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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 15

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

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Division on Earth and Life Studies

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Preface

Extremely hazardous substances (EHSs)[2] can be released accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars and trucks transporting EHSs. Workers and residents 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 or intentional releases by terrorists. 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. Subsequently, *Standard Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Substances* was published in 2001, providing updated procedures, methodologies, and other guidelines used by the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances and the Committee on Acute Exposure Guideline Levels (AEGLs) in developing the AEGL values.

Using the 1993 and 2001 NRC guidelines reports, the NAC—consisting of members from EPA, the Department of Defense (DOD), the Department of Energy (DOE), the Department of Transportation (DOT), other federal and state governments, the chemical industry, academia, and other organizations from the private sector—has developed AEGLs for more than 270 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 (COT) the Committee on Acute Exposure Guideline Levels, which prepared this report. This report is the fifteenth volume

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

in that series. AEGL documents for ethyl mercaptan, methyl mercaptan, phenyl mercaptan, tert-octyl mercaptan, lewisite, methyl isothiocyanate, and selected monoisocyanates are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes 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.

The committee's review of the AEGL documents involved both oral and written presentations to the committee by the authors of the documents. The committee examined the draft documents and provided comments and recommendations for how they could be improved in a series of interim reports. The authors revised the draft AEGL documents based on the advice in the interim reports and presented them for reexamination by the committee as many times as necessary until the committee was satisfied that the AEGLs were scientifically justified and consistent with the 1993 and 2001 NRC guideline reports. After these determinations have been made for an AEGL document, it is published as an appendix in a volume such as this one.

The interim reports of the committee that led to this report were reviewed in draft form 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 the committee interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for ethyl mercaptan (interim reports 19a, 20a, and 21a), methyl mercaptan (interim reports 15, 19a, 20a, and 21a), phenyl mercaptan (interim reports 19a, 20a, and 21a), tert-octyl mercaptan (interim reports 19a, 20a, and 21a), lewisite (interim reports 19a and 21a), methyl isothiocyanate (interim reports 20a and 21a), and selected monoisocyantes (interim reports 20a, 20b, 21a): Harvey Clewell (The Hamner Institutes for Health Sciences), Jeffrey Fisher (U.S. Food and Drug Administration), Sam Kacew (University of Ottawa), A. Wallace Hayes (Harvard School of Public Health), Rogene Henderson (Lovelace Respiratory Research Institute [retired]), James McDougal (Wright State University [retired], and Judith Zelikoff (New York 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 this volume before its release. The review of interim reports was overseen by Robert Goyer (University of Western Ontario [retired]). Appointed by the NRC, he was responsible for making certain that an independent examination of the interim reports was carried out in accordance with institutional procedures and that all review com-

ments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The committee gratefully acknowledges the valuable assistance provided by Ernest Falke and Iris A. Camacho from EPA. The committee also acknowledges Susan Martel, the project director for her work this project. Other staff members who contributed to this effort are James J. Reisa (director of the Board on Environmental Studies and Toxicology), Radiah Rose (manager of editorial projects), Mirsada Karalic-Loncarevic (manager of the Technical Information Center), and Tamara Dawson (program associate). Finally, I would like to thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

Edward C. Bishop, *Chair*
Committee on Acute Exposure
Guideline Levels

Contents

National Research Council Committee Review of Acute Exposure Guideline Levels of Selected Airborne Chemicals

This report is the fifteenth 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, or what steps to take in an 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 U.S. 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 values, developed by the National Institute for Occupational Safety and Health. Although several public and private groups, such as the Occupational Safety and Health Administration and the American Conference of Governmental Industrial Hygienists, 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 hour (h), and only once in a lifetime for the general population, which includes infants (from birth to 3 years of age), children, the elderly, and persons with diseases, such as asthma or heart 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 U.S. Department of Defense (DOD) and the National Aeronautics and Space Administration (NASA) (NRC 1968, 1972, 1984a,b,c,d, 1985a,b, 1986a, 1987, 1988, 1994, 1996a,b, 2000a, 2002a, 2007a, 2008a). COT has also published guidelines for developing emergency exposure guidance levels for military personnel and for astronauts (NRC 1986b, 1992, 2000b). 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 November 1995, the National Advisory Committee (NAC)[1] for Acute Exposure Guideline Levels for Hazardous Substances was established to identify, review, and interpret relevant toxicologic and other scientific data and to develop acute exposure guideline levels (AEGLs) for high-priority, acutely toxic chemicals. The NRC's previous name for acute exposure levels—community emergency exposure levels (CEELs)—was 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.

AEGLs represent threshold exposure limits (exposure levels below which adverse health effects are not likely to occur) for the general public and are applicable to emergency exposures ranging from 10 minutes (min) to 8 h. 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:

[1]NAC completed its chemical reviews in October 2011. The committee was composed of members from EPA, DOD, many other federal and state agencies, industry, academia, and other organizations. From 1996 to 2011, the NAC discussed over 300 chemicals and developed AEGLs values for at least 272 of the 329 chemicals on the AEGLs priority chemicals lists. Although the work of the NAC has ended, the NAC-reviewed technical support documents are being submitted to the NRC for independent review and finalization.

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 adverse 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 idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

As described in *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993) and the NRC guidelines report *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals* (NRC 2001a), the first step in establishing AEGLs for a chemical is to collect and review all relevant published and unpublished information. 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 for 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, data from the most sensitive animal species are used. 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 genders], developmental, 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, 2001a). The NRC assigned this project to the COT Committee on Acute Exposure Guideline Levels. The committee has expertise in toxicology, epidemiology, occupational health, pharmacology, medicine, pharmacokinetics, industrial hygiene, and risk assessment.

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

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

Because of the enormous amount of data presented in AEGL reports, the NRC committee cannot verify all of the data used by NAC. The NRC committee relies on NAC and the contractors for the accuracy and completeness of the toxicity data cited in the AEGL reports. Thus far, the committee has prepared fourteen reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009, 2010a,b, 2011, 2012a,b,c, 2013). This report is the fifteenth volume in that series. AEGL documents for ethyl mercaptan, methyl mercaptan, phenyl mercaptan, tert-octyl mercaptan, lewisite, methyl isothiocyanate, and selected monoisocyanates are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes 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

5

Lewisite[1]

Acute Exposure Guideline Levels

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P.L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review, and interpret relevant toxicologic and other scientific data and develop AEGLs for high-priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, 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 parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory

[1]This document was prepared by the AEGL Development Team composed of Cheryl Bast (Oak Ridge National Laboratory), Julie Klotzbach (SRC, Inc.), Chemical Manager Warren Jederberg (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (U.S. Environmental Protection Agency). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded 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).

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 the AEGL-1 represent exposure concentrations that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, nonsensory 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 concentrations 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 idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Because lewisite compounds were developed as chemical warfare agents, military literature is a major source of relevant toxicity data. Consequently, many of the study reports have “limited distribution", which is a separate issue from “classification”. For various reasons, sources may have a restricted distribution because of treaty restrictions on data access with allies, concerns regarding distribution of engineering information characterizing agent dissemination or generation in other sections of the same document, and related issues. To ensure public access to pertinent toxicity data originating from limited-distribution materials, pertinent data from those sources have been incorporated into this chapter.[2]

Lewisite-1 (L-1) is an organic arsenical with vesicant properties. It can exist as a *trans*-isomer or a *cis*-isomer; in aqueous solutions, the *cis*-isomer undergoes photoconversion to the *trans*-isomer. Lewisite causes local corrosive damage and may cause systemic poisoning after absorption through skin or mucous membranes. Exposure to lewisite causes almost immediate irritation and burning sensation in the eyes, skin, upper respiratory tract, and lungs. Death may result from direct pulmonary damage or from circulatory failure due to fluid loss and

[2]The NRC committee that reviewed this document was not provided with the limited-distribution materials, so it relied on the information as presented in the text.

arrhythmia. Death that occurs within 24 h of exposure is likely due to pulmonary damage (Lindberg et al. 1997). Lewisite-2 (L-2) and lewisite-3 (L-3) are co-products concurrently formed with L-1(Trammel 1992). L-1 yield is greater than 65%, and approximate yields of L-2 and L-3 are 7-10% and 4-12%, respectively (Lindberg et al. 1997). L-2 and L-3 are present in smaller quantities and have comparatively low volatility, so those compounds will be less toxicologically significant than L-1. Furthermore, the toxicity of L-2 and L-3 is comparable to L-1 (Lindberg et al. 1997). Therefore, AEGL values were derived for "lewisite", rather than for the individual lewisite compounds, and are considered protective for L-1, L-2, and L-3 compounds.

Appropriate data were not available for deriving AEGL-1 values for lewisite. Odor cannot be used as a warning for potential exposure. For L-1, the odor threshold is reported to be between 14-23 mg/m^3 (1.7-2.7 ppm), concentrations greater than those that are highly irritating and higher than the AEGL-2 and AEGL-3 values. Therefore, AEGL-1 values are not recommended.

No inhalation studies with both concentration and duration parameters and with effects consistent with the definition of AEGL-2 end points were available. Therefore, the AEGL-2 values for lewisite, were determined by taking a three-fold reduction in the AEGL-3 values; the resulting values are considered to be estimated thresholds for irreversible effects (NRC 2001). The reduction approach is considered appropriate because of the steep concentration-response curve for mortality from lewisite. In studies with mice, the 10-min LC_{50} (lethal concentration, 50% lethality) was 200 mg/m^3 [24 ppm], and the 10-min LC_{100} (lethal concentration, 100% lethality) was 240 mg/m^3 [28 ppm]. In dogs, no deaths occurred after a 7.5-min exposure to lewisite at 126 mg/m^3 [15 ppm], and the LC_{50} was 176 mg/m^3 [21 ppm]).

AEGL-3 values for lewisite were based on lethality data for L-1 in dogs (Armstrong 1923). Points of departure were the calculated LC_{01} values: 38.7 mg/m^3 (4.6 ppm) for the 10-min value, 14.0 mg/m^3 (1.7 ppm) for the 30-min value, 7.4 mg/m^3 (0.87 ppm) for the 1-h value, 2.1 mg/m^3 (0.25 ppm) for the 4-h value, and 1.1 mg/m^3 (0.13 ppm) for the 8-h value. The LC_{01} values are considered estimated lethality thresholds. Interspecies and intraspecies uncertainty factors of 3 each were applied. The interspecies uncertainty factor of 3 is supported by data suggesting little species variability with regard to lethality from inhalation exposure to lewisite; C × T values are relatively constant across species, except for the guinea pig, and the interspecies uncertainty factor of 3 encompasses the two- to three-fold difference in sensitivity between guinea pigs and rats, mice, rabbits, dogs, and goats. The intraspecies uncertainty factor of 3 is supported by the steep concentration-response curve with regard to lethality, which implies limited intraspecies variation. Thus, the total uncertainty factor was 10.

The AEGL values for lewisite are presented in Table 5-1.

TABLE 5-1 AEGL Values for Lewisite

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1[a] (nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (disabling)	1.3 mg/m^3 (0.15 ppm)	0.47 mg/m^3 (0.055 ppm)	0.25 mg/m^3 (0.030 ppm)	0.070 mg/m^3 (0.0083 ppm)	0.037 mg/m^3 (0.0044 ppm)	One-third of AEGL-3 values
AEGL-3 (lethal)	3.9 mg/m^3 (0.46 ppm)	1.4 mg/m^3 (0.16 ppm)	0.74 mg/m^3 (0.087 ppm)	0.21 mg/m^3 (0.025 ppm)	0.11 mg/m^3 (0.013 ppm)	Dog LC_{01} values (Armstrong 1923).

Abbreviations: LC_{01}, lethal concentration, 1% lethality; NR, not recommended.
[a]Absence of AEGL-1 values does not imply that exposure below the AEGL-2 values is without adverse effects.

1. INTRODUCTION

Lewisite is an organic arsenical with vesicant properties. It can exist as a *trans*- or *cis*-isomer; in aqueous solutions, the *cis*-isomer undergoes photoconversion to the *trans*-isomer. Pure lewisite is a colorless, odorless oily liquid; however, synthesized agent is an amber to dark brown liquid with a geranium-like odor (Munro et al. 1999). Lewisite causes local corrosive damage and may cause systemic poisoning after absorption through skin or mucous membranes. Exposure to lewisite causes almost immediate irritation and burning sensation of the eyes, skin, upper respiratory tract, and lungs. Death may result from direct pulmonary damage or circulatory failure from fluid loss and arrhythmia. Death that occurs within 24 h of exposure is likely due to pulmonary damage (Lindberg et al. 1997).

Lewisite was developed as a chemical warfare blister agent during the latter part of World War I and was named after its inventor Captain W. Lee Lewis. When the first ship loaded with lewisite reached Europe in 1918, the war ended, and the cargo was dumped into the sea. During the period between World War I and World War II, few studies on lewisite were conducted; however, when World War II began, the research efforts intensified. Results of those studies suggested that lewisite had limited utility as a war gas because of hydrolysis to a nonvolatile and water insoluble oxide, poor penetration of protective clothing, and difficulty in attaining lethal concentrations on the battle field (Lindberg et al. 1997). Also, lewisite is so immediately irritating at low concentrations (about 6-8 mg/m^3) that troops would be warned of its presence, even before detecting the geranium-like odor at 14-23 mg/m^3, and take protective action by deploying gas masks or retreating from the toxic atmosphere (Gates et al. 1946).

Lewisite-1 (L-1) is formed by the reaction of acetylene with arsenic trichloride using aluminum trichloride as a catalyst. Arsenic trichloride, lewisite-2 (L-2),

and lewisite-3 (L-3) are co-products concurrently formed with L-1 (Trammel 1992). L-1 yield is greater than 65%, and approximate yields of arsenic trichloride, L-2, and L-3 are 16-21%, 7-10%, and 4-12%, respectively (Lindberg et al. 1997). Therefore, an accidental release from storage tanks of L-1 will likely be the release of a mixture of L-1, L-2, L-3, and arsenic trichloride. Exposure will be to these compounds and to potential hydrolysis products, sodium arsenite ($NaAsO_2$) and arsenic acid (H_3AsO_4). Toxicologic data on arsenic trichloride are limited; however, effects are similar to those of L-1 (corrosiveness, damage to skin, eyes, and mucous membranes). With regard to lethality, arsenic trichloride appears to be approximately 2-3 times less toxic than L-1; the LCt_{50} (lethal concentration [product of concentration and time] that will cause death in 50% of the exposed population) for arsenic trichloride is 4,000-5,000 mg-min/m^3 whereas the LCt_{50} for L-1 is 1,200-1,500 mg-min/m^3 (Flury 1921). L-2 and L-3 will be less significant toxicologically because of their smaller quantities and comparatively low volatility. However, the toxicity of L-2 and L-3 is reportedly comparable to L-1 (Lindberg et al. 1997). Therefore, AEGL values were derived for "lewisite" rather than for the individual lewisite compounds, and are considered protective for L-1, L-2, and L-3. In addition, in the review of literature, L-1, L-2, and L-3 are discussed only if the primary literature makes a distinction.

A summary of the nomenclature for the lewisite compounds is presented in Table 5-2, and chemical and physical data are summarized in Table 5-3.

2.1. Acute Lethality

Gates et al. (1946) estimated (based on animal data presented later in this chapter) that the inhalation LC_{50} for lewisite vapor in humans was 120 mg/m^3 for 10 min and 50 mg/m^3 for 30 min. An LC_{50} of 3,300 mg/m^3 for 30 min for lewisite vapor absorption through the bare skin was also estimated. This estimate is based on animal data and assumes that absorption of lewisite through skin is a function of the ratio of surface exposed to body volume. A dermal LD_{50} of more than 40 mg/kg was also estimated by Gates et al. (1946) based on animal data presented later in this chapter.

TABLE 5-2 Nomenclature for Lewisite Agents

Common Name	Military Designator	Chemical Names and Synonyms	CAS Registry No.
Lewisite-1	L or L-1	2-Chlorovinyldichloroarsine; (2-chlorovinyl)arsenous dichloride; beta-chlorovinyldichloroarsine; dichloro(2-chlorovinyl) arsine; chlorovinylarsine dichloride; EA 1034	541-25-3
Lewisite-2	L-2	*bis*-(2-chlorovinyl)chloroarsine	40334-69-8
Lewisite-3	L-3	*tris*-(2-chlorovinyl)arsine	40334-70-1

Sources: Gates et al. 1946; Cookson and Nottingham 1969; USACHPPM 1996.

TABLE 5-3 Chemical and Physical Data for Lewisite Compounds

Parameter	Value	Reference
Chemical formula		
Lewisite-1 (L or L-1)	$ClCH=CHAsCl_2$	Gates et al. 1946
Lewisite-2 (L-2)	$(ClCH=CH)_2$ AsCl	Gates et al. 1946
Lewisite-3 (L-3)	$(ClCH=CH)_3As$	Gates et al. 1946
Molecular weight		
Lewisite-1 (L or L-1)	207.32	HSDB 2008;
Lewisite-2 (L-2)	233.32	Lindberg et al. 1997
Lewisite-3 (L-3)	259.35	
Physical state		
Lewisite-1 (L or L-1)	Oily liquid for all forms	Lindberg et al. 1997
Lewisite-2 (L-2)		
Lewisite-3 (L-3)		
Color		
Lewisite-1 (L or L-1)	Mixture: amber to brown	Munro et al. 1999
Lewisite-2 (L-2)	Colorless (pure)	Munro et al. 1999
Lewisite-3 (L-3)	–	
Melting point		
Lewisite-1 (L or L-1)	0.1°C	HSDB 2008
Lewisite-2 (L-2)	–	
Lewisite-3 (L-3)	–	
Boiling point		
Lewisite-1 (L or L-1)	190°C	Trammel 1992
Lewisite-2 (L-2)	–	
Lewisite-3 (L-3)	–	
Specific gravity (water = 1)		
Lewisite-1 (L or L-1)	1.888 at 20°C	HSDB 2008
Lewisite-2 (L-2)	–	
Lewisite-3 (L-3)	–	
Density (air = 1)		
Lewisite-1 (L or L-1)	7.1	Trammel 1992
Lewisite-2 (L-2)	–	
Lewisite-3 (L-3)	–	
Solubility		
Lewisite-1 (L or L-1)	Insoluble in water; soluble in most organic solvents	USACHHPM 1996
Lewisite-2 (L-2)	Insoluble in water; soluble in most organic solvents	USACHHPM 1996
Lewisite-3 (L-3)	Insoluble in water; soluble in most organic solvents	USACHHPM 1996
Vapor pressure		
Lewisite-1 (L or L-1)	0.34 mm Hg at 25°C; 0.22 mm Hg at 20°C	USACHHPM 1996
Lewisite-2 (L-2)	–	
Lewisite-3 (L-3)	–	
Conversion factors		
Lewisite-1 (L or L-1)	1 mg/m^3 = 0.118 ppm	
Lewisite-2 (L-2)	1 ppm = 8.48 mg/m^3	
Lewisite-3 (L-3)		

2. HUMAN TOXICITY DATA

2.2. Nonlethal Toxicity

2.2.1. Individual Studies

Lewisite is immediately and highly irritating at concentrations of about 6-8 mg/m^3. The geranium-like odor is reportedly detectable at 14-23 mg/m^3 (Gates et al. 1946).

Inhalation of lewisite at10 mg/m^3 for 30 min reportedly resulted in severe intoxication and incapacitation that lasted for several weeks, and exposure at 10 mg/m^3 for 15 min caused inflammation of the eyes and swelling of the eyelids (Franke 1968, as cited in Ottinger et al. 1973). Ottinger et al. (1973) is a review article, and did not provide experimental details or information regarding the severity of effects. No further details were available.

A dermal vapor study was conducted by Eldridge (1923). To select "men of average resistance" for the study, pin-point drops of 0.1 or 2% solutions of liquid lewisite in alcohol were applied to the forearms of 52 male volunteers at Edgewood Arsenal. If a subject showed no reaction to the 2% solution, he was classified as "resistant" and not used in the dermal vapor study. If a subject showed a marked reaction to the 0.1% solution, he was classified as "sensitive" and not used in the dermal vapor study. Of the 52 men, 14 were resistant and 3 were sensitive. Further dermal tests with liquid lewisite were done on the sensitive and resistant subjects; the tests showed that the sensitive subjects had no effects when treated with a 0.01% lewisite solution, and the resistant subjects developed blistering with a 5% solution. Dermal effects included blanching or graying of the skin, followed by severe erythema within 15-30 min. Vesication, accompanied by some edema, occurred within 12 h. Within less than 24 h, a raised area of redness measuring 2 × 2.5 inches in diameter appeared, accompanied by a 1.5-inch diameter blister surrounded by hundreds of minute vesicles. Forty-eight hours later, the raised area of redness had increased to 6 × 3.5 inches in diameter, and fluid seeped from the blister. The smaller vesicles also ruptured as the severity of the burns continued to increase up to the fourth day. No change was noted from days 4 to 7, and from day 7 onward improvement was observed until the burns were completely healed by the end of week 4. The men described a stinging sensation that lasted for 2 min and occurred within 2.5 min of exposure. No further sensation was noted until approximately 20 min later, when the stinging sensation was again reported and lasted for approximately 2 h. Five hours later, a "continuous feeling of discomfort" was described; burning lasted until the blister ruptured 22.5 h after lewisite was administered. Intermittent stinging and burning followed and the area became sore to the touch. By the end of day 6, the pain was more severe and occurred at shorter time intervals. By day 9, all pain had resolved.

Groups of 1-7 men (from the 35 male volunteers of average sensitivity described above) were exposed on their arms to varying concentrations of lewisite vapor for periods ranging from 10 min to 3 h to determine the concentration nec-

essary to produce blistering (Eldridge 1923). The exposure apparatus allowed for a constant stream of air-lewisite mixture to pass over a square centimeter area of the subject's forearm under atmospheric pressure. Lewisite concentrations were determined by dividing the loss in weight of the gas container by the total volume of air passing through the apparatus during the test. Skin burns ranged in severity from reddish discoloration to a clear watery blister over the entire burned area, accompanied by reddening, swelling, and hardening of the surrounding skin. The burns reached maximum severity in 36-48 h, and healing was complete in 6 days to 2 weeks. The men reported that the healed skin remained sensitive for several weeks after the healing was complete. Data from this study are summarized in Table 5-4.

Lewisite liquid at doses of 3.5, 7, and 14 μg produced erythema and vesication of human skin, and doses of 22, 32, and 40 μg produced vesication (NDRC 1944).

Davis (1943) analyzed fluid from human lewisite blisters and found arsenic at 0.8-1.3 mg/mL, equivalent to 2.5-4.0 mg of lewisite.

2.2.2. Case Report

A male worker at Pine Bluff Arsenal experienced lewisite burns over 20% of his body surface, with the majority of burns on his legs. He hadan anemia 10-15 days after the burn, but had no signs of systemic arsenic poisoning (Gates et al. 1946). No further information was available on this incident.

2.3. Developmental and Reproductive Effects

Human developmental and reproductive toxicity data concerning lewisite were not found.

2.4. Genotoxicity

Human genotoxicity toxicity data concerning lewisite were not found.

TABLE 5-4 Average Lewisite Concentration Causing Blistering on Human Forearm Skin

Duration of Exposure (min)	Average Blistering Concentration (mg/m^3)
5	2,090
10	1,040
30	340
60	150
120	62
180	26.2

Source: Eldridge 1923.

2.5. Carcinogenicity

In 1940, a World War II German soldier was accidentally exposed to lewisite on his lower right leg. The blistered lesion never healed, and was diagnosed as malignant in 1948. Bowen's disease (intraepidermal squamous cell carcinoma) was diagnosed 38 years later (Krause and Grussendorf 1978).

Wada et al. (1962) reported increased incidences of cancer mortality (14% respiratory tract; 9.6% digestive tract) in workers from the Okuno-Jima poison gas factory. When cancer rates were correlated with job classification, the frequency of respiratory and gastrointestinal tract neoplasms were highest in workers involved in the production of mustard gas or lewisite, followed by those who worked indirectly with mustard gas or lewisite, and the lowest frequency was found in those that had no direct contact with mustard or lewisite (Yamakido et al. 1985). However, this information is confounded by the fact that workers were also exposed to mustard gas in addition to lewisite, and the factory also produced hydrocyanic acid, diphenylcyanarsine, chloroacetophenone, and phosgene.

2.6. Summary

Exposure to lewisite in air and by contact to liquid causes immediate irritation, burning, and corrosive damage to the eyes and exposed skin; inhalation exposure may also affect the upper airway and lungs. Human exposure data are dated and studies are, in many cases, not well described. No information concerning developmental or reproductive toxicity or genotoxicity with regard to lewisite exposure in humans was identified. Information suggesting an increased cancer incidence in workers from a Japanese poison gas factory is confounded because workers were exposed to several chemicals. Selected data on humans exposed to lewisite by inhalation are summarized in Table 5-5, and selected data on human exposed to liquid lewisite are presented in Table 5-6.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Several inhalation LC_{50} values were identified in the literature. In some cases no detailed methods were presented; however, only data from studies where concentrations were reported to be analytically determined are presented in this chapter. Oral, dermal, subcutaneous, and intravenous LD_{50} values were also identified in a variety of species.

A 9-min LC_{50} of 166 mg/m^3 was reported for rats (Gates et al. 1946). An oral LD_{50} of 50 mg/kg (U.S. Army 1974), dermal LD_{50} of 24 mg/kg (Cameron et al. 1946), and subcutaneous LD_{50} of 1 mg/kg (Cameron et al. 1946) were reported for rats.

TABLE 5-5 Data on Humans Exposed to Lewisite in Air

Effect	Exposure Duration (min)	Concentration (mg/m^3)	C × T ($mg\text{-}min/m^3$)	Reference
Odor perception	Threshold	14-23	–	Gates et al. 1946
Nasal irritation, mild	Threshold	0.8	–	Prentis 1937
Irritation, pronounced	Threshold	2.0	–	Cherkes et al. 1965
Irritation, highly irritating	Threshold	6-8	–	Gates et al. 1946
Irritation, severe	Threshold	10-30	–	Cherkes et al. 1965
Ocular inflammation/ swelling	15	10	150	Ottinger et al. 1973
Incapacitation	30	10	300	Ottinger et al. 1973
Skin lesions (skin exposure)	5	2,090	10,450	Eldridge 1923
	10	1,040	10,400	
	30	340	10,200	
	60	150	9,000	
	120	62	7,440	
	180	26.2	4,716	
Estimated inhalation LC_{50}	10	120	1,200	Gates et al. 1946
Estimated inhalation LC_{50}	30	50	1,500	Gates et al. 1946
Estimated percutaneous LC_{50}	30	3,300	100,000	Gates et al. 1946

TABLE 5-6 Skin Effects in Humans Exposed to Liquid Lewisite

Dose (μg)	Effect	Incidence	Reference
3.5	Erythema	24/29	NRDC 1944
	Vesication	21/29	
7	Erythema	30/30	NRDC 1944
	Vesication	30/30	
14	Erythema	26/26	NRDC 1944
	Vesication	26/26	
22	Vesication	10/10	CWS 1944
32	Vesication	7/9	CWS 1944
40	Vesication	100%	CWS 1944

3.1.1. Rats

Olajos et al. (1998) exposed groups of six male and six female Sprague-Dawley rats (head-only) to product solution (waste stream) from the chemical neutralization of Chemical Agent Identification Sets (CAIS). The CAIS waste stream contained chloroform (vehicle), *t*-butanol (vehicle), and lewisite. Exposures to the CAIS waste stream were at 6,000, 12,000, 18,000, or 24,000 ppm and to the chloroform-butanol solvent were at 24,000 ppm for 1 h. The concen-

tration of lewisite in the test atmospheres was 0, 0.17, 0.67, 0.96, and 0.31 mg/m^3 for the vehicle controls and the 6,000, 12,000, 18,000, and 24,000 ppm groups, respectively. Toxic signs were consistent with those of chloroform and butanol, and were noted in the control (vehicle) and waste-stream exposed animals. Ocular effects (corneal opacity and erosion) and pulmonary function effects (decreased minute volume) were similar in control and waste-stream exposed groups. The authors concluded that effects were due to chloroform and butanol, not lewisite.

3.1.2. Mice

Silver and McGrath (1943) exposed groups of 20 male CF-1 mice to varying concentrations of *cis*- or *trans*-lewisite for 10 min. Animals were exposed in a 386-L continuous flow chamber. Lewisite was vaporized by passing 20-30 L of air per minute (L/min) through lewisite in a bubbler at room temperature. Chamber airflow was maintained at 250 L/min. Lewisite concentrations in the chamber were measured analytically using a wet test meter. No animals were placed in the chamber until the chamber atmosphere reached equilibrium (approximately 10 min). Ten-min mouse LC_{50} values of 190 and 200 mg/m^3 were determined for the *cis*- and *trans*-isomers, respectively. All mice exposed to lewisite for 10 min at 240 mg/m^3 died.

3.1.3. Dogs

In an acute inhalation toxicity study, Armstrong (1923) exposed groups of dogs (sex not reported) to varying concentrations of L-1(purity 99%) for 7.5, 15, 30, 60, 120, or 240 min. The number of dogs per group varied from 1 to 17 (see Table 5-7); no explanation for the variation was provided. The dogs were exposed in an air-tight glass chamber (74.9 × 69.6 × 71.2 cm) with a sliding front and entrance and exit ports for the air-lewisite mixture. Affluent air was supplied by an air pump and was passed through a series of drying bottles. Dried air was then passed through a flowmeter to regulate the amount entering the exposure chamber. This metered stream then entered a bubbler containing the lewisite; the bubbler was immersed in a water bath so that it could be heated or cooled. The temperature of the bath and flow rate was then adjusted to predetermined points (from blank runs) to obtain the desired chamber concentrations. Lewisite concentrations in the exposure chamber were determined analytically from samples aspirated from the chamber during exposures.

Clinical signs in dogs exposed for 7.5 or 15 min included detection of lewisite within 30 seconds, as evidenced by continual eye blinking, followed by excessive nasal secretion, lacrimation, and sneezing (Armstrong 1923). Vomiting occurred and ocular irritation was observed in some dogs before exposure ended. In dogs exposed for 30-min or longer, frequent retching, vomiting, extreme salivation, and labored breathing were observed, in addition to signs noted

for shorter exposure durations. Necropsy of dying animals revealed a thick membrane in the nostrils, larynx, and trachea, accompanied by purulent bronchitis, hemorrhage, pneumonia, inflammation of the entire respiratory tract, edema, and congestion of the lungs. Congestion of the liver and kidneys were also noted. Generally, all clinical signs and pathology increased in severity with increasing exposure duration and concentration. LC_{01} values for the five AEGL durations were calculated to be 38.7 mg/m^3 for 10 min, 14.0 mg/m^3 for 30 min, 7.4 mg/m^3 for 1 h, 2.1 mg/m^3 for 4 h, and 1.1 mg/m^3 for 8 h (ten Berge et al. 1986). Lethality data on lewisite are summarized in Table 5-7.

TABLE 5-7 Lethality Data from a Study of Dogs Exposed to Lewisite-1

Exposure Duration	Concentration (mg/m^3)	Mortality	LC_{50} (mg/m^3)	When Death Occurred
7.5 min	126	0/2	176	–
	176	7/12		15-69 h post-exposure
	231	10/17		13-57 h post-exposure
	274	4/4		12-37 h post-exposure
	330	1/1		14 h post-exposure
15 min	68.7	1/4	100	12 h post-exposure
	87.7	2/5		28 and 40 h post-exposure
	96	3/5		24-60 h post-exposure
	102	2/3		36 and 84 h post-exposure
	125	6/12		12-96 h post-exposure
	233	3/3		10-24 h post-exposure
30 min	11.5	0/1	48	–
	24.5	0/4		–
	30.6	0/2		–
	41.5	0/2		–
	48	2/3		14 and 44 h post-exposure
	58.6	4/4		24-84 h post-exposure
60 min	5.8	0/2	25.7	–
	8	0/5		–
	25	5/9		18-56 h post-exposure
	35	5/9		4-36 h post-exposure
	43	5/7		17-20 h post-exposure
	53	1/1		12 h post-exposure
120 min	4.8	0/4	11.8	–
	12.5	2/3		47 and 72 h post-exposure
	17.9	4/6		12-24 h post-exposure
	24.5	4/5		24-84 h post-exposure
	34.5	3/3		12-29 h post-exposure
240 min	2.1	0/3	6.6	–
	6.2	5/9		16-76 h post-exposure
	10	10/17		2-78 h post-exposure
	16.9	2/2		48 and 37 h post-exposure

Source: Armstrong 1923.

Harrison et al. (1946) exposed dogs to lewisite at 50 mg/m^3 for 30 min (8 dogs), 61 mg/m^3 for 30 min (9 dogs), or 121 mg/m^3 for 10 min (5 dogs). Clinical signs included vomiting, urination, defecation, salivation, and respiratory distress; 80% of the dogs died 3-48 h after exposure. No other information was available.

A dermal LD_{50} of 15 mg/kg (Cameron et al. 1946) and subcutaneous LD_{50} of 2 mg/kg (Cameron et al. 1946) were reported for dogs.

3.1.4. Rabbits

A 7.5-min LC_{50} of 160 mg/m^3 and a 60-min LC_{50} of 25 mg/m^3 was reported for rabbits (Gates et al. 1946). A dermal LD_{50} of 6 mg/kg (Cameron et al. 1946) and intravenous LD_{50} of 0.5 mg/kg (Cameron et al. 1946) were also reported.

3.1.5. Guinea Pigs

A 9-min LC_{50} of 111 mg/m^3 and a 60-min LC_{50} of 8 mg/m^3 were reported for guinea pigs (Gates et al. 1946). A dermal LD_{50} of 12 mg/kg (Cameron et al. 1946) and subcutaneous LD_{50} of 1 mg/kg (Cameron et al. 1946) were also reported.

3.1.6. Goats

A 100-min LC_{50} of 12.5 mg/m^3 (Gates et al. 1946) and a dermal LD_{50} of 15 mg/kg (Cameron et al. 1946) were reported for goats.

3.2. Nonlethal Toxicity

3.2.1. Rats

No treatment-related deaths occurred in rats exposed a CAIS waste stream (containing chloroform [vehicle], *t*-butanol [vehicle], and lewisite) at 6,000 or 12,000 ppm. The concentration of lewisite in these test atmospheres was 0.17 mg/m^3 for the 6,000 ppm group and 0.96 mg/m^3 for the 12,000 ppm group. This study is discussed in more detail in Section 3.1.1.

3.2.2. Dogs

Ocular lesions, but no deaths, were reported in dogs exposed to lewisite at 20 mg/m^3 for 30 min (Gates et al. 1946). No additional experimental details, including severity of effects, were reported.

3.2.3. Rabbits

Ocular lesions, but no deaths, were reported in rabbits exposed to lewisite at 1 mg/m^3 for 30 min (Gates et al. 1946). No additional experimental details, including severity of effects, were reported.

3.2.4. Pigs

Lindsay et al. (2004) dermally exposed three large white pigs to lewisite at 0.3 mg/cm^2. While under anesthesia, an area of dorsal skin (35 cm × 25 cm) was shaved. Exposures were then conducted using inverted glass chambers; lewisite (in hexane) was pipetted onto 10-cm^2 glass-fiber discs fitted tightly in the roof of each circular, glass chamber. The heat from the animals vaporized the lewisite so that the skin was exposed to vapor, but not lewisite liquid. Pigs were monitored in their pens for 24 h and were then killed. Full skin thickness samples from control (non-exposed) and lewisite-treated skin were excised to examine the degradative processes in connective tissue components of skin, especially glycoproteins, using immunostaining and gel electrophoresis. There was no evidence of cross linking of laminin or of type III or IV collagen in lewisite-treated pigs. There was evidence of degradation of laminin and type IV collagen only.

3.3. Developmental and Reproductive Effects

Hackett et al. (1987) administered lewisite to CD rats and New Zealand white rabbits by gastric intubation. Rats were dosed daily on days 6 through 15 of gestation with lewisite at 0, 0.5, 1.0, 2.0, or 2.5 mg/kg in a range-finding study and with 0, 0.5, 1.0, or 1.5 mg/kg in a teratology study. Rabbits were dosed on gestation days 6 through 19 with lewisite at 0, 0.5, 1.0, 1.5, and 2.0 mg/kg in a range-finding study and at 0, 0.07, 0.2, and 0.6 mg/kg in a teratology study. In rats, no maternal of fetal effects were noted at 1.5 mg/kg. At 2.0 mg/kg, maternal mortality (10%), decreased maternal and fetal body weight, and decreased numbers of viable fetuses were found. In rabbits, maternal mortality ranged from 13% in the 0.07-mg/kg group to 100% in the 2.0-mg/kg group. This mortality rate limited the sample size and made identification of other potential fetal or maternal effects difficult. However, at 0.07 mg/kg, only maternal mortality was noted. At 0.6 mg/kg (highest dose in the teratology study), effects included 86% maternal mortality, decreased maternal body weight gain, an increased incidence of fetal stunting, and a tendency toward decreased fetal body weight (Hackett et al. 1987).

In a 42-week, two-generation reproductive study in rats, parental males and females were administered lewisite in sesame oil by gastric intubation at 0, 0.10, 0.25, or 0.60 mg/kg/day for 5 days/week prior to mating, during mating, and after mating until the birth of offspring. Dams continued to be exposed to lewisite during lactation. After weaning, male and female offspring selected to

continue on the study were exposed similarly to lewisite. There were no treatment-related effects on reproductive performance, fertility, or reproductive organ weights of male or female rats through two consecutive generations. There were no treatment-related effects in offspring (Sasser et al. 1989).

3.4. Genotoxicity

Lewisite did not induce mutations in *Salmonella typhimurium* strains TA97, TA98, TA100, or TA102 with or without metabolic activation up to concentrations limited by toxicity (1.0 μg/plate) (Stewart et al. 1989). Lewisite was negative for mutation at the HGPRT locus in Chinese hamster ovary (CHO) cells at concentrations ranging from 0.12 to 2.0 μM (Jostes et al. 1989). However, lewisite induced chromosomal aberrations in CHO cells at concentrations of 0.50, 0.75, and 1.0 μM (Jostes et al. 1989). Lewisite was negative in the *Drosophilla melanogaster* sex-linked recessive lethal assay (Auerbach and Robson 1946, 1947) and negative in a dominant lethal assay in CD rats at concentrations of 0.375, 0.75, or 1.5 mg/kg (Bucci et al. 1993).

3.5. Carcinogenicity

No data were located regarding the carcinogenicity of lewisite in animals.

3.6. Summary

A summary of the acute inhalation data on lewisite is presented in Table 5-8, and Table 5-9 summarizes acute toxicity data by other routes of exposure. Animal data are limited but suggest that lewisite is highly irritating and corrosive, causing dermal and ocular lesions by contact with liquid or vapor. Inhalation LC_{50} values were identified in several species, and the weight of evidence suggests limited interspecies variability ($C \times T$ is relatively constant across species). There is no evidence that lewisite is a reproductive or developmental toxicant in rats or rabbits in the absence of maternal toxicity. Genotoxicity assay results were generally negative; the only positive result was in chromosome aberrations in CHO cells. No information concerning carcinogenicity in animals was found.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

According to a secondary source, lewisite is readily absorbed through the mucous membranes, and is also readily absorbed through the skin because of its lipophilicity (HSDB 2008).

TABLE 5-8 Summary of Acute Inhalation Data from Animals Exposed to Lewisite

Species	Exposure Duration (min)	Concentration (mg/m^3)	C × T ($mg\text{-}min/m^3$)	Effect	Reference
Lethal Effects					
Rat	9	166	1,494	LC_{50}	Gates et al. 1946
Mouse	10	190	1,900	LC_{50}	Silver and McGrath 1943
Mouse	10	200	2,000	LC_{50}	Silver and McGrath 1943
Mouse	10	240	2,400	LC_{100}	Silver and McGrath 1943
Guinea pig	9	111	999	LC_{50}	Gates et al. 1946
Guinea pig	60	8	480	LC_{50}	Gates et al. 1946
Rabbit	7.5	160	1,200	LC_{50}	Gates et al. 1946
Rabbit	60	25	1,500	LC_{50}	Gates et al. 1946
Dog	7.5	176	1,320	LC_{50}	Armstrong 1923
Dog	15	100	1,500	LC_{50}	Armstrong 1923
Dog	30	48	1,440	LC_{50}	Armstrong 1923
Dog	60	25.4	1,542	LC_{50}	Armstrong 1923
Dog	120	11.8	1,416	LC_{50}	Armstrong 1923
Dog	240	6.24	1,584	LC_{50}	Armstrong 1923
Goat	100	12.5	1,250	LC_{50}	Gates et al. 1946
Nonlethal Effects					
Rabbit	30	1	30	Ocular lesions, no death	Gates et al. 1946
Dog	30	20	600	Ocular lesions, no death	Gates et al. 1946

4.2. Mechanism of Toxicity

Dermal or intravenous exposure to lewisite leads to local skin edema and pulmonary edema due to increased capillary permeability. There is no evidence of edema or capillary permeability in any other part of the body. The increased capillary permeability results in blood plasma loss and leads to a sequence of physiological events termed "lewisite shock" which is similar to shock observed in severe burn cases. Functional changes in the lungs, kidneys, respiratory tract, cardiovascular system, and lymphatic system may be the result of a disturbance of osmotic equilibrium (Goldman and Dacre 1989).

TABLE 5-9 Summary of Acute Oral, Dermal, Subcutaneous, and Intravenous Data from Animals Exposed to Lewisite

Route of Administration	Species	LD_{50} (mg/kg)	Reference
Oral	Rat	50	U.S. Army 1974
Dermal	Rat	24	Cameron et al. 1946
	Guinea pig	12	Cameron et al. 1946
	Rabbit	6	Cameron et al. 1946
	Dog	15	Cameron et al. 1946
	Goat	15	Cameron et al. 1946
Subcutaneous	Rat	1	Cameron et al. 1946
	Guinea pig	1	Cameron et al. 1946
	Rabbit	2	Cameron et al. 1946
	Dog	2	Cameron et al. 1946
Intravenous	Rabbit	0.5	Cameron et al. 1946

As reviewed in Goldman and Dacre (1989) and Young (1999), the mechanism of toxicity of lewisite is the formation of stable complexes between the arsenite moiety of lewisite and sulfhydryls groups that are critical to the function of proteins and thiol cofactors (e.g., dihydrolipoic acid, keratin, alcohol dehydrogenase, pyruvate dehydrogenase, succinic dehydrogenase, succinic oxidase, hexokinase). The formation of stable complexes with protein thiols is also the primary mechanism of toxicity of arsenite. Although lewisite can hydrolyze to yield arsenite, the reaction occurs at alkaline conditions and/or high temperature and is unlikely to be important in lewisite toxicology (Goldman and Dacre 1989).

4.3. Structure-Activity Relationships

Lewisite and arsenite share a common mechanism of action in disruption of protein function by formation to complexes with protein sulfhydryls. Toxicologic data on arsenic trichloride, L-2 and L-3, co-products concurrently formed with L-1, are limited. However, effects are similar qualitatively to those of L-1 (corrosiveness, damage to skin, eyes, and mucous membranes). With regard to lethality, arsenic trichloride appears to be approximately 2-3 times less toxic than L-1; the LCt_{50} for arsenic trichloride is 4,000-5,000 mg-min/m^3 whereas the LCt_{50} for L-1 is 1,200-1,500 mg-min/m^3 (Flury 1921). The toxicity of L-2 and L-3 is reportedly comparable to L-1 (Lindberg et al. 1997). Silver and McGrath (1943) found no substantial difference in 10-min LC_{50} values (190 and 200 mg/m^3) for the *cis*- and *trans*-isomers of lewisite.

Inhalation data for sodium arsenite, a hydrolysis product of L-1, are not available. However, Inns et al. (1988) compared the acute intravenous toxicity of lewisite and sodium arsenite in New Zealand white rabbits. The LD_{50} of lewisite was 1.8 mg/kg. Rapid panting was noted 5 min after injection, and was followed by prostration and death within 4 h. By 24 h after injection, surviving rabbits appeared normal. The LD_{50} for sodium arsenite was 7.6 mg/kg, with hypoactivity noted 20 min after injection. On the basis of trivalent arsenic content, lewisite was 6.5 times more toxic than the inorganic sodium arsenite, and clinical signs and times of death and recovery differed between the compounds. Severe pulmonary damage (gross and histopathologic) was found in rabbits treated with lewisite, but not in animals treated with sodium arsenite. Also, arsenic levels in the liver, kidneys, brain, stomach, duodenum, spleen, and bladder were much greater in sodium arsenite-treated rabbits than in lewisite-treated rabbits. However, arsenic content in the lungs was similar. These data suggest different mechanisms of toxicity for lewisite and inorganic trivalent arsenic, and that arsenite is not an appropriate surrogate for lewisite.

4.4. Other Relevant Information

4.4.1. Species Variability

The selected animal mortality data presented in Table 5-8 show that the concentration-time products from LC_{50} data sets are relatively constant across species, except for the two guinea pig data points. This suggests that there is relatively little species variability with respect to lethal response to lewisite inhalation exposure. Findings are consistent with the expectation that little species variability will be observed for highly corrosive substances.

4.4.2. Concentration-Exposure Duration Relationship

The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases has been described by the relationship $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al. 1986). Using LC_{50} data from the dog (the species with the most robust data set, see Table 5-7), which included exposures ranging from 7.5 min to 4-h, an n value of 1.03 is derived (see Figure 5-1).

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No human data were relevant for establishing AEGL-1 values for lewisite.

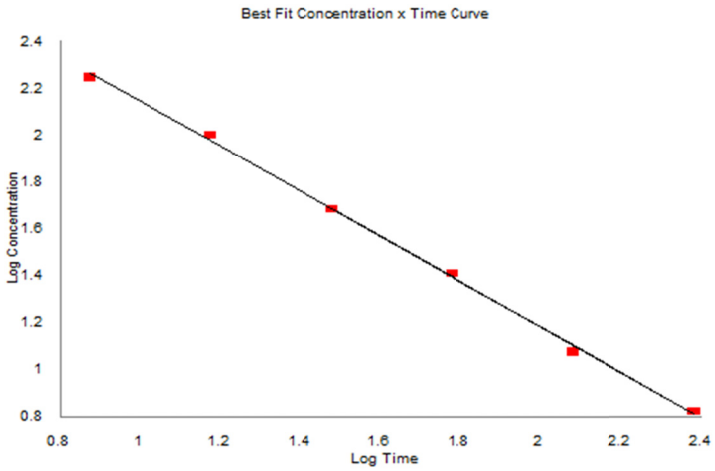

FIGURE 5-1 LC_{50} Data for Lewisite in Dogs. Source: Armstrong 1923.

5.2. Animal Data Relevant to AEGL-1

No animal data were relevant for establishing AEGL-1 values for lewisite.

5.3. Derivation of AEGL-1

Appropriate data were not available to derive AEGL-1 values for lewisite. Odor cannot be used as a warning for potential exposure, because the odor threshold (14-23 mg/m^3 for L-1) is higher than concentrations that are highly irritating and higher than the AEGL-2 and AEGL-3 values. Therefore, AEGL-1 values are not recommended. Lack of AEGL-1 values does not imply that exposure at concentrations below the AEGL-2 values is without effect.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data were available for establishing AEGL-2 values for lewisite.

6.2. Animal Data Relevant to AEGL-2

No animal data were available for establishing AEGL-2 values for lewisite. Ocular inflammation and lesions reported by Gates et al. (1946) and Ottinger et al. (1973) were considered an inappropriate basis for AEGL-2 values. The Ottinger et al. (1973) report is a review paper, which noted that "a lower concentration of 0.01 mg/L causes inflammation to the eyes and swelling of the lid after 15 minutes" (as

cited in Franke 1968); however, no experimental details were provided and attempts to obtain the Franke (1968) report were not successful. Because the primary data could not be obtained for review, the information was considered unsuitable for deriving AEGL-2 values. Gates et al. (1946) reported approximate concentrations necessary to produce ocular lesions in 30 min (0.001 mg/L in rabbits and 0.20 mg/L in dogs); however, no experimental details or descriptions of the lesions were reported. For both the Ottinger et al. (1973) and Gates et al. (1946) reports, sufficient detail is not available to determine the severity of effects and do not provide no-effect levels.

6.3. Derivation of AEGL-2

No inhalation data with both concentration and duration parameters and with effects consistent with the definition of AEGL-2 end points were available. Therefore, the AEGL-2 values for lewisite were determined by taking a three-fold reduction in the AEGL-3 values; the resulting values are considered to be estimated thresholds for irreversible effects (NRC 2001). The reduction approach is considered appropriate because of the steep concentration-response curve for mortality from lewisite. In studies with mice, the 10-min LC_{50} was 200 mg/m^3 and the 10-min LC_{100} was 240 mg/m^3. In dogs, no deaths occurred after a 7.5-min exposure to lewisite at 126 mg/m^3, and the LC_{50} was 176 mg/m^3.

AEGL-2 values for lewisite are presented in Table 5-10, and the calculations are presented in Appendix A.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data with concentration and duration parameters consistent with the definition of AEGL-3 were available.

7.2. Animal Data Relevant to AEGL-3

Gates et al. (1946) reported LC_{50} values for several test species: a 9-min LC_{50} of 166 mg/m^3 for rats; a 9-min LC_{50} of 111 mg/m^3 and a 60-min LC_{50} of 8 mg/m^3 for guinea pigs; a 7.5-min LC_{50} of 160 mg/m^3 and a 60-min LC_{50} of 25 mg/m^3 for rabbits; and a 100-min LC_{50} of 12.5 mg/m^3 in goats. Silver and McGrath (1943) reported 10-min LC_{50} values for mice of 190 and 200 mg/m^3 for *cis*- and *trans*-isomers of lewisite, respectively. Armstrong (1923) reported the following LC_{50} values for dogs: 176 mg/m^3 for 7.5 min, 100 mg/m^3 for 15 min, 48 mg/m^3 for 30 min, 25.4 mg/m^3 for 60 min, 11.8 mg/m^3 for 120 min, and 6.24 mg/m^3 for 240 min. The mouse study (Silver and McGrath 1943) and dog study (Armstrong 1923) were well-conducted and well-described, but the studies by Gates et al. (1946) were not well described.

TABLE 5-10 AEGL-2 Values for Lewisite

10 min	30 min	1 h	4 h	8 h
1.3 mg/m^3 (0.15 ppm)	0.47 mg/m^3 (0.055 ppm)	0.25 mg/m^3 (0.030 ppm)	0.070 mg/m^3 (0.0083 ppm)	0.037 mg/m^3 (0.0044 ppm)

7.3. Derivation of AEGL-3

The dog lethality study (Armstrong, 1923) was used as the basis of AEGL-3 values. Points of departure were the calculated LC_{01} values: 38.7 mg/m^3 for the 10-min value, 14.0 mg/m^3 for the 30-min value, 7.4 mg/m^3 for the 1-h value, 2.1 mg/m^3 for the 4-h value, and 1.1 mg/m^3 for the 8-h value. The LC_{01} values are considered estimates of lethality thresholds. Interspecies and intraspecies uncertainty factors of 3 each were applied. The interspecies uncertainty factor of 3 is supported by data that suggest little species variability with regard to lethality from inhalation exposure to lewisite; C × T values are relatively constant across species, except for the guinea pig, and the interspecies uncertainty factor of 3 encompasses the two- to three-fold difference in sensitivity between guinea pigs and rats, mice, rabbits, dogs, and goats (see Table 5-8 for summary of supporting data). The intraspecies uncertainty factor of 3 is supported by the steep concentration-response curve with regard to lethality, which implies limited intraspecies variation. In studies with mice, the 10-min LC_{50} was 200 mg/m^3 and the 10-min LC_{100} was 240 mg/m^3. In dogs, no deaths occurred after a 7.5-min exposure to lewisite at 126 mg/m^3, and the LC_{50} was 176 mg/m^3.

AEGL values were derived for lewisite as a mixture of L-1, L-2, and L-3, rather than for the individual lewisite compounds. L-2 and L-3 are co-products concurrently formed with L-1 (Trammel 1992). L-1 yield is greater than 65%, and approximate yields of L-2 and L-3 are 7-10% and 4-12%, respectively (Lindberg et al. 1997). L-2 and L-3, because of their smaller quantities and comparatively low volatility, will be less toxicologically significant than L-1. Furthermore, the toxicity of L-2 and L-3 is comparable to L-1 (Lindberg et al. 1997). Therefore, AEGL-values derived for lewisite are considered protective for L-1, L-2, and L-3 compounds. AEGL-3 values for lewisite are presented in Table 5-11, and the calculations are presented in Appendix A.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

A summary of the AEGL values for lewisite is presented in Table 5-12. Data were insufficient to derive AEGL-1 values. AEGL-2 values are based on a three-fold reduction in AEGL-3 values, and AEGL-3 values are based on lethality data in dogs.

TABLE 5-11 AEGL-3 Values for Lewisite

10 min	30 min	1 h	4 h	8 h
3.9 mg/m^3 (0.46 ppm)	1.4 mg/m^3 (0.16 ppm)	0.74 mg/m^3 (0.087 ppm)	0.21 mg/m^3 (0.025 ppm)	0.11 mg/m^3 (0.013 ppm)

TABLE 5-12 AEGL Values for Lewisite

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1[a] (nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (disabling)	1.3 mg/m^3 (0.15 ppm)	0.47 mg/m^3 (0.055 ppm)	0.25 mg/m^3 (0.030 ppm)	0.070 mg/m^3 (0.0083 ppm)	0.037 mg/m^3 (0.0044 ppm)
AEGL-3 (lethal)	3.9 mg/m^3 (0.46 ppm)	1.4 mg/m^3 (0.16 ppm)	0.74 mg/m^3 (0.087 ppm)	0.21 mg/m^3 (0.025 ppm)	0.11 mg/m^3 (0.013 ppm)

[a]NR, not recommended; absence of an AEGL-1 does not imply that exposure below the AEGL-2 values is without adverse effect.

8.2. Comparisons with Other Standards and Guidelines

No exposure standards or guidelines were for L-1, L-2, or L-3 were found.

8.3. Data Adequacy and Research Needs

Human data were insufficient for deriving AEGL values for lewisite. Mouse and dog lethality studies were well conducted and were not inconsistent with the limited lethality data in other species. No data on concentration-response relationships for AEGL-2 effects were suitable for deriving AEGL-2 values. Data were available only for L-1; however, given the low volatility and small volume of L-2 and L-3 in total lewisite and the similar toxicity of L-2 and L-3 with L-1 (Lindberg et al. 1997), AEGL-values derived for lewisite should be protective for L-1, L-2, and L-3 compounds.

9. REFERENCES

Because lewisite compounds were developed as chemical warfare agents, military literature is a major source of relevant toxicity data. Consequently, many of the study reports have “limited distribution", which is a separate issue from “classification”. For various reasons, sources may have a restricted distribution because of treaty restrictions on data access with allies, concerns regarding distribution of engineering information characterizing agent dissemination or generation in other sections of the same document, and related issues. To ensure

public access to pertinent toxicity data originating from limited-distribution materials, pertinent data from those sources have been incorporated into this chapter.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR LEWISITE

Derivation of AEGL-1 Values

The available data were insufficient to derive AEGL-1 values for lewisite.

Derivation of AEGL-2 Values

In the absence of relevant data to derive AEGL-2 values, a one-third reduction of the AEGL-3 values was used to derive AEGL-2 values (NRC 2001).

10-min AEGL-2: $3.9\ mg/m^3 \div 3 = 1.3\ mg/m^3$

30-min AEGL-2: $1.4\ mg/m^3 \div 3 = 0.47\ mg/m^3$

1-h AEGL-2: $0.74\ mg/m^3 \div 3 = 0.25\ mg/m^3$

4-h AEGL-2: $0.21\ mg/m^3 \div 3 = 0.070\ mg/m^3$

8-h AEGL-2: $0.11\ mg/m^3 \div 3 = 0.037\ mg/m^3$

Derivation of AEGL-3 Values

Key study: Armstrong, G.C. 1923. The toxicity of M-1 by inhalation for dogs. Chapter II in The Toxicity, Pathology, Chemistry, Mode of Action, Penetration, and Treatment for M-1 and its Mixtures with Arsenic Trichloride, Part 1. ADB954935. Edgewood Arsenal, Aberdeen Proving Ground, MD. August 13, 1923. (unclassified report/limited distribution).

Toxicity end point: Calculated LC_{01} values (estimated 1% lethality thresholds)

10-min	$38.7\ mg/m^3$
30-min	$14.0\ mg/m^3$
1-h	$7.4\ mg/m^3$
4-h	$2.1\ mg/m^3$
8-h	$1.1\ mg/m^3$

Uncertainty factors: 3 for interspecies differences
3 for intraspecies variability

	Appropriate chemical-specific data were not available to derive AEGL-3 values for L-2 or L-3. However, L-2 and L-3 exist as a small fraction of total lewisite (7-10% for L-2 and 4-12% for L-3) and have comparatively low volatilities. Because of these chemical characteristics, AEGL-3 values for L-1 were adopted as AEGL-3 values for the mixture of L-1, L-2, and L-3.

Calculations:

10-min AEGL-3:	$38.7\ mg/m^3 \div 10 = 3.9\ mg/m^3$
30-min AEGL-3:	$14.0\ mg/m^3 \div 10 = 1.4\ mg/m^3$
1-h AEGL-3:	$7.4\ mg/m^3 \div 10 = 0.74\ mg/m^3$
4-h AEGL-3:	$2.1\ mg/m^3 \div 10 = 0.21\ mg/m^3$
8-h AEGL-3:	$1.1\ mg/m^3 \div 10 = 0.11\ mg/m^3$

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR LEWISITE

Derivation Summary

AEGL-1 VALUES

The available data on lewisite were inadequate to derive AEGL-1 values.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
1.3 mg/m^3 (0.15 ppm)	0.47 mg/m^3 (0.055 ppm)	0.25 mg/m^3 (0.030 ppm)	0.070 mg/m^3 (0.0083 ppm)	0.037 mg/m^3 (0.0044 ppm)

Data adequacy: The available data on lewisite were inadequate to derive AEGL-2 values. When data are lacking and the concentration-response curve is steep, AEGL-2 values may be derived by dividing the AEGL-3 values by 3 (NRC 2001). A steep concentration-response curve has been demonstrated for lewisite. In studies with mice, the 10-min LC_{50} was 200 mg/m^3 and the 10-min LC_{100} was 240 mg/m^3. In dogs, no deaths occurred after a 7.5-min exposure to lewisite at 126 mg/m^3, and the LC_{50} was 176 mg/m^3.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
3.9 mg/m^3 (0.46 ppm)	1.4 mg/m^3 (0.16 ppm)	0.74 mg/m^3 (0.087 ppm)	0.21 mg/m^3 (0.025 ppm)	0.11 mg/m^3 (0.013 ppm)

Key reference: Armstrong, G.C. 1923. The toxicity of M-1 by inhalation for dogs. Chapter II in The Toxicity, Pathology, Chemistry, Mode of Action, Penetration, and Treatment for M-1 and its Mixtures with Arsenic Trichloride. Part 1. ADB954935. Edgewood Arsenal, Aberdeen Proving Ground, MD. August 13, 1923. (unclassified report/limited distribution).

Test species/Strain/Number: Dog; breed not specified; 1-17 per group.

Exposure route/Concentrations/Durations:
Inhalation; 126, 176, 231, 274, and 330 mg/m^3 for 7.5 min
Inhalation; 68.7, 87.7, 96, 102, 125, and 233 mg/m^3 for 15 min
Inhalation; 11.5, 24.5, 30.6, 41.5, 48, and 58.6 mg/m^3 for 30 min
Inhalation; 5.8, 8, 25, 35, 43, and 53 mg/m^3 for 1 h
Inhalation; 4.8, 12.5, 17.9, 24.5, and 34.5 mg/m^3 for 2 h
Inhalation; 2.1, 6.2, 10, and 16.9 mg/m^3 for 4 h

Effects:

Concentration (mg/m^3)	
176	7.5-min LC_{50}
100	15-min LC_{50}

48	30-min LC_{50}
25.7	1-h LC_{50}
11.8	2-h LC_{50}
6.6	4-h LC_{50}
38.7	10-min LC_{01}
14.0	30-min LC_{01}
7.4	1-h LC_{01}
2.1	4-h LC_{01}
1.1	8-h LC_{01}

End point/Concentration/Rationale: Calculated LC_{01} values, considered thresholds for lethality.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, data suggest little species variability with regard to lethality from inhalation exposure to L-1; C × T values are relatively constant across species, except for the guinea pig, and the interspecies uncertainty factor of 3 encompasses the 2- to 3-fold difference in sensitivity between guinea pigs and rats, mice, rabbits, dogs, and goats.
Intraspecies: 3, steep concentration-response curve with regard to lethality implies limited intraspecies variation. In studies with mice, the 10-min LC_{50} was 200 mg/m^3 and the 10-min LC_{100} was 240 mg/m^3. In dogs, no deaths occurred after a 7.5-min exposure to lewisite at 126 mg/m^3, and the LC_{50} was 176 mg/m^3.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: Points of departure were time-specific LC_{01} values.

Data adequacy: Data are adequate to derive AEGL-3 values for lewisite.

APPENDIX C

CALCULATION OF LC_{01} VALUE FOR DOGS

Data source: Armstrong (1923)
Filename: ten Berge Spreadsheet Data for Log Probit Model
Date: 15 October 2010 Time: 09:03:51

Sequence No.	Concentration (mg/m^3)	Minutes	Exposed	Responded
1	126	7.5	2	0
2	176	7.5	12	7
3	231	7.5	17	10
4	274	7.5	4	4
5	330	7.5	1	1
6	68.7	15	4	1
7	87.7	15	5	2
8	96	15	5	3
9	102	15	3	2
10	125	15	12	6
11	233	15	3	3
12	11.5	30	1	0
13	24.5	30	4	0
14	30.6	30	2	0
15	41.5	30	2	0
16	48	30	3	2
17	58.6	30	4	4
18	5.8	60	2	0
19	8	60	5	0
20	25	60	9	5
21	35	60	9	5
22	43	60	7	5
23	53	60	1	1
24	4.8	120	4	0
25	12.5	120	3	2
26	17.9	120	6	4
27	24.5	120	5	4
28	34.5	120	3	3
29	2.1	240	3	0
30	6.2	240	9	5
31	10	240	17	10
32	16.9	240	2	2

Used Probit Equation Y = B0 + B1*X1 + B2*X2
X1 = concentration mg/m^3, ln-transformed
X2 = minutes, ln-transformed

Chi-Square = 15.93
Degrees of freedom = 29
Probability Model = 9.76E-01

Ln(Likelihood) = -29.24

B 0 = -7.7323E+00 Student t = -3.1898
B 1 = 1.7999E+00 Student t = 5.3334
B 2 = 1.6615E+00 Student t = 5.2230

Variance B 0 0 = 5.8761E+00
Covariance B 0 1 = -8.1104E-01
Covariance B 0 2 = -7.6250E-01
Variance B 1 1 = 1.1390E-01
Covariance B 1 2 = 1.0355E-01
Variance B 2 2 = 1.0120E-01

Estimation ratio between regression coefficients of ln(conc) and ln(minutes)
Point estimate = 1.083
Lower limit (95% CL) = 0.976
Upper limit (95% CL) = 1.191

Estimation of concentration mg/m^3 at response of 1%
Minutes = 10
Point estimate concentration mg/m^3 = 3.869E+01 for response of 1%
Lower limit (95% CL) concentration mg/m^3 = 1.699E+01 for response of 1%
Upper limit (95% CL) concentration mg/m^3 = 5.741E+01 for response of 1%

Estimation of concentration mg/m^3 at response of 1%
Minutes = 30
Point estimate concentration mg/m^3 = 1.403E+01 for response of 1%
Lower limit (95% CL) concentration mg/m^3 = 6.185E+00 for response of 1%
Upper limit (95% CL) concentration mg/m^3 = 2.064E+01 for response of 1%

Estimation of concentration mg/m^3 at response of 1%
Minutes = 60
Point estimate concentration mg/m^3 = 7.400E+00 for response of 1%
Lower limit (95% CL) concentration mg/m^3 = 3.237E+00 for response of 1%
Upper limit (95% CL) concentration mg/m^3 = 1.094E+01 for response of 1%

Estimation of concentration mg/m^3 at response of 1%
Minutes = 120
Point estimate concentration mg/m^3 = 3.903E+00 for response of 1%
Lower limit (95% CL) concentration mg/m^3 = 1.682E+00 for response of 1%
Upper limit (95% CL) concentration mg/m^3 = 5.838E+00 for response of 1%

Estimation of concentration mg/m^3 at response of 1%
Minutes = 240
Point estimate concentration mg/m^3 = 2.058E+00 for response of 1%
Lower limit (95% CL) concentration mg/m^3 = 8.675E-01 for response of 1%
Upper limit (95% CL) concentration mg/m^3 = 3.138E+00 for response of 1%

Estimation of concentration mg/m^3 at response of 1%
Minutes = 480
Point estimate concentration mg/m^3 = 1.085E+00 for response of 1%
Lower limit (95% CL) concentration mg/m^3 = 4.447E-01 for response of 1%
Upper limit (95% CL) concentration mg/m^3 = 1.697E+00 for response of 1%

APPENDIX D

CATEGORY PLOT FOR LEWISITE

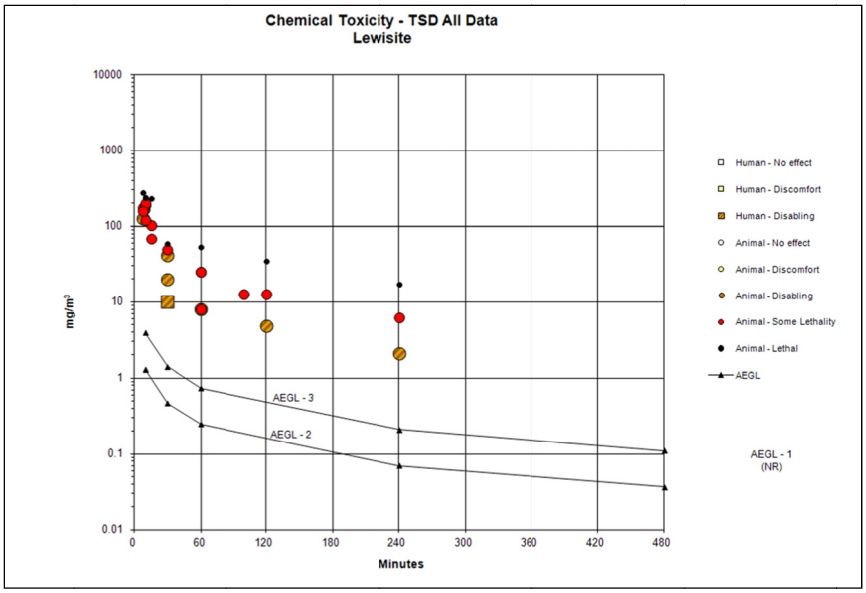

FIGURE D-1 Category plot of animal and human toxicity data and AEGL values for lewisite.

TABLE D-1 Data Used in the Category Plot for Lewisite

Source	Species	Sex	No. of Exposures	mg/m^3	Minutes	Category	Comments
AEGL-1				NR	10	AEGL	
AEGL-1				NR	30	AEGL	
AEGL-1				NR	60	AEGL	
AEGL-1				NR	240	AEGL	
AEGL-1				NR	480	AEGL	
AEGL-2				1.3	10	AEGL	
AEGL-2				0.47	30	AEGL	
AEGL-2				0.25	60	AEGL	
AEGL-2				0.070	240	AEGL	
AEGL-2				0.037	480	AEGL	
AEGL-3				3.9	10	AEGL	
AEGL-3				1.4	30	AEGL	
AEGL-3				0.74	60	AEGL	
AEGL-3				0.21	240	AEGL	
AEGL-3				0.11	480	AEGL	
Franke 1968	Human		1	10	30	2	Severe intoxication, incapacitation
Silver and McGrath 1943	Mouse	Male	1	240	10	3	Mortality (10/10)
Armstrong 1923	Dog		1	126	7.5	2	Mortality (0/2)
	Dog		1	176	7.5	SL	Mortality (7/12)
	Dog		1	274	7.5	3	Mortality (4/4)
	Dog		1	68.7	15	SL	Mortality (1/4)
	Dog		1	102	15	SL	Mortality (2/3)
	Dog		1	233	15	3	Mortality (3/3)

	Dog	1	41.5	30	2	Mortality (0/2)
	Dog	1	58.6	30	3	Mortality (4/4)
	Dog	1	8	60	2	Mortality (0/5)
	Dog	1	25	60	SL	Mortality (5/7)
	Dog	1	53	60	3	Mortality (1/1)
	Dog	1	4.8	120	2	Mortality (0/4)
	Dog	1	12.5	120	SL	Mortality (2/3)
	Dog	1	34.5	120	3	Mortality (3/3)
	Dog	1	2.1	240	2	Mortality (0/3)
	Dog	1	6.2	240	SL	Mortality (5/9)
	Dog	1	16.9	240	3	Mortality (2/2)
Harrison et al. 1946	Dog	1	50	30	SL	
	Dog	1	121	10	SL	
Gates et al. 1946	Dog	1	20	30	2	Ocular lesions
Silver and McGrath 1943	Mouse	1	240	10	3	100% mortality (10/10)
Gates et al. 1946	Rat	1	166	9	SL	LC_{50}
Silver and McGrath 1943	Mouse	1	190	10	SL	LC_{50}
Silver and McGrath 1943	Mouse	1	200	10	SL	LC_{50}
Silver and McGrath 1943	Mouse	1	240	10	3	100% mortality (10/10)
Gates et al. 1946	Guinea pig	1	8	60	SL	LC_{50}
Gates et al. 1946	Rabbit	1	160	7.5	SL	LC_{50}
Gates et al. 1946	Rabbit	1	25	60	SL	LC_{50}
Gates et al. 1946	Goat	1	12.5	100	SL	LC_{50}

For category: 0 = no effect, 1 = discomfort, 2 = disabling, 3 = lethal; SL = some lethality.