation, severe effects, mild effects, threshold effects).
[c] LD_{50}: Liquid dose causing lethality in 50% of the exposed animals.
[d] ED_{50}: Liquid dose causing a defined effect in 50% of the exposed animals.
[e] ID_{50}: Liquid dose causing incapacitation in 50% of the exposed population.

4—

Review of Acute Human-Toxicity Estimates for GD (Soman)

GD (Soman or 1,2,2-trimethyl propyl methylphosphonofluoridate) is an organophosphate nerve agent. It is a colorless, volatile liquid. The physical and chemical properties, toxicokinetics, and toxicity of GD are discussed in detail by CDEPAT (1994), Marrs et al. (1996), and Somani (1994). Human-toxicity estimates have been derived for percutaneous vapor exposures, vapor inhalation exposures, and percutaneous liquid exposures. Only a few toxicity end points were considered (for example, lethality in animals and incapacitation). The subcommittee's assessment of the scientific validity of CDEPAT's human-toxicity estimates for GD is discussed below.

PERCUTANEOUS VAPOR EXPOSURE

Lethal Effects (LCt_{50})

CDEPAT's proposed LCt_{50} estimate following percutaneous exposure to GD vapors is 2,500 mg-min/m^3, assuming that soldiers are wearing light clothing, temperatures are moderate, and exposure durations are 30 to 50

min. There is no existing LCt_{50} estimate for exposures to percutaneous vapor (CDEPAT 1994).

No human data on GD are available for this effect. LCt_{50} values derived from studies in monkeys range from 1,750 to 28,000 mg-min/m^3 (Cresthull 1957). Because data on the effects of percutaneous exposure to GD vapor are extremely limited and are insufficient for developing human-toxicity estimates, CDEPAT recommended that estimates for GD be based on toxicity information on GB, assuming that GD is 4 times more potent than GB. This assumption is supported by empirical evidence in dogs and rabbits, showing that the percutaneous potency of GD vapor is at least 2 times and maybe 5 times that of GB (Van de Wal and Zeffert 1970).

The subcommittee concludes that the approach used by CDEPAT to estimate the LCt_{50} of GD is scientifically valid and defensible, because (1) GD and GB belong to the same class of chemicals (organophosphates) and are structurally similar, and (2) animal data support the assumption that GD is 4 times more potent than GB. On the basis of the available data, the subcommittee concludes that the CDEPAT's LCt_{50} estimate of 2,500 mg-min/m^3 is scientifically valid.

ECt_{50} for Threshold Effects

CDEPAT's proposed estimate for the ECt_{50} for threshold (minimal) effects after percutaneous exposure to GD vapor is 300 mg-min/m^3, assuming light clothing, exposure durations of 30 to 50 min, and moderate temperatures. There is no existing toxicity estimate for threshold effects from exposure to percutaneous vapor (CDEPAT 1994).

No human data are available to estimate this effect level. In deriving the ECt_{50} for threshold effects, CDEPAT assumed that GD vapor is 4 times more potent than GB vapor (CDEPAT 1994). This assumption was based on a report (Cullumbine et al. 1954) showing that the LCt_{50} for GD was 4 times lower than GB. However, CDEPAT has a low degree of confidence in this estimate because of insufficient data.

The subcommittee agrees with CDEPAT's approach of basing the ECt_{50} estimate for GD on toxicity data from GB and assuming that GD is 4 times more potent than GB. The subcommittee also agrees with CDEPAT that the confidence in the ECt_{50} estimate is low to moderate because of sparse data on both compounds. The subcommittee recommends that CDEPAT's proposed estimate of 300 mg-min/m^3 serve as an interim value

until further research is conducted to establish the ECt_{50} estimate for thresh-old effects with a greater degree of confidence.

INHALATION VAPOR EXPOSURE

Lethal Effects (LCt_{50})

CDEPAT's proposed estimate for the LCt_{50} following inhalation exposure to GD vapor is 35 mg-min/m^3, assuming exposure durations of 2 to 10 min, minute volumes of 15 liters, and moderate temperatures. The existing toxicity estimate is 70 mg-min/m^3.

CDEPAT's proposed estimate for the LCt_{50} is based on the assumption that GD and GB are equipotent. The equipotency of GD and GB via inhalation is supported by recent data reported by Schoene et al. (1985).

The subcommittee agrees with CDEPAT's approach of basing the LCt_{50} estimate for GD on toxicity data from GB for reasons previously stated. The subcommittee also agrees with CDEPAT's conclusion that the confidence in the LCt_{50} estimate is low because the data on both compounds are sparse. Because the subcommittee recommends lowering the LCt_{50} estimate for GB, it also recommends that the estimate for GD be lowered correspondingly. The subcommittee recommends that further research be conducted to establish the LCt_{50} estimate with a greater degree of confidence.

ECt_{50} for Severe Effects

CDEPAT's proposed estimate for ECt_{50} for severe effects following inhalation exposure to GD vapor is 25 mg-min/m^3, assuming exposure durations of 2 to 10 min, minute volumes of 15 liters, and moderate temperatures. The existing toxicity estimate is 35 mg-min/m^3, (CDEPAT 1994).

The inhalation data needed to develop an estimate for the severe effects of GD are insufficient. CDEPAT assumed that the potencies of GD and GB via the inhalation route are comparable and proposed identical toxicity estimates.

The subcommittee agrees with CDEPAT's approach of basing the ECt_{50} estimate for GD on toxicity data from GB, because (1) GD and GB belong to the same class of chemicals (organophosphates) and are structurally similar, and (2) animal data support the assumption that GD is equipo

tent to GB for severe effects via the inhalation route (CDEPAT 1994). The basis of this assumption is a study by Cresthull et al. (1957) in which the ratio of ICt_{50} to LCt_{50} for GB was 0.7. Because GB and GD have similar structures and similar modes of action, CDEPAT assumed that the ratio of 0.7 for GB would also hold true for GD. However, the subcommittee concludes that the confidence in the ECt_{50} value is low because of sparse data on both compounds. The subcommittee recommends that CDEPAT's proposed estimate of 25 mg-min/m^3 be lowered to correspond to the subcommittee's recommendation for lowering the ECt_{50} for GB until further research is done to establish the estimate with a greater degree of confidence.

ECt_{50} for Mild Effects

CDEPAT's proposed estimate for ECt_{50} for mild (ocular and/or nasal) effects for GD is 0.2 mg-min/m^3, assuming exposure durations of 2 to 10 min and moderate temperatures. This local effect is not affected by minute volume. There is no existing ECt_{50} estimate for GD (CDEPAT 1994).

Sufficient human data are not available to calculate an ECt_{50} for mild effects following ocular exposure to GD. One study in which rabbits were exposed under identical conditions to GB and GD showed that GD is a 2.5-times more potent miotic agent than GB via inhalation exposure (Callaway and Dirnhuber 1971). Thus, in deriving the ECt_{50} estimate for GD, CDEPAT assumed that GD is 2.5 times more potent than GB for ocular effects (Callaway and Dirnhuber 1971).

The subcommittee agrees with CDEPAT's approach of assuming that the ocular toxicity of GD is 2.5 times greater than that of GB. The subcommittee also agrees with the conclusion of CDEPAT that the confidence in the ECt_{50} estimate is low because of sparse data on both compounds. In addition, because the subcommittee recommends raising the ECt_{50} for GB, it concludes that the estimate for GD should be raised correspondingly for ocular effects until further research is done to establish the estimate with a greater degree of confidence.

PERCUTANEOUS LIQUID EXPOSURE

Lethal Effects (LD_{50})

CDEPAT's proposed estimate for the LD_{50} value is 350 mg for a 70-kg

man, or 5 mg/kg. The existing LD_{50} estimate for GD following percutaneous liquid exposure is the same (CDEPAT 1994).

The available animal-toxicity data are insufficient for estimating the human LD_{50} for percutaneous exposure to GD liquid with any degree of confidence. The most often quoted estimate is 350 mg for a 70-kg man, an estimate based on a study by Cullumbine et al. (1954) investigating the effect of percutaneous exposure of rabbits to GD liquid. The rabbit is more sensitive to GD liquid than any other nonhuman species (Henry 1989). The reported LD_{50}s in animals range from < 1 to 14 mg/kg (< 70 to 980 mg for a 70-kg man). Given this wide range in LD_{50} values, the subcommittee's degree of confidence in CDEPAT's proposed estimate of 350 mg for a 70-kg man is moderately low. The subcommittee recommends that CDEPAT's proposed estimate serve as an interim value until further research is conducted to establish this estimate with a greater degree of confidence.

ED_{50} for Severe Effects

CDEPAT's proposed estimate for the ED_{50} for severe effects following percutaneous exposure to GD liquid on bare skin is 200 mg for a 70-kg man or approximately 3 mg/kg. There is no existing ED_{50} estimate for GD (CDEPAT 1994).

The available data are insufficient for estimating the human ED_{50} for severe effects (incapacitation, prostration, collapse, and convulsion) after percutaneous exposure to GD liquid. Data on exposure of pigs indicate that the slopes for lethality and severe effects are parallel and that the ID_{50}-to-LD_{50} ratio is about 0.8 (Manthei et al. 1988; CDEPAT 1994). Other data suggest that the ratio is approximately 0.6 (Reutter et al. 1992). On the basis of the more conservative ratio of 0.6, CDEPAT derived the human-toxicity estimate of 3 mg/kg (5 mg/kg (LD_{50}) × 0.6 = 3 mg/kg). In the absence of adequate human data or animal data on GD for this effect, the subcommittee accepts CDEPAT's approach of using the ID_{50}-to-LD_{50} ratio of 0.6 to derive the ED_{50} estimate. The subcommittee's degree of confidence in CDEPAT's proposed estimate is low to moderate because of the insufficient data. The subcommittee recommends that the proposed estimate serve as an interim value until further research is conducted to establish this estimate with a greater degree of confidence.

CONCLUSIONS AND RECOMMENDATIONS

The subcommittee's conclusions concerning CDEPAT's proposed estimates for GD are summarized in Table 4-1. Of the seven human-toxicity estimates for GD proposed by CDEPAT to protect soldiers from the toxic effects of CW agents, the subcommittee agrees that one estimate is scientifically valid. The subcommittee recommends that two of the estimates be lowered, and three be considered interim estimates. It also concludes that one estimate should be raised.

TABLE 4-1 Evaluation of Human-Toxicity Estimates for GD

		Human-Toxicity Estimates for GB			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GB	Rationale for Subcommittee's Evaluation
LCt_{50}[a]	Percutaneous, vapor	None	2,500 mg-min/m^3	Proposed estimate is scientifically valid	Proposed estimate based on assumption that GD is 4 times more toxic than GB for percutaneous exposure
	Inhalation, vapor	70 mg-min/m^3	35 mg-min/m^3	Proposed estimate should be lowered	Proposed estimate based on the assumption that GD and GB are equipotent via this route; subcommittee recommends that LCt_{50} estimate for GD be lowered to correspond to lowered estimate for GB; further research recommended
ECt_{50}[b]					
Threshold effects	Percutaneous, vapor	None	300 mg-min/m^3	Proposed estimate should serve as an interim value	In the absence of adequate human or animal data, proposed estimate based on assumption that GD is 4 times more toxic than GB for percutaneous exposure; further research recommended
Severe effects	Inhalation, vapor	35 mg-min/m^3	25 mg-min/m^3	Proposed estimate should be lowered	In the absence of adequate human or animal data, proposed estimate based on assumption that potenies of GD and GB are comparable; ECt_{50} estimate for GD should be lowered to correspond to the lowered estimate for GB; further research recommended
Mild effects	Inhalation, vapor	None	0.2 mg-min/m^3	Proposed estimate should be raised	In the absence of adequate human or animal data, proposed estimate based on assumption that GD is 2.5 times more potent than GB for miotic effects; subcommittee recommends that the LCt_{50} estimate for GD be raised to correspond to the recommended raised estimate for GB; further research recommended

		Human-Toxicity Estimates for GB			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GB	Rationale for Subcommittee's Evaluation
LD_{50}[c]	Percutaneous, liquid	350 mg for 70-kg man	350 mg for 70-kg man	Proposed estimate should serve as an interim value	Because of wide range of LD_{50} values in animals, subcommittee's confidence in the proposed estimate is low; CDEPAT's proposed estimate of 350 mg for 70-kg man should serve as an interim value; further research recommended
ED_{50}[d]					
Severe effects	Percutaneous, liquid	None	200 mg for 70-kg man	Proposed estimate should serve as an interim value	In the absence of adequate human or animal data, proposed estimate was derived using the ID_{50}[e]/LD_{50} ratio of 0.6; the subcommittee recommends that CDEPAT's proposed estimate serve as an interim value; further research recommended

[a] LCt_{50}: Vapor exposure that produces lethality in 50% of the exposed animals. Ct refers to the product of concentration (c) and exposure time (t). Note that Ct is not necessarily a constant.

[b] ECt_{50}: Percutaneous vapor exposure or inhalation vapor exposure causing a defined effect (e.g., incapacitation, severe effects, mild effects, threshold effects).

[c] LD_{50}: Liquid dose causing lethality in 50% of the exposed animals.

[d] ED_{50}: Liquid dose causing a defined effect in 50% of the exposed animals.

[e] ID_{50}: Liquid dose causing incapacitation in 50% of the exposed population.

5—

Review of Acute Human-Toxicity Estimates for GF

GF (cyclohexyl methylphosphonofluoridate) is an organophosphate nerve agent. The physical and chemical properties, toxicokinetics, and toxicity of GF are discussed in detail by CDEPAT(1994), Marrs et al. (1996), and Somani (1994). Human-toxicity estimates have been derived for percutaneous vapor exposures, vapor inhalation exposures, and for percutaneous liquid exposures. Only a few toxicity end points were considered; they include lethality and cholinesterase (ChE) inhibition in humans and animals. The subcommittee's assessment of the scientific validity of CDEPAT's proposed human-toxicity estimates for GF is discussed below.

PERCUTANEOUS VAPOR EXPOSURE

Lethal Effects (LCt_{50})

CDEPAT's proposed LCt_{50} estimate for percutaneous exposure to GF vapor is 2,500 mg-min/m^3, assuming exposure durations of 30 to 50 min and

moderate temperatures. The existing estimate is 15,000 mg-min/m^3 (CDEPAT 1994).

In a study conducted with rhesus monkeys, 10 animals each weighing 2.7 to 5.9 kg were exposed to GF vapor. An LCt_{50} value of 10,000 mg-min/m^3 was reported (McGrath et al. 1953). It is important to note that the animals were clipped, allowing for maximum skin exposure. Exposure durations varied from 31 to 345 min with an average atmospheric concentration of 105 mg/m^3. Animals were exposed until they died. That type of exposure is a serious limitation of the study, because exposure until death necessarily results in higher LCt_{50} values. Had animals been exposed to lower vapor Cts (concentration X exposure time) and followed for 24 to 48 hr, the LCt_{50} might be lower.

CDEPAT proposed lowering the existing estimate of 15,000 mg-min/m^3 to 2,500 mg-min/m^3. The subcommittee agrees with CDEPAT's proposal to lower the estimate, but it believes that insufficient evidence was provided for lowering the estimate to 2,500 mg-min/m^3. Therefore, the subcommittee recommends that CDEPAT's proposed estimate of 2,500 mg-min/m^3 serve as an interim value until further research is done. The subcommittee also recommends that a study be conducted at different exposure levels and observations made 24 to 48 hr after exposure to obtain data to more accurately determine the LCt_{50}.

ECt_{50} for Threshold Effects

CDEPAT's proposed ECt^{50} estimate for threshold (minimal) effects from exposure to GF is 300 mg-min/m^3, assuming exposure durations of 30 to 50 min and moderate temperatures. There is no existing ECt_{50} estimate for threshold effects (CDEPAT 1994).

No human or animal data are available for estimating the ECt_{50} for threshold effects (CDEPAT 1994). The proposed estimate is based on the assumption that GD and GF are equipotent (Cullumbine et al. 1954). The subcommittee believes that, in the absence of adequate data on GF exposure of humans and animals, CDEPAT's approach of assuming equipotencies for GF and GD and thus proposing the same ECt_{50} estimates is reasonable.

The subcommittee recommends that CDEPAT's proposed estimate of 300 mg-min/m^3 serve as an interim value until further research on GF is conducted to establish the ECt_{50} estimate with a greater degree of confidence.

INHALATION VAPOR EXPOSURE

Lethal Effects (LCt_{50})

CDEPAT's proposed LCt_{50} estimate for inhalation exposure to GF vapor is 35 mg-min/m^3, assuming exposure durations of 2 to 10 min, moderate temperatures, and minute volumes of 15 liters. There is no existing LCt_{50} estimate (CDEPAT 1994).

No data are available concerning the toxicity of GF in humans following inhalation exposures, and the animal data are insufficient for deriving an LCt_{50} estimate (CDEPAT 1994).

LCt_{50} studies were conducted in rats and monkeys. The LCt_{50}s for male and female Wistar rats exposed for 1 min were 181 mg-min/m^3 and 110 mg-min/m^3, respectively (Callaway and Blackburn 1954). In a study using 44 rhesus monkeys, the LCt_{50} was determined for 2-min and 10-min durations. The reported LCt_{50}s for GF were 130 mg-min/M ^{3} and 75 mg-min/m^3 for 2-min and 10-min exposures, respectively (Cresthull et al. 1957). These studies are considered inadequate for deriving human LCt_{50} estimate.

The proposed estimate of 35 mg-min/m^3 is based on the assumption that GF is as potent as GB or GD (CDEPAT 1994). That assumption is supported by animal studies (Cresthull et al. 1957) that show that GF, GB, and GD have equal potencies for this effect via inhalation vapor exposures (CDEPAT 1994). The subcommittee recommends that the proposed LCt_{50} estimate for GF be lowered to correspond to that recommended for GB. The subcommittee also recommends that further research on GF be conducted to establish this estimate with a greater degree of confidence.

ECt_{50} for Severe Effects

CDEPAT's proposed ECt_{50} estimate for severe effects from inhalation exposure to GF is 25 mg-min/m^3, assuming exposure durations of 2 to 10 min, moderate temperatures, and minute volumes of 15 liters. There is no existing ECt_{50} estimate (CDEPAT 1994).

No data are available on severe effects in humans, and the studies on severe effects following inhalation exposures in animals are inadequate.

In the absence of data in humans and animals, CDEPAT's proposed estimate of 25 mg-min/m^3 is based on the assumption that GF is as potent

as GD and GB (CDEPAT 1994) in monkeys and other species by the inhalation route. That assumption is supported by animal studies that show that GF, GB, and GD are equipotent for this effect via inhalation vapor exposures (Cresthull et al. 1957; CDEPAT 1994). In the absence of adequate data on GF for severe effects, the subcommittee recommends that CDEPAT's proposed ECt_{50} estimate be lowered to correspond to lowered estimates for GB and GD until further research on GF is conducted to establish the estimate with a greater degree of confidence.

ECt_{50} for Mild Effects

CDEPAT's proposed ECt_{50} estimate for ocular effects from exposure to GF is 0.2 mg-min/m^3, assuming exposure durations of 2 to 10 min and moderate temperatures. There is no existing ECt_{50} estimate (CDEPAT 1994).

No data are available on the ocular toxicity of GF in humans or experimental animals. The proposed estimate is based on the assumption that GF and GD are equipotent (Cullumbine et al. 1954). The subcommittee agrees with CDEPAT's approach. The subcommittee recommends that CDEPAT's ECt_{50} estimate for ocular effects be raised to correspond to the recommended raised estimate for GD until further research is conducted on GF to establish this estimate with a greater degree of confidence.

PERCUTANEOUS LIQUID EXPOSURE

Lethal Effects (LD_{50})

CDEPAT's proposed LD_{50} estimate for percutaneous exposure to GF vapor is 350 mg for a 70-kg man, assuming exposure at moderate temperatures. There is no existing LD_{50} estimate (CDEPAT 1994).

Limited human data are available, and the data that are available suggests a fourfold variation in ChE inhibition. Studies have been conducted in rabbits and pigs to determine the LCt_{50} of GF liquid after percutaneous exposure. In one study (Marzulli et al. 1952), rabbits were exposed at four levels. A similar protocol was used for pigs. The LD_{50} in rabbits was 1.3 mg/kg (91 mg for a 70-kg man); the LD_{50} in pigs was 16.5 mg/kg (1,155 mg for a 70-kg man). On the basis of the rabbit data, CDEPAT concluded that liquid GF poses a serious threat to soldiers in a moderate climate.

The proposed LD_{50} estimate assumes that GF and GD are equipotent

(Cullumbine et al. 1954). The subcommittee believes that, in the absence of adequate data, the use of this assumption is a reasonable approach. The subcommittee recommends that CDEPAT's estimate of 350 mg for a 70-kg man be considered an interim estimate until further research on GF is conducted to establish this estimate with a greater degree of confidence.

ED_{50} for Severe Effects

CDEPAT's proposed ED_{50} estimate for severe effects from percutaneous liquid exposure to GF is 200 mg for a 70-kg man, assuming exposure durations of 2 to 10 min and moderate temperatures. There is no existing ED_{50} estimate (CDEPAT 1994).

In the absence of adequate human and animal data on the severe effects following percutaneous exposure to GF liquid, CDEPAT (1994) assumed that GD and GF are equipotent. The subcommittee concludes that the approach used by CDEPAT (1994) to derive the ED_{50} is reasonable and recommends that the proposed estimate be considered an interim value until further research on GF is conducted to establish this estimate with a greater degree of confidence.

CONCLUSIONS AND RECOMMENDATIONS

The subcommittee's conclusions concerning CDEPAT's proposed estimates for GF are summarized in Table 5-1.

Of the seven acute human-toxicity estimates for GF proposed by CDEPAT (1994), the subcommittee agrees that the estimates are not scientifically valid or appropriate for protecting soldiers. Four estimates are recommended to serve as interim values until further research is conducted, one estimate should be raised, and two estimates should be lowered. The subcommittee recommends that further research be conducted to establish estimates with a greater degree of confidence.

TABLE 5-1 Evaluation of Human-Toxicity Estimates for GF

		Human-Toxicity Estimates for GF			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GF	Rationale for Subcommittee's Evaluation
LCt_{50}[a]	Percutaneous, vapor	15,000 mg-min/m^3	2,500 mg-min/m^3	Proposed estimate should serve as an interim value	Rationale for the CDEPAT estimate not supported by data; further research recommended
	Inhalation, vapor	None	35 mg-min/m^3	Proposed estimate should be lowered	In the absence of adequate data, proposed estimate based on assumption that GF, GD, and GB are equipotent; approach is reasonable; because LCt_{50} for GB was recommended to be lowered, proposed value for GF should be lowered correspondingly; further research recommended
ECt_{50}[b]					
Threshold effects	Percutaneous, vapor	None	300 mg-min/m^3	Proposed estimate should serve as an interim value	Proposed estimate based on assumption that GF and GD are equipotent; approach is reasonable; further research recommended
Severe effects	Inhalation, vapor	None	25 mg-min/m^3	Proposed estimate should be lowered	In the absence of adequate data, proposed estimate based on assumption that GF, GD, and GB are equipotent; approach is reasonable, because ECt_{50}s for severe effects for GB and GD were recommended to be lowered, proposed value for GF should be lowered correspondingly; further research recommended

Toxicity Type	Route and Form of Exposure	Human-Toxicity Estimates for GF: Existing Estimates	Human-Toxicity Estimates for GF: CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GF	Rationale for Subcommittee's Evaluation
Mild effects	Inhalation, vapor	None	0.2 mg-min/m^3	Proposed estimate should be raised	In the absence of adequate human or animal data, the proposed estimate based on assumption that GF and GD are equipotent; approach is reasonable; because ECt_{50} for mild effects for GD was recommended to be raised, proposed value for GF should be raised correspondingly; further research recommended
LD_{50}[c]	Percutaneous, liquid	None	350 mg for 70-kg man	Proposed estimate should serve as an interim value	In the absence of adequate human or animal data, proposed estimate based on assumption that GF and GD are equipotent; approach is reasonable; further research recommended
ED_{50}[d]					
Severe effects	Percutaneous, liquid	None	200 mg for 70-kg man	Proposed value should serve as an interim value	In the absence of adequate human or animal data, the proposed estimate based on assumption that GF and GD are equipotent; approach is reasonable; further research recommended

[a] LCt_{50}: Vapor exposure that produces lethality in 50% of the exposed animals. Ct refers to the product of concentration (c) and exposure time (t). Note that Ct is not necessarily a constant.
[b] ECt_{50}: Percutaneous vapor exposure or inhalation vapor exposure causing a defined effect (e.g., incapacitation, severe effects, mild effects, threshold effects).
[c] LD_{50}: Liquid dose causing lethality in 50% of the exposed animals.
[d] ED_{50}: Liquid dose causing a defined effect in 50% of the exposed animals.

6—

Review of Acute Human-Toxicity Estimates for VX

VX (*O*-ethyl-*S*-[2(diisopropylamino)ethyl]methylphosphonothioate) is an organophosphate nerve agent. It is less volatile than G-nerve agents, a property that might significantly affect its role in chemical warfare. The physical and chemical properties, toxicokinetics, and toxicity of VX are discussed in detail by CDEPAT (1994), Marrs et al. (1996), and Somani (1994). Human-toxicity estimates have been derived for percutaneous vapor exposures, vapor inhalation, and percutaneous liquid exposures. Only a few end points were considered—lethality in animals, changes in cholinesterase (ChE) activity in humans and animals, incapacitation, ocular toxicity, and rhinorrhea. The subcommittee's assessment of the scientific validity of CDEPAT's human-toxicity estimates for VX is discussed below.

PERCUTANEOUS VAPOR EXPOSURE

Lethal Effects (LCt_{50})

CDEPAT's proposed LCt_{50} estimate for percutaneous exposure to VX vapor is 150 mg-min/m^3 assuming exposure durations of 30 to 50 min and moderate temperatures. There is no existing LCt_{50} estimate (CDEPAT 1994).

The potency of VX is enhanced by increased ambient wind speed and aerosol particle size. Those factors are more noticeable with VX than with the other nerve agents because of the relatively low volatility of VX. The recommended percutaneous estimates for VX vapor are for no wind and for aerosol particles of ≤ 2 μm diameter (CDEPAT 1994). The estimates also take into consideration the areas of the body that are probably the most sensitive to VX, the head and neck, which are highly likely to be exposed to vapor (Bramwell et al. 1963; Sim 1962).

The most relevant human and animal studies for generating human LCt_{50} estimates are discussed below.

The percutaneous toxicity of VX vapor was investigated in mice and goats. The exposure duration was uncertain for goats (values were given, but uncertainty was associated with them) and unreported for mice (Koon et al. 1960). The LCt_{50} was 11.5 mg-min/m^3 for mice and 100 to 150 mg-min/m^3 for clipped goats (Koon et al. 1960).

The LCt_{50}s for clothed, depilated rabbits at 0-mph and 8-mph wind speeds were 814 mg-min/m^3 and 35 mg-min/m^3, respectively (Cresthull et al. 1963). The values for unclothed rabbits at 0-mph and 8-mph wind speeds were 28 mg-min/m^3 and 8.3 mg-min/m^3, respectively (Cresthull et al. 1963). Krackow (1956) studied the toxicity of VX in depilated rabbits. On the basis of his data, he proposed an LCt_{50} of 124 to 180 mg-min/m^3.

Animal data indicate that the highest observed LCt_{50} for no wind is 100 to 150 mg-min/m^3 (Koon et al. 1960). Human estimates vary from 6 to 3,600 mg-min/m^3 for various exposure conditions (Koon et al. 1960), and the human estimate depends on wind speed and particle size. Higher wind speed and larger particle size are more effective in producing toxicity of VX. The more credible animal studies estimated the LCt_{50} to be between 280 and 300 mg-min/m^3. CDEPAT estimated a LCt_{50} for percutaneous VX vapor of 150 mg-min/m^3 (slightly more protective given the sensitivity of the head region). The subcommittee agrees with CDEPAT's evaluation that the degree of confidence in that estimate is low. The subcommittee recommends that CDEPAT's proposed LCt_{50} estimate be considered an interim value until further research on VX is conducted to establish the LCt_{50} estimate with a greater degree of confidence.

ECt_{50} for Severe Effects

CDEPAT's proposed ECt_{50} estimate for severe effects from percutaneous

exposure to VX vapor is 25 mg-min/m^3, assuming exposure durations of 30 to 50 min and moderate temperatures. There are no existing ECt_{50} estimates (CDEPAT 1994).

In one study in humans, a spirometer mouthpiece was used for breathing; a clip was placed over the nose, and the eyes were kept closed (Bramwell et al. 1963). Percutaneous exposure of the head and neck to VX vapor at a rate of 1 mg-min and a temperature of 32°C resulted in miosis in almost all subjects even though the eyes were closed (Bramwell et al. 1963). The ECt_{50}s were 0.7 to 25.6 mg-min/m^3; exposure durations were 15 to 24 min and concentrations ranged from 0.23 to 5 mg/m^3. In one or more trials, five of eight individuals experienced local flushing (transient redness) over the face and neck. After 24 hr of exposure, the ChE activity ranged from 37% to 108% of baseline. Nausea, vomiting, cold sweats, and pallor were also observed. The effective dose for 50% inhibition of ChE activity was 27 mg-min/m ^{3} (Bramwell et al. 1963). This study did not identify a no-observed-adverse-effect level (NOAEL).

Because the subcommittee's degree of confidence in the proposed ECt_{50} estimate is low to moderate, the subcommittee recommends that the estimate of 25 mg-min/m^3 for severe effects serve as an interim value until further research on VX is conducted to establish the ECt_{50} estimate with a greater degree of confidence.

ECt_{50} for Threshold Effects

CDEPAT's proposed ECt_{50} estimate for threshold (minimal) effects from percutaneous exposure to VX vapor is 10 mg-min/m^3, assuming exposure durations of 30 to 50 min and moderate temperatures. There is no existing ECt_{50} estimate for threshold effects (CDEPAT 1994).

In one human study, exposures investigated for severe effects produced adverse effects at the highest exposure level, which was 25.6 mg-min/m ^{3} (Bramwell et al. 1963). At this exposure level, approximately 50% ChE inhibition occurred. This study did not identify a NOAEL.

The subcommittee's degree of confidence in the proposed estimate is low because a true NOAEL was not established. The subcommittee recommends that the proposed estimate be considered an interim value until further research on VX is conducted to establish the NOAEL.

INHALATION VAPOR EXPOSURE

Lethal Effects (LCt_{50})

CDEPAT's proposed LCt_{50} estimate for inhalation exposure to VX vapor is 15 mg-min/m^3, assuming exposure durations of 2 to 10 min, minute volumes of 15 liters, and moderate temperatures. The existing LCt_{50} estimate is 30 mg-min/m^3 (CDEPAT 1994).

There are a few reports on VX that provide definitive data about human inhalation toxicity. Most studies are in animals and often do not specify the duration of exposure.

CDEPAT's proposed human-toxicity estimates considered effects produced from inhalation exposures as well as from percutaneous vapor exposures. Bramwell et al. (1963) reported that the ECt_{50} for ChE inhibition following percutaneous vapor exposure to VX was 27 mg-min/m^3; one subject experienced systemic effects from vapor exposure at 25.6 mg-min/m^3. Bramwell et al. (1963) also reported a mean ChE inhibition of 26% in humans exposed to VX vapors by inhalation at 2.6 to 3.6 mg-min/m^3 for 1.5 min.

Studies performed in the rat reported LCt_{50} values for 1 min, 5 min, and 10 min at exposures of 17 mg-min/m^3, 8 mg-min/m^3, and 9 mg-min/m^3, respectively (Krackow 1956).

The vapor toxicity of VX was also investigated in mice for whole-body or head-only exposures (Koon et al. 1960). For a 10-min exposure, the LCt_{50} for whole-body exposure in mice was 4 mg-min/m^3. The LCt_{50} value for head only exposure was 13.6 mg-min/m^3. The LCt_{50} value reported for goats was 9.2 mg-min/m^3 (Koon et al. 1960).

In deriving the human-toxicity estimates for inhalation, CDEPAT assumed that the dose delivered to the target tissue is greater for inhalation than for percutaneous vapor exposure. Although humans tolerated (26% ChE inhibition) 3.6 mg-min/m^3 via inhalation for 1.5 min, higher exposures were not used. The subcommittee agrees with CDEPAT's evaluation that degree of confidence in the proposed estimate of 15 mg-min/m^3 is low to moderate. The subcommittee recommends that CDEPAT's proposed estimate of 15 mg-min/m^3 be lowered. The subcommittee also recommends that research on VX be done to establish the LCt_{50} estimate with a greater degree of confidence.

ECt_{50}, for Severe Effects

CDEPAT's proposed ECt_{50} estimate for severe effects is 10 mg-min/m ^{3}, assuming exposure durations of 2 to 10 min, minute volumes of 15 liters, and moderate temperatures. The existing ECt_{50} estimate for severe effects is 25 mg-min/m^3.

In one study, the ICt_{50} (exposure level producing incapacitation in 50% of a given population) for VX was estimated to be 13 mg-min/m ^{3} (Howd et al. 1986). That estimate was based on ChE inhibition in humans and animals. The available data to derive an ECt_{50} for severe effects are insufficient. CDEPAT used the ratio of ICt_{50}/LCt_{50} of 0.7 to 0.8 to derive the ECt_{50} for severe effects. The rationale for using this ratio is unclear. The subcommittee's degree of confidence in the CDEPAT's proposed ECt_{50} estimate of 10 mg-min/m^3 is low. Thus, the subcommittee recommends that the proposed ECt_{50} estimate for severe effects of 10 mg-min/m^3 serve as an interim value until further research on VX is conducted to establish the estimate with a greater degree of confidence.

Ect_{50} for Mild Effects

CDEPAT's proposed Ect_{50} estimate for ocular effects or rhinorrhea in humans is 0.09 mg-min/m^3, assuming exposure durations of 2 to 10 min and moderate temperatures. The existing estimate is the same (CDEPAT 1994).

Exposures of the head and neck of humans to VX vapor for 1.5 to 6 min resulted in Ect_{50} values of 0.6 to 6.4 mg-min/m^3, respectively (Bramwell et al. 1963). Transient respiratory signs occurred after exposure, but no systemic effects were observed. A vapor dose of 5.5 mg-min/m^3 produced a 70% ChE inhibition. Some miosis occurred after exposure. Rhinorrhea was reported in all but one subject.

The effects of wind speed on the miotic potencies of VX in humans and rabbits were also studied. A definite relationship was observed between impaction velocity on the cornea (exposure that reduces pupil size by 90%) and the Ect_{90}.

On the basis of the available data, the subcommittee concludes that the Ect_{50} estimate of 0.09 mg-min/m^3 for ocular effects is scientifically valid.

PERCUTANEOUS LIQUID EXPOSURE

Lethal Effects (LD_{50})

CDEPAT's proposed LD_{50} estimate for percutaneous exposure to VX liquid on bare skin is 5 mg for a 70-kg man. The existing estimate is 10 mg for a 70-kg man (CDEPAT 1994).

No human studies have been conducted for this effect and route of exposure. Most of the animal studies do not take into account the sensitivity of various areas of the human body to dermal penetration by toxicants.

Animal data indicate that CDEPAT's proposed estimate of 5 mg for a 70-kg man is too high because it underestimates the potency of VX liquid on bare skin. Studies have shown the LD_{50}s in clipped rabbits, pigs, and guinea pigs to be 0.02 mg/kg (1.4 mg for a 70-kg man), 0.12 mg/kg (8.4 mg for a 70-kg man), and 0.077 mg/kg (5.4 mg for a 70-kg man), respectively (Wiles and Shaw 1960).

No uncertainty factors were applied when extrapolating from animal data to compensate for the variability associated with dermal penetration of various areas of the human body. Thus, the subcommittee concludes that CDEPAT's proposed estimate of 5 mg for a 70-kg man (0.07 mg/kg) for percutaneous exposure to VX liquid is too high. The subcommittee also recommends that the proposed estimate be lowered. The subcommittee recommends that further research be conducted to establish the LD_{50} estimate with a greater degree of confidence.

ED_{50} for Severe Effects

CDEPAT's proposed ED_{50} estimate for severe effects from percutaneous exposure to VX liquid is 2.5 mg for a 70-kg man. The existing estimate is 5 mg/70-kg man (CDEPAT 1994).

There are no human data and few animal data for this end point by this route of exposure. A study in rabbits showed that the ratio of Ict_{50} to LD_{50} for VX is O.5 (Manthei and Callahan 1991). Therefore, in the absence of adequate human or animal data for severe effects via percutaneous exposure to VX liquid, the ratio was used to derive the ED_{50} for severe effects. The subcommittee agrees with this approach.

The subcommittee recommends that CDEPAT's ED_{50} estimate of 2.5

mg for a 70-kg man be lowered because of the subcommittee's recommendation for lowering the LD_{50} estimate. The subcommittee also recommends that further research on VX be conducted to establish an ECt_{50} estimate with a greater degree of confidence.

CONCLUSIONS AND RECOMMENDATIONS

The subcommittee's conclusions concerning the scientific validity of CDEPAT's proposed human-toxicity estimates for VX are summarized Table 6-1.

Eight human-toxicity estimates, instead of the seven proposed for the other organophosphate agents, were calculated for VX; an ECt_{50} for severe effects from percutaneous vapor exposure was also calculated. Of the eight human-toxicity estimates for VX proposed by CDEPAT, the subcommittee concludes that only one estimate is appropriate for protecting soldiers and is scientifically valid. The subcommittee recommends that four estimates serve as interim values until further research is conducted, and three estimates are to be lowered. The subcommittee recommends that further research be conducted on VX to establish the human-toxicity estimates with a greater degree of confidence.

TABLE 6-1 Evaluation of Human-Toxicity Estimates for VX

		Human-Toxicity Estimates for VX			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for VX	Rationale for Subcommittee's Evaluation
LCt_{50}[a]	Percutaneous, vapor	None	150 mg-min/m^3	Proposed estimate should be considered an interim value	Degree of confidence in data is low to moderate; further research recommended
	Inhalation, vapor	30 mg-min/m^3	15 mg-min/m^3	Proposed estimate should be lowered	Degree of confidence in data is low to moderate; further research recommended
ECt_{50}[b]					
Threshold effects	Percutaneous, vapor	None	10 mg-min/m^3	Proposed estimate should be considered an interim value	Degree of confidence in data is low; a no-observed-adverse-effect level (NOAEL) was not defined; further research recommended
Severe effects	Percutaneous, vapor	None	25 mg-min/m^3	Proposed estimate should be considered an interim value	Degree of confidence low to moderate; further research recommended
	Inhalation, vapor	25 mg-min/m^3	10 mg-min/m^3	Proposed estimate should be considered an interim value	Insufficient data; further research recommended
Mild effects	Inhalation, vapor	0.09 mg-min/m^3	0.09 mg-min/m^3	Proposed estimate is scientifically valid	Available human data support the proposed estimate
LD_{50}[c]	Percutaneous, liquid	10 mg/70-kg man	5 mg/70-kg man	Proposed estimate should be lowered	Animal data indicate that the proposed estimate is too high; furthermore, no uncertainty factor used in lieu of variability associated with dermal penetration of various regions of body; further research recommended

		Human-Toxicity Estimates for VX			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for VX	Rationale for Subcommittee's Evaluation
ED_{50}[d]					
Severe effects	Percutaneous, liquid	5 mg/70-kg man	2.5 mg/70-kg man	Proposed estimate should be lowered	The ED_{50} is based on the ID_{50}[e]/LD_{50} ratio; the subcommittee recommends that the LD_{50} be lowered, therefore, the ED_{50} should be lowered correspondingly; further research recommended

[a] LCt_{50}: Vapor exposure that produces lethality in 50% of the exposed animals. Ct refers to the product of concentration (c) and exposure time (t). Note that Ct is not necessarily a constant.
[b] ECt_{50}: Percutaneous vapor exposure or inhalation vapor exposure causing a defined effect (e.g., incapacitation, severe effects, mild effects, threshold effects).
[c] LD_{50}: Liquid dose causing lethality in 50% of the exposed animals.
[d] ED_{50}: Liquid dose causing a defined effect in 50% of the exposed animals.
[e] ID_{50}: Liquid dose causing incapacitation in 50% of the exposed population.

7—

Review of Acute Human-Toxicity Estimates for HD

HD (- ′-dichloroethyl sulfide or bis(2-chloroethyl)sulfide), also known as sulfur mustard, is a vesicant (blistering agent). The physical and chemical properties, toxicokinetics, and toxicity of sulfur mustard are discussed in detail by CDEPAT (1994), Marrs et al. (1996), and Somani (1994). Human-toxicity estimates have been derived for percutaneous vapor exposures, vapor inhalation exposures, and for percutaneous liquid exposures. Only a few toxicity end points were considered. End points of toxicity that were considered are lethality, vesication, erythema, burns on the skin, and ocular and pulmonary effects. The subcommittee's assessment of the scientific validity of CDEPAT's human-toxicity estimates for HD is discussed below.

PERCUTANEOUS VAPOR EXPOSURE

Lethal Effects (LCt_{50})

CDEPAT's proposed LCt_{50} estimate for percutaneous exposure to HD vapor is 5,000 mg-min/m^3, assuming exposure durations of 30 to 50 min. The existing estimate is 10,000 mg-min/m^3 (CDEPAT 1994).

The LCt_{50} value for humans is difficult to estimate from the available animal data, because the data indicate that animal species vary in their sensitivity to HD. The LCt_{50} ranged from > 6,300 to 20,000 mg-min/m^3 in monkeys (NDRC 1943a, 1944), from 2,948 to 4,885 mg-min/m ^{3} in mice (NDRC 1943b,c), and from 4,750 to 6,430 mg-min/m^3 in rabbits (NDRC 1943a, 1944). The current LCt_{50} estimate for HD exposure of humans is 10,000 mg-min/m^3. That estimate is based on data from monkeys—one of the least-sensitive species tested for lethality. The authors of the CDEPAT report recommend lowering the estimate to 5,000 mg-min/m ^{3}, an estimate that is more consistent with results from studies in other animal species. In the subcommittee's opinion, CDEPAT's approach is reasonable, but the estimate is not overly conservative, because data indicate that humans might be one of the most-sensitive species to HD exposure. Rats and mice are the most-sensitive animal species.

Although the proposed CDEPAT estimate is more appropriate than the existing estimate, the subcommittee believes that the new estimate might still be too high. Therefore, the subcommittee recommends that the proposed estimate be lowered. The subcommittee also recommends that further research be conducted to establish the LCt_{50} estimate with a greater degree of confidence.

ECt_{50} for Severe Effects

CDEPAT's proposed ECt_{50} estimates for severe effects from exposure to HD are 500 mg-min/m^3 for moderate temperatures and < 200 mg-min/m ^{3} for hot temperatures, assuming exposure durations of 30 to 50 min. The existing estimates for moderate and hot temperatures are 2,000 and 1,000 mg-min/m^3, respectively (CDEPAT 1994).

The estimates are derived from data reported in human studies conducted 50 years ago (CDEPAT 1994). The proposed estimate of < 200 mg-min/m ^{3} for hot-temperature exposures is supported by a study of 10 men (PCS 1946), who exercised and sweat profusely in perspiration-drenched clothing and were exposed to HD at 220 mg-min/m^3 at 90°F and 85% relative humidity for 57 min. All the men had severe scrotal burns. Thus, CDEPAT's recommended estimate is based on actual human data with a reasonable number of subjects.

CDEPAT's recommended estimate for exposures at moderate temperatures (70°F, 48% humidity) is 500 mg-min/m^3 and is supported by a study

of eight men (clothed, wearing protective gas masks, and not exercising) in which exposures of 500 mg-min/m^3 for over 1 hr produced severe scrotal effects in four of the eight men (Heinen et al. 1945). The estimate is supported by the results of exposure to lower concentrations of HD in the same study. The subcommittee concludes that the proposed estimates for hot and moderate temperatures are scientifically valid.

ECt_{50} for Threshold Effects

CDEPAT's proposed ECt_{50} estimates for threshold (minimal) effects from percutaneous exposure to HD vapor are 50 mg-min/m^3 for moderate temperatures and 25 mg-min/m^3 for hot temperatures, assuming exposure durations of 30 to 50 min. There are no existing estimates for the threshold effects of HD (CDEPAT 1994).

Human data used to support the proposed estimate, which apparently came from the Project Coordination Staff (PCS) report of 1946, were not given in sufficient detail in the CDEPAT report to allow for full evaluation. The PCS report concluded that the maximum safe exposure to HD for percutaneous exposure is 50 mg-min/m^3. At that exposure, HD was associated with no important injury. More data on the effects of low vapor doses would have to be available to evaluate these estimates fully. The subcommittee recommends that these ECt_{50} estimates (for hot and moderate temperatures) serve as interim values until further research is conducted to establish the estimates with a greater degree of confidence.

INHALATION VAPOR EXPOSURE

Lethal Effects (LCt_{50})

CDEPAT's proposed estimate for the LCt_{50} effects from inhalation exposures to HD vapor, assuming exposure durations of 2 to 10 min and minute volumes of 15 liters, was reduced from the existing value of 1,500 mg-min/m^3 to the value of 900 mg-min/m^3 (CDEPAT 1994).

Because of the nature of the end point (lethality), the LCt_{50} estimates were based on animal data. CDEPAT averaged the LCt_{50} from all the 10-min LCt_{50} data in different animal species to arrive at its estimate. No animal LCt_{50} studies on HD are adequate for use in estimating the human

LCt_{50}. CDEPAT had no confidence in any study. Therefore, CDEPAT had no basis for determining which animal species best reflected the human response. CDEPAT performed some modeling studies, but they did not provide useful information. In the absence of better data, CDEPAT averaged the toxicity data from several studies to estimate the human LCt_{50}. The subcommittee believes that this approach is reasonable. The subcommittee agrees with the proposed estimate but would prefer to see a range of proposed values to indicate the confidence bounds.

ECt_{50} for Severe Effects

CDEPAT's proposed ECt_{50} estimate for severe (ocular) effects from inhalation exposure to HD vapor, assuming exposure durations of 2 to 10 min, was lowered from the existing value of 200 mg-min/m^3 to the value of 100 mg-min/m^3 (CDEPAT 1994).

The eye is one of the organs that is most sensitive to the effects of HD vapors. Available data indicate that temporary blindness might be produced by HD vapor exposures of 200 mg-min/m^3, but other eye effects will be experienced at lower exposures. Therefore, the authors of the CDEPAT report reduced their estimates for severe nonlethal effects by 50%. From a battlefield perspective, the soldiers will first experience eye effects which will lead to the removal of soldiers from the battlefield. The subcommittee agrees with CDEPAT's proposed estimate.

ECt_{50} for Mild Effects

CDEPAT's proposed estimate for the ECt_{50} for mild (ocular) effects from exposure to HD is 25 mg-min/m^3, assuming exposure durations of 2 to 10 min. The existing estimate is > 50 mg-min/m^3 (CDEPAT 1994).

As with its ECt_{50} estimate for severe effects, CDEPAT based its ECt_{50} estimate for mild effects on the eye. Pre-1940 data indicate effects on the eye at vapor doses of 5 to 10 mg-min/m^3 (Reed 1920). Later studies, which are considered more reliable because of improved techniques, indicate that the eye can withstand a higher exposure (that is, 70 mg-min/m^3) (Guild et al. 1941). The subcommittee believes that CDEPAT's proposed estimate of 25 mg-min/m^3 for mild effects from inhalation exposure to HD vapor is supported by human data. Therefore, the subcommittee concludes that the proposed ECt_{50} estimate for mild effects is scientifically valid.

PERCUTANEOUS LIQUID EXPOSURE

Lethal Effects (LD_{50})

CDEPAT's LD_{50} estimate for percutaneous exposure to HD liquid is 1,400 mg for a 70-kg man. The existing estimate is 7,000 mg for a 70-kg man (CDEPAT 1994).

As for most LD_{50} estimates for humans, animal data must be relied on primarily. In this case, there is even a paucity of animal data. The Army's existing estimate was based on early data that indicated an LD_{50} of approximately 100 mg/kg for the rabbit; extrapolation to a 70-kg man yielded an estimated LD_{50} of 7,000 mg for a 70-kg man. CDEPAT (1994) chose to base its LD_{50} estimate on the LD_{50} of 20 mg/kg (1,400 mg for a 70-kg man) for the dog and guinea pig rather than the LD_{50} for the rabbit. Based on the data of Henry (1991), that choice is reasonable. The data indicate that rabbits are 10 times less sensitive to percutaneous HD than are humans. The subcommittee agrees with the proposed estimate of 1,400 mg for a 70-kg man.

ED_{50} for Severe Effects

The proposed ED_{50} for severe effects from percutaneous exposure to HD was estimated by CDEPAT to be 610 mg for a 70-kg man. There is no existing estimate (CDEPAT 1994). HD has a very low vapor pressure and stays on the ground for a long time. This persistence of HD on the ground can cause toxicity to people or animals over a long time. However, decontamination procedures can be followed to remove HD from the ground.

CDEPAT's proposed estimate is based on the observation of vesication of the human forearm (an area of moderate sensitivity to HD) following application of HD at a dose of 34 $\mu g/cm^2$ (Landhal 1945). Landhal (1945) collected data on hundreds of human exposures at the University of Chicago Toxicology Laboratory and concluded that 34 $\mu g/cm^2$ was the threshold blister dose on the volar forearm.

Extrapolation of that dose to the estimated 1.8 m^2 surface area of the average male yielded CDEPAT's proposed ED_{50} estimate of 610 mg for severe effects for a 70-kg man. Therefore, the subcommittee finds CDEPAT's proposed estimate to be scientifically valid. However, the proposed value of 610 mg should be rounded to 600 mg for a 70-kg man to avoid the appearance of precision that is not there.

CONCLUSIONS AND RECOMMENDATIONS

The subcommittee's conclusions concerning the scientific validity of CDEPAT's proposed estimates for HD are summarized in Table 7-1.

Of the 10 human-toxicity estimates for HD proposed by CDEPAT, the subcommittee concludes that seven of the estimates are appropriate for protecting soldiers and are scientifically valid. The subcommittee recommends that two estimates serve as interim values estimates until further research is conducted and one estimate be lowered.

In general, the subcommittee agrees that most of CDEPAT's proposed estimates for HD are reasonable and based on sound scientific judgments of the available data. The subcommittee is concerned that the estimates were central values and calculated without uncertainty factors. Such an approach might not be protective of all members of the military forces. Thus, the subcommittee recommends that further research be conducted to establish the estimates with a greater degree of confidence.

TABLE 7-1 Evaluation of Human-Toxicity Estimates for HD

		Human-Toxicity Estimates for HD			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for HD	Rationale for Subcommittee's Evaluation
LCt_{50}[a]	Percutaneous, vapor	10,000 mg-min/m^3	5,000 mg-min/m^3	Proposed estimate should be lowered	Estimate might be too high because data from the most-sensitive species (rats and mice) not used; further research recommended
	Inhalation, vapor	1,500 mg-min/m^3	900 mg-min/m^3	Proposed estimate is scientifically valid	CDEPAT averaged LCT_{50} data in several animal species; in the absence of data on humans, that approach is reasonable
ECt_{50}[b]					
Threshold effects	Percutaneous, vapor	None	50 mg-min/m^3 (moderate temperature); 25 mg-min/m^3 (hot temperature)	Proposed estimates should serve as interim values	In the absence of details on studies on value; which estimates were based, proposed estimate should be considered interim further research recommended
Severe effects	Percutaneous, vapor	2000, mg-min/ m^3 (moderate temperature 1000 mg-min/ m^3 (hot temperature	500 mg-min/m^3 (moderate temperature); <200 mg-min/m^3 (hot temperature)	Proposed estimated are scientifically valid	Estimates based on human studies

		Human-Toxicity Estimates for HD			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for HD	Rationale for Subcommittee's Evaluation
Severe effects	Inhalation vapor	200 mg-min-/m^3 (moderate temperature)	100 mg-min/m^3 moderate temperature)	Proposed estimate is scientifically valid	Proposed estimated supported by human data
Mild effects	Inhalation, vapor	>50 mg-min/m^3	25 mg-min/m^3	Proposed estimate is scientifically valid	Proposed estimate supported by human data
LD_{50}[c]	Percuataneous, liquid	7,000 mg for 70-kg man	1,400 mg for 70-kg man	Proposed estimate is scientifically valid	Proposed estimate supported by a study in dogs
ED_{50}[d]					
Severe effects	Percutaneous, liquid	None	610 mg for 70-kg man	Proposed estimate is scientifically valid; however, it should be rounded to 600 mg for a 70-kg man to avoid appearance of precision that is not there	Proposed estimate supported by human data

[a] LCt_{50}: Vapor exposure that produces lethality in 50% of the exposed animals. Ct refers to the product of concentration (c) and exposure time (t). Note that Ct is not necessarily a constant.
[b] ECt_{50}: Percutaneous vapor exposure or inhalation vapor exposure causing a defined effect (e.g., incapacitation, severe effects, mild effects, threshold effects).
[c] LD_{50}: Liquid dose causing lethality in 50% of the exposed animals.
[d] ED_{50}: Liquid dose causing a defined effect in 50% of the exposed animals.

8—

Evaluation of the Risk-Estimation Procedures Used in the CDEPAT Report

One of the Goals of the CDEPAT report was to provide dose-response information for various biological effects associated with acute exposure to chemical agents under investigation. Specifically, estimates of the proportion of individuals at risk as a function of exposure were based on log-probit analysis. In this chapter, the subcommittee evaluates this procedure for deriving human-toxicity estimates.

USE OF LOG-PROBIT ANALYSIS

Log-probit analysis assumes that the density distribution among individuals exposed at the exposures that produce a specified biological effect (for example, death or some incapacitating condition) can be described by a lognormal distribution. In other words, it assumes that the distribution of the log-exposure that produces an effect among individuals is normal. The lognormal distribution is a common and generally accepted approach for describing biological effects. Other statistical distributions could be selected and used, but many notable differences would likely not be observed because of the small numbers of exposure groups and individuals or animals

generally used per exposure. Thus, the subcommittee accepts the log-probit analysis approach as reasonable for these types of data.

USE OF THE ECT_{50}

The ECt_{50}, expressed as milligrams per cubic meter times exposure duration, is the effective vapor exposure at which 50% of the individuals exhibit a specified biological effect. The ECt_{50} is the concentration that causes an effect in 50% of the population (that is, the median exposure of the distribution). The ECt_x is the exposure causes an effect in x% of the population, a percentage obtained by integrating the lognormal density distribution until the cumulative distribution is x%. The ECt_{50} is the median of the Iognormal distribution. Integrating the area under the lognormal density distribution up to a specified log-exposure gives the cumulative lognormal distribution (that is, the proportion of individuals that show an effect at or below that exposure). The standard deviation (SD) of the lognormal distribution is the reciprocal of the slope of the probit log-exposure response line. The probit log-exposure response line is obtained by converting the percentage of responders to a probit for each exposure group. For a lognormal distribution, this provides a straight-line relationship between probits and log-exposure that can be estimated by weighted linear-regression techniques. This line provides point (best) estimates of risk as a function of log-exposure to be used in risk-benefit decisions.

For example, a slope of 5 indicates that a reduction of exposure by a factor of 10 (log 10 = 1 unit on a log-exposure scale) corresponds to a shift of 5 SDs. If ECt_{50} = 100 mg-min/m^3, 50% of the individuals would exhibit the specified biological effect at that dose. At $ECt_{50} \div 10 = 100 \div 10 = 10$ mg-min/m^3, the proportion of individuals responding at 5 SDs below the mean of a lognormal distribution is 3×10^{-7}. At $ECt_{50} \div 2 = 100 \div 2 = 50$ mg-min/m^3, the log-exposure is log(50) = 1.70. With a probit slope of 5, the SD of log-exposure is $1 \div 5 = 0.20$. Thus, $ECt_{50} \div 2$ is (log100 -log50) $\div$ 0.20 = (2.00-1.70) $\div$ 0.20 = 1.5 SDs below the mean, at which exposure 6.7% of the population of individuals are expected to respond. Therefore, a reduction in the exposure by a factor of 2 changes the risk from 50% to 6.7%. Similarly, an increase in the exposure by a factor of 2 to $2ECt_{50}$ = 200 mg-min/m^3 increases the risk from 50% to 93.3%. With an uncertainty of a factor of 2 in the ECt_{50}, the risk could vary from 6.7% to 93.3%.

The above example demonstrates an inherent uncertainty in risk estimates for steep dose-response lines. In the CDEPAT report, the confidence limits on the ECt_{50}s were often a factor of 2 (that is, $ECt_{50} \div 2$ to $2ECt_{50}$). For the above example, the estimated ECt_{50} could be 1.5 SDs above the true mean rather than at the geometric mean of the lognormal distribution. A log-exposure reduction of 1.645 SDs below the mean provides an estimate of the ECt_5 (exposure corresponding to a 5% risk). If the estimated mean is actually 1.5 SDs above the true mean, the estimated exposure is 1.500-1.645 = -0.145 SDs from the true geometric mean. That exposure has a risk of 44.2% rather than the expected risk of 5%.

The above example is illustrated in Figure 8-1. Suppose the ECt_{50} is estimated to be 60 mg-min/m^3 and the estimate of the slope (percentage responding plotted on a probit scale vs. log-dose) is 5, as represented by the solid line in Figure 8-1. The ECt_{05} is estimated to be 28 mg-min/m^3. Suppose, in fact, that the true ECt_{50} is lower by a factor of 2 and is 30 mg-min/m^3. That discrepancy between the estimated and true value would not be uncommon for the available data. Assuming the same slope (or same SD), the true dose-response relationship is represented by the dashed line. Note that the true proportion of individuals affected at the estimated ECt_{50} is not 50% but 94%. Further, the true proportion of responders at the estimated ECt_{05} is 44% rather than 5%. Hence, small differences in exposure can result in large differences in the proportion of individuals affected. This is due to the steep dose-response lines for these agents.

The above example does not take into account the uncertainty in the estimate of the slope. The slope is likely to be overestimated. The slope based on a homogenous group of inbred animals is likely to be steeper than the slope based on a group of heterogeneous individuals under battlefield conditions. Apart from that likelihood, the slope is expected to be overestimated 50% of the time because of random statistical variation. For the above example, suppose the ECt_{50} is estimated without error but the slope estimate is 7 rather than the true value of 5. Instead of the correct value of the ECt_5 being 47 mg-min/m^3, the estimate is 58 mg-min/m^3 with a risk of 12% rather than 5%. Note that a relatively small change in concentration (47 mg-min/m^3 to 58 mg-min/m^3) results in a considerable change in risk (5% to 12%).

With some human data available, exposure estimates of the ECt_{50} are probably within a factor of 2 of the true value. With this uncertainty and the steep dose-response curves observed, the true risk at the estimated ECt_5 for humans can vary from nearly 1% to nearly 99%. The true risk at the

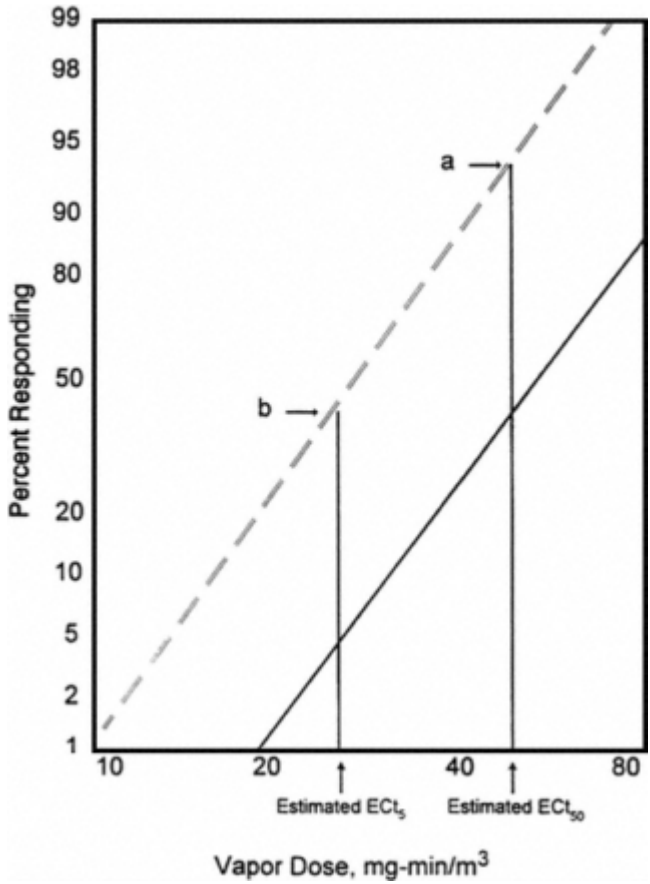

Figure 8-1
Probit log-exposure (slope = 5). Estimated exposure response, solid line; true dose response, broken line. (a) True percent at estimated ECt_{50} is 94%. (b) True percent at estimated ECt_5 is 44%.

estimated ECt_5 could vary from less than 1% to nearly 50%. With only sparse animal data, the uncertainty of exposure estimates might be as much

as a factor of 10. Typically, uncertainty factors of 10 are used when extrapolating from animal-toxicity data to humans. The uncertainty of exposure and risk estimates should be estimated for critical biological effects.

USE OF CONFIDENCE LIMITS

A shortcoming of the CDEPAT report is the failure to calculate confidence limits for the different exposures, such as ECt_5 and ECt_{16}. Point (best) estimates are needed to provide the best risk-benefit trade-offs, but the uncertainty of these estimates should be considered. Confidence intervals can be obtained for individual probit dose-response lines. The calculation of uncertainty becomes more complex when an average probit line is based on two or more sets of toxicity data. In that case, a central line might be chosen, as was done by CDEPAT for some of the estimates. If human data are not available, the line for the species most like humans may be selected. Various lines may be given more weight according to the quantity and quality of the data.

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Glossary

A

acetylcholinesterase True cholinesterase (ChE). Acetylcholinesterase hydrolyzes acetylcholine within the central nervous system and peripheral neuroeffector functions.

acute effect An effect that results from a brief exposure or shortly after an acute exposure (see below).

acute exposure A short-term exposure that lasts from minutes to hours (usually 1–24 hr).

aerosol Liquid or solid particles suspended in air.

C

ChE_{50} The vapor exposure producing significant cholinesterase (ChE) inhibition in 50% of the given population.

cholinesterase An enzyme capable of catalyzing the hydrolysis of acetylcholine.

chronic effect An effect of gradual onset and duration of months and years.

chronic exposure An exposure (usually at low concentrations) of long duration, such as months or years.

Ct Concentration × time. Note that Ct is not necessarily a constant. For example, a 2-min exposure to a concentration of 100 mg/m^3 (Ct = 200 $mg\text{-}min/m^3$) does not necessarily produce the same toxicological effects as a 50-min

exposure to a concentration of 4 mg/m^3 (Ct = 200 mg-min/m^3).

D

depiliation Removal of hair.

dose The amount of a substance that enters or interacts with organisms. An administered dose is the amount of substance administered to an animal or human, usually measured in milligrams per kilogram of body weight; milligrams per square meter of body-surface area; or parts per million of the diet, drinking water, or ambient air. An effective dose is the amount of the substance reaching the target organ.

E

ECt_{50} The vapor exposure causing a specifically defined effect in 50% of the given population. Within the context of this report, the route of exposure can be either inhalation or percutaneous.

ED_{50} The dose of liquid agent causing a specifically defined effect in 50% of the given population. In this report, ED_{50} refers to a percutaneous liquid exposure.

exposure duration The length of time that a receptor population is exposed to a contaminant.

exposure route The route by which a contaminant enters the body (dermal, inhalation, or oral).

I

ICt_{50} The vapor exposure causing incapacitation (see below) in 50% of the given population. Within the context of this report, the route of exposure can be either inhalation or percutaneous.

ID_{50} The dose of liquid agent causing a defined degree of incapacitation in 50% of the given population. Within this context, ID_{50} refers to a percutaneous liquid exposure. Unless otherwise specified, all ID_{50}s are for bare skin.

incapacitation An effect considered moderate to severe, unless otherwise specified. It might include prostration and convulsions.

L

LCt_{50} The vapor exposure causing lethality in 50% of the given population. Within the context of this report, the route of exposure can be either inhalation or percutaneous.

LD_{50} The dosage of liquid agent causing lethality in 50% of the given population. Within this context, LD_{50} refers to a percutaneous liquid exposure. Unless otherwise specified, all LD_{50}s are for percutaneous liquid contamination of bare skin.

M

microgram (μg) One millionth of a gram.

mild effects For the organophosphate nerve agents, mild effects are miosis and rhinorrhea. For HD, mild effects are slight ocular irritation.

milligram (mg) One thousandth of a gram.

minute volume The volume of air expelled from the lungs in a minute, which is assumed to be 15 liters unless otherwise stated.

miosis A decrease in pupil size.

N

no-observed-adverse-effect level (NOAEL) The highest dose of a substance that can be administered without observation of adverse effects in laboratory animals.

P

percutaneous vapor exposure Percutaneous vapor exposures are defined as vapor exposures to intact bare skin. Vapor inhalation is prevented by use of an appropriate protective mask and does not contribute to overall toxicity. Percutaneous vapor exposures can result from vapor dissemination of chemical agents or from liquid contamination of clothing with subsequent vapor penetration.

potency The degree to which an agent can cause strong or toxic effects.

R

rhinorrhea Running nose.

S

severe effects For the organophosphate nerve agents, severe effects are systemic, such as vomiting, involuntary urination, or defecation, prostration, incapacitation, tremors, collapse, and convulsions. Exposures that produce these effects might not be substantially different from exposures that produce lethality. For HD, severe nonlethal effects consist of skin burns, such as severe redness (erythema) and blistering (vesication).

T

threshold The lowest dose of a substance at which a specified measurable effect is observed and below which it is not observed. In this report, threshold effects refer to minimal or negligible effects.

toxic Harmful to living organisms.

toxicity The adverse effects of chemicals on living organisms.

toxicology The study of adverse effects of chemicals on living organisms.

toxic substance A substance that destroys life or injures health when introduced into or absorbed by a living organism.

U

uncertainty factors Factors used to divide a no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) to obtain a safe exposure level.

Appendix

Offensive Versus Defensive Use of Human-Toxicity Estimates for CW Agents

Perhaps the single most important factor to consider about many of the existing human estimates is that they appear to have been developed primarily for offensive purposes. This is summarized in the following paragraphs excerpted from Silver's (1953) report on GB (CDEPAT 1994):

> While it is possible to calculate, on a fairly logical basis, an LCt_{50} for resting man, it is not possible to give a single figure for the LCt_{50} which would apply to all other states of activity. The actions of soldiers in combat are so varied and unpredictable that the respiratory minute volume at the moment of chemical attack would be quite impossible to determine.
>
> At the risk of over-simplification, this problem can be solved for all practical purposes. Offensive tactics, to be successful, must be designed to produce the highest Cts necessary to cause casualties in all possible combat situations. In the case of toxic gas warfare, the highest LCt_{50} is required for resting men since their minute volume is the least. For all offensive calculations, therefore, the LCt_{50} for resting man should be used. Any extra casualties caused by increased respiration due to activity should merely be considered as bonus effects.
>
> On the other hand, for defensive uses, protective equipment should function under the most adverse conditions. For example,

leakages of gas masks should be so small that even men performing heavy work and breathing at high rates should suffer no ill effects. This same reasoning applies to all other protective devices. For all defensive calculations, therefore, the incapacitating exposure (ICt_{50}) for active man should be used.

Although much consideration has been given to the soldier's activity level and resultant respiratory minute volume in developing human toxicity estimates, little consideration has been given to the purpose of many of the existing human-toxicity estimates for CW agents: Many were probably formulated for offensive purposes. Offensive estimates are designed to produce the desired effect in at least the stated percentage of the population and to produce that effect quickly. The time required for CW agents to produce an effect is generally inversely proportional to the dose received. For defensive purposes, those factors (for example, high minute volume or the use of most resistant individuals in developing human toxicity estimates) result in an underestimation of the potency (toxicity) of the agents.

REFERENCE

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