Acute Exposure Guideline Levels for Selected Airborne Chemicals

Volume 3

Subcommittee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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Preface

Extremely hazardous substances (EHSs)[1] can be released accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars and trucks transporting EHSs. The people in communities surrounding industrial facilities where EHSs are manufactured, used, or stored and in communities along the nation's railways and highways are potentially at risk of being exposed to airborne EHSs during accidental releases. Pursuant to the Superfund Amendments and Reauthorization Act of 1986, the U.S. Environmental Protection Agency (EPA) has identified approximately 400 EHSs on the basis of acute lethality data in rodents.

As part of its efforts to develop acute exposure guideline levels for EHSs, EPA and the Agency for Toxic Substances and Disease Registry (ATSDR) in 1991 requested that the National Research Council (NRC) develop guidelines for establishing such levels. In response to that request, the NRC published *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* in 1993.

Using the 1993 NRC guidelines report, the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances—consisting of members from EPA, the Department of Defense (DOD), the Department of Energy (DOE), the Department of Transportation, other federal and state governments, the chemical industry,

[1]As defined pursuant to the Superfund Amendments and Reauthorization Act of 1986.

academia, and other organizations from the private sector—has developed acute exposure guideline levels (AEGLs) for approximately 80 EHSs.

In 1998, EPA and DOD requested that the NRC independently review the AEGLs developed by NAC. In response to that request, the NRC organized within its Committee on Toxicology the Subcommittee on Acute Exposure Guideline Levels, which prepared this report. This report is the third volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*. It reviews the AEGLs for the nerve agents (GA [tabun], GB [sarin], GD [soman], GF, and VX), sulfur mustard, diborane, and methyl isocyanate for scientific accuracy, completeness, and consistency with the NRC guideline reports.

This report was reviewed in draft by individuals selected for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report: Mohamed Abou-Donia of Duke University; Janice Chambers of Mississippi State University; and Sidney Green of Howard University.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by David Moore of Battelle Memorial Institute, appointed by the Division on Earth and Life Studies, who was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The subcommittee gratefully acknowledges the valuable assistance provided by the following persons: Roger Garrett (deceased, March 31, 2003), Paul Tobin, and Ernest Falke (all from EPA); George Rusch (Honeywell, Inc.); Po Yung Lu, Claudia Troxel, Robert Young, Carol Forsyth, Dennis Opresko, and Annetta Watson (all from Oak Ridge National Laboratory). Aida Neel was the project assistant. Kelly Clark edited the report. We are grateful to James J. Reisa, director of the Board on Environmental Studies and Toxicology (BEST), for his helpful comments. The subcommittee particularly acknowledges Kulbir Bakshi, project director for the subcommittee, for bringing the report to completion. Finally, we would like to thank all members of the subcommittee for their expertise and dedicated effort throughout the development of this report.

Daniel Krewski, *Chair*
Subcommittee on Acute Exposure
Guideline Levels

Bailus Walker, *Chair*
Committee on Toxicology

Dedication

The subcommittee dedicates this series of reports
to our late colleague and director of
the Acute Exposure Guideline Levels program,
Dr. Roger L. Garrett,
whose 27 years of distinguished service with the
U.S. Environmental Protection Agency
in the fields of toxicology and health-risk assessment
contributed significantly to scientific knowledge,
to the development of
the Acute Exposure Guideline Levels program,
and to the protection of public health and safety.

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Introduction

This report is the third volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*.

In the Bhopal disaster of 1984, approximately 2,000 residents living near a chemical plant were killed and 20,000 more suffered irreversible damage to their eyes and lungs following accidental release of methyl isocyanate. The toll was particularly high because the community had little idea what chemicals were being used at the plant, how dangerous they might be, and what steps to take in case of emergency. This tragedy served to focus international attention on the need for governments to identify hazardous substances and to assist local communities in planning how to deal with emergency exposures.

In the United States, the Superfund Amendments and Reauthorization Act (SARA) of 1986 required that the U.S. Environmental Protection Agency (EPA) identify extremely hazardous substances (EHSs) and, in cooperation with the Federal Emergency Management Agency and the Department of Transportation, assist Local Emergency Planning Committees (LEPCs) by providing guidance for conducting health-hazard assessments for the development of emergency-response plans for sites where EHSs are produced, stored, transported, or used. SARA also required that the Agency for Toxic Substances and Disease Registry (ATSDR) determine whether chemical substances identified at hazardous waste sites or in the environment present a public-health concern.

As a first step in assisting the LEPCs, EPA identified approximately 400 EHSs largely on the basis of their "immediately dangerous to life and health" (IDLH) values developed by the National Institute for Occupational Safety and Health (NIOSH) in experimental animals. Although several public and private groups, such as the Occupational Safety and Health Administration (OSHA) and the American Conference of Governmental Industrial Hygienists (ACGIH), have established exposure limits for some substances and some exposures (e.g., workplace or ambient air quality), these limits are not easily or directly translated into emergency exposure limits for exposures at high levels but of short duration, usually less than 1 h, and only once in a lifetime for the general population, which includes infants, children, the elderly, and persons with diseases, such as asthma, heart disease, or lung disease.

The National Research Council (NRC) Committee on Toxicology (COT) has published many reports on emergency exposure guidance levels and spacecraft maximum allowable concentrations for chemicals used by the Department of Defense (DOD) and the National Aeronautics and Space Administration (NASA) (NRC 1968, 1972, 1984a,b,c,d, 1985a,b, 1986a,b, 1987, 1988, 1994, 1996a,b, 2000). COT has also published guidelines for developing emergency exposure guidance levels for military personnel and for astronauts (NRC 1986b, 1992). Because of COT's experience in recommending emergency exposure levels for short-term exposures, in 1991 EPA and ATSDR requested that COT develop criteria and methods for developing emergency exposure levels for EHSs for the general population. In response to that request, the NRC assigned this project to the COT Subcommittee on Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. The report of that subcommittee, *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993), provides step-by-step guidance for setting emergency exposure levels for EHSs. Guidance is given on what data are needed, what data are available, how to evaluate the data, and how to present the results.

In November1995, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC)[1] was established to identify, review, and interpret relevant toxicologic and other scientific data and to develop acute exposure guideline levels (AEGLs) for high-

[1]NAC is composed of members from EPA, DOD, many other federal and state agencies, industry, academia, and other organizations. The roster of NAC is shown on page 8.

priority, acutely toxic chemicals. The NRC's previous name for acute exposure levelsCcommunity emergency exposure levels (CEELs)Cwas replaced by the term AEGLs to reflect the broad application of these values to planning, response, and prevention in the community, the workplace, transportation, the military, and the remediation of Superfund sites.

Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 min, 30 min, 1 h, 4 h, and 8 h) and are distinguished by varying degrees of severity of toxic effects.

> The three AEGLs are defined as follows:
>
> AEGL-1 is the airborne concentration (expressed as ppm [parts per million] or mg/m^3 [milligrams per cubic meter]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.
>
> AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.
>
> AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below AEGL-1 represent exposure levels that can produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, nonsensory adverse effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

As described in the *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993) and the NAC guidelines report *Standing Operating Procedures on Acute Exposure Guideline Levels for Hazardous Substances*(NRC 2001), the first step in establishing AEGLs for a chemical is to collect and review all relevant published and unpublished information available on a chemical. Various types of evidence are assessed in establishing AEGL values for a chemical. These include information from (1) chemical-physical characterizations, (2) structure-activity relationships, (3) in vitro toxicity studies, (4) animal toxicity studies, (5) controlled human studies, (6) observations of humans involved in chemical accidents, and (7) epidemiologic studies. Toxicity data from human studies are most applicable and are used when available in preference to data from animal studies and in vitro studies. Toxicity data from inhalation exposures are most useful for setting AEGLs for airborne chemicals because inhalation is the most likely route of exposure and because extrapolation of data from other routes would lead to additional uncertainty in the AEGL estimate.

For most chemicals, actual human toxicity data are not available or critical information on exposure is lacking, so toxicity data from studies conducted in laboratory animals are extrapolated to estimate the potential toxicity in humans. Such extrapolation requires experienced scientific judgment. The toxicity data from animal species most representative of humans in terms of pharmacodynamic and pharmacokinetic properties are used for determining AEGLs. If data are not available on the species that best represents humans, the data from the most sensitive animal species are used to set AEGLs. Uncertainty factors are commonly used when animal data are used to estimate risk levels for humans. The magnitude of uncertainty factors depends on the quality of the animal data used to determine the no-observed-adverse-effect level (NOAEL) and the mode of action of the substance in question. When available, pharmacokinetic data on tissue doses are considered for interspecies extrapolation.

For substances that affect several organ systems or have multiple effects, all end points—including reproductive (in both sexes), develop-mental, neurotoxic, respiratory, and other organ-related effects—are evaluated, the most important or most sensitive effect receiving the greatest attention. For carcinogenic chemicals, excess carcinogenic risk is estimated, and the AEGLs corresponding to carcinogenic risks of 1 in 10,000 (1×10^{-4}), 1 in

100,000 (1×10^{-5}), and 1 in 1,000,000 (1×10^{-6}) exposed persons are estimated.

REVIEW OF AEGL REPORTS

As NAC began developing chemical-specific AEGL reports, EPA and DOD asked the NRC to review independently the NAC reports for their scientific validity, completeness, and consistency with the NRC guideline reports (NRC 1993; NRC in press). The NRC assigned this project to the COT Subcommittee on Acute Exposure Guideline Levels. The subcommittee has expertise in toxicology, epidemiology, pharmacology, medicine, industrial hygiene, biostatistics, risk assessment, and risk communication.

The AEGL draft reports are initially prepared by ad hoc AEGL Development Teams consisting of a chemical manager, two chemical reviewers, and a staff scientist of the NAC contractor—Oak Ridge National Laboratory. The draft documents are then reviewed by NAC and elevated from "draft" to "proposed" status. After the AEGL documents are approved by NAC, they are published in the *Federal Register* for public comment. The reports are then revised by NAC in response to the public comments, elevated from "proposed" to "interim" status, and sent to the NRC Subcommittee on Acute Exposure Guideline Levels for final evaluation.

The NRC subcommittee's review of the AEGL reports prepared by NAC and its contractors involves oral and written presentations to the subcommittee by the authors of the reports. The NRC subcommittee provides advice and recommendations for revisions to ensure scientific validity and consistency with the NRC guideline reports (NRC 1993, 2001). The revised reports are presented at subsequent meetings until the subcommittee is satisfied with the reviews.

Because of the enormous amount of data presented in the AEGL reports, the NRC subcommittee cannot verify all the data used by NAC. The NRC subcommittee relies on NAC for the accuracy and completeness of the toxicity data cited in the AEGLs reports.

This report is the third volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*. AEGL documents for nerve agents (GA, GB, GD, GF, and VX), sulfur mustard, diborane, and methyl isocyanate are published as an appendix to this report. The subcommittee concludes that the AEGLs developed in those documents are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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Appendixes

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Sulfur Mustard (Agent HD)[1]

Acute Exposure Guideline Levels

SUMMARY

Sulfur mustard (agent HD) is an alkylating chemical vesicant that affects any epithelial surface it comes in contact with; it has been developed and used as a warfare agent. The active component is bis(2-chloroethyl)sulfide (CAS Registry No. 505-60-2). Although the chemical is a liquid at ordinary ambient temperatures, its volatility results in rapid generation of vapors that have a garlic-like odor. Due to its low aqueous solubility, it is

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[1]This document was prepared by the AEGL Development Team comprising Robert Young (Oak Ridge National Laboratory) and Kenneth Still (Chemical Manager) of the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances. The NAC reviewed and revised the document and the AEGL values as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Subcommittee on Acute Exposure Guideline Levels. The NRC subcommittee concludes that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

persistent in the environment. Odor thresholds of 1 mg·min/m^3, 0.15 mg/m^3, and 0.6 mg/m^3 have been reported. Among various U.S. Army facilities, there are currently approximately 17,018.1 tons of sulfur mustard (agent HD) awaiting disposal.

Exposure to sulfur mustard vapor may result in irritation and damage to the eyes, respiratory tract, and skin. The toxic effects of sulfur mustard are temperature- and humidity-dependent; for a given exposure, the effects could be greater with increasing temperature and humidity. An exposure-dependent latency period of hours to days is documented and is relevant for all routes of exposure but may be shorter for ocular and upper respiratory tract effects than for dermal and systemic responses. Both human and animal data indicate that the eyes are the most sensitive organ/tissue; deaths resulting from sulfur mustard exposure are more often the result of respiratory tract involvement. Because the toxic effects of sulfur mustard (at least for short time periods) appear to be a linear function of exposure duration and exposure concentration, most of the available exposure-response data are expressed as cumulative exposures (Ct).

Minor ocular irritation (conjunctival injection in the absence of irritation) occurs in humans following exposure at 12-30 mg·min/m^3. More severe effects develop at 60-75 mg·min/m^3 (conjunctivitis, irritation, photophobia) and at 100 mg·min/m^3 (severe ocular irritation). Vapor inhalation LCt_{50} estimates for humans range from 900 mg·min/m^3 to 1,500 mg·min/m^3.

Animal lethality following acute exposure to sulfur mustard occurs at cumulative exposures ranging from approximately 600 mg·min/m^3 to 1,500 mg·min/m^3. Nonlethal effects were similar to those observed in humans and included effects on the eyes, respiratory tract, and skin. Long-term exposure of dogs, rats, and guinea pigs to concentrations at 0.03 mg/m^3 produced only minor signs of ocular and respiratory tract irritation. One-hour (h) exposure of mice to concentrations up to 16.9 mg/m^3 resulted in notable effects on respiratory parameters, and acute exposures of rabbits (20 minutes [min]) to 12 h) to concentrations ranging from 58 mg/m^3 to 389 mg/m^3 (Ct $\geq$ 2,300 mg·min/m^3) resulted in severe respiratory tract damage.

Because exposure-response data were unavailable for all of the AEGL-specific exposure durations, temporal extrapolation was used in development of values for the AEGL-specific time periods. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data regarding AEGL-1-type effects reported by Reed (1918), Reed et al. (1918), Guild et al. (1941), and Anderson (1942) indicate that, for exposure periods up to several hours, the concentration-exposure time relationship is a near-linear function (i.e., Haber's law where $n = 1$ for $C^n \times t = k$) as shown by n values of 1.11 and 0.96. Therefore, the empirically derived, chemical-specific estimate of $n = 1$ was used for derivation of the AEGL-1 and AEGL-2 values. However, in the absence of chemical-specific lethality data, time scaling for AEGL-3 values was performed using exponential extrapolation ($n = 3$) for shorter time periods and linear extrapolation ($n = 1$) for longer time periods. This procedure provides a somewhat more conservative (i.e., protective) estimate of the AEGL-3 values than would be obtained using the single n value based upon ocular irritation.

The AEGL-1 values were based on data from Anderson (1942), who found that an exposure concentration-time product of 12 mg·min/m^3 represented a threshold for conjunctival injection and minor discomfort with no functional decrement in human volunteers acutely exposed to sulfur mustard. An intraspecies uncertainty factor (UF) of 3 was applied for protection of potentially sensitive individuals. This adjustment was considered appropriate for acute exposures to chemicals whose mechanism of action primarily involves surface contact irritation of ocular tissue rather than systemic toxicity. Anderson (1942) noted that there was little variability in the ocular responses among the subjects in his study, thereby providing additional justification for the intraspecies UF of 3.

The AEGL-2 values for sulfur mustard were also developed using the data from Anderson (1942). Anderson reported that a Ct value of approximately 60 mg·min/m^3 represented the lowest concentration-time product for which ocular effects were sufficiently severe (visual impairment and irritation) as to be characterized as military casualties. The 60-mg·min/m^3 exposure was used as the basis for developing the AEGL-2 values because it represented an acute exposure that caused an effect severe enough to impair escape and, although not irreversible, would result in the potential for additional injury. Anderson (1942) characterized the 60-mg·min/m^3 Ct as representing the lower margin of the concentration-effect zone that would result in ineffective military performance (i.e., performance necessary to complete a mission) and that might require treatment for up to 1 week (wk). The ocular irritation and damage were also considered appropriate as a threshold estimate for AEGL-2 effects because the eyes are generally considered the most sensitive indicator of sulfur mustard exposure, and irritation would likely occur in the absence of vesication effects and severe pulmonary effects. The fact that the AEGL-2 is based on human data precludes the use of an interspecies UF. A factor of 3 was applied for intraspecies variability (protection of sensitive populations). The factor was limited to 3 under the assumption that the primary mechanism of action of sulfur mustard involves a direct effect on the ocular surface and that the response will not vary greatly among individuals. Anderson also noted little variability in the ocular responses among the subjects in his study. A modifying factor of 3 was applied to accommodate potential onset of long-term ocular or respiratory effects. This was justified by the fact that there was no long-term follow-up reported by Anderson to confirm or deny the development of permanent ocular or respiratory tract damage. The total modifying factor adjustment was 10 (because the factors of 3 each represent a logarithmic mean [3.16] of 10, that is, $3.16 \times 3.16 = 10$).

For development of the AEGL-3, a 1-h exposure of mice at 21.2 mg/m^3 was used as an estimated lethality threshold (Kumar and Vijayaraghavan 1998). That value is also near the lower bound of the 95% confidence interval for the 1-h mouse LC_{50} of 42.5 mg/m^3 reported by Vijayaraghavan (1997). The intraspecies variability was limited to 3 because the lethality resulting from acute inhalation exposure to sulfur mustard appears to be a function of pulmonary damage resulting from direct contact of the agent with epithelial surfaces and would not likely exhibit an order-of-magnitude variability among individuals. A UF of 3 was also applied to account for possible interspecies variability in the lethal response to sulfur mustard. The resulting total UF adjustment was 10. The modifying factor of 3 used for AEGL-2 development to account for uncertainties regarding the latency and persistence of the irritant effects of low-level exposure to sulfur mustard was not applied for AEGL-3 because lethality of mice was assessed at 14 days (d) postexposure in a previous study by Vijayaraghavan (1997). Application of any additional UFs or modifying factors was not warranted because the AEGL-3 values are equivalent to exposures in humans that are known to produce only ocular and respiratory tract irritation.

The AEGL values for sulfur mustard are based on noncancer end points. Sulfur mustard is genotoxic and has induced carcinogenic responses in humans following single high-concentration exposure and following multiple exposures that were sufficient to produce adverse effects. Based on available sulfur mustard data and in the absence of clinical signs, carcinogenic responses in humans have not been observed following acute low-level or nonvesicating exposures. The human data summarizing cancer

TABLE 2-1 AEGL Values for Sulfur Mustard in Parts Per Million and Milligrams per Cubic Meter

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1[a]	0.06 ppm (0.40 mg/m^3)	0.02 ppm (0.13 mg/m^3)	0.01 ppm (0.067 mg/m^3)	0.003 ppm (0.017 mg/m^3)	0.001 ppm (0.008 mg/m^3)	Conjunctival injection and minor discomfort with no functional decrement in human volunteers (Anderson 1942)
AEGL-2[a]	0.09 ppm (0.60 mg/m^3)	0.03 ppm (0.20 mg/m^3)	0.02 ppm (0.10 mg/m^3)	0.004 ppm (0.025 mg/m^3)	0.002 ppm (0.013 mg/m^3)	Well-marked, generalized conjunctivitis, edema, photo-phobia, and eye irritation in human volunteers (Anderson 1942)
AEGL-3[a]	0.59 ppm (3.9 mg/m^3)	0.41 ppm (2.7 mg/m^3)	0.32 ppm (2.1 mg/m^3)	0.08 ppm (0.53 mg/m^3)	0.04 ppm (0.27 mg/m^3)	Lethality estimate in mice (Kumar and Vijayaraghavan 1998)

[a]AEGL-1 and AEGL-2 values, and the 4- and 8-h AEGL-3 values are at or below the odor threshold for sulfur mustard.

incidences among individuals exposed to sulfur mustard is primarily that for wartime gas-factory workers and for military personnel who sustained injury following direct contact with "battlefield concentrations" of sulfur mustard liquid and/or vapor. A cancer risk assessment based on a geometric mean of inhalation slope factors developed using various data sets and procedures indicated an excess cancer risk of 1 in 10,000 (10^{-4}) may be associated with exposures similar to the AEGL-3 values. The use of excess-cancer-risk estimates in setting AEGL values is precluded by the uncertainties involved in assessing excess cancer risk following a single acute exposure of 8 h or less, the relatively small population exposed in an emergency release situation, and the potential risks associated with evacuations.

The AEGL-1 and AEGL-2 values are based on human exposure data and are considered to be defensible estimates for exposures representing thresholds for the respective AEGL effect levels. Ocular irritation, which forms the basis for AEGL-1 and AEGL-2 values, is the most sensitive response to sulfur mustard vapor. The AEGL-3 values provide Ct products (approximately 39-130 mg·min/m^3) that are known to cause moderate to severe ocular irritation and possible respiratory tract irritation in human subjects but no life-threatening health effects or death. It must be noted that all of the AEGL-1 and AEGL-2 values and the 4- and 8-h AEGL-3 values are at or below the odor threshold for sulfur mustard. In consequence, there is considered to be a finite amount of time to don protective equipment and safeguard critical target tissues such as the eyes and respiratory tract.

Although the overall database for acute inhalation exposure to sulfur mustard is not extensive, the AEGL values appear to be supported by the available data. Extrapolation to exposure durations of less than 10 min is not recommended in the absence of careful evaluation of existing exposure-response data and comparison of any derivative values with these data.

I. INTRODUCTION

Sulfur mustard (agent HD) is an alkylating chemical vesicant that affects any epithelial surface it comes in contact with. It has been developed and used as a warfare agent. The active component is bis(2-chloroethyl)sulfide (CAS Registry No. 505-60-2). Although the chemical is a liquid at ordinary ambient temperatures, its volatility results in rapid generation of vapors (see review by Watson and Griffin [1992]). Ambient temperature and humidity govern the degree of "casualty effect." Under hot and humid conditions, much lower mustard concentrations generate debilitating effects. Sulfur mustard has a garlic-like odor and, due to its low aqueous solubility, is persistent in the environment. Watson and Griffin (1992) have summarized information on the distribution of unitary chemical weapon stockpiles in the United States. Among various U.S. Army facilities, there were approximately 17,018.1 tons of sulfur mustard (agent HD) awaiting disposal in September 2001 (DA 2001). Pertinent physicochemical data for sulfur mustard are summarized in Table 2-2.

TABLE 2-2 Physicochemical Data for Sulfur Mustard

Synonyms	Agent HD; sulfur mustard; dichloroethyl sulfide; yperite; mustard gas; Bis(2-chloroethyl) sulfide; sulfide, Bis(2-chloroethyl); 1,1'-thiobis[2-chloroethane]; yellow cross; LOST	DA 1996; Budavari et al. 1989; Büscher 1932
Chemical formula	$C_4H_8Cl_2S$	Budavari et al. 1989
Molecular weight	159.08	DA 1996
CAS Registry No.	505-60-2	Budavari et al. 1989
Physical state	Oily liquid	DA 1996
Solubility	Sparingly soluble in water; soluble in organic solvents	DA 1996; Budavari et al. 1989
Vapor pressure	0.072 mm Hg at 20°C 0.11 mm Hg at 25°C	DA 1996
Density	5.4	DA 1996
Boiling/melting point	215-217 °C/ 13-14 °C	DA 1996; Budavari et al. 1989
Conversion factors in air	1 ppm = 6.49 mg/m^3 1 mg/m^3 = 0.15 ppm	

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Either inhalation or percutaneous exposure to sulfur mustard vapor can result in lethality, although inhalation exposure is the more sensitive route. Estimates of human LCt_{50} values for agent vapor inhalation are several times lower than the estimated human percutaneous LCt_{50} (Robinson 1967; DA 1974). This contention is supported by animal LCt_{50} data (Robinson 1967; DA 1974; Watson and Griffin 1992). Human lethality data are available only as estimates attained by extrapolation from animal data. The estimated human LCt_{50} values in use by the U.S. Army are 1,500 mg·min/m^3 and 10,000 mg·min/m^3 for inhalation and percutaneous vapor exposure, respectively (DA 1974; NRC 1997).

Although lacking quantitative exposure terms, Warthin and Weller (1919) provided qualitative clinical information regarding two fatalities resulting from sulfur mustard exposures during manufacture of the agent. Both men were wearing gas masks, so ocular involvement was inconsequential, but the exposure concentrations were high enough to result in severe skin burns. Within hours, both victims exhibited lesions about the lips and necrotic lesions in the mouth and nasopharyngeal region. By 7 to 8 d postexposure, there was evidence of more severe respiratory involvement, as demonstrated by moist rales and physical signs indicative of bronchopneumonia. One victim died 8 d after the accident, and the other died 4 wk after the exposure.

Between 1919 and 1923, site remediation and scrap metal recovery operations at a vast (25 square miles) "gas dump" at Breloh, Germany, near Munster in what is now Lower Saxony, resulted in numerous cases of occupational exposure to warfare agents either manufactured or captured by German forces during World War I (Büscher 1932). Thousands of tons of "gas" munitions as well as tank cars and storage buildings containing sulfur mustard and other chemical warfare agents were involved. Summary reports for the years 1920-1923 by the primary-care physician at the site document "two or three" fatalities among workmen who had received concentrated sulfur mustard vapor exposures to the skin, eyes, and respiratory tract in combination. In these cases, "death came very soon" (Büscher 1932). Büscher (1932) was not equipped to gather source term information for any of these fatal episodes.

Estimated lowest lethal doses of 150 mg/m^3 (10 min) and 70 mg/m^3 (30 min) have been reported (Back et al. 1972; Inada et al. 1978). However, those values are not based on definitive exposure values or controlled exposure conditions.

Available hospital records from World War I and sketchy casualty reports from the Iran-Iraq conflict indicate mortality rates of 1-3% from acute sulfur mustard exposure (Blewett 1986; Dunn 1986). Actual battlefield concentrations have not been reported but may well have been in excess of 1,500 mg/m^3 (Watson and Griffin 1992).

Human lethalities were reported by a number of European physicians asked to provide humanitarian treatment for gas casualties arising from the Iran-Iraq conflict. Eisenmenger et al. (1991) treated sulfur-mustard exposed Iranian patients in a German hospital; one patient admitted 5 d postexposure in a semiconscious state with serious exfoliative lesions died during treatment. Other Iranian soldiers exhibiting the characteristic burns, edema, and damage to the respiratory tract associated with battlefield exposures to sulfur mustard died from various combinations of respiratory insufficiency and infection between 5 and 36 d postexposure (one on day 7, three on days 12-15, one on day 36; $N = 5$) (D'Halluin and Roels 1984; Mandl and Frielinger 1984). Sulfur mustard agent is a known immunosuppressant (IOM 1993); however, no exposure terms for any of these wartime cases were available.

In an effort to establish updated toxicity estimates for humans, the U.S. Army Chemical Defense Equipment Process Action Team (Reutter and Wade 1994) developed a revised estimated LCt_{50} of 900 mg·min/m^3 for human inhalation exposure from an average of animal LCt_{50} data. The National Research Council Committee on Toxicology (Subcommittee on Toxicity Values for Selected Nerve and Vesicant Agents) concluded that the 900 mg·min/m^3 estimate was scientifically valid (NRC 1997) but cautioned that the estimate was developed with reference to healthy male military personnel and is *not* applicable to civilians.

2.2. Nonlethal Toxicity

Clinical presentation in humans following acute exposure to sulfur mustard vapor may involve dermal, ocular, and respiratory tract effects, all of which are preceded by a latency period dependent on the exposure concentration and exposure duration (Eisenmenger et al. 1991). Systemic effects (nausea, vomiting, abdominal pain, headache, weight loss, hematopoietic effects) may also occur as a result of gastrointestinal involvement or deep penetration dermal involvement (Büscher 1932). The eye appears to be the most frequently affected and most sensitive organ and also has one of the shortest latency periods (Warthin and Weller 1919; Papirmeister et al. 1991). Latency periods vary with changes in exposure parameters but tend to be several hours to days for dermal effects, 2-8 h for ocular effects, and several hours for upper respiratory tract effects (up to several days for progression to full severity respiratory tract involvement). Studies involving controlled exposure of human volunteers as well as studies on war casualties and occupational exposures are available; the latter provide clinical information but lack quantitative exposure data.

Controlled human clinical trials conducted by Büscher (1932) to better define treatment regimens were confined to "drop" tests of sulfur mustard on various skin sites with observations of the time course under differing decontamination protocols. Inhalation exposures occurred to Breloh gas-dump workers as a consequence of munition explosions, inhalation of smoke plumes generated during primitive "bonfire" heat-cleaning of contaminated metal scrap, off-gassing of contaminated clothing in warm rooms, and the use of contaminated wood scraps as heating fuel in winter quarters. Büscher (1932) describes the clinical course of respiratory effects and their treatment but does not present dose-response data.

Reed (1918) conducted preliminary experiments in which he and another volunteer participated in exposure chamber experiments at a sulfur mustard concentration of 0.0012 mg/L (1.2 mg/m^3); mustard was generated as a spray in absolute ethanol for 45 min in a 10,000 L chamber. The subjects were clad in ordinary khaki uniforms, without blouses, and had no facial protection. A slight odor was initially detected but the olfactory response accommodated within 3 min for one subject and 8 min for the other. Slight irritation of the mucosa of the nose and nasopharyngeal regions occurred at 8 min and progressed in severity such that at 20 min one individual determined to be sensitive to HD on the basis of skin tests withdrew from the exposure chamber. At 25 min, the remaining subject experienced heavy eyelids and "huskiness" of the voice but no coughing or sneezing. At 3 h after the 45-min exposure and 6 h after the 20-min exposure a sudden and severe conjunctivitis developed that was accompanied by photophobia and blepharospasm. By 12 h postexposure, vision was severely impaired, and severe pain and rhinitis were experienced for 30 h. These effects were somewhat less severe in the subject originally classified as more sensitive. Conjunctival injection did not resolve for over a month. At 3 d postexposure, intense pruritus and erythema developed over the neck, shoulders, upper arms, and trunk. It began abating after 7 d. Ocular hypersensitivity and exercise-induced dermal wheals occurred for weeks after the exposure.

Reed (1918) conducted additional experiments using lower sulfur mustard concentrations. In those experiments, one to six volunteers were exposed at various low concentrations of sulfur mustard (0.0001-0.0043 mg/L, nominal; equivalent to 0.1-4.3 mg/m^3) for time periods of 5 to 45 min. The exposure atmospheres were generated by slowly spraying sulfur mustard in absolute alcohol and continually mixing the air with an electric fan. Subsequent investigations revealed that the actual exposure concentrations were $\leq$60-70% of nominal, although Reed (1918) freely admitted that "it is impossible to state what the actual concentration was" due to analytical limitations of the time. It is assumed from context that the volunteers were clothed similarly to those in initial trials (e.g., khaki uniforms without blouses) and wore no facial protection during the period of exposure. Of the 22 men participating in this series (see Table 2-3), a majority had been exposed to sulfur mustard before, and 12 had sustained "one or more burns" either experimentally or accidentally (Reed 1918). The most prominent effect of the controlled atmospheric exposures was ocular irritation (conjunctival injection, conjunctivitis, photophobia), which varied among individuals depending on exposure concentration and duration. The results of these experiments are summarized in Table 2-3.

Reed et al. (1918) also conducted experiments that utilized improved methods (e.g., hydrogen ion method) for measurement of exposure concentrations. To minimize hydrolysis, the HD was delivered in absolute alcohol.

Walker et al. (1928) reported that of seven men exposed to sulfur mustard at 0.001 mg/L (1 mg/m^3) for 5-45 min, four showed conjunctivitis and two exhibited skin burns. It was also reported that of 17 men exposed at 0.0005 mg/L (0.5 mg/m^3) for 10-45 min, six exhibited conjunctivitis, one had a skin burn, and that three of 13 men exposed for 10-30 min at 0.0001 mg/L (0.1 mg/m^3) showed slight but distinct conjunctivitis.

Guild et al. (1941) conducted experiments using human volunteers exposed to sulfur mustard at varying acute exposure regimens. The sulfur mustard vapor was generated by heat volatilization in a 100-m^3 exposure chamber. The subjects were male soldiers and officers and one civilian who had not had previous exposure to sulfur mustard. All subjects wore paint or "dope" spray respirators "to protect the lungs" (Guild et al. 1941). For each of the tests, two to six individuals were exposed. Guild et al. concluded that Ct is constant for ocular effects for exposure periods of 2 min to 20 h and for sulfur mustard concentrations of 0.07-65 mg/m^3. Based on the results of the experiments, it was reported that exposure at Ct values <70 mg·min/m^3 would result in mild conjunctival responses that would not be indicative of a casualty (defined by the authors as temporary loss of vision); Ct values at 70-100 mg·min/m^3 would produce some casualties; and Ct values at >100 mg·min/m^3 would be expected to produce disabling ocular effects for several days. In the military context of this study, Guild et al. (1941) defined "disablement" as "injury sufficient to prevent troops from taking an active part in operations for 1-2 weeks." Because the subjects wore respiratory protection, effects on the respiratory tract could not be determined and were not reported.

TABLE 2-3 Effects of Acute Exposure to Sulfur Mustard (Agent HD) in Human Volunteers

Nominal Concentration (mg/m^3)	Exposure Duration (min)	Number of Subjects	Results
0.1	10	6	No detectable effect
0.1	15	2	One of two subjects exhibited slight conjunctival injection
0.1	30	5	One of five showed marked bilateral conjunctival injection; one of five showed slight conjunctival injection
0.5	10	5	Two of five exhibited conjunctival injection
0.5	15	3	One of three exhibited slight conjunctival injection
0.5	30	8	One of eight exhibited conjunctivitis and experienced rhinitis; one of eight exhibited severe conjunctivitis, marked skin burn; one of eight exhibited marked conjunctivitis, slight facial burn
0.5	45	1	No effect
1.0	5	1	Marked conjunctivitis, photophobia, rhinitis, laryngitis, pulmonary congestion
1.0	10	2	One of two exhibited slight conjunctivitis
1.0	15	2	No effect
1.0	20	1	Exhibited severe conjunctivitis, severe skin burns
1.0	45	1	Very severe conjunctivitis, photophobia, skin burns, mucosal exfoliation in nasopharynx
2.6	5	1	No effect
4.3	10	1	Marked conjunctivitis, no pain

Note: Unprotected face assumed from study context.

Source: Reed 1918.

In a study reported by Anderson (1942) and performed as a follow-up to the Guild et al. (1941) recommendation to replicate the earlier Guild experimental design under tropical conditions, three to four human volunteers were exposed to each of several concentration-time regimens of agent HD "under Indian hot weather conditions." Sulfur mustard vapor was generated by heat volatilization in a 50-m^3 exposure chamber; mixing was accomplished by use of an electric fan in the chamber. Subjects included both British and Indian troops without respiratory protection who wore tropical service dress of drill shorts and open-necked cotton shirts. To minimize off-gassing exposure, subjects bathed and dressed in clean clothing upon completion of each experiment. Eyes of each subject were examined prior to the first experimental exposure; the author noted that a certain degree of fine conjunctival injection was a normal baseline condition for a large proportion of persons living in India at that time. Allowance was thus made for this baseline condition in assessing postexposure effects to sulfur mustard vapor. Effects on the respiratory tract were not reported.

Anderson (1942) determined HD concentrations by use of the gold-benzidine method and performed analysis in a "Spekker photoelectric absorptiometer." In an analysis of the data and cross-comparison with the temperate-zone results of Guild et al. (1941), Anderson determined that comparable eye effects of a particular degree of severity are usually produced at a lower Ct under tropical conditions. An exposure concentration-time product of 30 mg·min/m^3 represented the upper range for mild effects with no disability (conjunctival injection and minor discomfort with no functional decrement). Ct products slightly higher than that (e.g., 34-38.1 mg·min/m^3) were, however, also without appreciable casualty effects. A concentration-time product of 12 mg·min/m^3 was noted by Anderson (1942) as representing the limit for ocular effects as characterized by conjunctival injection in the complete absence of irritation. Ct values of 60-75 mg·min/m^3 were considered a danger zone for widespread conjunctivitis frequently accompanied by chemosis, photophobia, and irritation. At Ct values of 75-90 mg·min/m^3, more severe ocular effects would be expected, to the extent that several weeks of treatment would be necessary in a high proportion of subjects so exposed. At Ct values $\geq$ 100 mg·min/m^3, a 100% casualty rate (as determined by militarily disabling ocular effects) would be expected. The results of these experiments are summarized in Table 2-4.

Please note that the longest reported period of follow-up in the Anderson (1942) study was 36 d postexposure for a case requiring infirmary treatment and exhibiting conjunctivitis, photophobia, and injection with

TABLE 2-4 Effects of Acute Exposure to Sulfur Mustard (Agent HD) in Human Volunteers

Mean Concentration (mg/m^3)	Exposure Duration (min)	Number of Subjects	Cumulative exposure (Ct) ($mg{\cdot}min/m^3$)	Results
6.25	2	4	12.5	Three of four—band of fine injection across exposed bulbar conjuntiva; one of four—trace angular conjunctivitis; all noncasualties
7.0	3.3	4	23.1	Three of four—obvious band of injection across exposed bulbar conjuntiva; one of four—angular conjunctivitis; all noncasualties
10.0	2.75	3	27.5	Two of three—mild injection band over exposed sclera; one of three—band of injection with slight discomfort; all noncasualties
6.8	5	3	34.0	Three of three—well-marked injection of conjunctivae; slight edema in oneof three; all complaining of eye soreness; injection visible in one of three at 14 d postexposure; all noncasualties
12.7	3	3	38.1	Three of three—band of conjunctival injection over exposed sclera; no discomfort; all noncasualties
12.6	3.3	3	41.8	Three of three—effects slightly more marked than in previous experiment; mild discomfort in one of three; all noncasualties

11.0	4	3	44.0	Three of three—moderate injection of exposed bulbar conjunctiva and lower lids (to a lesser degree); one of three—slight edema; one of three—complained of sore eyes in first 24 h; all noncasualties
7.6	6	4	45.6	Three of four—widespread conjunctivitis involving lids and bulb; one of four—exhibiting trace chemosis; one of four—slight photophobia on days 2 and 3; one of four—moderate band of injection; all complaining of discomfort
13.0	3.75	3	48.8	Three of three—widespread moderate injection of conjunctiva; one of three—slight discomfort; one of three—transient edema; all noncasualties
10.5	4.75	3	49.8	Three of three—well-marked injection of lids and exposed conjunctiva; two of three—discomfort; all noncasualties
2.5	20	3	50.0	Three of three—band of moderate injection over exposed part of sclera; two of three—slight soreness
10.6	5	2	53.0	Two of two—widely generalized conjunctival injection visible after 14 d; one of three—complaining of sore eyes; all noncasualties
15.6	3.5	1	54.6	Band of injection across exposed part of sclera; slight conjunctival injection; soreness in one eye; noncasualty.

(Continued)

TABLE 2-4 *Continued*

Mean Concentration (mg/m^3)	Exposure Duration (min)	Number of Subjects	Cumulative exposure (Ct) ($mg{\cdot}min/m^3$)	Results
5.8	9.5	4	55.1	One of four—casualty; wide and intense redness over entire conjunctiva, slight photophobia, moderate chemosis and blepharospasm; three of four—just short of casualty with widespread conjunctival injection, slight edema, and mild photophobia in first 24 h, sore eyes for 2-3 d
14.0	4.0	3	56.0	Three of three—well-marked and widespread conjunctival injection, discomfort; all noncasualties
1.7	33	3	56.1	Three of three—fine injection band over exposed sclera; all noncasualties
2.9	20	3	58.0	Three of three—moderate and generalized conjunctival congestion; one of three—mild discomfort; all noncasualties
4.5	13.5	3	60.7	Three of three—band of moderate injection over exposed sclera; one of three—reported headache on day 1 and later developed generalized urticaria; all non-eye casualties

13.7	4.75	3	65.0	Two of three—widespread conjunctival injection, slight edema and mild discomfort; one of three—severe injection of conjunctiva, well developed edema, very near casualty, severe urticarial reaction first day post-exposure, positive reaction to 1:25,000 sulfur mustard after 1 mo
5	14	3	70	Two of three—well marked and generalized conjunctivitis with edema, photophobia, lacrimation and blepharospasm; sore eyes and frontal headache, casualties up to 1 wk; one of three—intense congestion of entire conjunctiva, lacrimation, chemosis and photophobia
15.6	4.5	2	70.2	One of two—injection of lids, well-marked band of injection across exposed sclera, soreness up to day 3, noncasualty; one of two—severe conjunctival injection, slight hazing of cornea with photophobia and soreness up to day 3 postexposure, lacrimation and slight interference with vision, casualty requiring 4-5 d treatment
4.7	15	3	70.5	Three of three—lids injected, well-marked and generalized conjunctivitis with edema, photophobia and eye soreness; one of three—headache; all near casualties requiring 3-5 d treatment

Note: No respiratory protection was worn during exposure periods.
Source: Anderson 1942.

corneal injury. By discharge on day 36, both eyes were reported "normal." It is observed that, during the 1940s, it was common practice to employ minimal long-term medical follow-up in studies of military personnel experimentally exposed to chemical warfare agents (IOM 1993). Short-term casualty effects were the primary focus of military investigators at the time.

Following a review and evaluation of all available data, an ECt_{50} of 100 mg·min/m^3 for severe ocular effects (for soldiers) was determined by Reutter and Wade (1994) and the NRC (1997). The estimate was based on an assumed exposure duration of 2 to 10 min and an effect severity consistent with that which would necessitate removal of soldiers from the battlefield. The assessment also affirmed that the eye is a sufficiently sensitive organ on which to base exposure estimates.

The percutaneous absorption of sulfur mustard vapor in human skin was studied by Nagy et al. (1946) to understand more fully the relationship between penetration rate and severity of toxicity. Using a carefully designed and tested technique and human volunteers, Nagy et al. determined the penetration rate of sulfur mustard for human skin. The application times studied using human skin were 3, 6, and 10-min exposures. A saturated atmosphere (under an application cup) of sulfur mustard was applied to a 1.3-cm^2 area of the flexor aspect of the forearm; lesions (pinhead vesicles, erythema, vesication) were evaluated at 48 h after application. Quantitation of agent that penetrated the skin was determined by comparing the quantity of HD vapor in the application cup before and after a given time interval. It was found that an increase in temperature (from 21-23 °C to 30-31 °C) produced an increase in the penetration rate from 1.4 µg/cm^2/min to 2.7 µg/cm^2/min.

Moore and Rockman (1950) studied variability in hypersensitivity reactions to sulfur mustard using human volunteers. A single drop (4.5 ± 0.22 mm^3) of various dilutions of purified sulfur mustard (1:500 to 1:8,000 in petroleum ether) was applied to each subject's volar forearm. The test area was examined at 24, 48, and 72 h, and a description of the reaction was recorded. About 25% of those given two exposures to sulfur mustard with a week exhibited a flare response at the first site even when the second application was at a different site (e.g., opposite arm). Although a conversion of this exposure regimen to an equivalent air concentration was not feasible, the results of the study provide evidence of possible dermal sensitization to sulfur mustard dermal exposure. Similar findings are reported in Büscher (1932), Sulzberger et al. (1945), and IOM (1993).

Warm, moist anatomical areas such as the axillae and groin are especially susceptible to sulfur mustard vapor injury (IOM 1993).

Eisenmenger et al. (1991) reported clinical and morphologic findings from 11 Iranian patients exposed to sulfur mustard during the Iran-Iraq conflict and treated in a German hospital. Quantitative exposure data are lacking for these case reports, but the information provides a clinical picture of the progression of sulfur mustard lesions. Upon admittance to the hospital (4-6 d or 17 d after exposure), all patients exhibited conjunctivitis and some also exhibited erosions and slight corneal opacity and reddened, blistered skin. The severity of respiratory tract involvement tended to be concentration-dependent, with only upper respiratory tract involvement at lower concentrations. The most serious respiratory effects were observed at 14 d postexposure. One patient admitted in a semiconscious state with serious exfoliative lesions observed at 5 d postexposure died, and several others likely would have died without medical intervention. No follow-up study was performed on these patients. Although lacking quantitative data useful for developing AEGL values, this clinical report provides qualitative information regarding human exposure to sulfur mustard and indicates that effects observed in humans are similar to those observed in animals.

Odor thresholds of 1 mg·min/m^3 (Bloom et al. 1944), 0.15 mg/m^3 (Ruth 1986), and 0.6 mg/m^3 (Dudley and Wells 1938; Bowden 1943; Fuhr and Krakow 1945) have been reported.

2.2.1. Epidemiologic Studies

Emad and Rezaian (1997) conducted a cross-sectional clinical study of late pulmonary sequelae exhibited by 197 Iranian military veterans 10 y after receiving a single, high-concentration sulfur mustard exposure in 1986 during the Iran-Iraq conflict. The control group consisted of 86 nonexposed veterans. In 1986, exposure to sulfur mustard had been initially confirmed at hospital admission by urine and vesicular fluid analysis (by the method of Heyndrickx et al. [1984]) and by presentation with respiratory symptoms that included rhinorrhea, sore throat, hoarseness, cough, chest tightness, and dyspnea. Participants were screened for asthma and prior exposures to environmental agents known to cause interstitial lung disease or extrinsic allergic alveolitis. In addition, participants were not allowed to have had jobs that might create interference with the study (e.g., woodworking, milling, welding, farming, sculpturing, painting, fire fighting, baking) since 1986. The incidences of asthma (10.65%), chronic bronchitis (58.88%), bronchiectasis (8.62%), airway narrowing due to scar or granulation tissue (9.64%), and pulmonary fibrosis (12.18%) in the sulfur mustard exposed group were all greater than those found in the referent group (0% in all categories except for one case of bronchitis [1%]). The investigators concluded that exposure to clinically significant sulfur mustard concentrations created greater potential for development of chronic destructive pulmonary sequelae. The authors further concluded that the relatively low incidence of pulmonary fibrosis resulted from the fact that the largest proportion of mustard agent was absorbed in the upper airways rather than in the alveoli. No bronchial carcinoma or lung malignancy has been observed to date in this group of veterans (Emad and Rezaian 1997).

2.3. Neurotoxicity

There are no data currently available regarding potential neurotoxic effects of inhaled sulfur mustard in humans.

2.4. Developmental and Reproductive Toxicity

There are no data currently available regarding potential developmental and reproductive toxicity of inhaled sulfur mustard in humans.

2.5. Genotoxicity

The International Agency for Research on Cancer (IARC) (1975, 1982, 1987a,b), Fox and Scott (1980), ATSDR (1992), Papirmeister et al. (1991), and Watson and Griffin (1992) summarized the evidence concerning genotoxicity of sulfur mustard. Because sulfur mustard is a potent DNA alkylating agent, genotoxic effects occur through cross-link formation, inhibition of DNA synthesis and repair, point mutations due to replication or repair errors, chromosome breaks, and chromatid aberrations. Some of those conditions have been observed in humans following exposure to sulfur mustard, others have occurred in various test systems including bacteria, yeast, insects, and mammalian cell cultures.

Retrospective studies have been conducted on Japanese workers who were employed at a chemical agent manufacturing plant from 1929 to 1945. Although sulfur mustard was the main product of the facility, lewisite, diphenylarsine, hydrocyanic acid, phosgene, and chloroacetophenone were also produced there (Inada et al. 1978), and it is not known to what degree those other chemicals contributed to the observed effects. In one study of the workers, Yanagida et al. (1988) found that the frequency of mutations to hypoxanthine-guanine-phosphoribosyl-transferase (HGPRT) deficiency in 28 exposed individuals was significantly elevated when compared with two control groups matched for age and smoking status. One control group consisted of healthy men and the other of individuals with bronchitis. The data also showed that the mutations were significantly more frequent in workers who had longer exposures. A chromosome study of 16 former workers of this same factory indicated a significantly higher incidence of sister chromatid exchanges (SCE) in peripheral lymphocytes when compared with a control group ($p < 0.03$) (Shakil et al. 1993). Two individuals with chronic myelocytic leukemia had an almost 3-fold higher SCE rate than controls and also a high (12.1%) incidence of chromosome abnormalities (Shakil et al. 1993). In an evaluation of the p53 mutations found in lung tumors of these workers, Takeshima et al. (1994) found that the mutations were similar to those in lung tumors of tobacco smokers (the factory workers were also tobacco smokers); however, the prominence of G:C to A:T transitions and the occurrence of double mutations in two of 12 cases suggested that exposures in the chemical agent manufacturing plant contributed to the development of the lung cancers.

Yamakido et al. (1985) studied the potential genotoxicity of sulfur mustard in children of workers previously exposed at a Japanese poison gas factory. The study utilized general health exams in conjunction with one-dimensional electrophoretic analysis of blood protein variants to identify gene mutations. Although variants were detected, the investigators considered the results inconclusive as to the potential genotoxicity of sulfur mustard in humans because of the small size of the population sampled.

Wulf et al. (1985) reported significant ($p < 0.001$) increases in sister chromatid exchanges in lymphocytes of 11 fisherman who had accidentally been exposed to sulfur mustard in sufficiently high concentrations to cause signs of acute toxicity. The fishermen received contact exposure to sulfur mustard from nets deployed in areas where World War II–era munitions had been dumped at sea.

Cytometric analysis of DNA damage was shown for cultured human epithelial cells exposed to sulfur mustard (Emison and Smith 1997). The cell cycle was found to be blocked at the G1-S interface at concentrations equivalent to an in vivo vesicating dose (>100 μM) and is blocked in the

G2 phase at concentrations below an equivalent vesicating concentration. At concentrations of 3 µM, the cell cycle was initially blocked at G2/M, but the cells recovered normal cell cycle progression. Quantitation of DNA strand breaks was possible at concentrations equivalent to both vesicating and nonvesicating exposures.

2.6. Carcinogenicity

Studies evaluating workers occupationally exposed to sulfur mustard indicate elevated risks of respiratory tract and skin tumors after long-term exposure. Genotoxicity and animal carcinogenicity data as well as information characterizing the alkylating properties of sulfur mustard provide supporting evidence for the carcinogenicity of sulfur mustard in humans. This work has been summarized in USACHPPM (2000).

IARC classified sulfur mustard as a Group-1 compound (carcinogenic to humans) (IARC 1987), and the National Toxicological Program (NTP) first categorized sulfur mustard gas (or mustard gas) as a substance "known to be a human carcinogen" in its *First Annual Report on Carcinogens, 1980*. Mustard gas is still listed in the same category in the *Ninth Report On Carcinogens, 2000* (DHHS 2000). The State of Maryland also considers mustard gas a "known human carcinogen" (a Class I.A. Toxic Air Pollutant as defined by the Code of Maryland Regulations, CMR Title 26 Subtitle 11, amended).

IARC (1975), Waters et al. (1983), Watson et al. (1989), and IOM (1993) summarized the epidemiological evidence concerning the potential carcinogenicity of sulfur mustard in humans. Those data are primarily from studies of soldiers exposed during World War I and from studies of workers at chemical warfare agent manufacturing facilities.

Individual case studies of World War I veterans include Case and Lea (1955) and Beebe (1960). Case and Lea (1955) reported that the mortality ratio (2.07) of 1,267 World War I United Kingdom veterans indicated a highly significant elevated risk for respiratory tract neoplasms ($p < 0.01$). A similar tumor incidence rate and mortality ratio (2.01) were found in a population of veterans who had never been exposed to mustard gas but were suffering from bronchitis. Case and Lea (1955) concluded that the evidence did not support the view that sulfur mustard was a direct carcinogen.

Beebe (1960) evaluated the occurrence of respiratory tract cancers among a group of 2,718 American soldiers exposed to sulfur mustard during World War I and found that the ratio of observed to expected cases was 1.47 (based on U.S. mortality rates) compared with 1.15 for wounded soldiers not exposed to sulfur mustard, and 0.81 for soldiers who had pneumonia but had not been exposed to mustard gas. Norman (1975) evaluated the same group of soldiers after a 10-y follow-up period (the study completed in 1965) and found that the exposed men had a 40% excess of lung cancer mortality, with an estimated relative risk of 1.3 (95% confidence limits of 0.9-1.9), compared with a control group consisting of wounded soldiers who were not exposured to mustard gas. The latency period was estimated at 22-37 y. Norman (1975) further concluded that there was no evidence in this limited data set that sulfur mustard exposure and cigarette smoking had a synergistic effect on lung cancer mortality.

Retrospective studies of Japanese workers who were employed at a chemical warfare agent manufacturing plant from 1929 to 1945 have revealed that those individuals have an increased risk of developing respiratory tract cancers (see Yamakido et al. [1996] for the most recent review). Although sulfur mustard was the main product of the facility, lewisite, diphenylarsine, hydrocyanic acid, phosgene, and chloroacetophenone were also produced (Inada et al. 1978). The concentration of sulfur mustard in the workplace was estimated to be as high as 50-70 mg/m^3 (Nakamura 1956), and workers frequently exhibited signs of sulfur mustard toxicity during the period of agent manufacture; those signs included acute conjunctivitis, acute rhinitis, acute bronchitis, and acute dermatitis with blister formation. Studies completed in the 1950s documented individual cases of bronchial and laryngeal carcinoma in this population of workers (Yamada et al. 1953, 1957; Yamada 1963) and an elevated incidence of deaths due to cancers of the respiratory tract and oropharynx (16.3% versus 0.4% in nonexposed inhabitants of the same geographic area). Elevated mortality rates among the former factory workers due to respiratory tract cancer was later confirmed by Wada et al. (1968). Neoplasms occurred in the tongue, pharynx, sphenoidal sinus, larynx, trachea, and bronchi; only one occurred peripherally in the lung. The median length of employment at the chemical warfare agent manufacturing facility was 7.4 y, and the median interval between first employment and death from cancer of the respiratory tract was 24.4 y (Wada et al. 1968).

Additional studies of this population of workers were conducted by Nishimoto et al. (1988) who incorporated histopathological and mortality data gathered between 1952 and 1986. For 1,632 of the workers, the overall standardized mortality ratio (SMR) for respiratory tract tumors was 3.9 (70 observed versus 17.8 expected, $p < 0.001$, based on data for the Japanese male population) and the overall SMR for all malignant tumors was 1.2 (173 observed versus 142 expected, $p < 0.01$). Age-adjusted SMRs for total malignancies, respiratory tract tumors, and gastrointestinal tract tumors showed significantly higher SMRs for the age-groups from 40 to 80 y.

Nishimoto et al. (1988) also found that the SMR was about 2.7 for individuals who had worked at the factory 0.5 to 5 y but was 7.17 for individuals who had been employed for more than 5 y. The SMR was not significantly elevated for individuals who had worked at the factory for 7 months (mo) or less.

Data on this same group of workers followed up to 1992 and has been summarized by Yamakido et al. (1996). The results do not differ substantially from those of Nishimoto et al. (1983, 1988).

Of 488 former workers who received dermatological examination, 115 had abnormal pigmentation and 22 had skin tumors, of which 8 were cases of Bowen's disease (intraepidermal squamous cell carcinoma) (Inada et al. 1978). Hyperkeratotic skin lesions, such as Bowen's disease, basal cell carcinomas, and hyperkeratotic papular eruptions, were present in 14 of 109 cases engaged only in sulfur mustard production and in 1 of 16 cases engaged only in lewisite production. No abnormalities were observed in 77 former factory workers who had no exposure to chemical agents (Inada et al. 1978). It was also observed that the longer an individual had been exposed to sulfur mustard, the more marked the skin lesions tended to become (Inada et al. 1978).

The studies of Yamakido et al. (1996), Nishimoto et al. (1988), Yamada (1974) and Inada et al. (1978) provide strong evidence for a causal link between chemical agent exposure and cancer of the respiratory tract; however, because the workers were potentially exposed to lewisite as well, it is not possible to state conclusively that the cancers were due solely to sulfur mustard. Furthermore, it should be noted that several possible confounding factors, such as tobacco smoking habits, preexisting health conditions, and postexposure occupational histories of the workers, were not evaluated. In addition, the SMR may not provide a good estimate of cancer risk, because it does not take into account the impact of medical intervention and socioeconomic factors that can affect survival rates.

Weiss and Weiss (1975) conducted studies evaluating the health of 271 workers employed for varying lengths of time between 1935 and 1945 at a munitions depot where the production, testing, and destruction of sulfur and nitrogen mustard (as well as bromoacetone, phosgene, chloropicrin, and organic arsenicals) had occurred. Ninety percent of the group had chronic health problems, and 114 had died by the end of 1974. Thirty-five percent died from cancer, of which 38% were bronchial cancers. The total number of deaths from cancer was significant ($p < 0.01$), and the number of bronchial cancers was also significant (11 observed versus 5 expected for the population of the geographic region where the facility was located). The number of cancers of the gastrointestinal tract was 35% greater than expected. The average tumor induction time was 21.6 y. IARC (1975) noted that the study was limited to workers with available medical records, which "raises the possibility that the proportion with cancer may have been inflated, since medical records or autopsy records would more likely have been preserved for workers with cancer." Furthermore, IARC (1975) does not mention whether Weiss and Weiss (1975) accounted for smoking habits and other confounding factors.

According to Klehr (1984), German workers involved in the dismantling of a sulfur mustard facility developed multiple skin lesions including basal cell carcinomas, Bowen's disease, Bowen's carcinomas, and carcinoma spinocellulare. The incidence rate for all tumors (including skin tumors) was 34% in 53 workers evaluated.

Manning et al. (1981) evaluated the incidence of cancer among former workers of a British sulfur mustard manufacturing facility (1939-1945). As of 1974, the number of deaths from all neoplasms combined (45) was slightly greater than that expected from national death rates, but the increase was not statistically significant. In follow-up investigations of this cohort, Easton et al. (1988) evaluated the mortality records of 3,354 workers and found greater numbers of cancer deaths when compared with national mortality rates. Significant increases were observed in deaths from cancer of the larynx, pharynx, and all other buccal cavity and upper respiratory sites combined. There were also elevated numbers of deaths from lung cancer compared with those expected ($p < 0.001$). It was reported that the risks of developing cancer of the lung and pharynx were significantly related to the duration of employment. Significant excess mortality was also observed for cancers of the esophagus and stomach, but there was no correlation with the time since first exposure or the duration of exposure.

Manning et al. (1981) concluded that it was very likely that the observed cancers of the pharynx, larynx, and other upper respiratory sites were due to exposure to sulfur mustard because the excesses were too large to be accounted for by confounding factors (the effects of smoking, however, were not evaluated). They increased with increasing duration of employment and were limited to the period >10 y after first employment. Evidence for a causal relationship between sulfur mustard exposure and other cancers, including lung cancer, was not considered to be as strong.

Although a large number of American military personnel were exposed to sulfur mustard in chamber and field tests conducted during World War II, the morbidity and mortality records of that cohort have not been adequately evaluated to document long-term health risks (IOM 1993).

Evaluations of available human and lab animal data sets have resulted in numerous estimates of a slope factor for sulfur mustard (Bakshi et al. 2000; McNamara et al. 1975; NRC 1999; Rosenblatt 1987; USACHPPM, 2000; USEPA 1991; Watson et al. 1989). The range of inhalation unit risk factors documented in this literature is 9.0×10^{-2} to 7.4×10^{-4} per µg/m^3 (geometric mean of 4.1×10^{-3} per µg/m^3) (USACHPPM 2000).

2.7. Summary

Human data regarding nonlethal effects of sulfur mustard are available from studies using volunteer subjects. Qualitative descriptions of the clinical presentation of injury following exposure to sulfur mustard vapor are also available for war casualties and occupational exposures. Lethality data for humans are not available, but LCt_{50} values have been estimated based on extrapolation from animal data.

The available data suggest that the location and severity of damage resulting from exposure to sulfur mustard are concentration-dependent and a function of the highly reactive nature of sulfur mustard (Papirmeister et al. 1991). Ocular surfaces appear to be a sensitive, rapidly responding target (Reed 1918; Reed et al. 1918; Anderson 1942) . At low exposures, sulfur-mustard-induced injury appears to be limited to the upper respiratory tract (Eisenmenger et al. 1991) and eyes (Reed 1918; Reed et al. 1918; Anderson 1942). Anderson (1942) considered Ct values of 60-75 mg·min/m^3 representative of exposures that would result in conjunctivitis, photophobia, and ocular irritation, while Ct values of 75-90 mg·min/m^3 would cause a high proportion of casualties, defined by more severe ocular damage requiring several weeks of treatment. At higher concentrations, the pulmonary regions are also affected (Eisenmenger et al. 1991). For all targets, there is a latency period between initial exposure and development of effects. The eyes and respiratory tract appear to have the shortest latency period; usually a matter of hours depending on the severity of exposure.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Fuhr and Krakow (1945) reported 2-, 30-, and 60-min LCt_{50} values of 1,512, 990, and 840 mg·min/m^3, respectively, for rats. However, data are unavailable for verifying the values or the analytical techniques utilized in their development.

3.1.2 Mice

Fuhr and Krakow (1945) also reported 2-, 30-, and 60-min LCt_{50} values of 4,140, 1,320, and 860 mg·min/m^3, respectively, for mice. As is the case for rats, data are unavailable for verification.

In a head-only inhalation study, groups of four adult female Swiss mice (24-26 g) were exposed to sulfur mustard (>99% purity) at concentrations of 8.5, 16.9, 21.3, 26.8, 42.3, or 84.7 mg/m^3 for 60 min (Vijayaraghavan 1997). A group of mice exposed to filtered air for 60 min served as controls, and mice exposed to acetone vapor served as vehicle controls. Respiratory patterns of the mice were monitored for 7 d, and the animals were observed for up to 14 d postexposure. Sulfur mustard vapor was generated using a known quantity of sulfur mustard diluted with acetone and pumped into a compressed air nebulizer. Pressure in the nebulizer was adjusted for complete evaporation of the acetone diluent. A constant air flow of 20 L/min was maintained in the 50 cm × 10 cm exposure chamber (constructed of PTFE). The chamber air was sampled at a rate of 50 mL/min for 5 min and analyzed by gas chromatography (flame ionization detector). The primary focus of the study was assessment of changes in respiratory patterns, and to that end, an RD_{50} of 27.4 mg/m^3 (RD_{50} is the exposure concentration necessary to evoke a 50% decrease in respiratory rate) was determined along with other effects on respiration described in Section

3.2.3. The study author noted that mice started dying 6 d after exposure to "higher concentrations," and the author provided a 60-min LC_{50} of 42.5 mg/m^3. No exposure-response data or other details regarding lethality were provided except the confidence interval for the LC_{50}, which was very large (13.5-133.4 mg/m^3) because sensory irritation and decreased respiratory frequency of mice in the higher exposure groups affected the actual intake and absorption of the sulfur mustard (most likely only for the latter half of the exposure period, because the mice did not exhibit notable decrement in respiratory function during the first 15-20 min of exposure).

Kumar and Vijayaraghavan (1998) provided additional information regarding the lethal response of mice exposed to sulfur mustard. Groups of 30 female albino mice were exposed (head only) for 1 h to sulfur mustard at concentrations of 21.2, 42.3, or 84.6 mg/m^3 (equivalent to 0.5, 1.0, and 2.0 LC_{50}) and sacrificed at 6, 24, or 48 h or 7 d after exposure. Three groups of 10 mice were exposed at each concentration. The exposure system was as previously described by Vijayaraghavan (1997). No mice died during the exposure and none of the mice in the lowest exposure group died prior to scheduled termination. Within 7 d, however, five mice from the 42.3 mg/m^3 group and eight mice from the 84.6 mg/m^3 group died. It was not stated when the mice expired, and because groups of mice were terminated at three time points prior to 7 d postexposure, it was not possible to determine the overall 7-d mortality rate.

3.1.3. Guinea pigs

Langenberg et al. (1998) provided data on the lethality of inhaled sulfur mustard in guinea pigs. In this study, which examined both the toxicity and toxicokinetics of sulfur mustard, male hairless guinea pigs (eight per group) were exposed to sulfur mustard by nose-only inhalation or by percutaneous exposure to vapors. The investigators reported the 96-h LCt_{50} for 5-min exposure to be 800 mg·min/m^3 (95% confidence interval of 700-920 mg·min/m^3). No percutaneous exposure lethality values were provided because of difficulties with the exposure system when exposing the guinea pigs to concentrations consistent with percutaneous LCt_{50} values (10,000 mg·min/m^3) previously reported in the literature. The vapor-generating system and exposure system were modified from those used in nerve agent studies. Modifications included replacement of portions of the chamber so that they would be inert to sulfur mustard and an increase in chamber temperature (thermostat controlled at 25-30 °C) to accommodate the lower vapor pressure of sulfur mustard.

Rosenblatt et al. (1987) cite an LCt_{50} value at 900 mg·min/m^3 for the rabbit for a 10-min exposure duration. However, data were unavailable to verify that value or the analytical techniques utilized in its development.

3.2. Nonlethal Toxicity

3.2.1. Dogs

McNamara et al. (1975) conducted long-term inhalation studies of sulfur mustard in several species, including dogs. In those experiments groups of dogs (gender and strain not specified) were exposed continuously at 0.001 mg of sulfur mustard per cubic meter or discontinuously (6.5 h/d, 5 d/wk) at 0.03 mg/m^3 for up to 52 wk (the latter group actually received 0.1 mg/m^3, 6.5 h/d and 0.0025 mg/m^3 for the remaining 17.5 h/d for a time-weighted average exposure of 0.029 mg/m^3 over a 24-h period; the study author referred to this latter group as the 0.1 mg/m^3 exposure group). Ocular effects including corneal opacities, pannus, chronic keratitis, vascularization, pigmentation and granulation were the only overt signs of toxicity observed in the course of the study, and were only observed in dogs in the 0.1 mg/m^3 exposure group. Clinical chemistry analysis revealed only a slight increase in serum glutamic oxaloacetic transaminase (SGOT) activity in the high-dose dogs, which was of no biologic consequence. Three of 10 dogs exposed at 0.1 mg/m^3 exhibited chronic keratitis and conjunctivitis that was considered to be treatment related following prolonged exposure (7.5 or 12 mo) to sulfur mustard. In addition, there was no evidence of respiratory sensitization in the sulfur-mustard-exposed dogs. Because the study did not provide acute exposure-response data and involved long-term, repeated exposures not consistent with the exposure scenarios for AEGL application, the data are not directly applicable to the development of AEGL values. However, the results of this long-term exposure study may be useful as reference points to assess the validity of AEGLs.

3.2.2. Rats

McNamara et al. (1975) conducted long-term inhalation studies of sulfur mustard in Sprague-Dawley–Wistar rats. In the experiments, groups of rats (gender not specified) were exposed continuously at 0.001 mg sulfur mustard per cubic meter or discontinuously (6.5 h/d, 5 d/wk) at 0.1 mg/m^3 (see Section 3.2.1) for up to 52 wk. In the 79 rats exposed at 0.1 mg/m^3, there were no compound-related overt signs of toxicity. Necropsy revealed keratitis, possibly compound-related, in five of the rats. Necropsy revealed squamous cell carcinomas (skin) considered treatment related in four rats and squamous or basal cell carcinomas considered possibly treatment related in five rats (see Section 3.5).

Anderson et al. (1996) reported on the pathologic changes in adult male rats following 50-min intratracheal administration of sulfur mustard (0.35 mg/100 µL absolute ethanol). The dose of sulfur mustard was selected based on preliminary studies (data not provided) indicating that such an exposure would produce consistent but nonlethal damage at 24 h postexposure. Controls were treated similarly with absolute ethanol without the involvement of sulfur mustard. During exposure, the rats were anesthetized with Ketamine and they were euthanized at 0, 1, 4, 6, 12, 18, or 24 h postexposure. At 6 h postexposure, gross pathology assessments revealed multifocal petechial hemorrhages on the pleural surface of the lungs. Atelectasis and edema of the accessory lobe and necrosis and sloughing of tracheal and bronchial epithelia were observed at 6-12 h postexposure. Analysis revealed that most histologically defined lesions were confined to the trachea, bronchi, and larger bronchioles rather than the pulmonary region. There were no findings in the control group and little or no effects were observed in the sulfur-mustard-treated rats during the first 4 h after exposure. A latent phase of 4-6 h following sulfur mustard exposure was required for development of histologic lesions (epithelial necrosis and sloughing). Lymphoid necrosis, loss of lymphocytes, and damage to tracheal cartilage were observed at 12 h postexposure. At 24 h postexposure, peribronchiolar and perivascular edema were detected, but small bronchioles and alveoli appeared to be unaffected, although they contained some cellular debris and inflammatory cells. Ultrastructural examination revealed an increased number of alveolar macrophages in some foci of mild edema at 6 h. At 12 h postexposure, injury to Type 1 pneumocytes was observed, and edematous material, cellular debris, extravasated erythrocytes, and fibrin were seen in scattered alveoli. Evidence of hyperplasia and hypertrophy of Type II pneumocytes was observed at 18-24 h postexposure. An actual administered concentration of sulfur mustard was not provided, and there were no provisions in the experimental apparatus for actual measurement of the test material. The results of this study are consistent with the pattern of respiratory tract injury observed in humans following low-level exposure to sulfur mustard. Because the study did not provide acute exposure-response data and involved long-term, repeated exposures not consistent with the exposure scenarios for AEGL application, the data are not directly applicable to the development of AEGL values. However, the results of this long-term exposure study may be useful as a reference point to assess the validity of AEGLs.

3.2.3. Mice

In the long-term inhalation study by McNamara et al. (1975), groups of A/J mice were exposed to sulfur mustard at 0.001 mg /m^3 continuously or discontinuously (6.5 h/d, 5 d/wk) at 0.1 mg/m^3 (see Section 3.2.1) for up to 52 wk. There were no overt signs of toxicity in the exposed mice during the treatment period. Deaths occured among the mice, but the investigators attributed those to adverse temperature extremes in the animal quarters, not to cumulative Ct for sulfur mustard. No clinical chemistry analyses were performed on the mice. There were no treatment-related tumors in mice exposed to sulfur mustard at 0.1 mg/m^3 (see Section 3.5). Because the study did not provide acute exposure-response data and involved long-term, repeated exposures not consistent with the exposure scenarios for AEGL application, the data are not directly applicable to the development of AEGL values. However, the results of this long-term exposure study may be useful as reference points to assess the validity of AEGLs.

Groups of four adult female Swiss mice (24-26 g) were exposed to sulfur mustard (>99% purity) at concentrations of 8.5, 16.9, 21.3, 26.8, 42.3, or 84.7 mg/m^3 for 60 min (Vijayaraghavan 1997). A group of mice exposed to filtered air for 60 min served as untreated controls, and mice exposed to acetone vapor served as vehicle controls. In this head-only exposure study, respiratory patterns of the mice were monitored for 7 d, and the animals were observed for up to 14 d postexposure. Sulfur mustard vapor was generated using a known quantity of sulfur mustard diluted with acetone and pumped into a compressed air nebulizer. Pressure in the nebulizer was adjusted for complete evaporation of the acetone diluent. A constant air flow of 20 L/min was maintained in the 50 cm × 10 cm exposure chamber. The chamber air was sampled at a rate of 50 mL/min for 5 min and analyzed by gas chromatography (flame ionization detector). At 15-20 min into the exposure, the mice exposed to sulfur mustard exhibited signs of sensory irritation and their respiratory rate progressively decreased until 30 min into the exposure after which no further decrement was detected. The RD_{50} was calculated to be 27.4 mg/m^3. By postexposure day 1, there was a concentration-dependent decrease in respiratory rate over the 7-d monitoring period that was statistically significant ($p < 0.05$) for the 21.3, 26.8, and 42.3 mg/m^3 groups relative to the unexposed controls. Decreases were as much as 40-60% of controls in the three exposure groups. Respiratory rate was also notably decreased (64.8% of that of controls) in the 16.9 mg/m^3 group, but the change was not statistically significant. Although exposure-response data were not provided, lethality was reported for mice in the "higher exposure" groups until 6 d postexposure.

Kumar and Vijayaraghavan (1998) provided additional information regarding nonlethal responses of mice to inhaled sulfur mustard. Groups of 30 female albino mice were exposed (head-only) for 1 h to sulfur mustard at concentrations of 21.2, 42.3, or 84.6 mg/m^3 (equivalent to 0.5, 1.0, and 2.0 LC_{50}) and sacrificed at 6, 24, or 48 h or 7 d after exposure. The exposure system was as previously described by Vijayaraghavan (1997). Even at the highest exposure, no mice died during exposure, although the mice did exhibit sensory irritation resulting in pauses between inspiration and expiration and decreased ventilatory frequency. Effects of sulfur mustard exposure on blood uric acid and urinary uric acid were also examined as an index of purine catabolism. Exposure to sulfur mustard at all concentrations tested resulted in significant increases in blood uric acid and urinary uric acid at all time points measured (except the 6-h time point for the low-dose group). The greatest concentration appeared to be at 24 h and generally decreased, although not to control levels, by 7 d. The increased blood uric acid was postulated as the result of catabolism of apurinated bases resulting from DNA adduct formation by sulfur mustard.

3.2.4. Rabbits

In an early study by Warthin and Weller (1919), rabbits (no information provided regarding gender, age, weight, or strain) were exposed to sulfur mustard at various concentrations and for various periods of time. The sulfur mustard concentrations were determined based on changes in weight of the sulfur mustard sample and the air flow and were simply expressed as ratios. The exposure regimen for eight rabbits and their respective responses are summarized in Table 2-5. The study authors concluded the following: (1) respiratory lesions are proportional to the concentration

TABLE 2-5 Effects on Rabbits of Acute Inhalation Exposure to Sulfur Mustard

Rabbit Number	Exposure[a]	Effects
32	58 mg/m^3 (1:110,000); 40 min	Signs of mild ocular and nasal irritation during exposure; increasing severity of conjunctival erythema and lacrimation up to sacrifice at 12 h; pulmonary congestion and edema
33	389 mg/m^3 (1:15,000); 20 min	Mild irritation during exposure; increased lacrimation and marked erythema of nostrils, mouth, ears, conjunctiva, and some dermal areas up to sacrifice at 36 h; evidence of edema and necrosis in nasal passages
30	389 mg/m^3 (1:15,000); 30 min	Signs of ocular irritation within 5 min after exposure; increased severity of ocular involvement progressing to extreme conjunctival edema and corneal ulceration; evidence of respiratory involvement by day 2; no increase in severity at time of sacrifice (4.25 d); marked congestion and edema in all areas of respiratory tract
31	214 mg/m^3 (1:30,000); 35 min	Minor nasal and ocular irritation immediately following exposure period that increased in severity up to sacrifice at 30 h; congestion in all areas of respiratory tract
46	130 mg/m^3 (1:50,000); 6 h	Signs of irritation during exposure; dead at 60 h postexposure (likely due to *Staphylococcus* infection)
45	130 mg/m^3 (1:50,000); 6 h	Similar effects and cause of death as noted for rabbit number 46
43	130 mg/m^3 (1:50,000); 12 h	Signs of ocular and nasal irritation, and lethargy during exposure; dead at 54 h postexposure; marked respiratory tract involvement and secondary infection in larynx and trachea
44	130 mg/m^3 (1:50,000); 12 h	Severe ocular effects and generalized dermal burns; congestion and necrosis in respiratory tract; congestion in other organs; secondary *Staphylococcus* infection involvement; sacrificed at 92 h postexposure

[a]Values in parentheses are the dilutions as reported by Warthin and Weller (1919).

and the length of exposure; (2) effects are mild following 10-15 min exposures at dilutions of 1:110,000 (58 mg/m^3) or following one to several exposures at higher concentrations; (3) nasal irritation is almost immediate and is followed by moderate ocular effects (photophobia, lacrimation) within 2-3 h and respiratory involvement at 2-3 h; (4) for prolonged or high-concentration exposures, pronounced respiratory effects occur somewhat later than ocular effects; (5) there are concentration- and time-dependent effects on severity of gross and histopathologic lesions such that long exposures or exposures to high concentrations will result in deeper tissue damage and damage to pulmonary regions, in addition to nasopharyngeal regions, and may increase susceptibility to secondary infection.

Rabbits exposed continuously to sulfur mustard at 0.001 mg/m^3 or discontinuously (6.5 h/d, 5 d/wk) at 0.1 mg/m^3 (see Section 3.2.1) for up to 52 wk exhibited no overt signs of toxicity (McNamara et al. 1975). Ocular sensitization tests were also performed on rabbits; the results were negative.

The effect of sulfur mustard vapor on rabbit eyes was examined by Laughlin (1944). In that study, rabbits were exposed to sulfur mustard (200-1,200 mg·min/m^3) for 30 or 60 min and observed for 24 h. Further details regarding experimental protocol are unavailable. Laughlin provided the following observations: redness and conjunctival edema but no corneal damage at 200 mg·min/m^3; some corneal opacity but no conjunctival discharge at 400 mg·min/m^3; excessive lacrimation with no purulent discharge at 600 mg·min/m^3; purulent discharge at 800 mg·min/m^3; and severe conjunctival edema at 1,200 mg·min/m^3. It was also reported that, for ocular effects, a Ct delivered over a 2-min period resulted in a more severe effect than the same Ct delivered over a 30-min or 60-min period and when the exposure duration was extended to 7 h, the severity of the effect was diminished (i.e., the 7-h Ct needed to be twice the 30- or 60-min Ct to obtain an equivalent effect). These observations imply that the concentration becomes less important over time and that there may be some form of a detoxification or recovery mechanism regarding ocular effects (Laughlin 1944; McNamara et al. 1975).

3.2.5. Guinea pigs

In the long-term inhalation study by McNamara et al. (1975), guinea pigs were used to assess the sensitization potential of sulfur mustard. For this phase of the study, the guinea pigs were exposed to sulfur mustard at 0.001 mg /m^3 continuously or discontinuously (6.5 h/d, 5 d/wk) at 0.1 mg/m^3 (see Section 3.2.1) for up to 52 wk. Groups of six animals were removed after 1, 2, 4, 8, 32, and 52 wk of exposure. There was no evidence of sensitization in any of the group following challenge with a 7.9-µg dermal application of sulfur mustard in olive oil. The challenge had been previously shown to induce erythema, edema, and necrosis in sensitized animals. Dermal application of sulfur mustard at 31.6 µg or 63.2 µg (shown to induce a response in normal animals) to the same guinea pigs produced responses similar to those of controls, indicating that a tolerance had not been developed. Respiratory patterns were also examined during the sensitization tests and found to be unaffected by the treatment. No other treatment-related effects were reported for the guinea pigs.

The effects of sulfur mustard injected intratracheally (0.3 mg/kg; equivalent to approximately 0.6 mg sulfur mustard per cubic meter based on a body weight of 0.84 kg and ventilatory rate of 0.40 m^3/d) into male Hartley guinea pigs were studied by Calvet et al. (1994). In the study, guinea pigs (five per group) received a single intratracheal injection. Lung mechanics, airway responsiveness, microvascular permeability, and neutral endopeptidase activity in tracheal epithelium were assessed 5 h and 14 d after administration of the test article. At 5 h postinjection there was a 3-fold increase in respiratory system resistance ($p < 0.05$) and a 2-fold increase in microvascular permeability ($p < 0.05$). Histopathologic findings included shedding of tracheal epithelium columnar cells and peribronchial edema. At 14 d postinjection, the guinea pigs exhibited airway hyperactivity to inhaled substance P (an endogenous vasoactive peptide) and histamine.

3.3. Neurotoxicity

There are no data available regarding the neurotoxic effects of inhaled sulfur mustard in animals.

3.4. Developmental and Reproductive Toxicity

In the McNamara et al. (1975) study, groups of 10 female rats were exposed to sulfur mustard at 0.001 or 0.1 mg/m^3 during the first, second, or third week of gestation or for the entire gestation period. No increase in fetal abnormalities was observed, and the fetal mortality rate was also within normal limits.

3.5. Genotoxicity

The potential genotoxicity of sulfur mustard was also examined by McNamara et al. (1975). Groups of 10 female rats were bred to males that had been exposed to sulfur mustard at 0.001 or 0.1 mg/m^3 for 1, 2, 4, 8, 12, 24, 36, or 52 wk. Based on number of live or dead fetuses and implantation sites, there was no evidence of dominant lethal mutagenesis.

3.6. Chronic Toxicity and Carcinogenicity

Animal carcinogenicity data have been summarized before in IARC (1975), Watson et al. (1989), IOM (1993), and USACHPPM (2000).

In a study reported by Heston and Levillain (1953), groups of 40 male and 40 female Strain A mice (2-3 mo old) were exposed for 15 min to sulfur mustard (0.01 mL) in an 8-liter desiccator while an equivalent number of control mice were exposed to air alone. At 4 mo after exposure, 30 test mice and 32 control mice were killed, and the lung tumor incidences were found to be 9/30 and 6/32. The remaining mice were killed at 11 mo postexposure, and the total tumor incidences (tumor type not specified) were found to be 33/67 and 21/77 for the treated and control groups, respectively. The incidences were significantly different at $p < 0.01$. The number of tumors per mouse was 0.66 and 0.31 in the treated and control groups, respectively.

McNamara et al. (1975) provided evidence of the tumorigenic potential of long-term exposure to sulfur mustard in Sprague-Dawley–Wistar rats. Seventy male and 70 female rats were continuously exposed to sulfur mustard at 0.001 mg/m^3 for 24 h/d, 5 d/wk, or at 0.1 mg/m^3 for 6.5 h/d followed by 0.0025 mg/m^3 for 17.5 h/d, 5 d/wk, for up to 12 mo. Both gross and microscopic examinations were conducted on major tissues and organs. Fifty subjects of each gender were maintained as controls. Results of this toxicity study are shown in Table 2-6. Lesions considered agent-related included squamous cell carcinomas and basal cell carcinomas of the skin.

EPA (1991) emphasized that the studies of McNamara et al. (1975) contain deficiencies that make a quantitative analysis difficult. The studies

TABLE 2-6 Rat Skin Tumor Data from the McNamara et al. (1975) Toxicity Study[a]

	Exposure Groups		
Gender	Control	Low Exposure[b]	High Exposure[c]
Males	0/11	0/10	4/11
Females	0/8	0/19	5/18
Both genders	0/19	0/29	9/29

[a]Includes only data for rats living longer than the time until first tumor appearance (12 mo exposure plus 70 d postexposure).
[b]0.001 mg/m^3 for 24 h/d, 5 d/wk.
[c]0.1 mg/m^3 for 6.5 h/d followed by 0.0025 mg/m^3 for 17.5 h/d, 5 d/wk.
Source: EPA 1991.

were conducted in 1970. They do not conform to current standards of experimental protocol and likely contain bias in the assignment of animals to test categories. In addition, many of the exposures were very brief and included only a few animals, many of which were sacrificed (and some were replaced) before their capacity to develop late-appearing tumors could be fully tested. Despite these shortcomings, EPA (1991) noted that the McNamara et al. (1975) data are the best available for directly estimating the carcinogenic potency of sulfur mustard.

In addition, a study specifically addressing carcinogenic potential was also conducted by McNamara et al. (1975) in which groups of rats were exposed for varying time periods up to 21 mo to the same sulfur mustard concentrations as used in the toxicity study. The animals were then observed for varying periods of time before being sacrificed. As is the case for the toxicity study, both gross and microscopic examinations of major tissues and organs were conducted in the carcinogenicity study. The results of the study are shown in Table 2-7. Agent-related lesions included squamous cell and basal cell carcinomas of the skin, trichoepitheliomas of the skin, and keratoacanthomas of the skin.

McNamara et al. (1975) also conducted carcinogenicity studies in ICR Swiss albino as well as strain A/J mice, dogs, rabbits, and guinea pigs exposed to the same sulfur mustard concentration protocols as in the previously described toxicity study for varying exposure durations up to 1 y. Necropsy protocols were the same as for the rat toxicity and carcinogenic-

TABLE 2-7 Rat Skin Tumor Data from McNamara et al. (1975) Cancer Study, By Increasing Lifetime Daily Exposure

Exposure Duration (wk)	Exposure Concentration[a]	Lifetime[b] Average Daily Exposure ($\mu g/m^3$)	Incidence of Skin Carcinomas
Control	0	0.0	0/27
1	Low	0.0096	0/5
2	Low	0.0192	0/5
4	Low	0.0385	0/5
8	Low	0.0769	0/4
12	Low	0.115	0/5
26	Low	0.250	0/4
1	High	0.279	0/5
39	Low	0.375	0/3
52	Low	0.500	0/17
2	High	0.558	0/5
4	High	1.12	0/6
8	High	2.23	0/4
12	High	3.35	4/5
26	High	7.25	4/5
39	High	10.9	4/4
52	High	14.5	10/23

[a]Low exposure was 0.001 mg/m^3 24 h/d, 5 d/wk; high exposure was 0.1 mg/m^3 for 6.5 h/d followed by 0.0025 mg/m^3 for the remaining 17.5 h/d, 5 d/wk.
[b]A 2-y lifetime was assumed
Source: EPA 1991.

ity studies. No exposure-related tumors were observed in any of the species.

A recent comparative analysis evaluated the tumorigenicity of sulfur mustard relative to alkylating compounds used in chemotherapy or treatment of other diseases (Nicholson and Watson 1993). By considering all possible combinations of experiments and several reference compounds, sulfur mustard tumorigenicity was determined to be comparable to nitrogen mustard (HN2 and HN2-HCl) tumorigenicity in laboratory rodents. Additional relative potency comparisons were made for the therapeutic nitrogen mustards melphalan and chlorambucil and the alkylating carcinogenic compound bis(chloromethyl) ether. Comparisons of laboratory rodent data indicated that sulfur mustard and nitrogen mustard had tumorigenic potencies comparable to melphalan and bis(chloromethyl) ether; the tumorigenic potencies of sulfur and nitrogen mustard were possibly greater than that of chlorambucil (Nicholson and Watson 1993).

3.7. Summary

The available acute lethality data in animals are summarized in Table 2-8. Lethality data from earlier reports were not verifiable but are not totally inconsistent with those from later studies. For example, the 1-h LC_{50} values of 14.0 mg/m^3 and 14.3 mg/m^3 for rats and mice derived, respectively, from the 840 mg·min/m^3 and 860 mg·min/m^3 60-min LCt_{50} values reported by Fuhr and Krakow (1945) are similar to the lower confidence limit of the mouse 1-h LC_{50} (13.5 mg/m^3) reported by Vijayaraghavan (1997) (i.e., 13.5 mg/m^3). The values are also similar to a 1-h LC_{50} of 13.3 mg/m^3 for guinea pigs that can be extrapolated (assuming $C^1 \times t = k$) from the 5-min LCt_{50} of 800 mg·min/m^3 reported by Langenberg et al. (1998). Anecdotal LCt_{50} values for the dog, cat, goat, and monkey were also reported by Rosenblatt et al. (1975). Those data are shown in Table 2-5, but details were unavailable for verification of the values. An overview of the data suggests that interspecies variability in the lethal response to sulfur mustard vapor is less than an order of magnitude.

Overall, the available animal data regarding nonlethal effects suggest that test species exhibit signs of toxicity that are qualitatively similar to those of humans when acutely exposed to sulfur mustard vapor. Ocular and respiratory tract irritation and the fact that those are primary targets are plainly evident in studies using dogs, rats, mice, rabbits, and guinea pigs. Long-term exposure of dogs, mice, and guinea pigs to concentrations at 0.03 mg/m^3 produced only minor signs of ocular and respiratory tract irritation, although similar exposures in rats were tumorigenic. One-hour exposure of mice to concentrations up to 16.9 mg/m^3 resulted in notable but not serious effects on respiratory parameters and acute exposures of rabbits (20 min to 12 h) to concentrations ranging from 58 mg/m^3 to 389 mg/m^3 (Ct $\geq$ 2,300 mg·min/m^3) resulted in severe respiratory tract damage. There are no

TABLE 2-8 Acute Lethality of Sulfur Mustard in Laboratory Species

Species	Lethality Value	Concentration (mg/m^3) and Exposure Duration (min)	Reference
Rat	2-min LCt_{50}: 1,512 mg-min/m^3 30-min LCt_{50}: 990 mg-min/m^3 60-min LCt_{50}: 840 mg-min/m^3	756 mg/m^3 (2 min) 33 mg/m^3 (30 min) 14 mg/m^3 (60 min)	Fuhr and Krakow 1945 (not verified)
Mouse	2-min LCt_{50}: 4,140 mg-min/m^3 30-min LCt_{50}: 1,320 mg-min/m^3 60-min LCt_{50}: 860 mg-min/m^3	2,070 mg/m^3 (2 min) 44 mg/m^3 (30 min) 14.3 mg/m^3 (60 min)	Fuhr and Krakow 1945 (not verified)
Mouse	60-min LC_{50}: 42.5 mg/m^3	42.5 mg/m^3 (60 min)	Vijayaraghavan 1997
Monkey	10-min LCt_{50}: 800 mg-min/m^3	80 mg/m^3 (10 min)	Rosenblatt et al. 1975
Dog	10-min LCt_{50}: 600 mg-min/m^3	60 mg/m^3 (10 min)	Rosenblatt et al. 1975
Cat	10-min LCt_{50}: 700 mg-min/m^3	70 mg/m^3 (10 min)	Rosenblatt et al. 1975
Goat	10-min LCt_{50}: 1,900 mg-min/m^3	190 mg/m^3 (10 min)	Rosenblatt et al. 1975
Guinea pig	5-min LCt_{50}: 800 mg-min/m^3 10-min LCt_{50}: 1,700 mg-min/m^3	160 mg/m^3 (5 min) 170 mg/m^3 (10 min)	Langenberg et al. 1998; Rosenblatt et al. 1975

data available regarding the neurotoxic effects of inhaled sulfur mustard toxicity in animals. Limited data in rats revealed no increase in fetal abnormalities or fetal mortality following exposure to sulfur mustard. The results of a single study in rats indicated no evidence of dominant lethal mutagenesis based on the numbers of live or dead fetuses and implantation sites.

There are data indicating the tumorigenic potential of sulfur mustard in laboratory species following inhalation exposure. A tentative quantitative assessment of cancer risk for a single acute exposure is presented in Appendix C. That assessment, following the NRC methodology for EEGLs, SPEGLs, and CEGLs (NRC 1986), is based on a geometric mean of slope factors developed using various data sets and indicates an excess cancer risk of 1 in 10,000. The resulting 10^{-4} excess cancer risk values are similar to the AEGL-3 values, and 10^{-5} and 10^{-6} excess cancer risk values would be considerably lower than the AEGL-3s. The use of excess cancer risk estimates in setting AEGL values is precluded by the uncertainties involved in assessing excess cancer risk following a single acute exposure of 8-h or less duration, by the relatively small population exposed in an emergency release situation, and by the potential risks associated with evacuations.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

A thorough understanding of the metabolism and disposition of sulfur mustard is not likely to be pivotal in the quantitative assessment of human health risk from acute exposures. One of the most important aspects of the disposition of sulfur mustard is that its lipophilic nature allows for toxicologically significant quantities to penetrate the skin (Papirmeister et al. 1991). In addition, its extreme cytotoxicity is not dependent on metabolism and disposition, and its toxic potential to primary targets is not significantly ameliorated via detoxification processes. The stratum corneum of the skin offers the greatest barrier to penetration by sulfur mustard, and it is the absence of this layer that make the eyes and respiratory tract so susceptible to toxic insult from the compound.

Papirmeister et al. (1991) have reviewed available studies regarding the absorption and distribution of sulfur mustard. Although only a relatively small amount of sulfur mustard is absorbed following percutaneous application, experiments with radio-labeled material have shown distribution to most tissues within short periods of time (e.g.,15 min). Henriques et al. (1943) estimated that about 12% of a dose absorbed into the skin actually reacts with tissue components and that it is this portion of the dose that is responsible for the vesicant effects.

The toxicokinetics of sulfur mustard and its DNA adduct, N7-hydroxyethylthioethyl guanine (SM-7-gua), were studied by Langenberg et al. (1998) in hairless guinea pigs exposed via nose-only inhalation, percutaneous exposure to vapors, or intravenous injection of sulfur mustard. The time course for sulfur mustard in the blood of guinea pigs following a single intravenous injection of 1 or 0.3 LD_{50} (96-h intravenous LD_{50} = 8.2 mg/kg) showed a rapid disappearance (>1,000-fold reduction) within 10 min and maintained this level or slightly less to 360 min. Overall, the toxicokinetics of intravenously administered sulfur mustard was biphasic and exhibited a very rapid distribution phase and a slow elimination phase. Significant partitioning of sulfur mustard into the lungs, liver, spleen, and bone marrow was also observed. At time points from 0.05 h to 48 h after intravenous administration, the concentration of SM-7-gua adducts (expressed per 10^7 nucleotides) was significantly greatest in the lung (10-400 adducts) but also detected (2-30 adducts) in all tissues examined (liver, spleen, bone marrow, small intestine, blood). Results of inhalation toxicokinetic studies using hairless guinea pigs exposed nose-only to 1 LCt_{50} for 5 min revealed sulfur mustard concentrations in the blood below detection limits (5 pg/ml). SM-7-gua adducts could not be detected in the spleen, bone marrow, or small intestine but very low levels (0.7 adducts per 10^7 nucleotides) were detected in the lung at 10 min and 48 h after exposure. Adducts were detected in the nasal, nasopharynx, larynx, trachea, and carina of the respiratory tract (50-80 adducts per 10^7 nucleotides) at 4 h after exposure. On the basis of these blood concentration and adduct distribution data the authors concluded that during acute inhalation exposure in guinea pigs most of the sulfur mustard reacts with upper airway tissues. For species with less complex nasal systems (such as humans), more sulfur mustard could conceivably reach the lungs.

Several studies have been conducted using intravenously administered ^{35}S-labeled sulfur mustard to assess metabolism and disposition. For intravenous studies in rabbits, Boursnell et al. (1946) reported that sulfur mustard was widely distributed and excreted primarily in the urine. The highest concentration of radio-label was detected in the lungs, liver, and kidneys. Similar excretory processes were observed for rats and mice. Results of these studies also identified thiodiglycol and conjugates, glutathione-bis-β-chloroethylsulphone conjugates, and bis-β-chloroethylsulphone and conjugates as urinary metabolites.

Studies using intravenously administered ^{35}S-labeled sulfur mustard (0.1 mg/kg in ethanol) were also conducted in human terminal-cancer patients (Davison et al. 1961). Within 24 h, 23% of the dose was excreted in the urine. Within 48 h, 27% was excreted in the urine. Based on chromatographic analysis, the metabolites were similar to those identified for rats and mice.

4.2. Mechanism of Toxicity

The principal mechanism of toxicity for sulfur mustard may be attributed to its capacity as an alkylating agent and consequent ability to react with DNA, RNA, and other macromolecules (reviewed by Watson and Griffin [1992]). Endothelial cells are a major target for sulfur mustard (Dabrowska et al. 1996). Because of the fundamental nature of these targets, the actual mechanism of toxicity may be complex. Cross-linking with DNA (Lohs 1975; Gross et al. 1985; Lin et al. 1996) and inhibition of enzymes such as hexokinase (Dixon and Needham 1946) have been reported, and sulfur mustard has been shown to be especially toxic to proliferating cells (Vogt et al. 1984; Gross et al. 1985). In addition, mechanisms such as the cell membrane modifications in the absence of DNA damage have been described (Levy 1934).

A hypothesis for the skin lesion and blistering effects of sulfur mustard has been provided by the U.S. Army Medical Research Institute of Chemical Defense (Papirmeister et al. 1985; Gross et al. 1985). This hypothesis contends that a depletion of NAD+ arising from efforts to repair extensive DNA damage results in inhibition of glycolysis. The inhibition of glycolysis stimulates the hexose monophosphate shunt, which causes a release of proteases that are instrumental in the skin damage associated with sulfur mustard exposure. More recently, Petrali and Oglesby-MeGee (1997) reported results from investigations using several animal models, cultured isolated human cells, and in vitro organotypic skin models. Histopathologic and ultrastructural analysis indicated that basal cells of the stratum basale layer is an early target of sulfur mustard and that resulting injury that is evident by 4-6 h after exposure represents a progressive and irreversible cell injury and death. In addition, there appears to be a disabling of anchoring hemidesmosome filaments resulting in microvesicle formation and interaction with various membrane proteins such that there is a loss of immunospecificity.

Using a chromogenic peptide substrate assay, Cowan et al. (1993) found that sulfur mustard enhanced proteolytic activity. A time-dependent and temperature-dependent proteolysis was observed for in vitro experiments using human peripheral blood lymphocytes. A similar response was also seen for in vivo exposures using the hairless guinea pig.

In vitro experiments conducted by Smith et al. (1990) and Smith and Smith (1997) using primary human epidermal keratinocytes provided results showing a concentration-dependent interference with cell cycling. At concentrations equivalent to those that would produce vesication, the cell cycle was blocked at the G1-S interface, although at subvesicant concentrations, the cell cycle was blocked in the G2 phase.

Using bovine pulmonary artery endothelial cells, Dabrowska et al. (1996) showed that sulfur mustard ($\leq$250 µM) induced apoptosis within 5 h. At concentrations $\geq$500 µM both apoptotic and necrotic cell death occurred after 5-6 h. Necrosis was accompanied by a significant depletion of intracellular ATP.

Most sulfur-mustard-induced fatalities have been due to respiratory tract involvement. The mechanism of sulfur-mustard-induced pulmonary damage was studied by Anderson et al. (1997) using lavage fluid from rats in which sulfur mustard (0.35 mg) was intratracheally intubated for 50 min. At 1, 4, or 24 h after the treatment, the rats were euthanized and the lungs lavaged with physiologic saline. Lactate dehydrogenase and γ-glutamyltransferase were increased ($p \leq 0.05$) at all time points, and total protein was increased ($p < 0.001$) at 4 and 24 h. The investigators contended that these indices were useful indicators of early pulmonary injury following low-dose exposure to sulfur mustard.

4.3. Structure-Activity Relationships

There are no structure-activity data that would be instrumental in the development of AEGL values for sulfur mustard.

4.4. Other Relevant Information

There are several important aspects of sulfur mustard toxicology that impact the toxic response and are relevant to assessing human health risk. They include the latency period between initial exposure and development of effects, the effect of temperature and humidity, the variable sensitivity among tissues and sites affected, and the sensitization potential for vesicating effects. First, it is well documented (summarized by Papirmeister et al.

[1991]) that a latency period exists between the initial exposure to sulfur mustard and the development of toxic effects. That pertains not only to onset of effects but also to development of full severity of effects. The ocular response appears to have the shortest latent period, sometimes as short as minutes, whereas dermal and respiratory effects following acute exposure may take days for full development. It is also known that higher ambient temperature and greater humidity enhance the dermal response to sulfur mustard (Nagy et al. 1946; Renshaw 1947; Papirmeister et al. 1991). Although the mechanism is unknown, increased temperature and humidity decrease the dose required for a given response and increase the severity of the response. In this respect, moisture (in addition to skin characteristics) is relevant to the greater sensitivity of certain anatomical areas (e.g., axial, interdigital, and popliteal areas, scrotum, and perineum). The eyes and respiratory tract are generally considered the most sensitive organs/tissues (eyes somewhat more so) for acute exposures to sulfur mustard. Both involve latency periods and a wide range of severity of effects depending primarily on the exposure concentration, but injury to the respiratory tract is considered more relevant regarding lethal responses. Sensitization to sulfur-mustard-induced dermal effects appears to be associated with repeated exposures and, according to McNamara et al. (1975), occurs after detectable insult (i.e., overt clinical signs). There tends to be a greater sensitivity to high exposures but no greater severity in response to lower exposures or greater likelihood of a response to lower exposures (Sulzberger et al. 1945).

4.4.1. Species Variability

All of the species tested exhibit qualitatively similar responses to sulfur mustard vapor and affirm that the eyes and respiratory tract are the most sensitive targets. Available lethality data (LC_{50} and LCt_{50}) are remarkably similar across species (see Section 3.1.4).

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

Walker et al. (1928) reported that four of seven men exposed to sulfur mustard at 0.001 mg/L (1 mg/m^3) for 5-45 min exhibited conjunctivitis, and two exhibited skin burns. It was also reported that, of 17 men exposed at 0.0005 mg/L (0.5 mg/m^3) for 10-45 min (5-22.5 mg·min/m^3), six exhibited conjunctivitis, and one had a skin burn. Three of 13 men exposed for 10-30 min at 0.0001 mg/L (0.1 mg/m^3; Ct of 1-3 mg·min/m^3) showed slight but distinct conjunctivitis. Although not of a severity consistent with an AEGL-2 level, those effects are of greater severity than would be acceptable for AEGL-1 development. Guild et al. (1941) also conducted experiments using humans and reported that (1) exposure to Ct values <70 mg·min/m^3 would result in mild conjunctival responses that would not be indicative of a casualty (temporary loss of vision); (2) Ct values of 70-100 mg·min/m^3 would produce some casualties and; (3) Ct values >100 mg·min/m^3 would be expected to produce disabling ocular effects of several days' duration. Because the subjects wore respiratory protection, effects on the respiratory tract could not be determined.

In experiments with human volunteers exposed to varying concentration-time regimens, Anderson (1942) found that an exposure concentration-time product of 12 mg·min/m^3 was without effects and 30 mg·min/m^3 represented the upper range for mild effects (conjunctival injection and minor discomfort with no functional decrement). Ct products slightly higher than that (e.g., 34-38.1 mg·min/m^3) were, however, also without appreciable effects, thereby indicating that the response to 30 mg·min/m^3 is consistent with AEGL-1 effects.

Odor thresholds of 1 mg·min/m^3 (Bloom 1944), 0.15 mg/m^3 (Ruth 1986) and 0.6 mg/m^3 (Dudley and Wells 1938; Bowden 1943; Fuhr and Krakow 1945) have been reported.

Analysis of the exposure-effect values from the human studies indicated that the 12-mg·min/m^3 value represented a defensible estimate of the threshold for effects consistent with the AEGL-1 definition. The 12-mg·min/m^3 exposure was without a symptomatic effect and, therefore, provides the basis for protective AEGL-1 values consistent with the AEGL-1 definition.

5.2. Summary of Animal Data Relevant to AEGL-1

The effects described in the animal studies tend to be a of greater severity than those associated with AEGL-1 (i.e., signs of severe ocular irritation, body weight loss, respiratory depression, evidence of respiratory tract histopathology, etc.). There were no definitive exposure-response data in animals that were considered appropriate for the development of AEGL-1 values.

5.3. Derivation of AEGL-1

The most tenable AEGL-1 values were developed using data reported by Anderson (1942) in which three to four human volunteers were exposed to agent HD at varying concentration-time regimens. In an analysis of those data, Anderson found that an exposure concentration-time product of 30 mg·min/m^3 represented the upper range for mild effects (conjunctival injection and minor discomfort with no functional decrement) and that 12 mg·min/m^3 represented a threshold for such effects. The 12 mg·min/m^3 represents a defensible estimate of the threshold for AEGL-1 effects. The 12-mg·min/m^3 exposure resulted in only minor conjunctival injection and no sensation of irritation. Ocular effects appear to be the most sensitive indicator of sulfur mustard exposure and toxicity, thereby justifying ocular irritation as an appropriate end point for development of AEGL values. All of the data considered were from human subjects, and, therefore, the uncertainty factor (UF) application to the 12-mg·min/m^3 value was limited to 3 for protection of sensitive individuals. The adjustment is considered appropriate for acute exposures to chemicals whose mechanism of action primarily involves surface contact irritation of ocular and/or respiratory tract tissue rather than systemic activity that involves absorption and distribution of the parent chemical or a biotransformation product to a target tissue. In addiction, Anderson (1942) noted that there was little variability in the ocular responses among the individuals participating in the study. That the AEGL-1 values are based on a sensitive end point is also reflected in that they are below reported odor thresholds (0.6 mg/m^3 and 1 mg·min/m^3).

Because exposure-response data were unavailable for all of the AEGL-specific exposure durations, temporal extrapolation was used in the development of AEGL-1 values for the AEGL-specific time periods. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases can be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Analysis of available data regarding AEGL-1 type effects reported by Reed (1918), Reed et al. (1918), Guild et al. (1941), and Anderson (1942) indicate that for the exposure periods up to several hours, the concentration-exposure time relationship is a near-linear function (i.e., Haber's law where $n = 1$ for $C^n \times t = k$) as shown by *n* values of 1.11 and 0.96 for various data sets consistent with AEGL-1 effects (Appendix B). Therefore, an empirically derived, chemical-specific estimate of *n* = 1 was used, rather than a default value, based on the ten Berge (1986) analysis. The derivation of the exponent (*n*) utilized human response data where 75-100% of the responders showed a mild response that would be consistent with the definition of AEGL-1 effects. In addition, the data provided by Anderson (1942) were indicative of a linear concentration-time relationship. The AEGL-1 values developed using the 12-mg·min/m^3 exposure value reported by Anderson (1942) are shown in Table 2-9. The AEGL-1 values are below the odor threshold for sulfur mustard (0.6 mg/m^3 and 1 mg·min/m^3).

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Quantitative data regarding the human experience and AEGL-2 level effects are limited to responses ranging from signs of mild ocular irritation to ocular irritation that impairs normal visual function. Reed (1918) reported that 20-45 min exposure of himself and a volunteer at 1.2 mg/m^3 resulted in severe ocular irritation and dermal lesions. In a report of a subsequent experiment, Reed et al. (1918) noted that exposure of human volunteers at 0.1-4.3 mg/m^3 for 5-45 min produced ocular irritation and skin burns (0.5 mg/m^3 for 30 min) and very severe conjunctivitis, photophobia, skin burns, and nasopharyngeal exfoliation (1.0 mg/m^3 for 45 min). The analytical techniques used in these experiments were suspect; actual exposures were likely 30-40% higher. The report by Guild et al. (1941) of human exposure experiments did not provide findings of effects consistent with the AEGL-2 definition. Anderson (1942) reported on a series of human exposures resulting in varying degrees of ocular responses ranging from nonsymptomatic ocular injection to ocular irritation that required medical treatments and was considered severe enough to impair normal function.

6.2. Summary of Animal Data Relevant to AEGL-2

With the exception of a study reported by Warthin and Weller (1919) regarding the effects in rabbits following acute exposure, there is little

TABLE 2-9 AEGL-1 Values for Sulfur Mustard (ppm [mg/m^3])[a]

10-min	30-min	1-h	4-h	8-h
0.06 (0.40)	0.02 (0.13)	0.01 (0.067)	0.003 (0.017)	0.001 (0.008)

[a]The AEGL-1 values are at or below the odor threshold for sulfur mustard.

exposure-response data for animals consistent with AEGL-2-severity effects. Weller and Warthin reported severe ocular effects and dermal burns in rabbits exposed for 12 h to sulfur mustard at 130 mg/m^3. That study, however, was compromised by the use of single animals and lacks detail. Kumar and Vijayaraghavan (1998) reported alterations in purine catabolism in mice exposed for 1 h to sulfur mustard at 21.2-84.6 mg/m^3, but those exposures also represented 0.5, 1.0, and 2.0 LC_{50} responses. Statistically significant reductions in body weights were also observed for the mice at 14 d following a 1-h exposure to concentrations at 16.9-42.3 mg/m^3; however, at least some of the exposures were also associated with lethality. Dogs, rats, mice, and guinea pigs exposed continuously to sulfur mustard at 0.001 mg/m^3 or discontinuously (6.5 h/d, 5 d/wk) at 0.1 mg/m^3 for up to 52 wk did not exhibit effects consistent with the AEGL-2 definition (McNamara et al. 1975).

6.3. Derivation of AEGL-2

The AEGL-2 values for sulfur mustard were developed using data from Anderson (1942). The study utilized three or four human volunteers exposed to varying concentrations of sulfur mustard (1.7-15.6 mg/m^3) for time periods varying from 2 to 33 min. Anderson considered a Ct value of 60 mg·min/m^3 as the lowest concentration-time product for which ocular effects could be characterized as military casualties and that personnel exposed might be ineffective for up to (but no more than) 7 d. Effects included irritation, soreness, and widespread conjunctivitis, frequently accompanied by chemosis and photophobia. The 60-mg·min/m^3 exposure was used as the basis for developing the AEGL-2 values because it is representative of an acute exposure causing an effect severe enough to impair normal visual function and, although not irreversible, would certainly result in potential for additional injury. The ocular irritation and damage were also considered appropriate as a threshold estimate for AEGL-2 effects, because

TABLE 2-10 AEGL-2 Values for Sulfur Mustard (ppm [mg/m^3])[a]

10-min	30-min	1-h	4-h	8-h
0.09 (0.60)	0.03 (0.20)	0.02 (0.10)	0.004 (0.025)	0.002 (0.013)

[a]The AEGL-2 values are at or below the odor threshold for sulfur mustard.

the eyes are generally considered the most sensitive indicator of sulfur mustard exposure, and irritation would likely occur in the absence of vesication effects and severe pulmonary effects. The fact that the AEGL-2 is based on human data precludes the use of an interspecies UF. A factor of 3 was applied for intraspecies variability (protection of sensitive populations). The factor was limited to 3 under the assumption that the primary mechanism of action of sulfur mustard involves a direct effect on the ocular surface and that the response will not vary greatly among individuals (as noted by Anderson [1942]). A modifying factor of 3 was applied to accommodate potential onset of long-term ocular or respiratory effects. It was justified by the absence of long-term follow-up in the subjects of the Anderson (1942) study to confirm or deny development of permanent ocular or respiratory tract damage. Because the factors of 3 each represent a logarithmic mean (3.16) of 10, their product is $3.16 \times 3.16 = 10$. Further reduction by the application of additional modifying factors was not warranted because of the use of a sensitive indicator representing an AEGL-2 effect of marginal severity. As is the case for AEGL-1 values, time scaling was conducted using an n of 1 for all time points (Appendix B). The resulting AEGL-2 values are shown in Table 2-10, and their derivation is presented in Appendix A. Similar to the AEGL-1 values, all of the AEGL-2 values are at or below the reported odor thresholds (0.6 mg/m^3 and 1 mg·min/m^3).

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

Human lethality data are limited to an inhalation LCt_{50} estimate of 1,500 mg·min/m^3 and percutaneous LCt_{50} estimate of 10,000 mg·min/m^3 estimated from animal data (DA 1974). The NRC (1997) concluded that an estimated LCt_{50} for humans of 900 mg·min/m^3 developed by the U.S.

Army based on an average of animal LCt_{50} data was scientifically valid but was developed in reference to healthy male military personnel and does *not* apply to civilians.

7.2. Summary of Animal Data Relevant to AEGL-3

Various lethality values have been reported for laboratory species acutely exposed to sulfur mustard. Vijayaraghavan (1997) reported a 1-h LC_{50} of 42.5 mg/m^3 for mice (head-only exposure). In a follow-up study reported by Kumar and Vijayaraghavan (1998), 1-h exposure of mice at 21.2 mg/m^3 did not result in lethality. Lethality estimates were based on deaths occurring up to 14 d after exposure. Langenberg et al. (1998) reported a 5-min LCt_{50} of 800 mg·min/m^3 for rabbits (deaths determined up to 96 h after exposure). These studies utilized up-to-date exposure and analytical systems and provided lethality estimates based on adequate numbers of animals evaluated at postexposure time frames appropriate for the known latency in sulfur-mustard-induced lethality.

7.3. Derivation of AEGL-3

As noted in Section 3.1.4, the lethality data from earlier reports were not verifiable but are not inconsistent with those from later studies. The 1-h LC_{50} values for rats and mice derived from the 840 and 860 mg·min/m^3 60-min LCt_{50} values reported by Fuhr and Krakow (1945) are similar to the lower confidence limit of the mouse 1-h LC_{50} reported by Vijayaraghavan (1997) (i.e., 14.0, 14.3, and 13.5 mg/m^3, respectively; the corresponding Ct values are 840, 858, and 810 mg·min/m^3). The values are also similar to a 1-h LC_{50} of 13.3 mg/m^3 for guinea pigs extrapolated (assuming $C^1 \times t = k$) from the 5-min LCt_{50} of 800 mg·min/m^3 reported by Langenberg et al. (1998). However, the values from the earlier studies are not verifiable. In the inhalation toxicity study by Vijayaraghavan (1997), mice were exposed (head only) for 60 min to sulfur mustard at concentrations of 0.0, 8.5, 16.9, 21.3, 26.8, 42.3 or 84.7 mg/m^3. The study investigator derived a 60-min LC_{50} of 42.5 mg/m^3 based on lethality at 14 d postexposure (95% confidence interval: 13.5-133.4 mg/m^3). In a follow-up study (Kumar and Vijayaraghavan 1998), there was no mortality in mice exposed at 0.5 LC_{50} (21.2 mg/m^3). Therefore, the 1-h exposure at 21.2 mg/m^3 was selected as an estimate of the lethality threshold in mice.

When compared with the human exposure-effect data, the 21.2-mg/m^3 concentration (Ct of 1,272 mg·min/m^3 for a 60-min exposure) is not an exposure that has been associated with lethality in humans (see Section 2.1). An intraspecies UF of 3 was applied for protection of sensitive individuals. This adjustment was considered appropriate for acute exposures to chemicals whose mechanism of action primarily involves surface contact irritation of ocular and/or respiratory tract tissue rather than systemic activity that involves absorption and distribution of the parent chemical or a biotransformation product to a target tissue. An interspecies UF was limited to 3 because available data do not suggest that humans are notably more sensitive than animals regarding lethality from inhalation exposure to sulfur mustard. The mechanism of pulmonary injury leading to lethality appears to be a function of the direct contact of an alkylating agent with epithelial tissue. This mechanism is likely to be more similar than different across mammalian species. Furthermore, the AEGL-3 values resulting from the aforementioned complement of UFs (total UF adjustment was 10; see Section 6.3) are equivalent to exposures known to cause only mild ocular effects in humans. The modifying factor of 3 utilized in the development of AEGL-2 values to account for uncertainties regarding the latency and persistence of the irritant effects of low-level exposure to sulfur mustard was not applied for AEGL-3 because lethality of the mice was assessed at 14 d postexposure in the key studies by Vijayaraghavan (1997) and Kumar and Vijayaraghavan (1998).

For derivation of the AEGL-3 values, there was uncertainty regarding the validity of applying linear extrapolation based on ocular effects to concentration-time extrapolations for lethality. As reported by ten Berge et al. (1986), the concentration-time relationship for many irritant and systemically acting vapors and gases can be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. Therefore, in the absence of chemical-specific lethality data, time scaling was performed using exponential extrapolation ($n = 3$) for shorter time periods and linear extrapolation ($n = 1$) for longer time periods, thereby providing a somewhat more conservative (i.e., protective) estimate of the AEGL-3 values than would be obtained using an n value based on ocular irritation. The AEGL-3 values were derived by scaling from the 1-h LC_{50} of 21.2 mg/m^3 reported by Kumar and Vijayarhagavan (1998) using $C^n \times t = k$ where $n = 1$ or 3 (Appendix A). The concentration-time constant, k, was 1,272 mg·min/m^3 where $n = 1$ and 571,687.68 mg·min/m^3 where $n = 3$. The AEGL-3 values are shown in Table 2-11, and their derivation is presented in Appendix A The 4-h and 8-h AEGL-3 values are at or below reported odor thresholds.

TABLE 2-11 AEGL-3 Values for Sulfur Mustard (ppm [mg/m^3])

10 min	30 min	1 h	4 h	8 h
0.59 (3.9)	0.41 (2.7)	0.32 (2.1)	0.08 (0.53)	0.04 (0.27)

Note: The 4-h and 8-h AEGL-3 values are below the odor threshold for sulfur mustard.

When comparing the Ct values generated by the draft AEGL-3 numbers with the human exposure data, any further reduction appears indefensible. The Ct values resulting from the AEGL-3 numbers (i.e., 39-130 mg·min/m^3) are similar to cumulative exposures shown to cause only ocular irritation in humans (Guild et al. 1941; Anderson 1942) and are similar to the ECt_{50} of 100 mg·min/m^3 for severe ocular effects (for soldiers) determined by Reutter and Wade (1994) and the NRC (1997). Furthermore, the AEGL-3 values are nearly similar to those developed using the human lethality estimate of 900 mg·min/m^3 (Reutter and Wade 1994) that was derived from multiple-species animal data. and reviewed by the NRC (1997). Assuming a 3-fold reduction for estimation of a lethality threshold ([900 mg·min/m^3] /3 = 300 mg·min/m^3) and another 3-fold reduction for consideration of sensitive populations ([300 mg·min/m^3]/3 = 100 mg·min/m^3), the resulting AEGL-3 values from the Reutter and Wade (1994) and NRC (1997) reports would be 4.8, 3.3, 1.7, 0.42, and 0.21 mg/m^3 for 10 min, 30 min, and 1, 4, and 8 h, respectively. These highly derivative estimates are comparable to, and supportive of, AEGL-3 estimates derived from the experimental data of Kumar and Vijayarhagavan (1998) (see Table 2-11).

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

Human data are available from several independent sources that define the exposure-response for AEGL-1 and AEGL-2 effects. Although a definitive demarcation of the exposure-response for sensitive populations was not provided by those data, the human data eliminated the uncertainties inherent in the use of data from animal studies. Both the AEGL-1 and AEGL-2 values were based on effect end points consistent with the respective AEGL definitions (i.e., threshold for barely discernible ocular irritation

[AEGL-1] and threshold for ocular irritation indicative of functional impairment [AEGL-2]). Areas of uncertainty were associated with the sensitive responders and the relationship between ocular effects and the onset of respiratory effects. Human data from which to develop AEGL-3 values were unavailable. The AEGL-3 was based on an estimated lethality threshold from studies in mice (Vijayaraghavan 1997; Kumar and Vijayaraghavan 1998). When compared with human exposure-response data and lethality estimates, the mouse lethality data were considered a defensible approach to AEGL-3 derivation. AEGL-3 values based on a human lethality estimate of 900 mg·min/m^3 (Reutter and Wade 1994; NRC 1997) were very similar to those developed using the animal data of Vijayaraghavan (1997) and Kumar and Vijayaraghavan (1998). An estimate of theoretical excess cancer risk based upon a geometric mean of inhalation slope factors developed using various data sets and procedures revealed that exposure concentrations representing a theoretical 10^{-4} lifetime risk were similar to the AEGL-3 exposure concentration values. The exposures for theoretical excess lifetime cancer risk at 10^{-5} and 10^{-6} levels would be correspondingly reduced. The use of excess cancer risk estimates in setting AEGL values is precluded by the uncertainties involved in assessing excess cancer risk following a single acute exposure of 8-h or less duration, by the relatively small population exposed in an emergency release situation, and by the potential risks associated with evacuations.

The AEGL values for sulfur mustard are summarized in Table 2-12. Extrapolation to exposure durations of less than 10 min is not recommended in the absence of careful evaluation of existing data and comparison of any derivative values with those data.

8.2. Comparison with Other Standards and Guidelines

Comparison of the draft AEGL values with other existing standards and guidelines is shown in Table 2-13. No other standards or guidelines from other agencies or programs (e.g., NIOSH, ERPG, ACGIH, MAK, MAC, OSHA) were available.

8.3. Data Adequacy and Research Needs

The AEGL-1 values are based on human data and are considered estimates for exposures that would cause no significant health effects or sensa-

TABLE 2-12 Summary of AEGL Values for Sulfur Mustard[a]

AEGL Level	10 min	30 min	1 h	4 h	8 h
AEGL-1[a] (Nondisabling)	0.06 ppm (0.40 mg/m^3)	0.02 ppm (0.13 mg/m^3)	0.01 ppm (0.067 mg/m^3)	0.003 ppm (0.017 mg/m^3)	0.001 ppm (0.008 mg/m^3)
AEGL-2[a] (Disabling)	0.09 ppm (0.60 mg/m^3)	0.03 ppm (0.20 mg/m^3)	0.02 ppm (0.10 mg/m^3)	0.004 ppm (0.025 mg/m^3)	0.002 ppm (0.013 mg/m^3)
AEGL-3[a] (Lethal)	0.59 ppm (3.9 mg/m^3)	0.41 ppm (2.7 mg/m^3)	0.32 ppm (2.1 mg/m^3)	0.08 ppm (0.53 mg/m^3)	0.04 ppm (0.27 mg/m^3)

[a]AEGL-1 and AEGL-2 values, and the 4- and 8-h AEGL-3 values are at or below the odor threshold for sulfur mustard.

tions of irritation beyond minimal conjunctivitis. The ocular irritation on which the AEGL-1 and AEGL-2 values are based is the most sensitive response to sulfur mustard vapor. The AEGL-2 values provide Ct exposures that are well below those known to induce severe ocular effects in normal humans (i.e., 70-90 mg·min/m^3). AEGL-3 values provide Ct values (39-130 mg·min/m^3) that are at levels known to cause moderate to severe ocular irritation and possible respiratory tract irritation in human subjects (Anderson 1942; Guild et al. 1941) but no life-threatening effects or death. Although the overall database for acute inhalation exposure to sulfur mustard is not extensive, the AEGL values are supported by the available data.

The absence of multiple-species lethality data for acute exposures limits a thorough understanding of variability. Data providing definitive demarcation of the threshold for serious and/or irreversible effects would provide a more complete picture of responses resulting from acute inhalation exposure to sulfur mustard. That is especially relevant to assessing the potential for serious respiratory tract damage or permanent ocular pathology following acute exposure. Although sulfur mustard is a genotoxic chemical capable of inducing tumors in animals and humans, the carcinogenic potential of acute inhalation exposures has not been defined.

TABLE 2-13 Comparison of AEGL Values for Sulfur Mustard with Other Extant Standards and Guidelines

Guideline	10 min	30 min	1 h	4 h	8 h	Other
AEGL-1	0.40mg/m^3 (0.06 ppm)	0.13 mg/m^3 (0.02 ppm)	0.067 mg/m^3 (0.01 ppm)	0.017 mg/m^3 (0.003 ppm)	0.008 mg/m^3 (0.001 ppm)	
AEGL-2	0.60 mg/m^3 (0.09 ppm)	0.20 mg/m^3 (0.03 ppm)	0.10 mg/m^3 (0.02 ppm)	0.025 mg/m^3 (0.004 ppm)	0.013 mg/m^3 (0.002 ppm)	
AEGL-3	3.9 mg/m^3 (0.59 ppm)	2.7 mg/m^3 (0.41ppm)	2.1 mg/m^3 (0.32 ppm)	0.53 mg/m^3 (0.08 ppm)	0.27 mg/m^3 0.04 ppm)	
Department of the Army/Civilian Occuptional WPL[a]					0.003 mg/m^3 (0.0005 ppm)	
Department of the Army/Civilian GPL[b]						0.0001 mg/m^3 (1.5x10^{-5} ppm)
CDC-CSEPP (Thacker, 1994)[c]						2.0 mg·min/m^3 (0.3 ppm)

[a]Worker Population Exposure Limit (DA 1991, 1997; DHHS 1988), 8-h TWA, 5 d/wk.
[b]General Population Limit (no observable effects), 24-h TWA, 7 d/wk.
[c]Recommended acute effects levels for determining emergency evacuation distances in the Chemical Stockpile Emergency Preparedness Program (CSEPP); no set exposure time.

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Appendixes

APPENDIX A

Derivations of AEGL Values

Derivation of AEGL-1

Key study:	Anderson (1942)
Toxicity end point:	Exposure concentration-time product of 12 mg·min/m^3 represented the threshold for ocular effects (conjunctival injection and minor discomfort with no functional decrement) for human volunteers exposed to agent HD at varying exposure regimens. The eye is generally considered to be the most sensitive organ/tissue relative to agent HD exposure.
Scaling:	The concentration-time relationship for many irritant and systemically acting vapors and gases can be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Analysis of available data indicated n to be near unity (Appendix B), hence, $C^1 \times t = k$.
Uncertainty factors:	Total adjustment of 3. A factor of 3 was applied for intraspecies variability (protection of sensitive populations). This factor was limited to 3 under the assumption that the primary mechanism of action of agent HD involves a direct effect on the ocular surface and that the response will not vary greatly among individuals. In addition, subjects in the Anderson (1942) study exhibited little variability in ocular response. Because the AEGL-1 is based on human data, the interspecies UF is 1.

10-min AEGL-1: $C^1 \times 10$ min = 12 mg·min/m^3
$C = 1.2$ mg/m^3
10-min AEGL-1 = (1.2 mg/m^3)/3 = 0.40 mg/m^3
(0.06 ppm)

30-min AEGL-1: $C^1 \times 30$ min = 12 mg·min/m^3
$C = 0.4$ mg/m^3
30-min AEGL-1 = (0.4 mg/m^3)/3 = 0.13 mg/m^3
(0.02 ppm)

1-h AEGL-1: $C^1 \times 60$ min = 12 mg·min/m^3
$C = 0.2$ mg/m^3
1-h AEGL-1 = (0.2 mg/m^3)/3 = 0.067 mg/m^3
(0.01 ppm)

4-h AEGL-1: $C^1 \times 240$ min = 12 mg·min/m^3
$C = 0.05$ mg/m^3
4-h AEGL-1 = (0.05 mg/m^3)/3 = 0.017 mg/m^3
(0.003 ppm)

8-h AEGL-1: $C^1 \times 480$ min = 12 mg·min/m^3
$C = 0.025$ mg/m^3
8-h AEGL-1 = (0.025 mg/m^3)/3 = 0.008 mg/m^3
(0.001ppm)

Derivation of AEGL-2

Key study: Anderson (1942)

Toxicity end point: A concentration-time product of 60 mg·min/m^3 was considered the lowest exposure causing ocular effects (well-marked, generalized conjunctivitis, edema, photophobia, and irritation) resulting in effective performance decrement and characterized as a military casualty requiring treatment for up to 1 wk.

Scaling: The concentration-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Analysis of available data indicated n to be near unity (Appendix B), hence, $C^1 \times t = k$.

Uncertainty factors: Total adjustment of 10.
A factor of 3 was applied for intraspecies variability (protection of sensitive populations). This factor was limited to 3 under the assumption that the primary mechanism of action of agent HD involves a direct effect on the ocular surface and that this response will not vary greatly among individuals. Because the AEGL-1 is based on human data, the interspecies UF is 1. A modifying factor of 3 was applied to accommodate potential onset of long-term ocular or respiratory effects.
Because the factors of 3 each represent a logarithmic mean (3.16) of 10, their product is 3.16 × 3.16 = 10.

10-min AEGL-2: $C^1 \times 10$ min = 60 mg·min/m^3
C = 6 mg
10-min AEGL-2 = (6 mg/m^3)/10 = 0.60 mg/m^3 (0.09 ppm)

30-min AEGL-2: $C^1 \times 30$ min = 60 mg·min/m^3
C = 2.00 mg
30-min AEGL-2 = (2.00 mg/m^3)/10 = 0.20 mg/m^3 (0.03 ppm)

1-h AEGL-2: $C^1 \times 60$ min = 60 mg·min/m^3
C = 1.00 mg/m^3
1-h AEGL-2 = (1.00 mg/m^3)/10 = 0.10 (0.02 ppm)

4-h AEGL-2: $C^1 \times 240$ min = 60 mg·min/m^3

$C = 0.25$ mg/m^3
4-h AEGL-2 = (0.25 mg/m^3)/10 = 0.025 mg/m^3 (0.004 ppm)

8-h AEGL-2: $C^1 \times 480$ min = 60 mg·min/m^3
$C = 0.125$ mg/m^3
8-h AEGL-2 = (0.125 mg/m^3)/10 = 0.013 mg/m^3 (0.002 ppm)

Derivation of AEGL-3

Key study: Kumar and Vijayaraghavan (1998)

Toxicity end point: Estimated lethality threshold of 21.2 mg/m^3 for 1 h based on no deaths in mice exposed to that concentration, which is 0.5 of the 1-h LC_{50} in mice reported by Vijayaraghavan (1997).

Scaling: The concentration-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Analysis of available data pertaining to ocular effects indicated n to be near unity (Appendix B). However, there was uncertainty regarding the validity of applying linear extrapolation based on ocular effects to concentration-time extrapolations for lethality. Therefore, in the absence of chemical-specific lethality data, time scaling was performed using exponential extrapolation (n = 3) for shorter time periods (<1 h) and linear extrapolation (n = 1) for longer time periods (>1 h), thereby providing a somewhat more conservative (i.e., protective) estimate of the AEGL-3 values than would be obtained using an n value based on ocular irritation. The concentration-time constant, k, was 1,272 mg·min/m^3 where n = 1 and 571,687.68 mg·min/m^3

where $n = 3$.

Uncertainty factors: Total UF was 10.
A UF for interspecies was limited to 3 because human data are available showing that exposures to the AEGL-3 values are more likely to produce only severe ocular irritation and possible minor or moderate irritation of the upper respiratory tract. Intraspecies variability was limited to 3 because lethality appears to be a function of extreme pulmonary damage resulting from direct contact of the agent with epithelial surfaces. No modifying factor was applied because the basis of lethality estimate was from a studies utilizing a 14-d observation period to assess the lethal response from a 1-h exposure.
Because the factors of 3 each represent a logarithmic mean (3.16) of 10, their product is 3.16 × 3.16 = 10.

10-min AEGL-3: $C^3 \times 10$ min = 571,687.68 mg·min/m^3
C^3 = 57,168.76 mg·min/m^3
C = 38.52 mg/m^3
10-min AEGL-3 = (38.52 mg/m^3)/10 = 3.9 mg/m^3 (0.59 ppm)

30-min AEGL-3: $C^3 \times 30$ min = 571,687.68 mg·min/m^3
C^3 = 19,056.26 mg·min/m^3
C = 26.7 mg/m^3
30-min AEGL-3 = (26.7 mg/m^3)/10 = 2.7 mg/m^3 (0.41 ppm)

1-h AEGL-3: $C^1 \times 60$ min = 1,272 mg·min/m^3
C = 21.2 mg/m^3
1-h AEGL-3 = (21.2 mg/m^3)/10 = 2.1 mg/m^3
(0.32 ppm)

4-h AEGL-3: $C^1 \times 240$ min = 1,272 mg·min/m^3
C = 5.3 mg/m^3

4-h AEGL-3 = (5.3 mg/m^3)/10= 0.53 mg/m^3
(0.08 ppm)

8-h AEGL-3: $C^1 \times 480$ min = 1,272 mg·min/m^3
C = 2.65 mg/m^3
8-h AEGL-3 = (2.65 mg/m^3)/10 = 0.27 mg/m^3
(0.04 ppm)

APPENDIX B

Determination of Temporal Scaling Factor (*n*) for AEGL Derivations

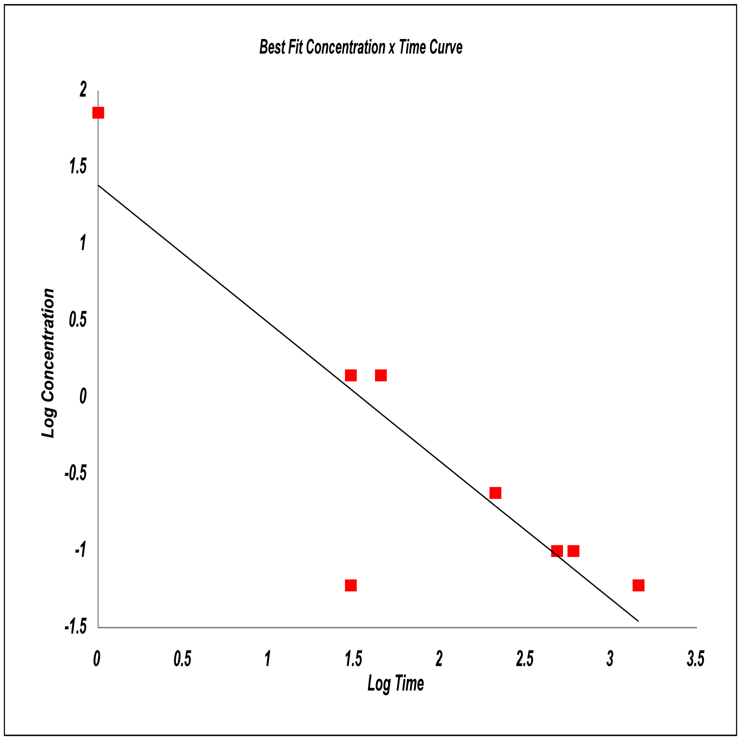
Derivation of n for $C^n \times t = k$; data points indicative of a 100% response for mild ocular irritation following exposure to sulfur mustard (agent HD) at various concentrations and times (Reed 1918; Reed et al. 1918; Guild et al. 1941; Anderson 1942)

Time	Concentration	Log Time	Log Concentration
1	72	0.0000	1.8573
30	1.4	1.4771	0.1461
30	0.06	1.4771	-1.2218
45	1.4	1.6532	0.1461
210	0.24	2.3222	-0.6198
480	0.1	2.6812	-1.0000
600	0.1	2.7782	-1.0000
1,440	0.06	3.1584	-1.2218

Regression output:	
Intercept	1.3852
Slope	-0.9002
R squared	0.7434
Correlation	-0.8622
Degrees of freedom	6
Observations	8

$n = 1.11$

$k = 34.58$


Best Fit Concentration x Time Curve
Log Concentration
2
1.5
1
0.5
0
-0.5
-1
-1.5
0
0.5
1
1.5
2
2.5
3
3.5
Log Time

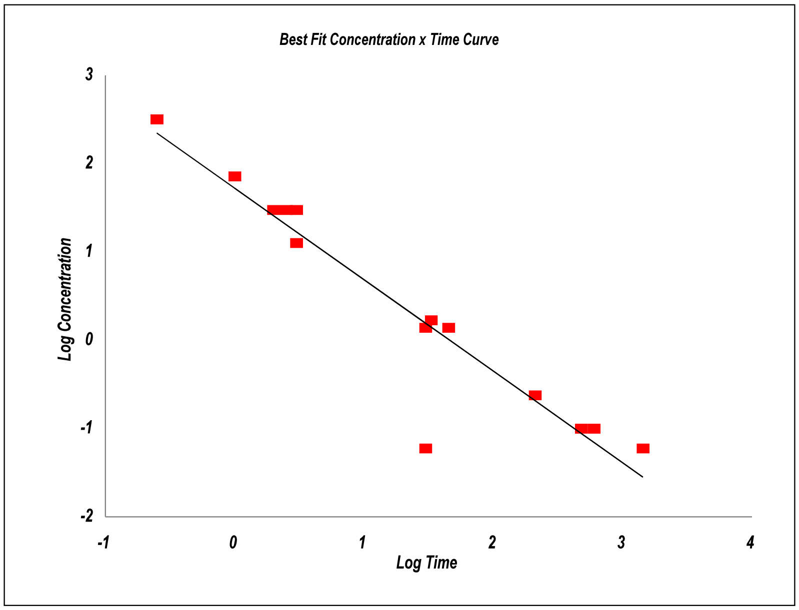
Derivation of n for $C^n \times t = k$; data points indicative of a 75-100% response for mild ocular irritation following exposure to sulfur mustard (agent HD) at various concentrations and times (Reed 1918; Reed et al. 1918; Guild et al. 1941; Anderson 1942)

Time	Concentration	Log Time	Log Concentration
1	72	0.0000	1.8573
30	1.4	1.4771	0.1461
30	0.06	1.4771	-1.2218
45	1.4	1.6532	0.1461
210	0.24	2.3222	-0.6198
480	0.1	2.6812	-1.0000
600	0.1	2.7782	-1.0000
1,440	0.06	3.1584	-1.2218
33	1.7	1.5185	0.2304
3	12.7	0.4771	1.1038
3	30	0.4771	1.4771
2.5	30	0.3979	1.4771
2	30	0.3010	1.4771
0.25	320	-0.6021	2.5051

Regression output:	
Intercept	1.7240
Slope	-1.0356
R squared	0.8891
Correlation	-0.9429
Degrees of freedom	12
Observations	14

n = 0.96

k = 46.05


Best Fit Concentration x Time Curve
Log Concentration
Log Time
3
2
1
0
-1
-2
-1
0
1
2
3
4

APPENDIX C

Carcinogenicity Assessment for Acute Exposure to Sulfur Mustard (Agent HD)

The cancer assessment for acute inhalation exposure to sulfur mustard was conducted following the NRC methodology for EEGLs, SPEGLs, and CEGLs (NRC 1986). The virtually safe dose (VSD) was determined from an inhalation slope factor of 14 $(\text{mg/kg/d})^{-1}$ for the general population (USACHPPM 2000). The slope factor was a geometric mean of slope factors developed using various data sets and procedures and was considered the most tenable quantitative assessment for potential cancer risk from inhalation exposure to sulfur mustard. The corresponding Inhalation Unit Risk was 0.0041 $(\mu\text{g/m}^3)^{-1}$ or 4.1 $(\text{mg/m}^3)^{-1}$ (USACHPPM 2000). The VSD was calculated as follows:

VSD = Risk Level /Unit Risk

$$\text{VSD} = \frac{1 \times 10^{-4}\ \text{risk}}{(4.1\ \text{mg/m}^3)^{-1}} = 2.5 \times 10^{-5}\ \text{mg/m}^3$$

Assuming the carcinogenic effect to be a linear function of cumulative dose (d), a single-day exposure is equivalent to $d \times 25{,}600$ d (average lifetime).

$$\begin{aligned} \text{24-h exposure} &= \text{VSD} \times 25{,}600 \\ &= (2.5 \times 10^{-5}\ \text{mg/m}^3) \times 25{,}600 \\ &= 0.64\ \text{mg/m}^3 \end{aligned}$$

Adjustment to allow for uncertainties in assessing potential cancer risks under short term exposures under the multistage model (Crump and Howe 1984).

$$\frac{\text{24-hr exposure}}{6} = \frac{0.64\ \text{mg/m}^3}{6} = 0.1\ \text{mg/m}^3$$

If the exposure is limited to a fraction (*f*) of a 24-h period, the fractional exposure becomes $1/f \times 24$ h (NRC 1985). For a 1×10^{-4}, 1×10^{-5}, and 1×10^{-6} risk, the fractional exposures are shown below.

Exposure Duration	10^{-4}	10^{-5}	10^{-6}
24-h	0.1 mg/m^3 (0.02 ppm)	0.01 mg/m^3 (0.002 ppm)	0.001 mg/m^3 (0.002 ppm)
8-h	0.3 mg/m^3 (0.05 ppm)	0.03 mg/m^3 (0.005 ppm)	0.003 mg/m^3 (0.0005 ppm)
4-h	0.6 mg/m^3 (0.09 ppm)	0.06 mg/m^3 (0.009 ppm)	0.006 mg/m^3 (0.0009 ppm)
1-h	2.4 mg/m^3 (0.36 ppm)	0.24 mg/m^3 (0.036 ppm)	0.024 mg/m^3 (0.0036 ppm)
30-min	4.8 mg/m^3 (0.72 ppm)	0.48 mg/m^3 (0.072 ppm)	0.048 mg/m^3 (0.0072 ppm)
10-min	14.1 mg/m^3 (2.16 ppm)	1.41 mg/m^3 (0.22 ppm)	0.141 mg/m^3 (0.022 ppm)

Because the derivation of the cancer slope factor requires conversion of animal doses to human equivalent doses, no reduction of exposure levels is applied to account for interspecies variability. With the exception of the 10-min, 30-min, and 1-h values for 10^{-4} risk and the 10-min 10^{-5} risk, these exposures are at or below the odor threshold for sulfur mustard. A cancer risk assessment based on a geometric mean of inhalation slope factors developed using various data sets and procedures indicated an excess cancer risk of 1 in 10,000 (10^{-4}) may be associated with exposures similar to the AEGL-3 values. The use of excess cancer risk estimates in setting AEGL values is precluded by the uncertainties involved in assessing excess cancer risk following a single acute exposure of 8-h or less duration, by the relatively small population exposed in an emergency release situation, and by the potential risks associated with evacuations.

APPENDIX D

DERIVATION SUMMARY FOR ACUTE EXPOSURE GUIDELINES LEVELS

Sulfur Mustard (CAS NO. 505-60-2)

AEGL-1				
10 min	30 min	1 h	4 h	8 h
0.40 mg/m^3 (0.06 ppm)	0.13 mg/m^3 (0.02 ppm)	0.067 mg/m^3 (0.01 ppm)	0.017 mg/m^3 (0.003 ppm)	0.008 mg/m^3 (0.001 ppm)
Key reference: Anderson, J.S. 1942. The effect of mustard gas vapour on eyes under Indian hot weather conditions. CDRE Report No. 241. Chemical Defense Research Establishment (India)				
Test species/strain/gender/number: 3-4 human volunteers				
Exposure route/concentrations/durations: Vapor exposure to varying concentrations (1.7-15.6 mg/m^3) for varying durations (2-33 min)				
Effects: Mild ocular effects (mild injection to notable conjunctivitis)				
End point/concentration/rationale: Concentration-time threshold of 12 mg·min/m^3 for ocular effects (conjunctival injection with minor discomfort and no functional decrement)				
Uncertainty factors/rationale: Interspecies: 1 (human subjects) Intraspecies: A factor of 3 was applied for intraspecies variability (protection of sensitive populations). This factor was limited to 3 under the assumption that the primary mechanism of action of agent HD involves a direct effect on the ocular surface and that the response will not vary greatly among individuals. Furthermore, little variability was observed in the tested subjects regarding ocular responses.				
Modifying factor: None applied				
Animal to human dosimetric adjustment: Not applicable				
Time Scaling: $C^n \times t = k$, where $n = 1$ based on analysis of available human exposure data for ocular effects.				
Data adequacy: The key study was conducted using human volunteers thus avoiding uncertainties associated with animal studies. Ocular irritation is considered the most sensitive end point for assessing the effects of acute exposure				

AEGL-1 *Continued*
to sulfur mustard and the available data were sufficient for developing AEGL-1 values.

AEGL-2				
10 min	30 min	1 h	4 h	8 h
0.60 mg/m^3 (0.09 ppm)	0.20 mg/m^3 (0.03 ppm)	0.10 mg/m^3 (0.02 ppm)	0.025 mg/m^3 (0.004 ppm)	0.013 mg/m^3 (0.002 ppm)
Key reference: Anderson, J.S. 1942. The effect of mustard gas vapour on eyes under Indian hot weather conditions. CDRE Report No. 241. Chemical Defense Research Establishment (India).				
Test species/strain/gender/number: 3-4 human volunteers				
Exposure route/concentrations/durations: Vapor exposure to varying concentrations (1.7-15.6 mg/m^3) for varying durations (2-33 min)				
Effects: Ocular effects ranging from mild injection to notable conjunctivitis, photophobia, lacrimation, blepharospasm				
End point/concentration/rationale: Exposure-concentration time product of 60 mg·min/m^3 representing exposure at which ocular irritation (well-marked, generalized conjunctivitis, edema, photophobia, and irritation) will occur resulting in performance decrement and necessitating medical treatment				
Uncertainty factors/rationale: Interspecies: 1 (human subjects) Intraspecies: A factor of 3 was applied for intraspecies variability (protection of sensitive populations). This factor was limited to 3 under the assumption that the primary mechanism of action of agent HD involves a direct effect on the ocular surface and that this response will not vary greatly among individuals. Furthermore, little variability was observed in the tested subjects regarding ocular responses.				
Modifying factor: A modifying factor of 3 was applied to accommodate uncertainties regarding the onset of potential long-term ocular effects or respiratory effects				
Animal to human dosimetric adjustment: Not applicable				
Time scaling: $C^n \times t = k$, where $n = 1$ based on analysis of available human exposure data for ocular effects				
Data adequacy: The key study was conducted using human volunteers, thus avoiding uncertainties associated with animal studies. The AEGL-2 values are based on ocular effects that may be considered severe enough to impair vision. The data were considered sufficient for developing AEGL-2 values.				

AEGL-3				
10 min	30 min	1 h	4 h	8 h
3.9 mg/m^3 (0.59 ppm)	2.7 mg/m^3 (0.41 ppm)	2.1 mg/m^3 (0.32 ppm)	0.53 mg/m^3 (0.08 ppm)	0.27 mg/m^3 (0.04 ppm)
Key reference: Kumar, O., and R. Vijayaraghavan. 1998. Effect of sulphur mustard inhalation exposure on some urinary variables in mice. J. Appl. Toxicol. 18: 257-259.				
Test species/strain/gender/number: Swiss mice/female/4 per exposure group				
Exposure route/concentrations/durations: Head-only inhalation exposure for 1 h to sulfur mustard (>99% purity) at 21.2, 42.3, or 84.6 mg/m^3 (equivalent to 0.5, 1.0, and 2.0 LC_{50}). Subjects were sacrificed at 6, 24, or 48 h or 7 d after exposure. Three groups of 10 mice were exposed at each concentration and observed for up to 14 d.				
Effects: Lethality assessed up to 14 d postexposure				
End point/concentration/rationale: No mortality in mice at 14 d following 1-h exposure at 21.2 mg/m^3. The exposure was considered an estimate of the lethality threshold in mice.				
Uncertainty factors/rationale: Total uncertainty factor: 10 Interspecies: An uncertainty factor of 3 was applied to account for possible interspecies variability in the lethal response to sulfur mustard. Application of any additional uncertainty factors or modifying factors was not warranted because the AEGL-3 values are equivalent to exposures in humans that are known to produce only ocular and respiratory tract irritation. Intraspecies: Intraspecies variability was limited to 3 because lethality appears to be a function of extreme pulmonary damage resulting from direct contact of the agent with epithelial surfaces.				
Modifying factor: No modifying factor was applied because the basis of lethality estimate was from a study utilizing a 14-d observation period to assess the lethal response from a 1-h exposure				
Animal to human dosimetric adjustment: Insufficient data				
Time scaling: $C^n \times t = k$, where n = 1 or 3. The concentration-time relationship for many irritant and systemically acting vapors and gases can be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of chemical-specific lethality data, time scaling was performed using exponential extrapolation (n = 3) for shorter time periods and linear extrapolation (n = 1) for longer time periods, thereby providing a somewhat more conservative (i.e., protective) estimate of the				

AEGL-3 *Continued*
AEGL-3 values than would be obtained using an *n* value of 1 based on ocular irritation.
Data adequacy: Uncertainties exist regarding a definitive lethality threshold for single acute exposures to sulfur mustard. However, the key study appeared to be well-designed and properly conducted and is considered sufficient for developing AEGL-3 values.