Immediately Dangerous to Life or Health (IDLH) Value Profile

for

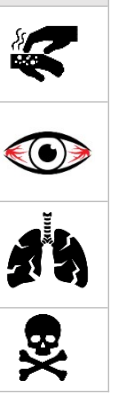
Lewisite

[CAS No. 541-25-3]

Department of Health and Human Services
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

Worker Summary for the IDLH Value for Lewisite

CAS Number: 541-25-3
IDLH Value: 0.03 parts per million (ppm) or 0.25 milligrams per cubic meter (mg/m^3)

General Substance Information	Health Effects of Lewisite	
Other names: • 2-chlorovinyldichloroarsine • Arsonous dichloride [(1E)-2-chloroethenyl] **Lewisite:** • is **not** flammable • is an oily substance that fumes into a colorless gas • can be odorless or smell herbaceous, peppery, or geranium-like depending on purity and humidity • was developed as a blister agent during World War I • is officially decommissioned, but unregistered "small finds" may still be encountered	**Short-term exposure causes:** • stinging, burning pain in eyes, nose and throat • skin contact causes blistering and pain • inhalation causes fluid in lungs (edema) • inhalation or absorption through skin can cause circulatory shock and death • effects become more severe as exposure continues **Long-term:** • injuries can recover if exposure is managed in time	

For more information on Lewisite visit: LINK TO CHEMICAL DOCUMENT

What is an IDLH Value?

NIOSH develops IDLH values for workplace conditions carrying immediate, unacceptable risks. As a safety margin, IDLH values are based on the effects that might occur from 30-minute exposures. Workers should not stay in an IDLH environment longer than absolutely necessary. **EVERY EFFORT SHOULD BE MADE TO EXIT IMMEDIATELY!** Short exposures to highly concentrated chemicals in the air can quickly overwhelm workers and harm worker health. Harmful effects may include:

- Long-term health issues
- Inability to escape the area
- Death

Workers should **never** be exposed to air concentrations that exceed the IDLH value without proper respiratory protection. NIOSH sets IDLH values to make sure that a worker can escape **immediately** from an area before severe injuries occur.

Employers **must require workers** to wear a NIOSH Approved® full facepiece self-contained breathing apparatus (SCBA) or a combination supplied air respirator with SCBA when entering IDLH conditions. These respirators deliver clean air to the worker in dangerous conditions, and these provide the greatest protection.

NIOSH Approved is a certification mark registered in the United States and several international jurisdictions.

Basis for IDLH Value: The IDLH value for lewisite is based on experiments done in the past when the US Army was considering whether to develop lewisite-based weapons. These included a range of experiments done on animals as well as very carefully controlled experiments involving human adults. Because potential injuries from lewisite are so severe, NIOSH sought to base the IDLH value on the lowest level at which human subjects began to experience any kind of symptoms. In the US Army experiments, human subjects were exposed to increasing concentrations of lewisite vapor for very short time periods until subjects reported stinging and burning sensations in the nose and throat. The concentration causing these symptoms was used to estimate the concentration that would cause stinging and burning given a 30-minute exposure, yielding a value of 0.03 ppm. Because the effects of lewisite rapidly become worse as exposure continues, unprotected workers should exit the area to avoid injury even if they do not immediately notice any symptoms.

Foreword

Chemicals are a frequent component of the modern workplace. Occupational exposures to chemicals have long been recognized as having the potential to adversely affect the lives and health of workers. Acute or short-term exposures to high concentrations of some airborne chemicals can quickly overwhelm workers, affecting their ability to escape from the exposure environment. These exposures can result in a range of negative health outcomes—from eye and respiratory tract irritation to severe, irreversible health effects—and in extreme cases, death.

Airborne concentrations of chemicals capable of causing such adverse health effects or impeding escape from high-risk conditions may come from a number of nonroutine workplace situations affecting workers. These may include special work procedures (e.g., in confined spaces), industrial incidents (e.g., chemical spills or explosions), and chemical releases into the community (e.g., during transportation incidents or other uncontrolled-release scenarios).

This technical report presents the scientific basis, toxicologic data, and risk assessment methodology used to derive a health-based immediately dangerous to life or health (IDLH) value for lewisite (CAS No. 541-25-3). The IDLH values are based on the scientific rationale and logic outlined in *Current Intelligence Bulletin (CIB) 66: Derivation of Immediately Dangerous to Life or Health Values* [NIOSH 2013].

This approach is intended to (1) update the scientific basis and risk assessment methodology used to derive IDLH values from quality toxicity and human health effects data and (2) provide transparency behind the rationale and derivation process for IDLH values. The IDLH value for lewisite has been established through the approach outlined in CIB 66. This value is intended to protect against health effects that impair escape, are irreversible, or result in death from exposures of 30 minutes or less.

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Abbreviations

ACGIH®	American Conference of Governmental Industrial Hygienists
AEGLs	acute exposure guideline levels
AIHA®	American Industrial Hygiene Association
Atm	atmosphere (a unit of pressure)
BMC	benchmark concentration
BMD	benchmark dose
BMCL	benchmark concentration lower confidence limit
BMD	benchmark dose
BMR	benchmark response
C	ceiling value
°C	degrees Celsius
CAS®	Chemical Abstracts Service, a division of the American Chemical Society
CIB	Current Intelligence Bulletin
DoA	Department of the Army (US)
DoD	Department of Defense (US)
DoE	Department of Energy (US)
ERPGs™	Emergency Response Planning Guidelines
°F	degrees Fahrenheit
g/mL	grams per milliliter
hr	hour(s)
IFA	Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (Institute for Occupational Safety and Health of the German Social Accident Insurance)
IDLH	immediately dangerous to life or health
LC	lethal concentration
LC_{01}	1% lethal concentration
LC_{50}	median lethal concentration
LC_{LO}	lowest concentration that caused death in humans or animals
LCt_{50}	median lethal concentration per min exposure
LD_{50}	median lethal dose
LD_{LO}	lowest dose that caused death in humans or animals
LEL	lower explosive limit
LOAEL	lowest observed adverse effect level
MCL	median lethal concentration
mg/L	milligram(s) per liter
mg/m^3	milligram(s) per cubic meter
min	minute(s)
mm Hg	millimeter(s) of mercury
NAS	National Academy of Sciences
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
NOAEL	no observed adverse effect level
NRC	National Research Council

OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
ppm	parts per million
RD_{50}	concentration of a chemical in the air that is estimated to cause a 50% decrease in the respiratory rate
REL	recommended exposure limit
RfC	reference concentration
STEL	short-term exposure limit
TEEL	temporary emergency exposure limit
TERA	Toxicology Excellence for Risk Assessment
TLV®	threshold limit value
TWA	time-weighted average
UEL	upper explosive limit
UF	uncertainty factor
WEEL®	Workplace Environmental Exposure Level

Glossary

Acute exposure: Exposure by the oral, dermal, or inhalation route for 24 hours (hr) or less.

Acute exposure guideline levels (AEGLs): Threshold exposure limits for the general public, applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hr. AEGL-1, AEGL-2, and AEGL-3 are developed for five exposure periods (10 min, 30 min, 1 hr, 4 hr, and 8 hr) and are distinguished by varying degrees of severity of toxic effects, ranging from transient, reversible effects to life-threatening effects [NRC 2013]. AEGLs are intended to be guideline levels used during rare events or single once-in-a-lifetime exposure to airborne concentrations of acutely toxic, high-priority chemicals [NRC 2013]. The threshold exposure limits are designed to protect the general population, including the elderly, children, and other potentially sensitive groups who are generally not considered in the development of workplace exposure recommendations. (Additional information available at https://www.epa.gov/aegl.)

Acute reference concentration (Acute RfC): An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure for an acute duration (24 hr or less) of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark concentration, with uncertainty factors (UFs) generally applied to reflect limitations of the data used. Generally used in EPA noncancer health assessments [EPA 2022].

Acute toxicity: Any poisonous effect produced within a short period of time following an exposure, usually 24 to 96 hr [EPA 2022].

Adverse effect: A substance-related biochemical change, functional impairment, or pathologic lesion that affects the performance of an organ or system or alters the ability to respond to additional environmental challenges.

Benchmark dose/concentration (BMD/BMC): A dose or concentration that produces a predetermined change in response rate of an effect (called the benchmark response, or BMR) compared with background [EPA 2022]. (Additional information available at https://www.epa.gov/bmds.)

Benchmark response (BMR): An adverse effect, used to define a benchmark dose from which a reference dose or concentration can be developed. The change in response rate over background of the BMR is usually in the range of 5%–10%, which is the limit of responses typically observed in well-conducted animal experiments [EPA 2022].

Benchmark concentration lower confidence limit (BMCL): A statistical lower confidence limit on the concentration at the BMC [EPA 2022].

Bolus exposure: A single, relatively large dose.

Ceiling value ("C"): Term in occupational exposure indicating the airborne concentration of a potentially toxic substance that should never be exceeded in a worker's breathing zone.

Chronic exposure: Repeated exposure for an extended period of time. Typically, exposures are more than approximately 10% of life span for humans and >90 days to 2 years for laboratory species.

Critical study: The study that contributes most significantly to the qualitative and quantitative assessment of risk [EPA 2022].

Dose: The amount of a substance available for interactions with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism [EPA 2022].

ECt_{50}: A combination of the effective concentration of a substance in the air and the exposure duration that is predicted to cause an effect in 50% of the experimental test subjects.

Emergency Response Planning Guidelines (ERPGs™): Maximum airborne concentrations below which nearly all individuals can be exposed without experiencing health effects for a 1-hr exposure. ERPGs are presented in a tiered fashion, with health effects ranging from mild or transient to serious, irreversible, or life-threatening (depending on the tier). ERPGs are developed by the American Industrial Hygiene Association [AIHA 2016].

Endpoint: An observable or measurable biological event or sign of toxicity, ranging from biomarkers of initial response to gross manifestations of clinical toxicity.

Exposure: Contact made between a chemical, physical, or biological agent and the outer boundary of an organism. Exposure is quantified as the amount of an agent available at the exchange boundaries of the organism (e.g., skin, lungs, gut).

Extrapolation: An estimate of the response at a point outside the range of the experimental data, generally through the use of a mathematical model, although qualitative extrapolation may also be conducted. The model may then be used to extrapolate to response levels that cannot be directly observed.

Hazard: A potential source of harm. Hazard is distinguished from risk, which is the probability of harm under specific exposure conditions.

Immediately dangerous to life or health (IDLH) condition: A condition that poses a threat of exposure to airborne contaminants when that exposure is likely to cause death or immediate or delayed permanent adverse health effects or prevent escape from such an environment [NIOSH 2004, 2013].

IDLH value: A maximum (airborne concentration) level above which only a highly reliable breathing apparatus providing maximum worker protection is permitted [NIOSH 2004, 2013]. IDLH values are based on a 30-min exposure duration.

LC_{01}: The statistically determined concentration of a substance in the air that is estimated to cause death in 1% of test animals.

LC_{50}: The statistically determined concentration of a substance in the air that is estimated to cause death in 50% of the test animals; median lethal concentration.

LC_{LO}: The lowest lethal concentration of a substance in the air reported to cause death, usually for a small percentage of test animals.

LD_{50}: The statistically determined lethal dose of a substance that is estimated to cause death in 50% of the test animals, i.e., the median lethal concentration.

LD_{LO}: The lowest dose of a substance that causes death, usually for a small percentage of the test animals.

Lethality: Pertaining to or causing death; fatal; referring to the deaths resulting from acute toxicity studies. May also be used in a lethality threshold to describe the point of sufficient substance concentration to begin to cause death.

Lower explosive limit (LEL): The minimum concentration of a gas or vapor in air, below which propagation of a flame does not occur in the presence of an ignition source.

Lowest observed adverse effect level (LOAEL): The lowest tested dose or concentration of a substance that has been reported to cause harmful (adverse) health effects in people or animals.

Median lethal concentration: A concentration observed or estimated to cause death in 50% of test animals, functionally equivalent to an LD_{50} concentration.

Mode of action: The sequence of significant events and processes that describes how a substance causes a toxic outcome. By contrast, the term "mechanism of action" implies a more detailed understanding on a molecular level.

No observed adverse effect level (NOAEL): The highest tested dose or concentration of a substance that has been reported to cause no harmful (adverse) health effects in people or animals.

Occupational exposure limit (OEL): Workplace exposure recommendations developed by governmental agencies and nongovernmental organizations. OELs are intended to represent the maximum airborne concentrations of a chemical substance below which workplace exposures should not cause adverse health effects. OELs may apply to ceiling limits, short-term exposure limit (STELs), or time-weighted average (TWA) limits.

Peak concentration: Highest concentration of a substance recorded during a certain period of observation.

Permissible exposure limits (PELs): Occupational exposure limits developed by OSHA (29 CFR § 1910.1000) or Mining Safety and Health Administration (30 CFR § 57.5001) for allowable occupational airborne exposure concentrations. PELs are legally enforceable and may be designated as ceiling limits, STELs, or TWA limits [OSHA 2019].

Point of departure (POD): The point on the dose-response curve from which dose extrapolation is initiated. This point can be the lower bound on dose for an estimated incidence or a change in response level from a concentration-response model (BMC). It can also be a NOAEL or LOAEL for an observed effect selected from a dose evaluated in a health effects or toxicology study.

RD_{50}: The statistically determined concentration of a substance in the air that is estimated to cause a 50% decrease in the respiratory rate.

Recommended exposure limit (REL): Recommended maximum exposure limit to prevent adverse health effects, based on human and animal studies and established for occupational (up to 10-hr shift, 40-hr week) inhalation exposure by NIOSH. RELs may be designated as ceiling limits, STELs, or TWA limits.

Short-term exposure limit (STEL): An exposure concentration limit that shall not be exceeded at any time during a workday, usually based on a 15-min TWA unless otherwise noted.

Target organ: Organ in which the toxic injury manifests in terms of dysfunction or overt disease.

Threshold limit values (TLVs®): Recommended guidelines for occupational exposure to airborne contaminants, published by the American Conference of Governmental Industrial Hygienists (ACGIH®). TLVs refer to airborne concentrations of chemical substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed, day after day, over a working lifetime, without adverse effects. TLVs may be designated as ceiling limits, STELs, or 8-hr TWA limits [ACGIH 2021].

Time-weighted average (TWA): A worker's 8-hr (or up to 10-hr) time-weighted average exposure concentration that shall not be exceeded during an 8-hr (or up to 10-hr) work shift of a 40-hr week. The average concentration is weighted to take into account the duration of different exposure concentrations [ACGIH 2021].

Toxicity: The degree to which a substance can cause an adverse effect on an exposed organism.

Uncertainty factors (UFs): Mathematical adjustments applied to the POD when developing IDLH values. The UFs for IDLH value derivation are determined by considering the study and effect used for the POD, with further modification based on the overall database.

Workplace Environmental Exposure Levels (WEELs®): Exposure levels developed by the American Industrial Hygiene Association (AIHA®) that provide guidance for protecting most workers from adverse health effects related to occupational chemical exposures, expressed as TWA or ceiling limits.

Acknowledgments

This document was developed by the Division of Science Integration, Christine Whittaker, PhD, Director. The authors of this report are Evan Frank, PhD, DABT; Melissa Edmondson, PhD, CIH; R. Todd Niemeier, PhD, CIH; and Molly Leshner, MPH.

NIOSH would like to acknowledge the contribution of the following subject matter experts for their critical technical review of this report: [*Reviewers to be added*.]

IDLH Value for Lewisite

IDLH Value: 0.03 ppm (0.25 mg/m^3)
Basis for IDLH Value: The immediately dangerous to life or health (IDLH) value for lewisite is based on respiratory irritation in human subjects. In experiments by Sherwood and Snyder [1918, as cited in Wardell 1941], human subjects experienced pronounced irritation of upper airways following exposure to 0.94 parts per million (ppm) lewisite for 1 minute. The detailed review by Wardell [1941] concluded that the exposure measurements originally reported in these studies are sufficiently accurate for the purpose of characterizing hazards. Considering the severity of lesions produced by lewisite contact, these data were selected to derive an IDLH value to protect against potentially severe respiratory irritation and avoid frank injury in any tissue. A 30-min adjusted equivalent concentration of 0.03 ppm was derived using the ten Berge method [ten Berge et al. 1986]. There were no significant areas of uncertainty using these data, and no further adjustment was necessary.

1.0 Introduction

1.1 Purpose

This *Immediately Dangerous to Life and Health* (*IDLH) Value Profile* presents (1) a brief summary of technical data associated with acute inhalation exposures to lewisite and (2) the scientific rationale behind the IDLH value for lewisite. IDLH values are developed based on the scientific rationale and logic outlined in the *Current Intelligence Bulletin (CIB) 66: Derivation of Immediately Dangerous to Life or Health (IDLH) Values* [NIOSH 2013]. NIOSH performs in-depth literature searches (outlined generally in CIB 66 and further described in Section 1.2 of this document) to ensure that all relevant data from human and animal studies with acute exposures to the substance are identified. The data identified in this literature search were evaluated for relevance by considering the methods used in the studies (i.e., species, study protocol, exposure concentration, and duration), the health endpoint(s) evaluated, and the critical effect levels (e.g., NOAELs, LOAELs, LC_{50} values).

1.2 How IDLH Values Are Set

An IDLH situation is one that poses a threat of exposure to airborne contaminants when that exposure is likely to cause death or immediate or delayed permanent adverse health effects or prevent escape from such an environment [NIOSH 2004]. An IDLH value is a maximum (airborne concentration) level above which only a highly reliable breathing apparatus providing maximum worker protection is permitted [NIOSH 2004]. IDLH values are based on a 30-minute (min) exposure duration and signal that every effort should be made to evacuate the area. These values are designed to protect workers from acute or short-term exposures to high concentrations of airborne chemicals that could quickly overwhelm them, affecting their ability to escape. These exposures could result in a range of undesirable outcomes from eye and respiratory irritation to severe, irreversible health effects, and in extreme cases, death. IDLH values also protect workers against non-toxicological safety hazards, including deprivation of oxygen, impairment of visibility, and ignition in the air.

1.2.1 Health Effects Considered

For the purposes of setting an IDLH value, NIOSH typically considers health effects data for the following acute health endpoints [NIOSH 2013]:

- Lethality/death
- Acute deficits in neurological and/or psychomotor functions that impair escape by interfering with workers' ability to recognize escape routes and any actions needed to get away through those routes, such as the operation of lifts, elevators, and door mechanisms
- Eye irritation that is severe enough to affect workers' ability to see adequately and escape the area
- Respiratory irritation severe enough to impair breathing, assuming a non-rest scenario, or that results in long-term respiratory complications
- Cardiac and hematological effects, including cardiac sensitization
- Any other specific target organ effects that are incapacitating and escape impairing or have the potential for long-term injury, disability, or deficits in function

1.2.2 Time Scaling

Effect levels for acute exposures are adjusted to 30-min effect levels when needed using the ten Berge et al. [1986] method, where a "k" constant value is calculated from concentration (C) and time (t) using the equation $C^n \times t = k$. When the value of the exponent *n* can be derived from data, the data-based *n* is used. Otherwise, default values of "1" for adjusting from a shorter exposure to 30-min and "3" for adjusting from longer exposures are used as described in CIB 66. For effects that are understood to occur based on threshold concentration regardless of exposure duration, time scaling may not be required.

1.2.3 Uncertainty Factor Considerations

The time-scaled effect levels for immediately dangerous health effects are modified by an uncertainty factor (UF) to estimate the concentration correlating to an unacceptable risk of immediately dangerous health effects in workers and account for the possibility of underestimating the degree of risk. When estimating an overall UF, NIOSH considers the following types of uncertainty and variability [NIOSH 2013, 2020]:

- Interspecies differences in sensitivity: When the effect level is obtained from animal data, the potential difference between animal and human responses should be accounted for. When data specific to the chemical are available, a factor may be calculated based on the known magnitude of toxicokinetic and/or toxicodynamic differences. If chemical-specific data are not available, NIOSH typically selects a value between 1 and 10 depending on the expectation of animal-to-human differences in toxic susceptibility.
- Human variability in sensitivity: To account for potential differences in sensitivity between individuals, NIOSH typically selects a value between 1 and 10 depending on the mode-of-action considerations in humans and, in cases where IDLH values are based directly on human subject data, whether variability among workers can be assessed from the experimental sample population. Because NIOSH generally assumes workers to be adults and in reasonable health, UFs for IDLH values generally do not account for particularly sensitive subgroups such as those with preexisting conditions.
- Severity of effect: A UF may be applied when the IDLH is based on health effects severe enough that overestimation of the threshold of immediately dangerous or lethal effects in workers

becomes a concern. This may be done to ensure that the IDLH is sufficiently protective of workers' health when the boundary between adverse and immediately dangerous risk is difficult to interpret.

- Other factors or database deficiencies: If gaps in the database create the possibility of significantly overestimating the IDLH value, UFs may be used to account for this. In special cases, other factors may arise that warrant inclusion of a UF.

1.3 Literature Search

Primary Literature Search

NIOSH performed an initial primary literature search and screened literature during December 2022 as outlined in NIOSH Current Intelligence Bulletin 66: Derivation of immediately dangerous to life or health (IDLH) values [NIOSH 2013]. This included several public databases consisting of non-peer reviewed literature that were reviewed for toxicity information on lewisite.

For searching the peer-reviewed primary literature, the following literature databases were used based on relevance and current availability. They were searched without limitations on publication date:

- PubMed/Medline
- Scopus
- Embase

Search terms used to search the primary literature for effect level data for animal and human endpoints relevant to the IDLH assessment are given in Table 1.1. These terms were used in conjunction with the chemical identifiers of "lewisite" and "2-chlorovinyldichloroarsine." The search terms were selected to best reflect the body of literature specific to lewisite and most effectively retrieve relevant toxicity data.

Table 1.1: Search Terms Used to Find Human and Animal Acute Toxicity Data

Search terms		
Acute	Symptoms	Accident
Irritation	Lethality	Confusion
Behavioral	LC_{50}	Toxicity
Neuro*	RD_{50}	Occupational
Psycho*	Poisoning	Volunteers
Subjects	Clinical	Animal
Inhalation	ppm	Fatality

*Denotes terms searched as prefixes

Tree Search for Government Reports and Non-peer Reviewed Literature

In addition to the primary literature searches, NIOSH reviewed references cited in authoritative reviews and other literature to identify relevant toxicity data. For lewisite, NIOSH used a combination of U.S. Department of Defense (DoD) toxicology reviews [Bakshi et al. 1999; Gates et al. 1946] and the acute exposure guideline level (AEGL) documentation for lewisite [NRC 2013]. The REACH database, which lists lewisite as a restricted substance under classification as an arsenic compound [ECHA 2020], was also reviewed for any toxicity data related to lewisite. All datasets identified through these means were reviewed by NIOSH to identify effect levels from endpoints relevant to the IDLH assessment.

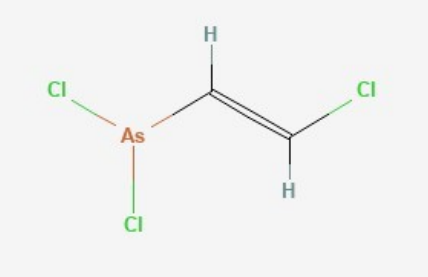
Screening Methods and Study Inclusion Criteria

NIOSH used the following inclusion criteria to screen for relevant datasets:

- Populations included in the review were human adults, workers, and mammalian test species.
- Exposures included in the review were acute exposures, meaning less than ~1 day for reports and <8 hr for experiments by any route where dose/concentration is known or estimated. Reports were excluded when the exposure concentration and/or duration were not estimated or reported.
- Comparators/controls included any comparisons between known doses/concentrations including comparisons between nonexposed, lower-exposed, and baseline prior to acute exposure.
- Outcomes included escape-impairing signs, symptoms, and endpoints in humans or animals; persistent adverse signs or symptoms in humans; persistent adverse effects in any organ/species; lethality; or RD_{50} values. For the purposes of the IDLH assessment, "escape-impairing" endpoints include acute neurological symptoms (e.g., recognition of letters and numbers, reaction time, psychomotor performance), irritation of the eyes and/or airways, or self-reported symptoms of the same.

2.0 General Substance Information

Chemical: Lewisite
CAS No: 541-25-3, also appears as 50361-05-2
Synonyms*: 2-chlorovinyldichloroarsine, arsonous dichloride ([1E]-2-chloroethenyl)
Chemical category*: Chemical warfare agents
Structural formula*:



*Reference: NLM 2023

Lewisite is a volatile, oily substance that fumes into a colorless gas that can be odorless or smell herbaceous, peppery, or geranium-like depending on purity and humidity [Wardell 1941]. It was developed and weaponized as a World War I-era blister agent similar to sulfur mustard, although these compounds have distinct chemical and toxicological differences. Lewisite was produced in substantial quantities by the United States during the first half of the 20th century; however there is no record of it being used on the battlefield by the United States or its allies [Goldman and Dacre 1989]. Table 2.1 summarizes the physicochemical properties of lewisite relevant to IDLH conditions.

The United States committed to destroying its stockpiles of lewisite as a part of the Chemical Weapons Convention treaty in 1997 [NRC 2012]. Although the DoD reported the elimination of all declared stockpile materials in 2023, the United States must also dispose of non-stockpile lewisite existing in various other forms. These include contaminated sites of former manufacture, testing, or storage;

improperly disposed material in trenches and pits; and previously mislabeled or uncatalogued "small finds" in various storage sites [NRC 2012]. The disposal of non-stockpile lewisite is expected to continue for the foreseeable future as these occasions arise and are addressed.

Table 2.1 Physicochemical Properties of Lewisite

Property	Value
Molecular weight	207.3[*]
Description	Colorless gas[*†‡]
Odor	Odorless or having a pungent geranium-like odor[*†‡]
Upper explosive limit	Not flammable[‡]
Lowe explosive limit	Not flammable[‡]
Vapor pressure	0.58 mm Hg at 25°C[*]
Flash point	Not flammable[‡]
Ignition temperature	Not flammable[‡]
Solubility	Negligibly soluble[*]
Relative gas density	7.1[‡§]
Incompatibilities and reactivities	None[*†‡]

[*]Bakshi et al. [1999]; [†]Goldman and Dacre [1989]; [‡]NOAA [2023]; [§]Wardell [1941]

There is little evidence indicating or ruling out lewisite as a carcinogen. Several organic and inorganic arsenic compounds are known carcinogens, but lewisite is not specified among these [IARC 2012]. An EPA provisional peer-reviewed toxicity value document for lewisite found inadequate evidence to evaluate carcinogenicity [EPA 2015]. An epidemiological study of Japanese poison gas factory workers suggested a correlation between sulfur mustard exposure and lung cancer but did not suggest a correlation for lewisite [Doi et al. 2011].

Several agencies and other safety and health organizations develop occupational exposure limits (OELs) based on the human health effects of exposure to chemicals. These range from OELs for daily full-shift (8–10 hr) exposures (NIOSH REL, OSHA PEL, AIHA TLV) to short-term acute exposures (AIHA ERPGs). For the most part, such values have not been determined for lewisite. In 1988, the CDC published a prevention guideline recommendation of 0.003 milligrams per cubic meter (mg/m^3, equivalent to 0.00035 ppm) to be applied to both the general population and occupational workers [CDC 1988]. This guideline value used a 72-hr averaging time. It was based on the lower detection limit and existing health protection guidelines for arsenic-containing compounds rather than the toxicology of lewisite itself.

The U.S. Department of the Army (DoA) used this limit as an interim IDLH guideline until updating their guidance to a "toxicologically-derived" IDLH of 0.36 mg/m^3 (0.042 ppm) in 2009 [DoA 2009]. This value was based on interpolation of the 30-min AEGL-2 and AEGL-3 values for lewisite described below. The Department of Energy (DoE) lists a level-1 temporary emergency exposure limit (TEEL-1) of 0.023 mg/m^3 (0.0027 ppm) for lewisite, denoting an estimation of the level causing no more than temporary, non-incapacitating effects given a 1-hr exposure period [DoE 2015].

AEGL values are emergency safety limits developed by the National Research Council (NRC) designed to protect members of the general public from adverse health effects for periods ranging from 10 min to 8 hr. AEGL values are estimated for three ranges of effects: nondisabling (AEGL-1), disabling (AEGL-2), and lethal (AEGL-3). The AEGL value most analogous to the IDLH is the 30-min AEGL-2 value, which is estimated to protect people from irreversible, serious, or escape-impairing effects, including in susceptible individuals. AEGL-2 and AEGL-3 values for lewisite are listed Table 2.2 [NRC 2013].

Table 2.2 Acute Exposure Guideline Level Values for Lewisite* Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	Not determined	Not determined	Not determined	Not determined	Not determined	N/A
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 [Armstrong 1923]
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)	Lethality in dogs [Armstrong 1923]

*[NRC 2013]

3.0 Health Effects of Lewisite

Lewisite is a powerful cytotoxic that has both highly irritating and profoundly injurious effects on any tissue it contacts as well as systemically [Wardell 1941].

3.1 Physical Safety

Lewisite is not flammable and does not deplete oxygen.

3.2 Lethality

Overview

The lethality of lewisite has been investigated in detail in animal studies, largely done by the US military during the first half of the 20th century. The available information gives an indication of the lethal dose

range and the pathophysiological events leading to death. Selected data from relevant dermal and intravenous studies have also been included in this assessment.

Quantitative lethality data for lewisite inhalation were identified for dogs and mice and are listed in Table 3.1. The only lethality value derived from 30-min inhalation data was 5.7 ppm in dogs [Armstrong 1923]. Gates et al. [1946] include a summary of lethality values expressed as LCt_{50} (median lethal concentration per min exposure) in various species. These values are transformed to 30-min LC_{50} values and listed in Table 3.2 for comparison with 30-min datasets. The values here range from 1.8 ppm in guinea pigs to 11 ppm in mice.

Data indicate that the lethality of acute lewisite exposure is dependent on the total absorbed dose, with the lethal concentration decreasing steadily in proportion to increasing exposure time. In the dog study by Armstrong [1923], each doubling of the exposure time reduced the median lethal concentration (MCL, equivalent to an LC_{50}) by half across the range of durations from 7.5 to 240 min. The absorbed dose at the MCL in the Armstrong study was calculated to fall between 3.7 and 4.2 mg for all groups regardless of duration [Lawson 1923, as cited in Wardell 1941]. The consistency in lethal dose over a wide range of exposure duration is evident in all species with lethality data, primarily demonstrated in Gates et al. [1946].

The cause of death by lewisite exposure via inhalation involves both local and systemic effects. Damage directly to the respiratory tract results in desquamation of epithelium, formation of membranous plaques, and pulmonary edema. Internal organs such as heart, liver, and kidneys are congested in deceased animals [Wardell 1941]. Absorbed lewisite by any route is highly toxic to vasculature and can cause severe, precipitous fall in plasma volume due to loss of capillary integrity. This was demonstrated as the cause of death in lethal applications of lewisite to skin [Cameron et al. 1947]. In inhalation experiments, bronchopneumonia is most proximal cause of death in the majority of fatalities in test animals, while the remainder die from circulatory shock [Cameron et al. 1946]. After 2–4 days, plasma volume and protein concentrations begin to return to normal levels, and subjects reaching this point generally were able to recover.

The majority of data indicate minimal interspecies differences in sensitivity to lewisite toxicity, with the exception of rabbits. Rabbits were reported to be 2–4 times more sensitive to lewisite compared with guinea pigs, dogs, rats, and goats in terms of LD_{50} values using skin application, but this was not true for subcutaneous administration [Cameron et al. 1946]. In skin reaction tests done in rabbits and human subjects, the lowest observed concentration of lewisite gas causing skin lesions was seven times lower in rabbits relative to humans [Eyster 1919, as cited in Wardell 1941]. However, rabbits do not appear particularly sensitive to inhaled lewisite compared with dogs, rats, guinea pigs, or mice in the table of LCt_{50} values reported by Gates et al. [1946]. Overall, the body of data does not indicate that humans are especially sensitive relative animal test species.

3.2.1 Human Lethality Data

No well-described reports of lethal effects in humans related to lewisite exposure were identified. The median lethal concentration in human adults on a time-unit basis (LCt_{50}) has been estimated to be between 1,200–1,500 mg-min/m^3 (142–177 ppm-min or 4.7–5.9 ppm 30-min LC_{50}) [DoA 1974; Prentiss 1937].

3.2.1 Animal Lethality Data

The DoD conducted animal lethality studies for lewisite during and following World War I. This work was summarized in detail in a government report by Wardell [1941]. The relevant studies from the Wardell report are given below along with other lethality data identified for lewisite. Table 3.1 lists the lethality effect levels found in the available data. Data informing the pathophysiology of lethal exposures to lewisite are also summarized below.

Kuhn [no date, as cited in Wardell 1941] exposed mice in groups of three to lewisite concentrations ranging from 0.05 to 0.8 mg/L (50–800 mg/m^3, 5.9–94 ppm) for 10 min and recorded deaths. The lowest concentration that caused death in a majority of animals was 0.3 mg/L (300 mg/m^3, 35 ppm), and the highest concentration causing no deaths was 0.1 mg/L (100 mg/m^3, 12 ppm). Deaths occurred within 48 hr following exposure. Linthicum [1933, as cited in Wardell 1941] used the data from the Kuhn study to statistically derive a 10-min median lethal concentration of 0.25 mg/L (250 mg/m^3, 29 ppm) for lewisite in mice.

Eyster [1919, as cited in Wardell 1941] exposed groups of 3, 7, and 24 dogs to 0.02, 0.03, or "0.03–0.13" mg/L (20, 30, and 30–130 mg/m^3, equivalent to 2.4, 3.5, 3.5–15 ppm, respectively) lewisite for 30 min. Two out of three dogs in the low concentration group survived. All dogs in the remaining groups died within 35 hr. Wardell commented that due to the analytical methods, the concentration estimates were "probably less reliable" than those taken under better controlled conditions.

Eyster and Loevenhart [1919, as cited in Wardell 1941] reviewed the comparative respiratory toxicity of lewisite, estimating a 30-min median lethal concentration of 0.03 mg/L (30 mg/m^3, 3.5 ppm) for lewisite in dogs. Wardell commented that this estimate was undoubtedly low and that the best estimate was closer to 0.045 mg/L (45 mg/m^3, 5.3 ppm). The authors hypothesized based on the body of data that humans were probably not more susceptible to the lethal inhalation effects of lewisite than dogs. Wardell commented that this conclusion was based on limited data at that point.

Armstrong [1923] exposed dogs to inhaled lewisite via whole-body exposure in groups ranging in size from 16 to 36 animals for time periods of 7.5, 15, 30, 60, 120, and 240 min. Animals were exposed individually to concentrations ranging from about 0.005 to 0.25 mg/L (5 mg/m^3 and 250 mg/m^3, 0.59 ppm and 29.5 ppm). The author determined the minimal lethal concentrations for each time period based on deaths observed in the 96 hr following exposure. The minimum lethal concentration was defined as the "lowest concentration which will cause a majority of deaths" during that period. In the results, concentrations measured for each animal exposure for a given duration fell along a gradient and clusters of similar concentration values were averaged together in groups ranging in size from 1 to 12 data points. The minimum lethal concentration was the lowest average concentration observed among groups wherein at least half the animals expired. For the 30-min experimental group, this value was 0.048 mg/L (48 mg/m^3 or 5.7 ppm). The group, made up of three animals, were exposed to a concentration measured to be 0.048 mg/L. All three animals died between 14 and 44 hr following the 30-min exposure at this concentration. No deaths were observed at concentrations below this. The next lowest group average measured for 30 min was 0.0415 mg/L (41.5 mg/m^3 or 4.9 ppm) and involved two animals that both recovered. All animals exposed to concentrations higher than 0.048 mg/L for 30 min died.

Lawson [1923, as cited in Wardell 1941] estimated absorbed median lethal dose in dogs assuming a 30-min ventilation volume of 100 liters and 85% absorption. This produced values between 3.7 and 4.2 mg total for exposure times ranging from 7.5 min to 4 hr using the Armstrong [1923] lethality study.

Silver and McGrath [1943] exposed CF-1 mice to both cis- and trans- stereoisomeric gases of lewisite for 10 min in separate experiments to derive an LC_{50} given a 10-day observation period. The experiments also tested several study parameters thought to impact the analytical versus nominal exposure concentrations. The study found essentially equivalent LC_{50} values of 0.28 and 0.25 mg/L (280 and 250 mg/m^3, 33 and 29 ppm), respectively, for the two stereoisomers. These values were based on nominal (target) concentrations, while analytical concentrations (measured in the exposure chamber) were 0.20 and 0.19 mg/L (200 and 190 mg/m^3, 24 and 22 ppm), respectively. The authors of this study determined experimentally that the difference observed between the nominal and measured concentrations was caused by adsorption and hydrolysis of lewisite by surfaces in the live animal chamber, concluding that the nominal concentrations provided the best estimate of the actual exposure levels.

Gates et al. [1946] cited several inhalation lethality values for mice, rats, guinea pigs, rabbits, dogs, and goats in the LCt_{50} format. Most of the reports from which these values are sourced are not available. Table 3.2 presents those LCt_{50} values as 30-min LC_{50} values to provide for comparison with the LC_{50} values from available studies.

Wardell [1941] reviewed the pathophysiology of lewisite evident in dogs exposed to lewisite in the studies by Eyster [1919] and Eyster and Loevenhart [1919]. In dogs succumbing to lewisite inhalation, respiratory tract lesions were pronounced in the trachea and bronchi and included membrane formation (similar to diphtheritic), hemorrhage, edema, emphysema, atelectasis, and bronchopneumonia. The prevalence of bronchopneumonia increased with time elapsed prior to death. Hydropic degeneration (cell swelling/blebbing) of cardiac fibers near the endocardium was seen in virtually all cases, and the right sides of the heart were often dilated. Abdominal organs were congested and showed "tendency towards hemorrhage" with diffuse degeneration and necrotic cells observed. Interestingly, in some cases, animals that succumbed did not show significant lesioning of the trachea, bronchi, or lungs.

Vedder [1925] described thick membrane formation in the respiratory tract similar to that described above. Vedder also described "intense congestion" of the liver and kidneys. Bronchopneumonia was determined to be the cause of death in 23 of 29 animals that succumbed to acute lewisite exposure. Cameron et al. [1946] also reviewed the pathology associated with lethal lewisite inhalation and described lesions similar to Wardell [1941].

Wardell [1941] also reviewed the pathology of animals that recovered from lewisite exposure based on an Edgewood Arsenal report (EAMRD 27) by Koontz et al. [1925]. In 45 dogs that survived acute exposure, varying degrees of congestion, hemorrhage, edema, and emphysema were present for up to 6 weeks after exposure. Large airways showed prominent desquamated airway epithelial cells and debris. Areas of chronic inflammation were seen only occasionally. These pathologies were markedly improved after 6 weeks of recovery, although one quarter of animals that survived the initial post-exposure period eventually succumbed within this time period [Koontz et al. 1925, as cited in Wardell 1941].

Cameron et al. [1947] exposed rabbits, goats, and dogs to lewisite via skin application in a series of experiments studying the systemic effects of acute exposure. Blood chemistry, vascular damage/loss of fluid, renal function, and lymph drainage were examined. In rabbits and goats, application of lewisite to the skin resulted in a precipitous decrease in plasma volume and plasma protein levels. Other metrics such as hemoglobin and red blood cell counts were normal or transiently increased due to the lost blood volume. This state of "lewisite shock" was observed to coincide with clinical signs that included ill appearance, fall in peripheral body temperature, and lack of appetite. Authors reported difficulty in

gathering venous blood from these animals. Animals that did not survive succumbed during this period, which lasted around 3 days. Animals surviving to this point began to recover volume and plasma protein and returned to normal levels in 5–7 days.

Based on the concordance of decreased plasma and protein with clinical signs and mortality, the authors believed lewisite circulatory shock to be a key event in lewisite mortality, with the proximal cause of death being circulatory collapse. Lewisite shock was attributed to loss of vascular capillary integrity, allowing large amounts of fluid to leave circulation. Although massive edema from wounding at the site of application itself doubtlessly contributed to this loss, authors found similar results when goats were intravenously administered lewisite oxide (the immediate degradation product of lewisite in tissues). This indicated that the circulatory shock effects could be caused by systemic effects of lewisite regardless of whether grievous wounding occurred at the site of absorption.

In dogs, authors sampled the flow and protein content of lymph to ascertain the fate of lost plasma and circulatory proteins. They found that lymph draining from sites of lewisite application was dramatically increased and similar to plasma in protein content. Similar changes in lymph draining from the lungs were seen in dogs intravenously given lewisite oxide. This indicated that loss of capillary integrity was the cause of lewisite shock, and that the lung capillaries were a sensitive target of systemically absorbed lewisite. Investigation of renal functions in exposed dogs indicated that the kidneys were affected secondarily to circulatory effects and not the reverse.

Table 3.1 Lethal Concentration Data for Lewisite

Species	LC_{50} (mg/m^3)*	LC_{50} (ppm)	Time (min)	Reference
Dog	45	5.3	30	[Wardell 1941]
Dog	176	21	7.5	[Armstrong 1923]
Dog	96	11	15	[Armstrong 1923]
Dog	48	5.7	30	[Armstrong 1923]
Dog	25	2.9	60	[Armstrong 1923]
Dog	13	1.5	120	[Armstrong 1923]
Dog	6.2	0.7	240	[Armstrong 1923]
Mouse	190	22	10	[Silver and McGrath 1943]

*Values expressed as mg/L in sources have been expressed as mg/m^3 in this table.

Table 3.2 LCt_{50} Values Reported in Gates et al. [1946]

Species	LCt_{50} ($mg\text{-}min/m^3$)*	LCt_{50} (ppm-min)	30-min LC_{50}† (ppm)
Dog	1,400	165	5.5
Mouse	900	106	3.5
Mouse	2,800	330	11
Mouse	1,500	177	5.9
Mouse	2,500	295	9.8
Mouse	500	59	2.0
Rat	1,500	177	5.9
Rat	580	68	2.3
Guinea pig	1,000	118	3.9
Guinea pig	470	55	1.8
Rabbit	1,200	142	4.7
Rabbit	1,500	177	5.9
Goat	1,250	147	4.9

*Values expressed as mg-min/L in sources have been expressed as $mg\text{-}min/m^3$ in this table.

[†]LCt_{50} values in ppm-min were divided by 30 min to derive 30-min LC_{50} values.

3.3 Neurotoxicity

There are no known neurological or neurotoxic effects of lewisite exposure.

3.3.1 Human Neurotoxicity Data

No reports of neurological effects in humans were found.

3.3.2 Animal Neurotoxicity Data

No reports of neurological effects in animals were found.

3.4 Respiratory and Eye Irritation

Lewisite gas is a powerful eye, respiratory, and skin irritant. It is perceived by human subjects as being strongly pungent and chemesthetic, and respiratory and eye irritation symptoms occur immediately upon exposure [Goldman and Dacre 1989; Wardell 1941]. Irritation effects are described as stinging and burning sensations of the nose and throat that increase in severity with continued exposure. The effect of lewisite gas or vapor on exposed skin is similar in kind to the effect on eye and respiratory tissues, but the concentration threshold for skin irritation is orders of magnitude higher than that of respiratory and eye irritation. Detailed data for irritation effects are summarized below, consisting of one human subject study that found a 1-min exposure to 0.94 ppm elicited pronounced respiratory irritation in addition to an eye irritation study in rabbits that found effect levels of 2 and 4.5 ppm corresponding to mild and severe ocular edema, respectively, following 30 min of exposure.

3.4.1 Human Irritation Data

Sherwood and Snyder [1918, as cited by Wardell 1941] conducted human subject studies with volunteers wearing face masks to determine the minimum concentration of lewisite evoking sensations of odor or irritation, exposing subjects for 60 seconds followed by 5 min of observation. Subjects reported that the sensation brought on by exposure was chemesthetic or pungent rather than odorous, and at least half of the individuals reported irritation of the nose at a concentration of 0.0057 mg/L (5.7 mg/m^3 or 0.67 ppm). Subjects did not report irritation at 0.0036 mg/L (3.6 mg/m^3 or 0.42 ppm). Irritation at a level of 0.0080 mg/L (8 mg/m^3 or 0.94 ppm) was pronounced after 1 min in six out of nine subjects and appeared to subside within the 5-min observation. There was no information given on whether subjects experienced further effects following the 5-min observation. A concentration of 0.011 mg/l (11 mg/m^3 or 1.3 ppm) was described as irritating immediately and affected 100% of subjects. The concentrations were assumed by Wardell to be based on the amount of lewisite volatized and considered to be sufficiently accurate estimations of the true exposure concentrations.

3.4.2 Animal Irritation Data

Eyster [1919, as cited in Wardell 1941] contains an experiment that attempted to identify the lowest concentration of lewisite or mustard vapor causing eye lesions in animals. Rabbits were exposed for durations ranging from 5 to 60 min. A concentration of 0.033 mg/L (33 mg/m^3 of 3.9 ppm) lewisite resulted in mild reactions following a 5-min exposure, while 0.031 mg/L (31 mg/m^3 or 3.7 ppm)

produced no effects. In animals exposed for 30 min, the lowest dose tested of 0.0011 mg/L (11 mg/m^3 or 1.3 ppm) lewisite produced similar mild reactions, described as slight edema and lacrimation. Corneal opacity was observed at concentrations 0.0017 mg/L (17 mg/m^3 or 2 ppm) and higher, but observations of opacity were sporadic and not consistent with increasing concentrations. Animals exposed at 0.0038 mg/L (38 mg/m^3 or 4.5 ppm) for 30 min showed severe edema of eyelids and could not keep their eyes open.

3.5 Cardiac and Hematological Effects

Lewisite is highly toxic to vasculature, and vascular capillaries are particularly sensitive both in directly exposed tissue and systemically [Cameron et al. 1947]. In lethal inhalation exposures in dogs, degeneration of cardiac fibers was often seen [Wardell 1941]. In addition, in several experimental deaths, it was noted that lung and respiratory lesions were not of "sufficient seriousness" to be lethal and that severe bronchopneumonia was not present [Eyster 1919, as cited by Wardell 1941]. This suggests that the cause of death in these cases was due to lewisite shock and circulatory collapse as described by Cameron et al. [1947].

The only quantitative effect level data available for changes in hematological parameters come from Cameron et al. [1946] who reported "definite blood changes" in rabbits occurring at one-third the LD_{50}. The blood changes induced by lewisite exposure are characterized in Cameron et al. [1947] and consist primarily of a precipitous loss of plasma volume and protein content due to tissue edema. As these changes represent an advanced stage of lewisite injury and the onset of shock, NIOSH interprets blood changes occurring at one-third the LD_{50} to be immediately dangerous in an occupational context. Because the effect on blood chemistry is a systemic endpoint, taking one-third the median lethal value by other routes may be assumed to approximate the level at which blood changes occur.

3.5.1 Human Cardiac and Hematological Effect Data

No data in humans were identified.

3.5.2 Animal Cardiac and Hematological Effect Data

Cameron et al. [1946] determined dermal and subcutaneous LD_{50} values for dogs, rabbits, guinea pigs, and rats. In rabbits administered lewisite via skin application, one-third the LD_{50} was found to be the lowest dosage inducing "definite blood changes." The blood changes induced in rabbits exposed to liquid lewisite via the skin at a dosage two-thirds the LD_{50} were elaborated on in Cameron et al. [1947]. These consisted primarily of loss of both plasma volume and plasma protein content. Because this was a lethal dose range that resulted in lethality, this study is summarized in detail in Section 3.3 concerning lethality.

3.6 Other Relevant Health Effects

Cameron et al. [1946] report "striking changes" in the bile duct, gall bladder, and liver of guinea pigs exposed to lewisite via skin application. These changes consisted of intense congestion and hemorrhagic necrosis and were observed to occur as low as one-fifth the dermal LD_{50}. Although the authors concluded that these changes were the likely cause of death in guinea pigs succumbing to dermal lewisite exposure, this effect appeared to be restricted to guinea pigs. The biliary lesions in goats, rabbits, and dogs were far less severe while mice and rats showed no appreciable changes. Because this

finding is limited to one species and is not associated with guinea pigs being more susceptible to lewisite relative to other species, NIOSH did not consider this outcome for deriving an IDLH value for humans.

4.0 Determination of IDLH Value

4.1 Selection of Critical Data

Lewisite in the air readily absorbs into tissues and enters circulation, and it is immediately toxic to virtually all tissue types on contact. The immediately dangerous effects of lewisite are a combination of local and systemic effects ranging from immediate sensory irritation to widespread systemic toxicity. The mode of toxic action and the relationship between cumulative dose and toxic effects are consistent regardless of the route of exposure or toxic endpoint. In all cases, the lethal and non-lethal effects of lewisite begin their onset immediately upon contact with tissue. These effects increase in severity over time and are dependent on the total amount of lewisite exposure regardless of exposure duration. This is true regarding skin, eye, and respiratory irritation [Wardell 1941] as well as lethality by inhalation [Armstrong 1923]. NIOSH considered determining an IDLH value for lewisite based on the following outcomes. Table 4.1 presents candidate IDLH values based on these outcomes with application of time adjustment and uncertainty factors as detailed below.

Lethality: The most quantitatively well-supported lethality value for lewisite is Wardell's revised estimate of the 30-min LC_{50} in dogs using data collected by Armstrong [1923], determined as 5.3 ppm. This value is comparable to the majority of LCt_{50} concentrations reported by Gates et al. [1946] in several species (see Table 3.2). Because the veracity of individual datasets from this time period is often subject to question due to method variations in measuring exposure concentrations, the most well-described datasets were considered more valuable for the purposes of deriving an IDLH. Wardell [1941] was particularly rigorous in considering the impact of inaccurate exposure measurements, so the 5.3 ppm LC_{50} in dogs is considered the best estimate for lethality.

Eye Irritation: Rabbits developed corneal lesions during 30-min exposures to concentrations as low as 2 ppm and could not open their eyes following exposure to 4.5 ppm. A concentration of 1.3 ppm for this time period produced only slight edema and lacrimation [Eyster 1919, as cited by Wardell 1941]. This was considered a no-effect level for the purpose of setting a potential IDLH value as these effects are reversible and do not appear to be escape-impairing.

Respiratory Irritation: Human subject studies demonstrated pronounced irritation of the nose and throat following a 1-min exposure to 0.94 ppm [Sherwood and Snyder 1918, as cited by Wardell 1941]. The steep concentration-response profile evident in symptoms reported in the range from 0.42 to 1.3 ppm in these experiments indicates that the effects caused by a 1-min exposure to 0.94 ppm lewisite reflect scenarios likely approaching immediately dangerous in an occupational setting. This takes into consideration that lewisite is extremely toxic to tissues. It is presumed that acute irritation symptoms may be occurring concomitantly with injury to airways that may result in deficits of function or secondary escape-impairing effects. The irritation symptoms reported in these exposures were reversible after several minutes.

NIOSH considered the properties of lewisite that originally motivated its development as a weapon. These include its low detectability by odor and relatively low margin between immediately irritating concentrations and LC_{50} values (as summarized by Wardell [1941]). Therefore, NIOSH conservatively interprets the effects of exposure to levels above 0.94 ppm for 1 min as immediately dangerous.

Cardiovascular Toxicity (Lewisite Shock): Cameron et al. [1946] reported changes to hematology in rabbits at one-third the LD_{50} by skin application. NIOSH considered deriving an IDLH based on changes to blood chemistry, but determined there was insufficient dose-response data to draw on. An IDLH based on hematological changes would be functionally identical to a value based on lethality data.

4.2 Application of Time Scaling

Lethality: The LC_{50} in dogs reported by Armstrong [1923] was based on a 30-min exposure, so no time adjustment is necessary.

Eye Irritation: The no-effect level for immediately dangerous eye effects in rabbits reported by Eyster [1919, as cited by Wardell 1941] was based on a 30-min exposure, so no time adjustment is necessary.

Respiratory Irritation: Effect levels for respiratory irritation in humans were only available for 1-min exposures reported by Sherwood and Snyder [1918, as cited by Wardell 1941]. NIOSH protocol to extrapolate this effect level to 30 min would use an *n* exponent of 1 (i.e., an unmodified application of Haber's law). The concentration-response data available for lewisite supports this approach because the severity of effects is dependent on accumulated exposure over all of the immediately dangerous outcomes observed. As studies summarized by Wardell [1941] demonstrated that concentrations of lewisite gas causing skin irritation and lethality effects consistently have a linear relationship with exposure time, NIOSH infers that this is true of respiratory effects as well. Because of the risk of escape-impairing effects, deficits in function, and secondary effects during a full 30-min exposure, NIOSH applies the default approach that adjusts the concentration linearly with respect to time.

Using the equation: 0.94 ppm × 1 min = (C) × 30 min

The adjusted 30-min effect level for pronounced irritation is 0.03 ppm.

4.3 Application of Uncertainty Factors

A total factor of 30 was applied to the LC_{50} value in dogs. The Armstrong [1923] dataset, from which this value was derived, showed that the onset of lethal effects with increasing concentration occurs over a fairly narrow dose range well within an order of magnitude. So a factor of 30 is assumed sufficient to considering a factor of 10 to approximate a non-lethal value with a factor of 3 to account for any possible species differences.

A factor of 3 was applied to the 30-min effect level for non-immediately dangerous eye irritation in rabbits to account for any species differences.

No uncertainty factor was necessary for the IDLH value based on respiratory irritation because the value was derived from experimentation in humans. In addition, the value was based on irritation of the nose and throat that was pronounced but reversible and not immediately dangerous or incapacitating.

Table 4.1 Potential IDLH Values Based on the Expected Immediately Dangerous Health Outcomes of Lewisite Exposure

Health outcome	Immediately dangerous effect level (ppm)	30-min adjusted value (ppm)	Uncertainty factor	Candidate IDLH value (ppm)
Lethality	5.3	5.3	30	0.18
Eye Irritation	1.3*	1.3	3	0.43
Respiratory Irritation	0.94*	0.03	N/A	0.03

*No observed dangerous effect level

4.4 Final IDLH Calculation

NIOSH chose the IDLH value based on respiratory irritation because of the severity of the lesions produced by lewisite contact. Because of the potential for harm and the rapid escalation of injury with increasing exposure, the IDLH estimate for lewisite is made with the aim of preventing any health-related effects from arising. The respiratory irritation value is the most sensitive value in this regard. It is based on human experimentation and offers the best estimate for avoiding injury in any tissue. This value is lower than the 30-min AEGL-2 value of 0.055 ppm, which was based on the AEGL-3 lethality data [NRC 2013], and above the 2.7 parts per billion (0.0027 ppm) 1-hr TEEL [DoE 2015]. The IDLH for lewisite is set at 0.03 ppm.

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