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Chemical Warfare Agents: Current Status of Oral Reference Doses

Dennis M. Opresko, Robert A. Young, Annetta P. Watson, Rosemarie A. Faust, Sylvia S. Talmage, Robert A. Ross, Kowetha A. Davidson, Joseph King, and Veronique Hauschild

Contents

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D.M. Opresko, R.A. Young, A.P. Watson (✉) R.A. Faust, S.S. Talmage, R.A. Ross, K.A. Davidson
Oak Ridge National Laboratory, Life Sciences Division, 1060 Commerce Park Drive, Oak Ridge, TN 37830-6480, U.S.A.

J. King
U.S. Army Environmental Center, ATTN: SFIM-AEC-IR-P, Bldg. E-4480, Aberdeen Proving Ground, MD 21010-5401, U.S.A.

V. Hauschild
Environmental Health Engineering, U.S. Army Center for Health Promotion and Preventive Medicine, ATTN: MCHB-TS-EES, Bldg. E-1675, Aberdeen Proving Ground, MD 21010-5403, U.S.A.

I. Introduction

A 1998 paper published in *Reviews in Environmental Contamination and Toxicology* (Opresko et al. 1998) documented the development of oral reference doses (RfDs) for several groups of chemical warfare agents; i.e., sulfur mustard agents, nitrogen mustard agents, organophosphate nerve agents, the arsenical lewisite, and cyanogen chloride. The development of these reference doses was initiated by the U.S. Army Environmental Center (USAEC) to support its continuing task of remediating sites potentially contaminated by past releases of hazardous substances. This action was taken under general provisions of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). The USAEC, which functions as the program manager for the Army's Installation Restoration Program (IRP), determined that responsible and efficient cleanup of both active installations and formerly used defense sites (FUDS) contaminated with chemical warfare agent residues required key toxicological parameters for performing IRP site health risk assessments.

II. Background

A. Methods

For any environmental contaminant, potential health risks are determined by comparing estimates of exposure during current or future use of the sites with some measure of the toxic potency of each of the individual contaminants. Exposure through inhalation of contaminated air, absorption through the skin, and ingestion of contaminated media such as soil particles or groundwater are common routes of potential concern in environmental health risk assessments. For inhalation exposures to chemical warfare agents, the U.S. Department of the Army (DA) has used airborne exposure limits for protecting the potentially exposed public as well as personnel in the workplace or on the battlefield (DA 1987, 1990). The U.S. Department of Health and Human Services (DHHS) has also published chemical warfare agent inhalation exposure limits for civilians and workers (Fed. Reg. 52:48458, 53:8504). The air exposure limits for organophosphate nerve agents and sulfur mustard originally promulgated by DHHS have recently been reevaluated (Mioduszewski et al. 1998; Reutter et al. 2000; USACHPPM 2000a). The results of these reevaluations have been recommended to the Office of the Army Surgeon General (OTSG) by the U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM 2000a,b). Per the Army Surgeon General's request, (OTSG 2000a, 2001), the reports are currently undergoing review by the National Center for Environmental Health of the DHHS Centers for Disease Control and Prevention (CDC). While existence of these airborne exposure limits has allowed evaluation of chemical warfare agent inhalation risks, standard toxicological criteria to evaluate other routes of chemical warfare agent exposure (such as incidental ingestion of contaminated groundwater or soil particles) were not available before 1996, at which time interim RfD values for chemical warfare agents were established (OTSG 1996).

Exposure criteria for contaminated soil or water are determined on a site-by-site basis and are highly dependent on the characteristics of the exposed population and on the frequency and duration of exposure. A key step in this process is a comparison of the expected exposure levels with reference toxicity values, the standard approach used in Superfund risk assessments (USEPA 1989). For assessing noncancer health risks, the relevant toxicity value for each contaminant is expressed as a reference dose (RfD), which is derived from experimental or epidemiological data. An RfD is an estimate of the daily exposure level or dose (usually expressed as mg/kg body wt/d) for the general population, including sensitive subpopulations, that is likely to be without an appreciable risk of deleterious effects (USEPA 1989). RfDs can be calculated for a subchronic exposure duration (i.e., 2 wk to 7 yr) or for a chronic exposure duration (i.e., 7 yr to a lifetime). A daily exposure at or below the RfD is not likely to be associated with health risks, but as the amount of chemical that an individual is exposed to increases above the RfD, the probability that an adverse effect will occur also increases (Cicmanec et al. 1996). The USEPA has developed and used RfDs extensively in evaluating and making remedial decisions regarding sites contaminated with toxic industrial chemicals and posts approved values on its Integrated Risk Information System (IRIS; USEPA 2000). Before the development of RfDs for the chemical warfare agents however, there was not a consistent way for assessing potential environmental (e.g., soil, water) contamination by these compounds.

B. Applications

The use of standardized (default) exposure scenario assumptions, along with RfD estimates for toxic industrial chemicals, has allowed the USEPA to establish nonsite-specific environmental screening levels for many industrial contaminants. These environmental screening levels, also referred to as Risk-Based Concentrations (RBCs; USEPA 1996a) and Preliminary Remediation Goals (PRGs; USEPA 1996b), have been shown to be useful in prioritizing and expediting environmental investigations and remediation, as well as in identifying laboratory detection requirements. Recent availability of chemical warfare agent RfDs has allowed the setting of similar prioritization and evaluation goals for chemical warfare agents.

Specifically, the USACHPPM published a technical evaluation of existing USEPA environmental screening level models and documented the assumption rationale used in calculating screening level estimates specific to each chemical warfare agent; interim estimates of the chemical warfare agent RfDs were employed in these calculations (OTSG 1996; USACHPPM 1999). This health-based environmental screening level technical report has been officially endorsed by the Office of the Assistant Secretary of the Army (OASA 1999) for use throughout the Army during investigations of environmental media potentially contaminated with chemical warfare agents.

Beyond their application in developing screening levels, oral RfDs are also necessary to site-specific health risk assessments.

III. Derivation of Oral Reference Doses

Under sponsorship of the U.S. Army Environmental Center (USAEC), staff of the Life Sciences Division of Oak Ridge National Laboratory (ORNL) evaluated the available scientific literature and, where possible, derived oral reference doses for select chemical warfare agents (Opresko et al. 1998). The evaluation found that toxicological data were insufficient to derive oral RfDs for the sulfur mustard agents code-named HT and T; the representative nitrogen mustard agent code-named HN2; and the arsenical lewisite. Opresko et al. (1998) determined that sufficient toxicological data existed for deriving reference doses for agent HD (sulfur mustard); the organophosphorous nerve agents VX, GA (tabun), GB (sarin), and GD (soman); and the cyanide-based compound cyanogen chloride. The proposed oral RfDs and uncertainty factors (UF) for these chemicals, as documented in Opresko et al. (1998), are listed in Table 1. It should be emphasized that RfDs are only toxicity *estimates*, and are not expected to be precise levels above which effects would occur. RfDs are specifically designed to be protective to accommodate variations in population susceptibility, as well as to ensure that sensitive subpopulations are protected when these estimates are used in risk-based decision making.

Table 1. Reference doses (RfDs) and total uncertainty factors (UFs) proposed for chemical warfare agents.

Chemical agent	RfD (mg/kg/d)	Total UF	Reference for critical study
GA (tabun)	4×10^{-5}	3000	Bucci et al. (1992a)
GB (sarin)	2×10^{-5}	3000	Bucci and Parker (1992)
GD (soman)	4×10^{-6}	3000	Bucci et al. (1992b)
VX	6×10^{-7}	100	Rice et al. (1971)
HD (sulfur mustard)	7×10^{-6}	3000	Sasser et al. (1989a)
HT	NV[a]	—	—
T	NV[a]	—	—
HN2	NV[a]	—	—
Lewisite	NV[a]	—	—
Cyanogen chloride[b]	3×10^{-2}	30	Ministry of Health, Mozambique (1984a,b)
Cyanogen chloride[c]	3×10^{-2}	300	NTP (1993)

NV, not verifiable; insufficient data for calculating a RfD.
[a]A RfD of 0.1 μg/kg/d was calculated for lewisite from the rat oral data of Sasser et al. (1989b), but because of data deficiencies, this RfD was considered to be nonverifiable. It was recommended that the comparable RfD for inorganic arsenic, 0.3 μg/kg/d, be used as a surrogate for lewisite.
[b]Derived from human epidemiological data.
[c]Derived from animal data.
Source: Opresko et al. (1998).

IV. Review Process

The proposed oral RfDs derived for the chemical warfare agents have undergone an extensive review process that is outlined more fully in Opresko et al. (1998). The process included evaluation by the Material/Chemical Risk Assessment (MCRA) Working Group of the Environmental Risk Assessment Program (ERAP) in 1996. ERAP was a component of the Strategic Environmental Research Development Program (SERDP), a multiagency effort addressing agency-specific risk assessment needs.

The proposed RfDs for agent HD (sulfur mustard), GA (tabun), GB (sarin), GD (soman), VX, and lewisite (but not cyanogen chloride or the nitrogen mustard compounds) were then submitted to the U.S. Department of the Army, Office of the Surgeon General, for consideration as criteria for conducting risk assessments at Army sites. In a memorandum dated August 19, 1996, the OTSG approved the proposed RfDs for these agents as interim criteria (OTSG 1996). These interim values are listed in Table 2. It should be noted that, in the case of lewisite, the OTSG adopted the calculated value of 0.1 μg/kg/d as the RfD for lewisite, rather than following the recommendation of the MCRA Working Group (to use the comparable RfD of 0.3 μg/kg/d for inorganic arsenic as a surrogate for lewisite because the calculated value was considered nonverifiable due to data deficiencies).

The OTSG asked the National Research Council (NRC) to examine the scientific validity of the interim values before making a final determination. The NRC assigned this task to the Committee on Toxicology, Subcommittee on Chronic Reference Doses for Selected Chemical Warfare Agents. The Subcommittee published its appraisal in July 1999 (*Review of the U.S. Army's Health Risk Assessments for Oral Exposure to Six Chemical-Warfare Agents*; NRC 1999; see also Bakshi et al. 2000). The recommendations of the NRC are listed in Table 2 and compared with the OTSG interim values. A summary of uncertainty factors (UF) used by the NRC in their appraisal of RfDs and those used in establishing the interim OTSG values are presented in Table 3. It should be

Table 2. Interim Army (OTSG) and NRC recommended RfDs for six chemical warfare agents.

Agent	Army interim RfD (mg/kg/d)	NRC recommended RfD (mg/kg/d)
GA (tabun)	4×10^{-5}	4×10^{-5}
GB (sarin)	2×10^{-5}	2×10^{-5}
GD (soman)	4×10^{-6}	4×10^{-6}
VX	6×10^{-7}	5×10^{-7}
HD (sulfur mustard)	7×10^{-6}	7×10^{-6}
Lewisite	1×10^{-4}	1×10^{-5}

Sources: OTSG (1996); NRC (1999); see also Bakshi et al. (2000).

Table 3. Uncertainty factors (UF) used by the Army and NRC to estimate agent RfDs.

Uncertainty factor	Description	GA		GB and GD		VX[a]		HD		Lewisite[a]	
		Army	NRC	Army	NRC	Army	NRC	Army	NRC	Army	NRC
UF_A	Animal-to human extrapolation	10	10	10	10	1	1	10	3	10	3
UF_H	Intraspecies variability (sensitive subpopulation)	10	10	10	10	10	10	10	10	10	3
UF_L	LOAEL-to-NOAEL extrapolation	1	1	3	3	3	10	3	10	1	10
UF_S	Subchronic-to-chronic extrapolation	3	3	3	3	3	10	10	10	10	10
UF_D	Database adequacy	3	3	3	3	1	3	1	1	3	10
MF	Modifying factor	3	3	1	1	1	1	1	1	1	1
Total UF		3000[b]	2700	3000[b]	2700	100	3000	3000	3000	3000	9000

[a]Different studies were used by the Army and the NRC to derive the RfD estimates.

[b]It is assumed that the range of a UF is distributed log normally, and that reduction by one-half in the default value of 10 results in a UF of approximately 3 (geometric mean of 10 is 3.16). Thus the UF composite product of 3×3 is considered to equal 10.

Sources: OTSG (1996); NRC (1999).

noted that the NRC (1999) also addressed the topic of sulfur mustard carcinogenic potency and recommended that a specific slope factor of 1.6 per mg/kg/d be used in health risk assessments for this agent. Issues surrounding the carcinogenic potency of sulfur mustard were not previously addressed in Opresko et al. (1998), and the NRC consideration of this topic is more fully described elsewhere (Bakshi et al. 2000; NRC 1999).

V. Summary of NRC Review

The NRC (1999) found that the guidelines used to derive the Army's interim chronic oral RfDs were consistent with the guidelines used by the USEPA for deriving RfDs for other environmental contaminants. The NRC (1999) further stated that these methods were appropriate for deriving RfDs for the chemical warfare agents.

The NRC (1999) concurred with the Army's interim RfDs for the nerve agents GA (tabun), GB (sarin), GD (soman), and the vesicant agent HD. For the nerve agent VX, the NRC recommended a slightly lower RfD value based on a different critical study than that used by the Army. For the vesicant lewisite, the NRC (1999) recommended a substantially lower RfD based on a different critical study than that used by the Army. The recommendations of the NRC are discussed in more detail next.

A. Agent GA (Tabun)

The Army's interim RfD of 4×10^{-5} mg/kg/d was based on a subchronic intraperitoneal study in rats (Bucci et al. 1992a) in which depression of plasma cholinesterase (plasma-ChE) was considered the critical effect. The OTSG (2000b) noted that this endpoint is a biomarker of exposure rather than an adverse effect; this position is consistent with that recently recommended by the USEPA Office of Pesticide Programs *Science Policy on the Use of Data on Cholinesterase Inhibition for Risk Assessments of Organophosphorous and Carbamate Pesticides* (announced in 65 FR 54521–54523; 8 Sept. 2000). The NRC (1999) acknowledged that blood ChE inhibition, either plasma or RBC-ChE, is "typically considered a biomarker of exposure to organophosphate agents," but also noted that "it is generally agreed that inhibition of ChE contributes to the overall hazard identification of ChE-inhibiting agents." NRC (1999) noted that this endpoint has been used in the past by USEPA for establishing RfDs for organophosphate insecticides, and concluded that it would also be appropriate for deriving an RfD for GA. Although the NRC identified several weaknesses in the critical study (i.e., inappropriate exposure route, short treatment duration, inconsistent results, and less than ideal methods for measuring blood ChE), it concluded that the Bucci et al. (1992a) study was the best available for deriving an RfD for GA. The NRC (1999) concurred with the Army's selection of the uncertainty factors used in the derivation of the interim RfD and considered the interim OSTG value of 4×10^{-5} mg/kg/d as scientifically valid.

A major data gap identified by the NRC is a lack of subchronic or chronic oral toxicity studies to serve as the basis for a direct RfD derivation for agent GA (NRC 1999). The Subcommittee acknowledges that this need could be appropriately addressed by a two-species subchronic oral study specifically designed to evaluate the effects of agent GA on ChE activity in both plasma and RBCs. If the experimental data for GA or any other nerve agent can determine that "significant toxic effects" occur at doses less than those significantly inhibiting ChE, the estimated RfD should then be reevaluated (NRC 1999).

B. Agent GB (Sarin)

The Army's interim RfD of 2×10^{-5} mg/kg/d was based on a subchronic oral study in rats (Bucci and Parker 1992) in which inhibition of RBC-ChE was considered the critical effect. As in the case of GA, the NRC (1999) stated that, although either plasma or RBC-ChE inhibition is typically considered a biomarker of exposure rather than an adverse effect, it was an appropriate endpoint for deriving an RfD for GB. The NRC (1999) noted several weaknesses in the Bucci and Parker study including short treatment duration, inconsistent results, and less than ideal methods for measuring blood ChE; however, the NRC (1999) concluded that, of the available studies, Bucci and Parker (1992) was the most appropriate for deriving an RfD for GB. The NRC (1999) concurred with the selection of the uncertainty factors used in the derivation of the interim RfD and considered the interim OTSG RfD of 2×10^{-5} mg/kg/d as scientifically valid.

The NRC considered the primary gap in the GB analysis to be the lack of a chronic or subchronic oral study demonstrating a clear LOAEL or NOAEL (NRC 1999). Experimental evaluation of the effects of agent GB on ChE activity in the RBCs and plasma of two species (preferred) is recommended. Further, the Subcommittee recommends an experimental dose regimen that includes one or more doses between 0.00 and 0.075 mg/kg/d. As earlier pointed out for agent GA, the current estimated RfD should be reevaluated if significant toxic effects are observed during experimental determination of the oral LOAEL or NOAEL for ChE inhibition (NRC 1999).

C. Agent GD (Soman)

The Army's interim RfD of 4×10^{-6} mg/kg/d was based on a subchronic oral study in rats (Bucci et al. 1992b) in which inhibition of plasma ChE was considered the critical effect. As in the case of GA and GB, the NRC (1999) acknowledged that either plasma ChE or RBC-ChE inhibition is only a biomarker of exposure but considered it to be an appropriate endpoint for deriving an RfD for GD. Although the NRC (1999) noted several weaknesses in the critical study (subchronic duration, variable results, no clear dose–response relationship, and less than ideal methods for measuring blood ChE), it concluded that the Bucci et al. (1992b) study was the most appropriate of the available studies for deriving a RfD for GD. The NRC (1999) concurred with the selection of the Uncertainty

Factors used in the derivation of the interim RfD and considered the OTSG interim RfD of 4×10^{-6} mg/kg/d to be scientifically valid.

The NRC considered the primary gap in the GD analysis to be the lack of any chronic or subchronic oral study demonstrating a dose response between GD exposure and ChE inhibition (NRC 1999). To determine this parameter, experimental evaluation of the effects of agent GD on ChE activity in RBCs and plasma of two species (preferred) is recommended. Further, the NRC recommends an experimental dose regimen that includes one or more doses between 0.00 and 0.0175 mg/kg/d. As earlier pointed out for the other nerve agents, the current estimated RfD should be reevaluated if significant toxic effects are observed during experimental determination of ChE inhibition (NRC 1999).

D. Agent VX

The Army's interim RfD of 6×10^{-7} mg/kg/d was based on a subchronic oral study in sheep (Rice et al. 1971) in which depression of whole blood cholinesterase was considered the critical effect. As in the case of G agents, the NRC (1999) agreed with the Army that either plasma or RBC-ChE inhibition is a valid endpoint for deriving an RfD for VX. The NRC (1999), however, noted several weaknesses in the selection of the Rice et al. study as the critical study, the most notable being the uncertainties about whether sheep are at least as susceptible as humans to VX. The NRC (1999) acknowledged that sheep lack plasma ChE and have lower levels of RBC ChE than humans, that there was *in vitro* evidence that rumen fluid would not detoxify VX, and that retention of VX in the rumen might result in increased absorption. These observations could support the supposition that sheep are at least as susceptible as humans to VX. Other weaknesses in the Rice et al. (1971) study identified by the NRC (1999) included the small number of test animals, the fact that the controls were older than the treated animals, the short exposure duration (8 wk), the lack of dose adjustments for weight, and the large variation in animal body weights. The NRC (1999) concluded that there was no good evidence that shows that sheep are more sensitive than humans to VX.

The NRC (1999) considered other possible studies for deriving an RfD for VX and concluded that a study in which human volunteers were exposed to VX in drinking water (Sim et al. 1964) was the most appropriate. In the Sim et al. study, 16 male volunteers were given drinking water solutions containing VX at concentrations that resulted in daily doses of 1.43 μg/kg for 7 d. No signs or symptoms of toxicity occurred in any of the test individuals; however, mean RBC-ChE activity was reduced to 60% of baseline values. Weaknesses identified by the NRC (1999) in the Sim et al. study included the small number of test subjects and the very short exposure duration (7 d, versus 56 d for sheep). The NRC (1999) applied a UF_H of 10 for sensitive subpopulations, a UF_L of 10 for extrapolating from a LOAEL to a NOAEL, a UF_S of 10 for extrapolating from a short-term study to a potentially chronic exposure, and a UF_D of 3 for database inadequacies. When the total UF of 3000 is applied to the LOAEL

identified in the Sim et al. study, the resulting RfD recommended by the NRC is 5×10^{-7} mg/kg/d, a value only slightly lower than the interim Army RfD of 6×10^{-7} mg/kg/d (OTSG 1996). It should be noted that the NRC (1999) stated that because ChE inhibition is a biomarker of exposure rather than a toxic effect, use of this endpoint overestimates the oral toxicity of VX.

The NRC considered the primary gap in the VX analysis to be the lack of a chronic or subchronic oral study demonstrating a clear dose–response relationship (NRC 1999). Experimental evaluation of anti-ChE activity in the RBC and plasma ChE of two species (preferred) is recommended. Further, the NRC recommends an experimental dose regimen that includes one or more doses between 0.00 and 0.00143 mg/kg/d. As earlier pointed out for the other nerve agents, the current estimated RfD should be reevaluated if significant toxic effects are observed during experimental determination of the oral LOAEL or NOAEL for ChE inhibition (NRC 1999).

E. Agent HD (Sulfur Mustard)

The Army's interim RfD of 7×10^{-6} mg/kg/d was based on a two-generation reproductive study in which rats were intragastrically intubated with agent HD dissolved in sesame oil (Sasser et al. 1989a). Forestomach lesions (epithelial acanthosis, an increase in the thickness of the stratum spinosum of the epithelial tissue) were identified as the critical effect. These effects occurred in the exposed parents and not in the offspring; i.e., no adverse reproductive effects were reported. The NRC (1999) considered other possible studies to use as the critical study for deriving the RfD, but concluded that the two-generation study of Sasser et al. (1989a) was the most appropriate. The NRC (1999) noted that although epithelial acanthosis can be used as the critical noncancer effect in deriving the RfD, that endpoint resulting from direct administration to the forestomach is likely to overestimate the toxicity of sulfur mustard, resulting in an RfD that might be overprotective for noncancer health effects. The NRC (1999) applied a UF_A of 3 for extrapolation from animals to humans, a UF_H of 10 for sensitive subpopulations, a UF_L of 10 for extrapolating from a LOAEL to a NOAEL, a UF_S of 10 for extrapolating from a short-term study to a potentially chronic exposure, and a UF_D of 1 for database inadequacies. When the total UF of 3000 is applied to the time-weighted LOAEL of 0.022 mg/kg/d identified in the Sasser et al. (1989a) study, the resulting RfD recommended by the NRC is 7×10^{-6} mg/kg/d, which is identical to the interim Army RfD (OTSG 1996). Therefore, NRC used the same study and the same LOAEL as OTSG for deriving the RfD, but applied a slightly different set of UFs (see Table 3).

The NRC identified as a major data gap the lack of long-term oral toxicological studies for direct derivation of an RfD for sulfur mustard (NRC 1999). As a consequence, the RfD can only be estimated from subchronic animal studies. The NRC recommends that long-term, low-dose oral exposure studies be performed to address this need.

F. Agent L (Lewisite)

The Army's interim RfD of 1×10^{-4} mg/kg/d (OTSG 1996) was based on a two-generation reproductive study in rats (Sasser et al. 1989b) in which the highest oral dose (0.6 mg/kg/d, administered 5 d/wk for 13 wk before mating, 7 d/wk during gestation, and at least 4 d/wk during lactation) did not produce gastric lesions (necrosis and hyperplasia). Such gastric lesions had been observed in other rat studies using larger doses of lewisite (1.0 mg/kg/d and higher; see Sasser et al. 1989c, 1996). In the two-generation study, no significant adverse effects on reproductive performance or fertility were found through two consecutive generations, and no other toxic effects were observed. The time-weighted average dose was 0.44 mg/kg/d and the composite applied uncertainty factors and modifying factor (MF) was 3000 (see Table 3). The NRC (1999) considered other possible critical studies and concluded that a rabbit developmental study (Hackett et al. 1987) was more appropriate for deriving an RfD for lewisite, because of evidence that the rabbit appears to be more susceptible than the rat to lewisite.

In the Hackett et al. study, gastric lesions (mucosal inflammation, edema, necrosis, and mucosal sloughing) and mortality occurred at the lowest test dose of 0.07 mg/kg/d. As in the rat studies, the lewisite was administered to the rabbits by intragastric intubation. Although the NRC (1999) noted several weaknesses in the study, including the short treatment period of 14 d, it considered the range of test doses and the number of animals in each test group as credible. The NRC (1999) also noted that there was the possibility that the effects observed in the Hackett et al. study were caused by the direct intragastric administration of the lewisite to the stomach, and concluded that the RfD calculated from such an endpoint might therefore be overprotective of noncancer health effects. However, the NRC (1999) further stated that there are two reasons for applying such a conservative value . . . first, the available dose–response data are too sparse to establish conclusively that the dose-administered process is responsible for the observed effects; second, the available data on lewisite are inadequate for determining its carcinogenic potential. Furthermore, the NRC expressed the concern that lewisite might be degraded in the environment or be metabolized into inorganic arsenic, and that vinyl chloride might be formed. Both inorganic arsenic and vinyl chloride are considered to be human carcinogens. To the LOAEL of 0.07 mg/kg/d that was identified in the Hackett et al. study, the NRC (1999) applied a UF_A of 3 for extrapolation from animals to humans, a UF_H of 3 for sensitive subpopulations, a UF_L of 10 for extrapolating from a LOAEL to a NOAEL, a UF_S of 10 for extrapolating from a short-term study to a potentially chronic exposure, and a UF_D of 10 for database inadequacies. The composite UF calculated by the NRC was 9000, and when applied to the LOAEL of 0.07 mg/kg/d, the resulting RfD recommended by the NRC is 1×10^{-5} mg/kg/d, an order of magnitude lower than the interim Army RfD of 1×10^{-4} mg/kg/d (OTSG 1996).

The NRC expressed concern about the "less-than-ideal" animal studies, and

that available data do not provide sufficient information to make a clear determination regarding whether the rabbit is a more appropriate animal model than the rat for lewisite RfD determination (NRC 1999). There are also gaps regarding the currently unknown implications of short-term intragastric lewisite administration, as well as the complete absence of chronic oral toxicity data. These deficiencies could be remedied by conducting subchronic oral toxicity studies in rabbits and rats under modern protocols of good laboratory practice and animal use. These studies should compare and contrast low-dose chronic oral exposure to short-term, small-volume intragastric administration (NRC 1999).

Further, the NRC notes that the metabolic and environmental degradation products of lewisite are poorly defined, and expresses concern that inorganic arsenic and perhaps even vinyl chloride may be generated by the lewisite degradation process. The fact that these compounds are carcinogens is also noted by the Subcommittee, which recommends experimental determination of lewisite degradation to reduce the current lack of clarity in the process and its products. If these experiments verify degradation to carcinogens, the Subcommittee recommends evaluation of the carcinogenic potential for these products as well as for the parent compound, lewisite.

VI. Army Evaluation of NRC Recommendations

The Army (U.S. Army Environmental Center and U.S. Army Center for Health Promotion and Preventive Medicine) requested that the Life Sciences Division of ORNL provide technical support in preparation of the Army response to the NRC recommendations. The following is a summary of the resulting collaborative response. The final decision of the U.S. Army Office of the Surgeon General concerning the toxicological criteria for these chemical warfare agents was issued in February 2000 (OTSG 2000b).

A. Agents GA, GB, and GD

In the case of RfDs for the organophosphate agents GA, GB, and GD, the NRC (1999) concurred with the interim Army RfDs (OTSG 1996) and with the uncertainty factors used in their derivation. The Army accepts the NRC findings.

B. Agent VX

The Army interim RfD value of 6.0×10^{-7} mg/kg/d for VX (OTSG 1996) was based on a subchronic (8-wk) oral feeding study in sheep (Rice et al. 1971) in which a dose response in whole-blood ChE inhibition was observed. The logic for this selection is more fully documented in a recently published paper by Young et al. (1999), which had been provided in draft form to the NRC for their use in evaluating the VX RfD estimate.

Citing concerns regarding the selection of a sheep model as well as the study design employed by Rice et al. (1971), the NRC (1999) chose as the critical

study the Sim et al. (1964) experiment in which human volunteers were dosed with VX in drinking water. The RfD derived by the NRC from these human data has an inherently higher total uncertainty (3000) than the RfD estimate based on the sheep data (total UF 100; see Table 3). Specifically, the NRC (1999) used higher UFs for extrapolating from a LOAEL to a NOAEL (10) and from short-term to long-term exposures (10). In addition, the NRC included a database UF of 3.

The only effect observed in the Sim et al. (1964) study was blood ChE inhibition (no toxic effects were observed). In the case of the derivations of the RfDs for agents GB and GD in which blood ChE inhibition was also the only effect seen, the NRC (1999) endorsed the use of a LOAEL to NOAEL UF_L of 3, citing the fact that ChE inhibition, in the absence of adverse effects, is only a biomarker of exposure. It is the Army's position that this same assumption would also apply in the case of VX, and if a UF_L of 3 were used instead of 10 with the Sim et al. data, the resulting RfD would be 1.5×10^{-6} mg/kg/d, a value larger than that derived from the sheep data (6×10^{-7} mg/kg/d; see Table 2). The NRC (1999) used a factor of 10 for extrapolating from the 7-d experimental human exposure to a potentially chronic exposure (UF_S). The Army notes that short-term human exposure data have been used by USEPA to derive RfDs for other organophosphate ChE inhibitors using a UF_S of 1 for extrapolating to a chronic exposure because of the unlikelihood that the ChE inhibition endpoint would change over time. The logic for using a UF_S of 1 in such cases is more fully documented in Young et al. (1999). The NRC (1999) also applied a factor of 3 for database inadequacies (UF_D) "to account for the absence of long-term oral studies of VX in humans or a relevant animal model." The Army position is that the lack of long-term studies on VX would be accounted for in the UF_S of 10 used by the NRC for extrapolating from a short-term to a potentially chronic exposure.

The NRC (1999) considered that there was insufficient evidence demonstrating that sheep were more sensitive to the effects of VX than humans. While the Army acknowledges that human data are generally preferred, sheep and man could be considered approximately similar in sensitivity to the anticholinesterase activity of nerve agent VX. Further, the sheep study extended over a lengthy exposure period (56 d) and the resulting data are of good quality.

The development of RfDs for VX using either human or animal data has resulted in very similar values (0.0000006 mg/kg/d by the Army from sheep data vs. 0.0000005 mg/kg/d by the NRC from human data). Given that RfDs are defined as estimates with an uncertainty spanning perhaps an order of magnitude or greater (USEPA 1989), these two estimates are not considered by the Army to be significantly different from one another. Thus, both the animal and human data are mutually supportive of the same RfD, and it might be argued that the human data might indeed support a higher RfD. In as much as the NRC (1999) has stated that the use of blood ChE inhibition overestimates the oral toxicity of VX, the Army considers the interim RfD of 6×10^{-7} mg/kg/d, the interim OTSG (1996) estimate, as an adequately protective value.

C. Agent HD (Sulfur Mustard)

In the case of the RfD for agent HD, the NRC (1999) endorsed the use of the critical study and critical effect selected by the Army as the basis for the interim RfD. The NRC (1999) did recommend changes in two of the UFs: a change from 10 to 3 for the UF for extrapolation from animals to humans and a change from 3 to 10 for the extrapolation from a LOAEL to a NOAEL. The combined application of the UFs recommended by the NRC results in no net change to the composite uncertainty factor (equal to 3000; see Table 3). The Army concurs with the recommendations of the NRC in this regard.

D. Agent L (Lewisite)

The NRC (1999) proposed an alternate RfD for lewisite based on a different key study [rabbit developmental study of Hackett et al. (1987)]. There are several issues revolving around the applicability of using the Hackett et al. (1987) data for deriving an RfD and the selection of values for UFs (see Table 3) used in the RfD derivation. These issues are largely the consequence of differences in opinion regarding sensitive species selection and choice of critical study.

Sensitive Species and Critical Study Selection. A reason given by the NRC (1999) for selecting the Hackett et al. (1987) study to derive a RfD for lewisite is that the rabbit appears to be more susceptible than the rat to lewisite. In the Hackett et al. (1987) study, rabbits were dosed with lewisite by intragastric intubation. The difficulties encountered in dosing this species by intragastric intubation can be seen by comparing the results of the Hackett et al. (1987) rabbit teratology study with the results of a range-finding study conducted in the same laboratory (Hackett et al. 1987; see Table 31, p. 109 and text on pp. 105–106 of Opresko et al. 1998). In the range-finding study performed by Hackett et al., no deaths were attributed to lewisite toxicity at a dose of 0.5 mg/kg/d, but there was a 63% mortality rate (5/8) attributed to dosing trauma (dose delivered into lungs or perforation of the lung or trachea). In the phase of the study designed to investigate teratogenic potential and using a greater number of rabbits ($n = 18$/group), an unexpected increased mortality occurred at even lower doses (0.07 and 0.2 mg/kg). At least some of these deaths were again attributed to dosing trauma. Based on the overall results of the Hackett et al. (1987) study, it appears that accurate assessment of the dose response in rabbits is tenuous using a gastric intubation dosing protocol with a very corrosive agent such as lewisite. As reported elsewhere by Feldman (1977), gastric intubation of the rabbit is difficult due to limited oral space, and both esophageal perforation and intratracheal intubation are possible. Furthermore, the LOAEL of 0.07 mg/kg/d identified in the Hackett et al. study represents a frank effect level of increased mortality concurrent with the gastric lesions, and represents an effect in the dose–response continuum that is an extreme departure from determination of a NOAEL.

As a consequence of these concerns, the reported rabbit data were judged to

be inconsistent and unsuitable for use in developing an Army-wide RfD (OTSG 2000b).

Total Uncertainty. The NRC (1999) used a total UF adjustment of 9000 in its derivation of the RfD from the Hackett et al. (1987) rabbit data. In contrast, a total UF adjustment of 3000 was used in the derivation of the Interim RfD using the multigeneration study in rats (Sasser et al. 1989b; see Table 3). The total UF of 9000 estimated in the NRC analysis indicates that the NRC considers the rabbit data set to be less robust than the rat data set. Greater certainty in the rat data set is provided by the fact that similar NOAEL values (0.5 and 0.44 mg/kg/d, respectively) were identified in a 13-wk gavage study of rats (Sasser et al. 1989c, 1996) and in the two-generation study of rats (Sasser et al. 1989b).

The same logic developed by the USEPA for derivation of Reference Concentrations (RfC; USEPA 1988, 1994) is also applicable to RfD derivations. In general, a RfC is not derived when use of the selected data set involves greater than four areas of uncertainty; the NRC analysis involves five areas of uncertainty. Further, the composite UF for four areas of uncertainty is generally maximized at 3000 (e.g., reduced from 10^4) in recognition of the lack of independence between and among individual UFs (USEPA 1994). Even so, the use of a total UF of 3000 or greater is a recognized mark of a weak data set. Application of a composite UF equaling 9000 by the NRC (1999) indicates a nonverifiable estimate (USEPA 1994).

Environmental Fate of Lewisite. Under field conditions in which moisture is present, lewisite will hydrolyze to its degradation products. In an aqueous solution, to include soil with significant moisture, the primary lewisite degradation product expected is 2-chlorovinyl arsonous acid (CVAA; $C_2H_4AsClO_2$) (USACHPPM 1999). Lewisite oxide (chlorovinyl arsenous oxide; C_2H_2ClAsO) occurs only as a dehydration reaction product and may therefore be expected in drier environmental media. It should be noted that both CVAA and lewisite oxide will further degrade and result in the formation of inorganic arsenic (USACHPPM 1999). Also note that, although vinyl chloride can be produced from *cis*-lewisite oxide under extreme laboratory conditions [40 °C and reaction with sodium hydroxide (Rosenblatt et al. 1975; Hewett 1948)], vinyl chloride is not expected to be formed in amounts of any concern under normal environmental conditions. Further, the synthesized agent used as munition fill is composed of *cis* and *trans* isomers with the ratio of 10:90 (Hewett 1948). Degradation of the *trans* isomer does not generate vinyl chloride. Thus, the potential for vinyl chloride generation is low in that only about 10% of any lewisite originally present would be expected to slowly form vinyl chloride under extreme conditions, and after initial reduction of lewisite concentrations via dispersion. Any vinyl chloride formed would be additionally dispersed because of its gaseous nature. The combined result of all these factors (low availability of necessary lewisite isomer, slow reaction to form vinyl chloride, extremely low yield of that reaction expected under ambient conditions, and dispersion of both reactants and

product) would serve to further reduce the probability of vinyl chloride detection to negligible levels. As a consequence, inorganic arsenic is the more likely primary constituent of concern when evaluating environmental media for potential lewisite contamination. Overall, the Army does not view as realistic the probability that any residual concentration of vinyl chloride could be found in the environment as the result of a lewisite release.

Additionally, because lewisite has not been a standard agent in the Army inventory for more than 40 years and its manufacture ceased well before that, most significant releases to the environment would have occurred decades ago. Thus, in most cases involving a release of lewisite to the environment, there will have been more than sufficient time for natural dispersion processes to have reduced concentrations of any residual lewisite agent or specific degradation products to a level such that no exposures of any health significance should be expected.

VII. Final Army Toxicological Criteria for Chemical Warfare Agents

In a memorandum dated February 16, 2000, the Department of the Army Office of the Surgeon General issued its final decision on "Chronic Toxicological Criteria for Chemical Warfare Compounds" (OTSG 2000b). These final criteria represent the Army's current position as to the most appropriate oral toxicity reference values for use in environmental risk assessments (Table 4).

The OTSG (2000b) supports its decision by noting that NRC (1999) concurred with the values calculated as Army interim RfDs for the nerve agents GA, GB, and GD and the vesicant HD (sulfur mustard). For VX and lewisite, OTSG notes that the NRC estimates were all within one order of magnitude of

Table 4. Final Army toxicological criteria for chemical warfare agents recommended by OTSG.

Agent	RfD (mg/kg/d)	Comments
GA	4×10^{-5}	
GB	2×10^{-5}	
GD	4×10^{-6}	
VX	6×10^{-7}	
HD	7×10^{-6}	
Lewisite	1×10^{-4}	Appropriate when presence of L, CVAA or lewisite oxide is known. However, most environmental evaluations should focus on the more likely degradates ("arsenicals") and use the RfD for inorganic arsenic from IRIS (3×10^{-4} mg/kg/d).

Source: OTSG (2000b).

the interim Army estimates, and further states that, given the uncertainties and variables involved, a range of values within an order of magnitude can be considered appropriate representation of a chemical's toxicity. Specifically, for the nerve agent VX, OTSG endorses the continued use of the interim RfD of 6×10^{-7} mg/kg/d, pointing out that this value is only minimally different from that derived by the NRC (1999). Furthermore, the OTSG cites the NRC (1999) statement that RfDs based on ChE inhibition in the absence of toxic effects overestimate the oral toxicity of VX, and concludes that the interim value is adequately protective and no change is warranted. The Army further acknowledges that, although human data are generally preferred, the sheep oral exposure study (Rice et al. 1971) extended over a more lengthy exposure period [56 d vs. 7 d for human subjects in Sim et al. (1964)], and contains data of generally better quality than the human exposure study.

In the case of lewisite, the OTSG notes that, although data gaps associated with the derivation of an RfD from either the rat or rabbit studies are significant, the limitations associated with the rabbit data are believed to be of even greater uncertainty. Specifically, the rabbit data are complicated by dosing trauma, inconsistencies, and a total calculated uncertainty three times greater than that associated with the rat data (OTSG 2000b). The OTSG acknowledges the NRC (1999) recommendation that additional data would reduce overall uncertainties in the lewisite RfD estimate, but believes that the interim Army RfD is a more appropriate estimate of the chronic oral toxicity when it is known that lewisite or its degradation products, chlorovinyl arsonous acid (CVAA) or lewisite oxide, are present in the environment. However, due to the physical and chemical properties of these compounds (see Section VI. D.), it is highly unlikely that they would be expected to be present in most circumstances involving potential long-term exposure. Instead, inorganic 'arsenicals' are the most likely lewisite residuals in environmental media. Therefore, the use of the existing RfD for inorganic arsenic as posted on the USEPA Integrated Risk Information System (IRIS; 3×10^{-4} mg/kg/d) is recommended for use in most circumstances. This recommendation is consistent with that previously made by the Material/Chemical Risk Assessment Program (MCRA) Working Group of the Environmental Risk Assessment Program in 1996 (ERAP; a component of the multiagency Strategic Environmental Research Development Program). In any case, it should be noted that the RfD for inorganic arsenic is comparable to the Army's originally proposed RfD for lewisite (1×10^{-4} mg/kg/d). Thus, defaulting to the use of the arsenic RfD would reasonably assure public health protection. Ultimately, decisions regarding lewisite RfD selection are not entirely those of risk assessment, but include consideration of risk management in that identification of the compounds of concern will be necessary.

Summary

The NRC concluded that the method used to derive the Army's interim RfDs is scientifically sound and is consistent with the guidelines and process used by

the EPA. Nevertheless, there were differences in the approaches taken by the OTSG and the NRC, particularly in the RfD derivations for the arsenical vesicant lewisite and the nerve agent VX. These differences were in the selection of critical study and the accompanying Uncertainty Factors. The NRC further identified a number of agent-specific data gaps and provided detailed recommendations regarding improved experimental protocols that would resolve areas of uncertainty.

The OTSG acknowledges weaknesses in the traditional RfD approach employed, which involves a series of systematic extrapolations. Of particular concern to the OTSG and the NRC is the use of a NOAEL from experimental data for which the timing and/or spacing of the dose is inappropriate or that contain small sample sizes. The OTSG further acknowledges that use of the experimental NOAEL provides no characterization of data variability or slope in the dose–response curve; this is also true for industrial compounds that undergo RfD evaluation. To address these issues, the NRC recommends consideration of the benchmark dose approach in deriving future RfDs for these agents and encourages comparison of the conventional and benchmark dose methods.

While recognizing the limits in currently applied models as well as the data sets available for analysis, the OTSG nevertheless now considers the chemical warfare agent RfD estimates to be validated to the limits of current science. As a consequence, the RfD values presented here are being applied on an Army-wide basis in the calculation of health-based environmental screening levels.

The OTSG is now giving consideration to the prioritization and performance of toxicological studies and assessment protocols recommended by the NRC, and acknowledges the potential for reevaluating chemical warfare agent RfD estimates with alternate models and when new data become available.

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