DEPARTMENT OF THE ARMY
OFFICE OF THE SURGEON GENERAL
5109 LEESBURG PIKE
FALLS CHURCH, VA 22041-3258

REPLY TO
ATTENTION OF

MCHB-CG-PPM (40) 16 February 2000

MEMORANDUM THRU Assistant Surgeon General for Force Projection, Office of The Surgeon General, 800 Army Pentagon, Washington, DC 20310-0800

FOR SEE DISTRIBUTION

SUBJECT: Chronic Toxicological Criteria for Chemical Warfare Compounds

1. Reference memorandum, USACHPPM (MCHB-TS), 31 January 2000, SAB (enclosed).

2. To ensure that consistent health-based standards are available for application to the management of items and media contaminated with chemical warfare compounds, the OTSG concurs with the Chronic Toxicological Criteria for Chemical Warfare Agents cited in the reference above. These criteria represent the Army's position as to the most appropriate reference values to be used in environmental risk assessments.

3. Direct questions and/or concerns to COL Evenson, Occupational Medicine Staff Officer, OTSG, DSN 761-0022 or commercial (703) 681-0022.

FOR THE SURGEON GENERAL:

Encl

LESTER MARTINEZ-LOPEZ
Brigadier General, MC
Functional Proponent for
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DEPARTMENT OF THE ARMY
U.S. ARMY CENTER FOR HEALTH PROMOTION AND PREVENTIVE MEDICINE
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REPLY TO
ATTENTION OF

MCHB-TS (40) 31 January 2000

MEMORANDUM FOR Office of The Surgeon General
(ATTN: DASG-PM) 5113 Leesburg Pike, Falls Church, VA 22041-5000

SUBJECT: Recommendations Regarding Chronic Toxicological Criteria for Chemical Warfare Compounds

1. References. See Enclosure.

2. Purpose. This memorandum is to recommend final, Army-endorsed chronic oral toxicological criteria to be used in environmental health risk assessments.

3. Background.

a. Chronic oral toxicological criteria include Reference Doses (RfDs) and Slope Factors (SFs). An oral RfD represents the daily exposure level (in units of mg/kg/day) of a chemical at, or below, which no adverse (non-cancer) effects would be expected to occur in members of the general population after daily lifetime ingestion. The oral SF represents the potency (per mg/kg/day) of a chemical that causes cancer when it is ingested (the larger the value of the SF, the greater the cancer potency). Both the RfD and SF are used to assess health risks associated with long-term ingestion of contaminated media (such as soil or water). They are *estimates* of toxicity and are not precise levels above which effects would necessarily occur. Rather, they are specifically designed to be protective in order to accommodate variations in population susceptibility as well as to ensure that sensitive sub-populations are also protected when these estimates are used in risk-based decision-making. According to the definition (Reference a), RfD estimates reflect "an uncertainty spanning an order of magnitude or greater." The RfD and SF are an integral component of the environmental risk assessment methodology. Without these estimates, the Army would not be able to quantify risks from the critical oral exposure route during

site remediation and restoration or preventive planning assessments for demilitarization processes.

b. The Army Office of The Surgeon General (OTSG) proposed interim chronic oral toxicity values in 1996 (Reference b). These values were to remain as "interim" pending a formal review by the Committee on Toxicology (COT) of the National Research Council (NRC). The NRC has completed its review (Reference c) and the USACHPPM has, in turn, evaluated the NRC report.

c. To assist the evaluation, the USACHPPM requested input from the Life Sciences Division of Oak Ridge National Laboratory (ORNL) and U.S. Army Environmental Center (AEC) as the initial authors and proponent for the technical derivation document supporting the Army's interim chronic oral toxicological criteria (References d and e). The ORNL technical evaluation (reference f) provides detailed supporting rationale for the recommendations that follow.

4. Summary of Findings.

a. In summary, the NRC found that the guidelines used to derive the Army's interim chronic oral toxicological criteria were consistent with guidelines used by the U.S. Environmental Protection Agency (USEPA), and were appropriate. Within the application of those guidelines, the NRC calculated somewhat different estimates for the RfDs for VX and Lewisite. The NRC concurred with the values calculated as Army interim RfDs for the nerve agents GA, GB, and GD and the vesicant agent HD. The NRC did, however, calculate a different oral SF estimate for HD.

b. The NRC estimates for VX, Lewisite, and the SF for HD were all at or within one order of magnitude of the interim Army estimates. 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. However, in order to ensure consistent guidance for application in risk assessment, specific estimates must be chosen. The following briefly summarizes the basis for the selection of a specific estimate:

(1) VX. The interim Army RfD (0.0000006 mg/kg/day) was based on extrapolation of data from a subchronic (8 week) oral-feeding study in sheep. The NRC suggested the extrapolation should instead be made from a 7-day study in male volunteers ingesting drinking water to calculate their estimate (0.0000005 mg/kg/day). The uncertainties and extrapolations used with each study are somewhat different - for instance, though human data are generally preferred, the animal study extended over a more lengthy exposure period (56 days) and is considered by the Army to include higher quality data. However, despite the totally different basis, the RfD values resulting from the two sets of calculations are minimally different. The NRC acknowledges the similarity and notes "because ChE inhibition [the critical effect used in the analysis] is a biomarker of exposure rather than a toxic effect, use of this end point overestimates the oral toxicity of VX." Since the Army value is adequately protective, recommendations for change are not considered warranted.

(2) Lewisite. As with VX, the NRC calculated an RfD for Lewisite using a different critical study as a basis for extrapolations. Though both studies were animal studies, the Army interim RfD (0.0001 mg/kg/day) was based on two separate studies in rats while the NRC chose a single study in rabbits to base their RfD (0.00001 mg/kg/day). Though the data gaps associated with either approach 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. As recommended by the NRC, additional data would reduce the overall uncertainties with the Lewisite RfD (Reference c). Nevertheless, given the current need to chose specific estimates on the basis of the best available data, the interim Army RfD is considered a more appropriate estimate of chronic oral Lewisite toxicity when it is known that Lewisite agent, or its degradation products chlorovinyl arsonous acid (CVAA) or Lewisite oxide, are present in the environment. However, due to the physical characteristics of these chemicals, it is highly unlikely that they would be

expected in most circumstances. Instead, other Lewisite degradation products (i.e., "arsenicals") are the most likely residual in environmental media. Therefore, the use of the existing RfD for inorganic arsenic as posted on the USEPA Integrated Risk Information System (IRIS) is recommended.

(3) HD. The NRC-recommended SF for HD of 1.6 per mg/kg/day is a less conservative estimate which considers HD to be of lower carcinogenic potency than the previously noted Army interim value of 95 per mg/kg/day (reference b). This value was derived utilizing the same method as used for the Army value but incorporated recently available data. Alternative methods for estimating cancer SFs are also currently being considered by the scientific community. In an initial evaluation of one such alternative approach, the Army recently proposed a cancer SF for HD of 7.7 per mg/kg/day (Reference g). The NRC value of 1.6 per mg/kg/day is also less conservative than this revised Army estimate. However, given the obvious uncertainties and ongoing evaluation of alternative methods for estimating cancer SFs, the revised Army estimate of 7.7 per mg/kg/day is recommended at this time.

5. Conclusions and Recommendations.

a. The USACHPPM recommends finalizing the existing Army interim RfDs for the subject chemical warfare agents as "final" Army-endorsed values. These values (Table) are considered adequately protective of the general population, including sensitive sub-populations. Differences with the values calculated by the NRC are within the realm of scientific certainty that such types of toxicological values represent. As new data and analyses become available in the future, these criteria will be reevaluated as necessary.

b. It is recommended that the oral SF for HD be further evaluated within the context of the alternative approaches being addressed in the scientific community. In the interim, a value of 7.7 per mg/kg/day is considered to be appropriately conservative estimate of the oral cancer potency of HD.

c. In fulfillment of their charge from The Army Surgeon General to "identify data gaps and make recommendations for future research," the NRC has developed a number of excellent recommendations to address database inadequacies and confirm the safety of the recommended chronic toxicological criteria (Reference c). Serious consideration is being given to prioritization and performance of these studies.

TABLE. Final Army Recommended Chronic Oral Toxicological Criteria for CWA

Agent	Recommended RfD mg/kg/day	Comments
GA	4×10^{-5} (0.00004)	
GB	2×10^{-5} (0.00002)	
GD	4×10^{-6} (0.000004)	
VX	6×10^{-7} (0.0000006)	
HD (sulfur mustard)	7×10^{-6} (0.000007)	Carcinogenic; Oral SF of 7.7 per mg/kg/day is considered protective and therefore recommended at this time.
L (Lewisite)	1×10^{-4} (0.0001)	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/day).

MCHB-TS
SUBJECT: Recommendations Regarding Chronic Toxicological Criteria for Chemical Warfare Compounds

6. The point of contact is Ms. Veronique Hauschild who can be reached at DSN 584-5213, commercial (410) 436-5213. Additional concerns may be addressed to Dr. Coleen Weese at DSN 584-2714, commercial (410) 436-2714.

FOR THE COMMANDER:

Stephen L. Kistner

Encl

STEPHEN L. KISTNER
Deputy for Technical Services

References

a. *Risk Assessment Guidance for Superfund, Volume 1 Human Health Evaluation Manual (Part A)*, EPA/540/1-89/002, Office of Emergency and Remedial Response.

b. Memorandum, DASG-HS, subject: Interim Toxicological Criteria for Chemical Warfare Compounds; 19 August 1996.

c. *Review of the U.S. Army's Health Risk Assessments for Oral Exposure to Six Chemical-Warfare Agents*, Subcommittee on Chronic Reference Doses for Selected Chemical Warfare Agents, National Research Council, National Academy Press, July 1999.

d. Data Analyses and Derivations of Reference Doses for Sulfur Mustard (HD), Lewisite, and Nerve Agents GA, GB, GD, and VX; prepared by ORNL for the U.S. Army Environmental Center, under Interagency Agreement No. 1769-1769-A1, January 1996. See also: Opresko, DM et. al., 1998, Chemical Warfare Agents: Estimating Reference Doses, *Reviews of Environmental Contamination and Toxicology* 156: 1-183.

e. Young, RA et. al. 1999, Deriving Toxicity Values for Organophosphorous Nerve Agents: A Position Paper in Support of the Procedures and Rationale for Deriving Oral RfDs for Chemical Warfare Agents, *Human and Ecological Risk Assessment*, 5(3): 589-634.

f. Technical Memorandum; Subject: NRC Review of CW Agent Chronic Oral Toxicological Criteria; Life Sciences Division, Oak Ridge National Laboratory, August 1999.

g. *Derivation of Health-Based Environmental Screening Levels for Chemical Warfare Agents: A Technical Evaluation;* Prepared by the US Army Center for Health Promotion and Preventive Medicine in conjunction with Life Sciences Division, Oak Ridge National Laboratory; March 1999.