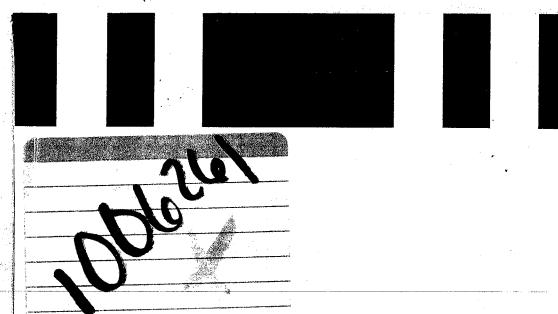
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Review of Acute Human-Toxicity Estimates for Selected Chemical-Warfare Agents



COMMITTEE ON TOXICOLOGY NATIONAL RESEARCH COUNCIL



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

100626

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

NATIONAL ACADEMY PRESS WASHINGTON, D.C., 1997

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

Summary

O RELIABLE ACUTE-EXPOSURE¹ 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.

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

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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 1 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.