ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

LEWISITE L-1 (CAS Reg. No. 541-25-3)
$ClCH=CHAsCl_2$

LEWISITE L-2 (CAS Reg. No. 40334-69-8)
$(ClCH=CH)_2$ AsCl

LEWISITE L-3 (CAS Reg. No. 40334-70-1)
$(ClCH=CH)_3As$

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 to 8 hours. Three levels — AEGL-1, AEGL-2 and AEGL-3 — are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) 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, non-sensory 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 levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory 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.

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SUMMARY

Because of the nature of the chemicals under review, military literature is a major source of the relevant toxicity data. Consequently, much of the data sources possess "limited distribution", which is a separate issue from "classification". For various reasons, sources may possess 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 the technical support document.

Lewisite-1 (L-1; 2-chlorovinyldichloroarsine) 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 circulatory failure due to fluid loss and arrythmia. Death that occurs within 24 hours of exposure is likely due to pulmonary damage (Lindberg et al., 1997).

Lewisite-2 (L-2; *bis*-(2-chlorovinyl)chloroarsine) and lewisite-3 (L-3; *tris*-(2-chlorovinyl)arsine) are co-products concurrently formed with lewisite-1(Trammel, 1992). Lewisite-1 yield is >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 smaller quantities and comparatively low volatility, will be less toxicologically significant than L-1.

Appropriate data were not available for derivation of AEGL-1 values for lewisite-1 (L-1), lewisite-2 (L-2), or lewisite-3 (L-3). Odor cannot be used as a warning for potential exposure. For lewisite-1, the odor threshold is reported to be between 14-23 mg/m^3, a value above highly irritating concentrations and above proposed AEGL-2 and AEGL-3 values. Therefore, AEGL-1 values are not recommended.

No inhalation data consistent with the definition of AEGL-2 with both concentration and duration parameters were available. Therefore, the AEGL-2 values for lewisite-1, were based upon a 3-fold reduction in the AEGL-3 values for L-1; this is considered an estimate of a threshold for irreversible effects and is considered appropriate given the extremely steep concentration-response curve (10-min mouse LC_{50} = 200 mg/m^3, 10-min 100% mortality in mice = 240 mg/m^3; no mortality in dogs at 126 mg/m^3 for 7.5-min, LC_{50} = 176 mg/m^3). Additionally, a modifying factor of 2 was applied to account for the sparse data set for effects defined by AEGL-2.

Appropriate chemical-specific data were not available for derivation of AEGL-2 values for lewisite-2 (L-2) or lewisite-3 (L-3). However, L-2 and L-3 exist as a small fraction of total lewisite and have comparatively low volatilites. Because of these chemical characteristics, AEGL-2 values for L-1 were adopted as AEGL-2 values for the mixture of L-1, L-2, and L-3.

The AEGL-3 values for lewisite-1 (L-1) were based on dog lethality data (Armstrong, 1923). Points-of-departure were the calculated LC_{01} values: 38.7 mg/m^3 for the 10-minute value, 14.0 mg/m^3 for the 30-minute value, 7.4 mg/m^3 for the 1-hr value, 2.1 mg/m^3 for the 4-hour value, and 1.1 mg/m^3 for the 8-hr AEGL-3 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 the fact that data suggest little species variability with regard to lethality from inhalation exposure to lewisite; c x 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. The intraspecies uncertainty factor of 3 is supported by the steep concentration-response curve with regard to lethality, which implies limited intraspecies variation (10-min mouse LC_{50} = 200 mg/m^3, 10-min 100% mortality in mice = 240 mg/m^3; no mortality in dogs at 126 mg/m^3 for 7.5-min, LC_{50} = 176 mg/m^3). Thus, the total uncertainty factor is 10.

Appropriate chemical-specific data were not available for derivation of AEGL-3 values for lewisite-2 (L-2) or lewisite-3 (L-3). However, L-2 and L-3 exist as a small fraction of total lewisite and have comparatively low volatilites. 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. The derived AEGL values for these lewisite compounds are shown in the following table.

Summary of AEGL Values for Lewisite-1 and the Mixture of Lewisite-1, Lewisite-2, and Lewisite-3

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data for derivation of AEGL-1 values
AEGL-2 (Disabling)	0.65 mg/m^3	0.23 mg/m^3	0.12 mg/m^3	0.035 mg/m^3	0.018 mg/m^3	⅓ of AEGL-3 values
AEGL-3 (Lethal)	3.9 mg/m^3	1.4 mg/m^3	0.74 mg/m^3	0.21 mg/m^3	0.11 mg/m^3	Dog LC_{01} values (Armstrong, 1923)

NR = Not recommended.

[a] Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

References

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.Edgewood Arsenal, Aberdeen Proving Ground, MD. August 13, 1923. ADB954935. Unclassified Report/ Limited Distribution.

Lindberg, G., Runn, P, Winter, S., and Fallman, A. 1997. Basic information on lewisite- a chemical warfare agent with effects similar to mustard gas. Defense Research Establishment, Division of NBC Defense, S-901 82 UMEA, Sweden.

Trammel, G.L. 1992. Toxicodynamics of organoarsenical chemical warfare agents. In: Somani, S.M., Ed. Chemical Warfare Agents. Academic Press, Inc.: New York, pp. 255-270.

1. INTRODUCTION

Lewisite (2-chlorovinyldichloroarsine; CAS Registry No. 541-25-3) 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. 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 due to fluid loss and arrythmia. Death that occurs within 24 hours 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 highly irritating at low concentrations (estimated 6-8 mg/m^3) that troops would be warned of the presence of gas, even before detection of 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 or L-1) is formed by the reaction of acetylene with arsenic trichloride using aluminum trichloride as a catalyst. Arsenic trichloride, lewisite-2 [$(ClCH=CH)_2$ AsCl] and lewisite-3 [$(ClCH=CH)_3As$] are co-products concurrently formed with lewisite-1 ($ClCH=CHAsCl_2$) (Trammel, 1992). Lewisite-1 yield is >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 and arsenic acid. Toxicological data on arsenic trichloride are very limited; however, qualitatively, effects are similar to those of L-1 (corrosiveness, damage to skin, eyes, and mucous membranes). Quantitatively with regard to lethality, arsenic trichloride appears to be approximately 2 to 3 times less toxic than L-1 (LCt_{50} for arsenic trichloride: 4000-5000 $mg \cdot min/m^3$; LCt_{50} for L-1:1200-1500 $mg \cdot min/m^3$) (Flury, 1921). L-2 and L-3 will be less significant because of 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). Because of these chemical characteristics, AEGL values for L-1 should be protective for L-2, L-3, and the mixture.

A summary of nomenclature for the chemicals of concern is presented in Table 1 and chemical/physical data are summarized in Table 2.

TABLE 1. Nomenclature of Lewisite Agents

Common name	Military Designator	Chemical name/Synonyms	CAS Registry No.
Lewisite-1	L (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

NDRC (1946); Cookson and Nottingham (1969); USACHPPM (1996)

TABLE 2. Chemical And Physical Data for Lewisite Compounds

Parameter	Value	Reference
Molecular formula		
Lewisite-1 (L or L-1)	$ClCH=CHAsCl_2$	NRDC, 1946
Lewisite-2 (L -2)	$(ClCH=CH)_2$ AsCl	NRDC, 1946
Lewisite-3 (L -3)	$(ClCH=CH)_3As$	NRDC, 1946
Molecular weight		
Lewisite-1 (L or L-1)	207.32	
Lewisite-2 (L -2)	233.32	
Lewisite-3 (L -3)	259.35	
Physical state	oily liquid for all forms	Lindberg et al., 1997
Lewisite-1 (L or L-1)		
Lewisite-2 (L -2)		
Lewisite-3 (L -3)		
Color	Mixture: amber to brown	Munro et al., 1999
Lewisite-1 (L or L-1)	colorless (pure)	Munro et al., 1999
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 @ 25EC; 0.22 mm Hg @ 20EC	USACHHPM, 1996
Lewisite-2 (L -2)	-	
Lewisite-3 (L -3)	-	
Specific gravity (water = 1)		
Lewisite-1 (L or L-1)	1.888 @ 20EC	HSDB, 2004
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)	-	
Melting point		
Lewisite-1 (L or L-1)	0.1EC	HSDB, 2004
Lewisite-2 (L -2)	-	
Lewisite-3 (L -3)	-	
Boiling point		
Lewisite-1 (L or L-1)	190EC	Trammel, 1992
Lewisite-2 (L -2)	-	
Lewisite-3 (L -3)	-	
Flammability limits		
Lewisite-1 (L or L-1)	-	
Lewisite-2 (L -2)	-	
Lewisite-3 (L -3)	-	

Conversion factors		
Lewisite-1 (L or L-1)	NA- aerosol atmosphere	
Lewisite-2 (L -2)	NA- aerosol atmosphere	
Lewisite-3 (L -3)	NA- aerosol atmosphere	
Volatility		
Lewisite-1 (L or L-1)	0.77- 2.5 g/m^3 at 20EC	Lindberg et al., 1997
Lewisite-2 (L -2)	0.043 g/m^3 at 20EC	Lindberg et al., 1997
Lewisite-3 (L -3)	-	-

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Gates et al. (1946) estimated (based on animal data in Table 8) that the inhalation LC_{50} for lewisite vapor in humans may be 120 mg/m3 for 10 minutes and 50 mg/m^3 for 30 minutes. Gates et al. (1946) also estimated an LC_{50} of 3300 mg/m^3 for 30 minutes for lewisite vapor absorption through the bare skin. 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 >40 mg/kg was also estimated by Gates et al. (1946) based on data in Table 9.

2.2. Nonlethal Toxicity

2.2.1. Individual Studies

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

Inhalation of 10 mg/m^3 lewisite for 30 minutes reportedly results in severe intoxication and incapacitation that lasts for several weeks, and inhalation of 10 mg/m^3 for 15 minutes causes inflammation of the eyes and swelling of the eyelids (Ottinger et al., 1973). No further details were available.

In order to select "men of average resistance" for a dermal vapor 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 (Eldridge, 1923). 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. Out of the 52 men, 14 were found to be resistant, and 3 were found to be sensitive. Further dermal liquid tests were done on the sensitive and resistant subjects ; these tests showed that the sensitive subjects showed no effect when treated with a 0.01% lewisite solution, and the resistant subjects showed blistering with a 5% solution. Dermal effects included blanching or graying of the skin, followed by severe erythema within 15-30 minutes. Vesication, accompanied by some edema, occurred within 12 hours, and within less that 24-hours, a raised area of redness measuring 2 x 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 x 3.5 inches in diameter, and fluid seeped from the blister. The smaller vesicles also ruptured as the severity of burns continued to increase up to the forth day. No change was noted from days 4 to 7, and from day seven onward, improvement was noted, with complete healing by the end of week 4. The men described a "stinging sensation" that lasted for two minutes and occurred within 2.5 minutes of exposure. No further sensation was noted until approximately 20 minutes later, when the stinging sensation was again reported; this stinging lasted for approximately 2 hours. Five hours later, a "continuous feeling of discomfort" was reported; this burning lasted until the blister ruptured 22.5 hours after lewisite administration. 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 nine, all pain had resolved.

The arms of groups of 1 to 7 men (from the 35 male volunteers of average sensitivity described above) were exposed to varying concentrations of lewisite vapor for periods ranging from 10-minutes to three hours in order to determine the concentration of lewisite in air necessary 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. The 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. The 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 to 48 hours, and healing was complete in six days to two weeks. The men reported that the healed skin remained sensitive for several weeks after the healing was complete. Data are summarized in Table 3.

Table 3. Average Lewisite Concentration Causing Blistering on Human Forearm Skin*

Length of Exposure (min)	Average Blistering Concentration (mg/m^3)
5	2090
10	1040
30	340
60	150
120	62
180	26.2

*Eldridge, 1923

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 0.8 to 1.3 mg arsenic/mL, equivalent to 2.5 to 4.0 mg of original lewisite

2.2.2. Case Report

A male worker at Pine Bluff Arsenal experienced lewisite burns over 20% of the body surface, the majority of burns being on the legs. He showed an anemia 10 to 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/Reproductive Effects

Human developmental/reproductive toxicity data concerning lewisite were not located.

2.4. Genotoxicity

Human genotoxicity toxicity data concerning lewisite were not located.

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 in 1948, was diagnosed as malignant. 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 (respiratory tract: 14%; digestive tract: 9.6%) 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 the workers who were 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 noted 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

Lewisite vapor and liquid causes immediate irritation, burning, and corrosive damage to eyes and exposed skin, and vapor may also effect the upper airway and lungs. Human exposure data are dated and studies are, in many cases, not well described. No information concerning developmental/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 numerous chemicals. Selected human vapor (inhalation) data are summarized in Table 4, and selected human liquid exposure data are summarized in Table 5.

Table 4. Summary of Data for Humans Exposed to Lewisite Vapor

Effect	Exposure duration (min)	Concentration (mg/m^3)	C x T ($mg \cdot min/m^3$)	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., 1964
Irritation- highly irritating	threshold	6-8	-	Gates et al., 1946
Irritation- severe	threshold	10-30	-	Cherkes et al., 1964
Eye inflammation/swelling	15	10	150	Ottinger et al., 1973
Incapacitation	30	10	300	Ottinger et al., 1973
Skin lesions (Skin exposure)	5 10 30 60 120 180	2090 1040 340 150 62 26.2	10,450 10,400 10,200 9000 7440 4716	Eldridge, 1923
Estimated Inhalation LC_{50}	10	120	1200	Gates et al., 1946
Estimated Inhalation LC_{50}	30	50	1500	Gates et al., 1946
Estimated Percutaneous LC_{50}	30	3300	100,000	Gates et al., 1946

Table 5. Summary of Skin Effects for Humans Exposed to Lewisite Liquid

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

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 report. These data are summarized in Table 7. Oral, dermal, subcutaneous, and intravenous LD_{50} values were also identified in a variety of species. These data are summarized in Table 8.

3.1.1. Rats

A 9-minute 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.

Olajos et al. (1998) exposed groups of 6 male and 6 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) and *t*-butanol (vehicle) and lewisite. Exposures were to 6000, 12,000, 18,000, or 24,000 ppm CAIS waste stream or to 24,000 ppm chloroform/butanol solvent for 1 hour. The concentration of lewisite in the test atmospheres was 0, 0.17, 0.67, 0.96, or 0.31 mg/m^3, respectively, for the vehicle control, 6000, 12,000, 18,000, or 24,000 ppm CAIS test groups. Toxic signs were consistent with chloroform/butanol and were noted in 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 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 minutes. Animals were exposed in a 386 liter continuous flow chamber. The lewisite was vaporized by passing 20-30 liters of air per minute through the 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 had reached equilibrium (approximately 10 minutes). Ten-minute mouse LC_{50} values of 190 and 200 mg/m^3 were determined for the cis- and trans-isomers, respectively. All mice exposed to 240 mg/m^3 lewisite for 10 minutes died

3.1.3. Dogs

In an acute inhalation toxicity study, Armstrong (1923) exposed groups of dogs (sex not reported) to varying concentrations of lewisite (purity 99%) for 7.5, 15, 30, 60, 120, or 240 minutes. The dogs were exposed in an air-tight glass chamber 74.9 x 69.6 x 71.2 cm with a sliding front and entrance and exit ports for the air-lewisite mixture. The affluent air was supplied by an air pump and was passed through a series of drying bottles. The dried air was then passed through a flowmeter in order 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) in order to obtain the desired chamber concentrations. The concentration of lewisite in the exposure chamber was determined analytically from samples aspirated from the chamber during exposures.

Clinical signs in dogs exposed for 7.5 or 15-minutes included detection of lewisite within 30 seconds, as evidenced by continual eye blinking, followed by excessive nasal secretion, lacrymation, and sneezing (Armstrong, 1923). In some cases, ocular inflammation was noted before the end of exposure. Vomiting was also noted before the end of the 7.5- and 15-min exposures. In dogs exposed for 30-minutes or longer, frequent retching, vomiting, extreme salivation, labored breathing, inflammation of the entire respiratory tract were noted, in addition to signs noted for shorter exposure durations. At necropsy in animals dying from lewisite exposure, a thick membrane in the nostrils, larynx, and trachea, accompanied by purulent bronchitis, hemorrhage, pneumonia, edema, and congestion of the lungs were noted. Liver and kidney congestion were also noted. Generally, all clinical signs and pathology increased in severity with increasing exposure duration and concentration. Calculated LC_{01} values for AEGL time points are: 38.7 mg/m^3 for 10-minutes, 14.0 mg/m^3 for 30-minutes, 7.4 mg/m^3 for 1-hr, 2.1 mg/m^3 for 4-hours, and 1.1 mg/m^3 for 8-hours (ten berge et al., 1986). Data are summarized in Table 6.

Table 6. Dogs Exposed to Lewisite for 7.5 to 240 Minutes (Armstrong, 1923)

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

Harrison et al.(1946) exposed dogs to 50 mg/m^3 lewisite for 30 minutes (8 dogs), 61 mg/m^3 for 30-minutes (9 dogs), or 121 mg/m^3 for 10 minutes(5 dogs). Clinical signs included vomiting, urination, defecation, salivation, and respiratory distress; 80% of the dogs died 3 to 48 hours 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-minute LC_{50} of 160 mg/m^3 and a 60-minute LC_{50} of 25 mg/m^3 were 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 reported for rabbits.

3.1.5. Guinea Pigs

A 9-minute LC_{50} of 111 mg/m^3 and a 60-minute 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 reported for guinea pigs.

3.1.6. Goats

A 100-minute LC_{50} of 12.5 mg/m^3 was reported for goats (Gates et al., 1946).

A dermal LD_{50} of 15 mg/kg was reported for goats (Cameron et al., 1946).

3.2. Nonlethal Toxicity

3.2.1. Rats

No treatment-related deaths were noted in rats exposed to 6000 or 12,000 CAIS waste stream containing chloroform (vehicle) and *t*-butanol (vehicle) and lewisite. The concentration of lewisite in these test atmospheres was 0.17 mg/m^3 for the 6000 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

Eye lesions, but no deaths, were reported in dogs exposed to 20 mg/m^3 lewisite for 30 minutes (Gates et al., 1946).

3.2.3. Rabbits

Eye lesions, but no deaths, were reported in rabbits exposed to 1 mg/m^3 lewisite for 30 minutes (Gates et al., 1946).

3.2.4. Pigs

Lindsay et al. (2004) dermally exposed three large white pigs to 0.3 mg/cm^2 lewisite. While under anaesthesia, an area of dorsal skin (35 cm x 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. The animals were monitored in their pens for 24 hours and were then scarificed. 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/Reproductive Effects

Hackett et al. (1987) administered lewisite to CD rats and New Zealand white rabbits by gastric intubation. Rats were dosed daily from days 6 through 15 of gestation with 0, 0.5, 1.0, 2.0, or 2.5 mg/kg lewisite in a range-finding study and with 0, 0.5, 1.0, and 1.5 mg/kg in the teratology study. Rabbits were dosed from gestation days 6 through 19 with 0, 0.5, 1.0, 1.5, and 2.0 mg/kg in a range-finding study and 0, 0.07, 0.2, and 0.6 mg/kg in the 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 noted. In rabbits, maternal mortality was noted and 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, and at 0.6 mg/kg (highest teratology study dose) 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 concentrations of 0, 0.10, 0.25, or 0.60 mg/kg/day, 5 days/week prior to mating, during mating, and after mating until the birth of offspring. Dams continued to receive lewisite during lactation. After weaning, male and female offspring were selected to continue on the study and similarly received 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 did induce 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

Animal data are limited but suggest that lewisite is highly irritating and corrosive, causing both dermal and ocular lesions by liquid or vapor contact. Inhalation LC_{50} values were identified in several species, and the weight-of-evidence of these data suggest limited interspecies variability (C x T is relatively constant across species). There is no evidence that lewisite is a reproductive or developmental toxicant in rats or rabbit in the absence of maternal toxicity. Genotoxicity assay results were generally negative, the only positive being in chromosome aberrations in CHO cells. No information concerning carcinogenicity in animals was located.

Table 7. Summary of Inhalation Data for Animal Species Exposed to Lewisite (L)

Species	Exposure duration (min)	Concentration (mg/m^3)	C x T ($mg \cdot min/m^3$)	Effect	Reference
Lethal Effects					
Rat	9	166	1494	LC_{50}	Gates et al., 1946
Mouse	10	190	1900	LC_{50}	Silver and McGrath, 1943
Mouse	10	200	2000	LC_{50}	Silver and McGrath, 1943
Mouse	10	240	2400	100% mortality (10/10)	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	1200	LC_{50}	Gates et al., 1946
Rabbit	60	25	1500	LC_{50}	Gates et al., 1946
Dog	7.5	176	1320	LC_{50}	Armstrong, 1923
Dog	15	100	1500	LC_{50}	Armstrong, 1923
Dog	30	48	1440	LC_{50}	Armstrong, 1923
Dog	60	25.4	1542	LC_{50}	Armstrong, 1923
Dog	120	11.8	1416	LC_{50}	Armstrong, 1923
Dog	240	6.24	1584	LC_{50}	Armstrong, 1923
Goat	100	12.5	1250	LC_{50}	Gates et al., 1946
Non-lethal Effects					
Rabbit	30	1	30	Eye lesions, no death	Gates et al., 1946
Dog	30	20	600	Eye lesions, no death	Gates et al., 1946

Table 8. Summary of Acute Oral, Dermal, Subcutaneous, and IV Data for Animal Species 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

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Lewisite is readily absorbed through the mucous membranes, and because of its lipophilicity, is also readily absorbed through the skin (HSDB, 2004).

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 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, and lymphatic systems may be the result of a disturbance of osmotic equilibrium (Goldman and Dacre, 1989).

The vesicant and other toxicological effects of lewisite are ultimately due to the ability to combine with thiol groups necessary for activity of a number of enzyme systems (Goldman and Dacre, 1989). The interaction with enzyme sulfhydryl groups may lead to inhibition of enzyme function by forming stable cyclic structures with arsenic. This is as a result of the arsenic reacting with the sulfhydryl groups of organic compounds, such as those present in dihydrolipoic acid and in reduced keratin (Young, 1999). Dihydrolipoic acid is a dithiol cofactor in several enzyme systems required for cellular respiration, and lewisite combines with dihydrolipoic acid to form stable six member ring structures. It is these ring structures that inactivate the enzymes. The ultimate result of these thiol interactions is energy depletion which results in cell death (Young, 1999).

4.3. Structure-Activity Relationships

Toxicological data on arsenic trichloride, lewisite-2 and lewisite-3, co-products concurrently formed with lewisite-1, are limited. However, qualitatively, effects are similar to those of L-1 (corrosiveness, damage to skin, eyes, and mucous membranes). Quantitatively with regard to lethality, arsenic trichloride appears to be approximately 2 to 3 times less toxic than L-1 (LCt_{50} for arsenic trichloride: 4000-5000 mg·min/m^3 ; LCt_{50} for L-1:1200-1500 mg·min/m^3) (Flury, 1921), and 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-minute 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 lewisite-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, and at 5 minutes after injection, rapid panting was noted, followed by prostration and death within 4 hours. By 24-hours after injection, surviving rabbits appeared normal. The LD_{50} for sodium arsenite was 7.6 mg/kg, with hypoactivity noted 20 minutes after injection. On the basis of trivalent arsenic content, lewisite was 6.5 times more toxic than the inorganic sodium arsenite, and the clinical signs and times of death and recovery differed between the compounds. Severe pulmonary damage was noted (gross and histopathological) in the lewisite-injected animals, but not in the sodium arsenite-injected animals. Also, arsenic levels in liver, kidney, brain, stomach, duodenum, spleen, and bladder were much greater in sodium arsenate-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 8 show that the concentration x 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, as would be expected for such a corrosive substance.

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). When dog (the most robust data set) LC_{50} data (from Table 8) ranging from 7.5 minutes to 4-hours exposure duration are utilized, an 'n' value of 1.03 is derived (Figure 1).

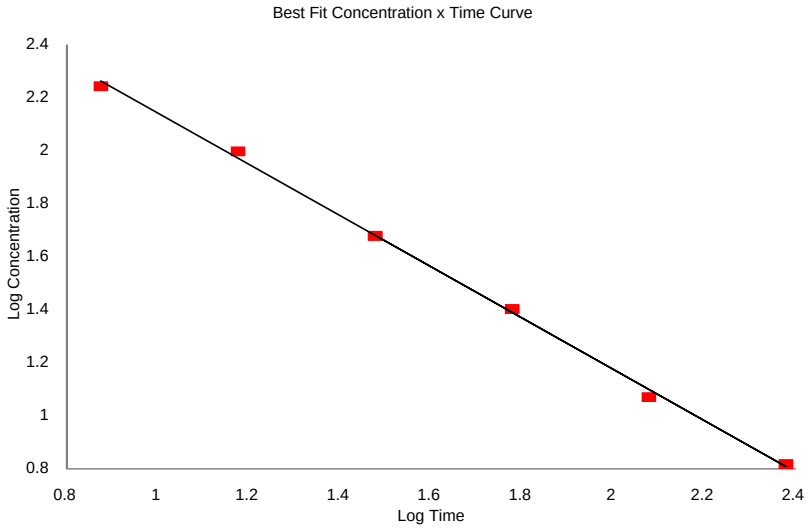

Figure 1. Dog LC_{50} data-Lewisite (Armstrong, 1923)

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 (L-1), lewisite-2 (L-2), or lewisite-3 (L-3).

5.2. Animal Data Relevant to AEGL-1

No animal data were relevant for establishing AEGL-1 values for lewisite (L-1), lewisite-2 (L-2), or lewisite-3 (L-3) .

5.3. Derivation of AEGL-1

Appropriate data were not available for derivation of AEGL-1 values for lewisite-1 (L-1), lewisite-2 (L-2), or lewisite-3 (L-3). Odor cannot be used as a warning for potential exposure. The odor threshold for L-1 is reported to be between 14-23 mg/m^3, a value above highly irritating concentrations and above proposed AEGL-2 and AEGL-3 values. Therefore, AEGL-1 values are not recommended.

TABLE 9. AEGL-1 Values For Lewisite-1 (L-1), Lewisite-2 (L-2), and Lewisite-3 (L-3)

	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1(Nondisabling)	NR*	NR	NR	NR	NR

[a] NR: Not recommended. Numeric values for AEGL-1 are not recommended because data are not available. The fact that AEGL-1 values are not recommended does not imply that concentrations below AEGL-2 are 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 (L-1), lewisite-2 (L-2), or lewisite-3 (L-3).

6.2. Animal Data Relevant to AEGL-2

No animal data were available for establishing AEGL-2 values for lewisite (L-1), lewisite-2 (L-2), or lewisite-3 (L-3).

6.3. Derivation of AEGL-2

No inhalation data consistent with the definition of AEGL-2 with both concentration and duration parameters were available. Therefore, the AEGL-2 values for lewisite-1, were based upon a 3-fold reduction in the AEGL-3 values for L-1; this is considered an estimate of a threshold for irreversible effects and is considered appropriate given the extremely steep concentration-response curve (10-min mouse LC_{50} = 200 mg/m^3, 10-min 100% mortality in mice = 240 mg/m^3;

no mortality in dogs at 126 mg/m^3 for 7.5-min, LC_{50} = 176 mg/m^3). Additionally, a modifying factor of 2 was applied to account for the sparse data set for effects defined by AEGL-2.

Appropriate chemical-specific data were not available for derivation of AEGL-2 values for lewisite-2 (L-2) or lewisite-3 (L-3). However, L-2 and L-3 exist as a small fraction of total lewisite and have comparatively low volatilites. Because of these chemical characteristics, AEGL-2 values for L-1 were adopted as AEGL-2 values for the mixture of L-1, L-2, and L-3.

The AEGL-2 values for Lewisite are presented in Table 10, and the calculations for these AEGL-2 values are presented in Appendix A.

TABLE 10. AEGL-2 Values For Lewisite-1 and the Mixture of Lewisite-1, Lewisite-2, and Lewisite-3

Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	0.65 mg/m^3	0.23 mg/m^3	0.12 mg/m^3	0.035 mg/m^3	0.018 mg/m^3

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

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

7.2. Animal Data Relevant to AEGL-3

A 9-min rat LC_{50} of 166 mg/m^3 was reported by Gates et al. (1946). Gates et al. (1946) also reported a 9-min LC_{50} of 111 mg/m^3 and a 60-min LC_{50} of 8 mg/m^3 in guinea pigs; a 7.5-min LC_{50} of 160 mg/m^3 and a 60-min LC_{50} of 25 mg/m^3 in rabbits; and a 100-min LC_{50} of 12.5 mg/m^3 in goats. Silver and McGrath (1943) reported ten-minute mouse LC_{50} values 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) are well-conducted, well-described studies. The data of Gates et al. (1946) are not well-described.

7.3. Derivation of AEGL-3

The dog lethality study (Armstrong, 1923) will be used as the basis of AEGL-3 values. Points-of-departure will be the calculated LC_{01} values: 38.7 mg/m^3 for the 10-minute value, 14.0 mg/m^3 for the 30-minute value, 7.4 mg/m^3 for the 1-hr value, 2.1 mg/m^3 for the 4-hour value, and 1.1 mg/m^3 for the 8-hr AEGL-3 value. The LC_{01} values are considered estimates of lethality thresholds. Interspecies and intraspecies uncertainty factors of 3 each will be applied. The interspecies uncertainty factor of 3 is supported by the fact that data suggest little species variability with regard to lethality from inhalation exposure to lewisite; c x 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. The intraspecies uncertainty factor of 3 is supported by the steep concentration-response curve with regard to lethality, which implies limited intraspecies variation (10-min mouse LC_{50} = 200 mg/m^3, 10-min 100% mortality in mice = 240 mg/m^3; no mortality in dogs at 126 mg/m^3 for 7.5-min, LC_{50} = 176 mg/m^3). Thus, the total uncertainty factor is 10.

Appropriate chemical-specific data were not available for derivation of AEGL-3 values for lewisite-2 (L-2) or lewisite-3 (L-3). However, L-2 and L-3 exist as a small fraction of total lewisite and have comparatively low volatilites. Because of these chemical characteristics, AEGL-3 values for L-1 will be adopted as AEGL-3 values for the mixture of L-1, L-2, and L-3. The AEGL-3 values for Lewisite are presented in Table 11, and the calculations for these AEGL-3 values are presented in Appendix A.

TABLE 11. AEGL-3 Values For Lewisite-1 (L-1) and the Mixture of Lewisite-1, Lewisite-2, and Lewisite-3

Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	3.9 mg/m^3	1.4 mg/m^3	0.74 mg/m^3	0.21 mg/m^3	0.11 mg/m^3

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

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

TABLE 12. Summary/Relationship of AEGL Values

Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1(Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	0.65 mg/m^3	0.23 mg/m^3	0.12 mg/m^3	0.035 mg/m^3	0.018 mg/m^3
AEGL-3 (Lethal)	3.9 mg/m^3	1.4 mg/m^3	0.74 mg/m^3	0.21 mg/m^3	0.11 mg/m^3

NR: Not recommended. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

8.2. Comparisons with Other Standards and Guidelines

No other extant standards were located for lewisite-1, lewisite-2, or lewisite-3.

8.3. Data Adequacy and Research Needs

Human data were not sufficient for deriving AEGL values. Most animal studies are dated; however, mouse and dog lethality studies are well conducted and are not inconsistent with the limited lethality data in other species. Data were available only for lewisite-1 (L-1); however, given the low volatility and small volume of lewisite-2 and lewisite-3 in total lewisite, AEGL-values derived for lewisite-1 should be protective.

9. REFERENCES

Because of the nature of the chemicals under review, military literature is a major source of the relevant toxicity data.. Consequently, much of the data sources possess "limited distribution", which is a separate issue from "classification". For various reasons, sources may possess 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 the technical support document.

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APPENDIX A: Derivation of AEGL Values for Lewisite Compounds

Derivation of AEGL-1 for Lewisite Compounds

LEWISITE-1 (L-1) (2-chlorovinyldichloroarsine):

Data were insufficient for derivation of AEGL-1 values for L-1. AEGL-1 values for L-1 are not recommended.

LEWISITE-2 (L-2) (*bis*-(2-chlorovinyl)chloroarsine)

Data were insufficient for derivation of AEGL-1 values for L-2. AEGL-1 values for L-2 are not recommended.

LEWISITE-3 (L-3) (*tris*-(2-chlorovinyl)arsine)

Data were insufficient for derivation of AEGL-1 values for L-3. AEGL-1 values for L-3 are not recommended.

Derivation of AEGL-2 for Lewisite Compounds

Key study: Armstrong, 1923

Toxicity endpoint: ⅓ of the AEGL-3 values

Modifying Factor: 2: Sparse data set for AEGL-2 effects

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

10-min AEGL-2: 10-min AEGL-2 = 3.9 ÷ 3 ÷ 2 = 0.65 mg/m^3

30-min AEGL-2: 30-min AEGL-2 = 1.4 ÷ 3 ÷ 2 = 0.23 mg/m^3

1-hr AEGL-2: 1-hr AEGL-2 = 0.74 ÷ 3 ÷ 2 = 0.12 mg/m^3

4-hr AEGL-2: 4-hr AEGL-2 = 0.21 ÷ 3 ÷ 2 = 0.035 mg/m^3

8-hr AEGL-2: 8-hr AEGL-2 = 0.11 ÷ 3 ÷ 2 = 0.018 ppm

Derivation of AEGL-3 for Lewisite Compounds

Key study: Armstrong, 1923

Toxicity endpoint: Calculated LC_{01} values (Estimated lethality thresholds)

10-min:	38.7 mg/m^3
30-min:	14.0 mg/m^3
1-hr:	7.4 mg/m^3
4-hr:	2.1 mg/m^3
8-hr:	1.1 mg/m^3

Uncertainty factors: 3 for interspecies variability
3 for intraspecies variability

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

Calculations:

10-minute AEGL-3 38.7 mg/m^3 ÷ 10 = 0.39 mg/m^3

30-minute AEGL-3 14.0 mg/m^3 ÷ 10 = 1.4 mg/m^3

1-hour AEGL-3 7.4 mg/m^3 ÷ 10 = 0.74 mg/m^3

4-hour AEGL-3 2.1 mg/m^3 ÷ 10 = 0.21 mg/m^3

8-hour AEGL-3 1.1 mg/m^3 ÷ 10 = 0.11 mg/m^3

APPENDIX B: Derivation Summary Tables for Lewisite Compounds

AEGL-1 VALUES FOR LEWISITE-1 (L-1), LEWISITE-2 (L-2), AND LEWISITE-3 (L-3)				
10 minute	**30 minute**	**1 hour**	**4 hour**	**8 hour**
Not Recommended	**Not Recommended**	**Not Recommended**	**Not Recommended**	**Not Recommended**
Key Reference: NA				
Test Species/Strain/Number: NA				
Exposure Route/Concentrations/Durations: NA				
Effects: NA				
Endpoint/Concentration/Rationale: NA				
Uncertainty Factors/Rationale: NA Total uncertainty factor:				
Modifying Factor: NA				
Animal to Human Dosimetric Adjustment: NA				
Time Scaling: NA				
Data Quality and Research Needs: Data were insufficient for derivation of AEGL-1 values for Lewisite-1 (L-1), Lewisite-2 (L-2), and Lewisite-3 (L-3)				

AEGL-2 VALUES FOR LEWISITE-1 AND THE MIXTURE OF LEWISITE-1, LEWISITE-2 AND LEWISITE-3				
10 minute	**30 minute**	**1 hour**	**4 hour**	**8 hour**
0.65 mg/m^3	**0.23 mg/m^3**	**0.12 mg/m^3**	**0.035 mg/m^3**	**0.018 mg/m^3**

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.Edgewood Arsenal, Aberdeen Proving Ground, MD. August 13, 1923. ADB954935. Unclassified Report/ Limited Distribution.

Test Species/Strain/Number: See AEGL-3 Derivation summary table

Exposure Route/Concentrations/Durations: See AEGL-3 Derivation summary table

Effects: See AEGL-3 Derivation summary table

Endpoint/Concentration/Rationale: 3-fold reduction of AEGL-3 values. Considered threshold for the inability to escape. Approach supported by steep concentration-response curve (10-min mouse LC_{50} = 200 mg/m^3, 10-min 100% mortality in mice = 240 mg/m^3; no mortality in dogs at 126 mg/m^3 for 7.5-min, LC_{50} = 176 mg/m^3).

Uncertainty Factors/Rationale: See AEGL-3 Derivation summary table
Total uncertainty factor:
Interspecies:
Intraspecies:

Modifying Factor: 2- Sparse data base for effects defined by AEGL-2

Animal to Human Dosimetric Adjustment: NA

Time Scaling: See AEGL-3 Derivation summary table.

AEGL-3 VALUES FOR LEWISITE-1 AND THE MIXTURE OF LEWISITE-1, LEWISITE-2 AND LEWISITE-3

10 minute	30 minute	1 hour	4 hour	8 hour
3.9 mg/m^3	**1.4 mg/m^3**	**0.74 mg/m^3**	**0.21 mg/m^3**	**0.11 mg/m^3**

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.Edgewood Arsenal, Aberdeen Proving Ground, MD. August 13, 1923. ADB954935. Unclassified Report/ Limited Distribution.

Test Species/Strain/Number: Dog/ strain not reported/1-17 per group

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

Effects:
7.5 minute $LC_{50:}$ 176 mg/m^3
15 minute $LC_{50:}$ 100 mg/m^3
30 minute $LC_{50:}$ 48 mg/m^3
1-hour $LC_{50:}$ 25.7 mg/m^3
2-hour $LC_{50:}$ 11.8 mg/m^3
4-hour $LC_{50:}$ 6.6 mg/m^3

10 minute $LC_{01:}$ 38.7 mg/m^3
30 minute $LC_{01:}$ 14.0 mg/m^3
1-hour $LC_{01:}$ 7.4 mg/m^3
4-hour $LC_{01:}$ 2.1 mg/m^3
8-hour $LC_{01:}$ 1.1 mg/m^3

Endpoint/Concentration/Rationale: Calculated LC_{01} values/ considered a threshold for lethality

Uncertainty Factors/Rationale:
Total uncertainty factor: 10

Interspecies: 3- data suggest little species variability with regard to lethality from inhalation exposure to lewisite-1; c x 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 (10-min mouse LC_{50} = 200 mg/m^3, 10-min 100% mortality in mice = 240 mg/m^3; no mortality in dogs at 126 mg/m^3 for 7.5-min, LC_{50} = 176 mg/m^3)

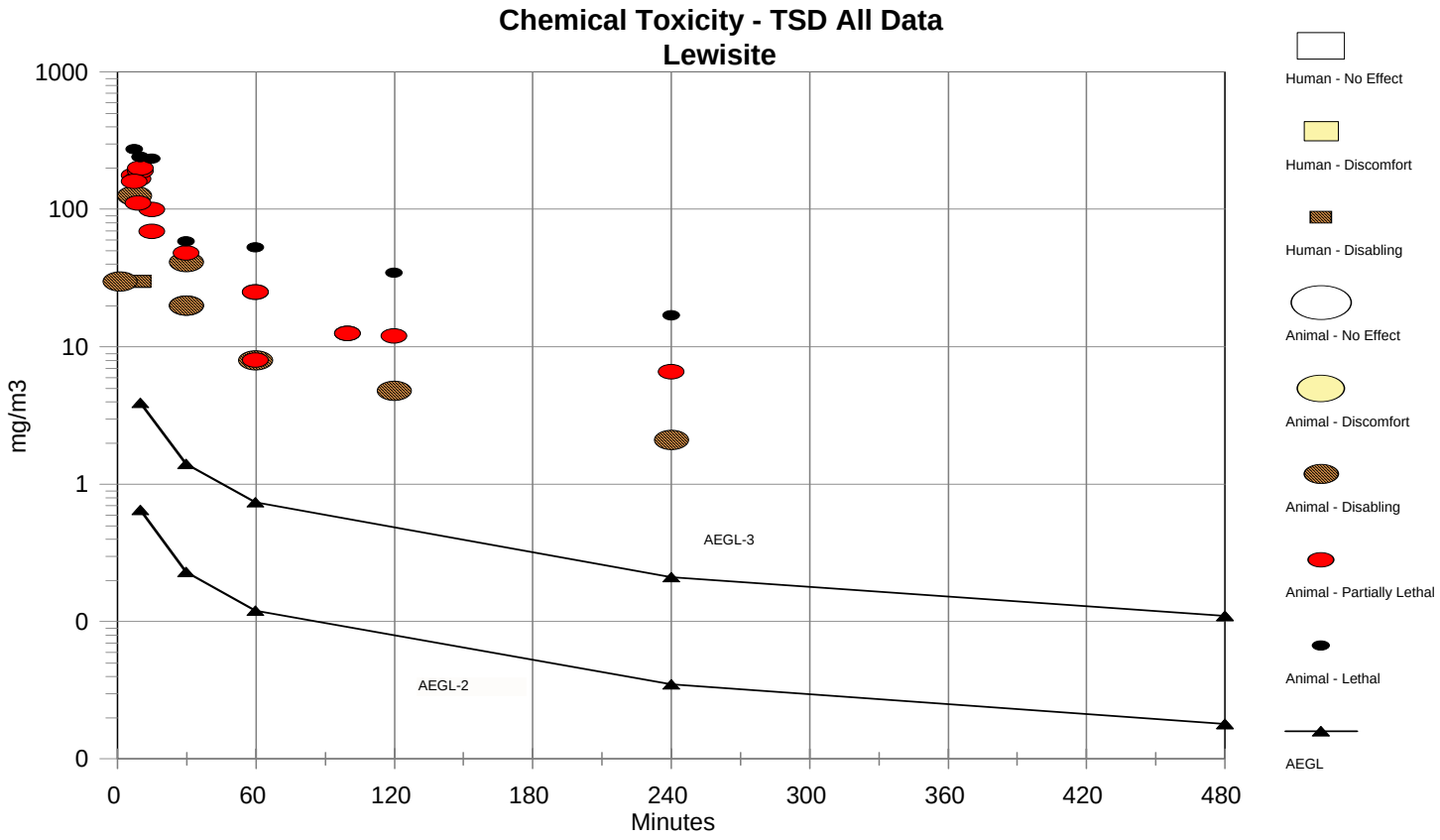
Modifying Factor: NA-

Animal to Human Dosimetric Adjustment: NA

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

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

Appendix C: Category Plot for Lewisite


Chemical Toxicity - TSD All Data
Lewisite
1000
100
10
1
0
0
mg/m3
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Partially Lethal
Animal - Lethal
AEGL

1