INTERIM ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

ADAMSITE (CAS Reg. No. 578-94-9) (DM)

ETHYLDICHLOROARSINE (CAS Reg. No. 598-14-1) (ED)

METHYLDICHLOROARSINE (CAS Reg. No. 593-89-5) (MD)

PHENYLDICHLOROARSINE (CAS Reg. No. 696 -28-6) (PD)

DIPHENYLCHLOROARSINE (CAS Reg. No. 712-48-1) (DA)

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.

TABLE OF CONTENTS

LIST OF TABLES

SUMMARY

The arsenical agents for which AEGL analysis have been performed include adamsite (DM), ethyl dichloroarsine (ED), methyldichloroarsine (MD), phenyldichloroarsine (PD), and diphenylchloroarsine (DA). Adamsite (diphenylaminochloroarsine; CAS Registry No. 578-94-9) is often referred to as a vomiting agent. Although it has been used as a riot control agent, it is generally considered too toxic for this application. The name, adamsite, was applied to this chemical primarily during World War I; the DM designation is currently used. DA, ED, MD, and PD were also developed for possible military applications and have been referred to as riot control agents, harassing agents, and short-term incapacitating agents. They have also been categorized based upon the physiologic response they induce, i.e., sternutators, lacrimators. For the most part, these agents were found to be of limited military use.

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.

All human exposure studies presented in this evaluation meet the criteria for acceptance for use in the AEGL process (e.g., there is evidence that subjects provided informed consent and that the studies were performed under appropriate clinical supervision (NRC 2001).

Adamsite (DM)

Studies with human volunteer subjects affirm nasal and ocular irritation as the primary effect from short term low level exposure to DM. Exposures of 0.68 to 60 minute durations with Ct products of 3.1 to 144 mg • min/m^3 produced effects ranging from negligible (nasal and throat irritation) to severe distress for 2 to 3 hours (burning and tightness in the chest, persistent rasping cough, burning sensation in the upper respiratory tract, depression). Nausea tended to occur in about 10% of the subjects and only at the higher Ct exposures. There was full recovery from all effects for all subjects. A latency period (approximately 10 minutes) was frequently reported. Based upon human volunteer studies, exposure thresholds of 0.38, 0.5, and 0.75 mg/m^3 have been estimated for irritation of the throat, lower respiratory tract and initiation of the cough reflex, respectively.

Animals studies in multiple species have provided data affirming the respiratory tract as the initial and primary target of DM, the latency in manifestation of some effects, and recovery from mild to moderate effects. Studies with nonhuman primates provided data for both lethal and nonlethal effects.

The human experience data reported by Lawson and Temple (1922) and analyzed by Craighill and Folkoff (1922) were the most relevant for AEGL-1 development. Because the effects were likely of greater severity than would be considered consistent with the definition of AEGL-1 (i.e., 60-minute exposure to 0.14 mg/m^3 was a tolerance limit), the exposure concentration was reduced three-fold to approximate an exposure (0.047 mg/m^3) resulting in effects of less severity and more consistent with those associated with AEGL-1.

An assessment by ten Berge et al. (1986) of LC_{50} data for certain chemicals revealed chemical-specific relationships between exposure concentration and exposure duration that were often exponential. This relationship can be expressed by the equation $C^n \times t = k$, where n represents a chemical specific exponent. Available data suggest that exposure duration may be more relevant than exposure concentration with respect to DM. Analysis of human tolerance limits for DM based on average response of 1 to 6 volunteer

subjects. (Lawson and Temple,1922; Craighill and Folkoff, 1922) resulted in an empirically-derived exponent (*n*) of 0.71.

Uncertainty factor application was limited to 3 for individual variability. Qualitatively, the human response to DM is well characterized but uncertainty exists regarding a precise threshold for minor irritation. As previously explained, the concentrations selected as point-of-departures were decreased threefold to estimate an exposure producing a less severe response. Therefore, there were no additional uncertainty adjustments.

AEGL-2 values were developed using data reported by Striker et al. (1967b) for monkeys exposed to DM at various concentration-time regimens and exhibiting various physiological/behavioral responses (hyperactivity, blinking, nasopharyngeal irritation, ocular irritation) and gross pathological effects (tracheal, bronchial and pulmonary edema). Necropsy findings at 12, 24, or 72 hours, or 1 or 30 days post exposure indicated sequential resolution of DM-induced pulmonary damage for all exposure groups. Although exposure durations were all 60 minutes or less, some (10 and 60 minutes) coincided with AEGL-specific time points. The response of monkeys exposed to 291 mg DM/m^3 for 10 minutes served as the basis for the 10- and 30-minute AEGL-2 values and response to 77 mg DM/m^3 for 60 minutes was utilized for developing the 1-, 4-, and 8-hr AEGL-2 values. Time scaling was performed using an empirically-derived *n* of 0.71 as described for AEGL-1 development. Qualitative evaluation of the responses of humans and animals to DM indicate that the range of effects is a function of severity of irritation and subsequent damage to respiratory tract epithelium. Therefore, it is assumed that the exposure time relationship may be similar across the effect continuum for DM.

A total uncertainty factor adjustment of 30 was applied in development of the AEGL-2 values. This included an intraspecies adjustment of 3 to account for individual variability in response to a direct-acting irritant. Agent DM appears to damage epithelial tissue which it contacts, which subsequently results in tissue damage especially in the respiratory tract. This process is supported by clinical observations in humans and animals and by pathological findings in animals exposed to sufficiently high concentrations of DM. An interspecies uncertainty factor of 10 was applied because available data suggest notable variability among the species tested. Data from a study with nonhuman primates (cynomolgus monkey, *Macaca mulatta*) was used for developing the AEGL-2. While not the most sensitive species, the cynomolgus monkey was considered more appropriate due to greater similarities with humans in respiratory anatomy and physiology than other species. Early studies with human volunteer subjects indicated very low tolerance to DM at low concentrations for very short durations which would preclude reduction of uncertainty in animal-to-human extrapolation.

AEGL-3 values were based upon data in monkeys (Striker et al., 1969a and McNamara et al., 1969). Striker et al. (1967a) provided data involving both lethal and nonlethal responses of monkeys (10/group) exposed to DM aerosols for 3, 5, or 11 minutes. The exposure resulting in serious but nonlethal effects (1708 mg/m^3 for 5 minutes) was considered appropriate as a point-of-departure for developing AEGL-3 values for 10 minutes. Extrapolation of this exposure/duration value to 30-minute and greater time periods was tenuous and, therefore, not used for development of the remaining AEGL-3 values. The 30-minute, 1, 4, and 8-hour AEGL-3 values, were also based upon a nonlethal exposure of monkeys (279 mg/m^3 for 46 minutes) (McNamara et al., 1969). The exposures defined in these studies resulted in Ct products of 986.36 and 2,506.89 mg•min/m^3 with which to develop the AEGL-3 values for 10-minute values and 30-minute and greater values, respectively.

Time scaling was performed using the empirically-derived exponent (*n*) of 0.71. Because lethality studies in multiple species indicated irritation and subsequent damage to respiratory tract epithelium as the prominent mode of action, it was assumed that the exposure time relationship would be similar across the effect continuum for DM. As for AEGL-2 development, uncertainty factor adjustment consisted of 10 for

interspecies variability due to uncertainties in extrapolating from animal lethality to exposures resulting in human deaths. An uncertainty factor of 3 was applied to account for individual variability in response to a direct-acting irritant.

Summary of AEGL Values for Adamsite (DM)

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	0.20 mg/m^3	0.041 mg/m^3	0.016 mg/m^3	0.0022 mg/m^3	0.00083 mg/m^3	irritation threshold for human volunteers (Lawson and Temple, 1922 as analyzed by Craighill and Folkoff, 1922)
AEGL-2 (Disabling)	9.7 mg/m^3	6.8 mg/m^3	2.6 mg/m^3	0.36 mg/m^3	0.14 mg/m^3	respiratory tract effects in monkeys (Striker et al., 1967b)
AEGL-3 (Lethality)	21 mg/m^3	17 mg/m^3	6.4 mg/m^3	0.91 mg/m^3	0.34 mg/m^3	notable pulmonary damage with no lethality in monkeys (Striker et al., 1967a); estimated lethality threshold in monkeys (McNamara et al., 1969)

Diphenylchloroarsine (DA)

Data were unavailable with which to develop AEGL-1 and AEGL-2 values for DA. The overall data on DA were not considered sufficient to support development of AEGL-1 values by extrapolation from other data or exposure values. Due to the quantitatively and qualitatively poor data base for DA, development of AEGL-2 values by extrapolation from AEGL-3 values is not recommended.

The AEGL-3 values for DA were based upon the rat data reported in MMW (1918) which are supported by similar findings in rabbits and cats (MMW, 1918). For rats, rabbits and cats, 30-minute exposure to 236 mg/m^3 and 60 minute exposure to 118 mg/m^3 did not result in the death of any of the animals (4 rats and rabbits/group, 2 to 4 cats/group). These 10-minute data were used as the point-of-departure for the 10 and 30-minute AEGL-3 values for DA, while the 60-minute data point was used for developing the 1-, 4-, and 8-hour AEGL-3 values for DA. Data were unavailable with which to derive a value for the exponent, *n*, in the equation $C^n \times t = k$. Consistent with AEGL methodologies (NRC, 2001), an *n* of 1was used in extrapolating from the 60-minute experimental exposure period to the 4 and 8 hour AEGL-3 time periods, and an *n* of 3 was used for extrapolating from the 30-minute experimental period to the 10-minute AEGL-3 exposure.

Uncertainty factor adjustment consisted of 10 for interspecies variability due to uncertainties in extrapolating from animal lethality to exposures resulting in human deaths. Due to insufficient data with which to assess individual variability in the toxic response to DA., an uncertainty factor of 10 was retained to account for possible intraspecific variability.

Summary of AEGL Values for Diphenylchloroarsine (DA)

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Insufficient data.
AEGL-2 (Disabling)	1.1 mg/m^3	0.79 mg/m^3	0.39 mg/m^3	0.098 mg/m^3	0.049 mg/m^3	Estimated as 1/3 reduction of AEGL-3
AEGL-3 (Lethality)	3.4 mg/m^3	2.4 mg/m^3	1.2 mg/m^3	0.30 mg/m^3	0.15 mg/m^3	Lethality threshold in rats (MMW, 1918)

NR = Not recommended.

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

Ethyldichloroarsine (ED)

Data were unavailable with which to develop AEGL-1 and AEGL-2 values for ED. Due to the deficient data base for ED, development of AEGL-2 values by extrapolation from AEGL-3 values is not recommended. Consistent with AEGL procedures and methodologies (NRC, 2001), the AEGL-2 values (10-minute, 30-minute and 1-hour only) for ED were estimated as a three-fold reduction of the AEGL-3 values.

AEGL-3 values for 10 and 30 minutes, and 1 hour were developed based on a lethality threshold estimated as a 3-fold reduction of a mouse 10-minute LCt_{50} of 1555.5 mg • min/m^3 (equivalent to a 10-minute LC_{50} of 155.5 mg/m^3) (Hutchens et al., 1943). The resulting point-of-departure was 51.8 mg/m^3. Assuming similarity in activity to other dichloroarsines, uncertainty factors of 10 for interspecies variability (uncertainties in extrapolating from animal lethality to exposures resulting in human deaths) and 10 (insufficient data with which to assess individual variability in the toxic response to ED), and a modifying factor (MF) of 2 were used in the development of the AEGL-3 values. Time scaling from the 10-minute experimental time point to the 30- and 60-minute AEGL-3 time frames utilized a default *n* of 1 (NRC, 2001). Limited data and uncertainties in extrapolating to exposure durations 24-fold and 48-fold greater than the 10-minute experimental time frame, preclude development of the 4-hour and 8-hour AEGL-3 values.

Summary of AEGL Values for Ethyldichloroarsine (ED)

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Insufficient data.
AEGL-2 (Disabling)	0.17 mg/m^3	0.057 mg/m^3	0.029 mg/m^3	NR[b]	NR[b]	Estimated as 1/3 reduction of AEGL-3
AEGL-3 (Lethality)	0.52 mg/m^3	0.17 mg/m^3	0.086 mg/m^3	NR[b]	NR[b]	Estimated lethality threshold in mice (Hutchens et al., 1943)

NR = Not recommended.

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

[b] 10-minute experimental data point is insufficient to support extrapolation to 4-hour and 8-hour exposure

Methyldichloroarsine (MD)

Data were insufficient for development of AEGL-1 values or by extrapolation from AEGL-2 values. Toxicity data for MD were limited to lethality studies in dogs (Allen et al., 1922) and mice (Wells, 1924) which did not address nonlethal effects. Consistent with AEGL procedures and methodologies (NRC, 2001), the AEGL-2 values for MD were estimated as a three-fold reduction of the AEGL-3 values.

The AEGL-3 values for MD were developed using the multiple time-point dog lethality data provided by Allen et al. (1922) who reported LC_{50} values for 7.5, 15, 30, 60, and 120-minute exposure durations (815, 303, 125, 47, and 31 mg/m^3, respectively), two of which (those for 30 and 60 minutes) are AEGL-specific time frames and were used as such. The 7.5-minute value served as the basis for the 10-minute AEGL-3 while the 120-minute LC_{50} was used as the basis for the 4-hr and 8-hr AEGL-3 values. These LC_{50} values were decreased 3-fold as an estimate of the lethality threshold (NRC, 2001).

Time scaling was performed using the empirically-derived exponent (*n*) of 0.82 from multiple time-point dog LC_{50} values of Allen et al. (1922). Uncertainty factor adjustment consisted of 10 for interspecies variability due to uncertainties in extrapolating from animal lethality to exposures resulting in human

deaths. An uncertainty factor of 10 accounted for uncertainties regarding individual variability in the toxic response to MD.

Summary of AEGL Values for Methyldichloroarsine (MD)						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Insufficient data
AEGL-2 (Disabling)	0.63 mg/m^3	0.14 mg/m^3	0.053mg/m^3	0.015 mg/m^3	0.0063 mg/m^3	Estimated as 1/3 reduction of AEGL-3
AEGL-3 (Lethality)	1.9 mg/m^3	0.42 mg/m^3	0.16 mg/m^3	0.044 mg/m^3	0.0 19 mg/m^3	Lethality threshold estimated as 1/3 reduction of 7.5-min., 30-min., 60-min., and 120-min LC_{50} values for dogs (Allen et al., 1922)

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

Phenyldichloroarsine (PD)

Data were unavailable with which to develop AEGL-1 or AEGL-2 values for PD. Consistent with AEGL procedures and methodologies (NRC, 2001), the AEGL-2 values for PD were estimated as a three-fold reduction of the AEGL-3 values.

The AEGL-3 values for PD were derived by assuming a 3-fold reduction of the mouse 10-minute LC_{50} of 330 mg/m^3 reported by Skipper et al. (1942) as an estimate of a lethality threshold (NRC, 2001). The resulting point-of-departure is 110 mg/m^3. Because no data were available with which to empirically derive an exponent for $C^n \times t = k$, a default of $n = 1$ was used for scaling from the 10-minute experimental value to longer AEGL-specific time periods. Due to the limited data and the uncertainties regarding extrapolation to exposure durations that are 24-fold and 48-fold greater than the 10-minute experimental time frame, the 4-hour and 8-hour AEGL-3 values are not recommended. Assuming similarity in activity to other dichloroarsines, uncertainty factors of 10 for interspecies variability (uncertainties in extrapolating from animal lethality to exposures resulting in human deaths) and 10 for intraspecific variability (insufficient data with which to assess individual variation in the toxic response to PD) were applied.

Summary of AEGL Values for Phenyldichloroarsine (PD)						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Insufficient data
AEGL-2 (Disabling)	0.37 mg/m^3	0.12 mg/m^3	0.061 mg/m^3	NR[b]	NR[b]	Estimated as 1/3 reduction of AEGL-3
AEGL-3 (Lethality)	1.1 mg/m^3	0.37 mg/m^3	0.18 mg/m^3	NR[b]	NR[b]	Estimated lethality threshold in mice (Skipper et al., 1942)

NR = Not recommended.
[a] Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.
[b] 10-minute experimental data point is insufficient to support extrapolation to 4-hour and 8-hour exposure

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1. INTRODUCTION

Adamsite (DM), diphenylchloroarsine (DA), ethyldichloroarsine (ED), methyldichloroarsine (MD), and phenyldichloroarsine (PD) are aromatic and alkyl derivatives of arsenic trichloride. Although varying in their toxic manifestation and potency, all are known for disabling effects upon contact with the skin, eyes, or respiratory tract and all were developed as anti-personnel agents (e.g., warfare agents, riot-control agents, harassing agents). Agents DA and DM are often classified as irritant arsenical smokes and were originally developed as "mask breakers" intended to penetrate the cannister portion of World War I type protective masks resulting in removal of the mask with subsequent exposure to more toxic agents. Although riot-control agents are frequently considered nonlethal, this is not necessarily the case (Cookson and Nottingham , 1969). The particulate clouds resulting from release of these agents is not persistent (NDRC, 1946).

Adamsite (diphenylaminechlorarsine; CAS Registry No. 578-94-9) is a heterocyclic chloroarsine produced as an irritant "smoke" (NDRC, 1946). The name, adamsite, was applied to this chemical primarily during World War I; the DM designation is currently more commonly used. Agent DM is often referred to as a vomiting agent. Although not considered effective as a warfare agent, at one time it was used as a riot control agent but was later considered too toxic for this application and its use discontinued. Ethyldichloroarsine (ED; CAS Registry No. 598-14-1) was developed in Germany in 1918 and, due to its capabilities as a skin and lung irritant, was used briefly as a warfare agent. Methyldichloroarsine (MD; CAS Registry No. 593-89-5) was developed by the United States Chemical Warfare Service in 1918 but not used. Phenyldichloroarsine (PD; CAS Registry No. 696-28-6) was also utilized by Germany as a warfare agent in World War I. As warfare agents, ED, MD, and PD were operationally less effective than lewisite.

In the aftermath of terrorist attacks in the United States, the reporting of numbers of munitions and bulk containers of chemical agents, and of storage quantities of agents has been suspended.

A summary of nomenclature for the chemicals of concern is presented in Table 1 and chemical/physical data for these chemicals are summarized in Tables 2-5. The hydrolysis of solid adamsite is generally considered negligible due to the formation of an oxide coating, but aerosols of adamsite hydrolyze rapidly (Salem et al., 2001). Ethyldichloroarsine and phenyldichloroarsine hydrolyze to hydrogen chloride and ethyl or phenylarsenious oxide (Sullivan and Krieger, 1992).

TABLE 1. Nomenclature of Chloroarsenical Agents

Common name	Military Designator	Chemical name/Synonyms	CAS Registry No.
Adamsite	DM	diphenylaminechlorarsine; diphenylaminochloroarsine; diphenylaminechlororarsine; diphenylaminearsine 10-chloro-5, 10-dihydrochlorphenarsazine phenarsazine chloride 5-aza-10-arsenaanthracene chloride	578-94-9
Diphenylchloroarsine	DA	diphenylchloroarsine; diphenylarsinous chloride Clark I; Blue Cross	712-48-1
Ethyldichloroarsine	ED	ethyldichloroarsine	598-94-9
Methyldichloroarsine	MD	methyldichloroarsine	593-89-5
Phenyldichloroarsine	PD	phenyldichloroarsine; dichlorophenylarsine phenyl-arsenous dichloride	696-28-6

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

TABLE 2. Chemical And Physical Data for Adamsite (DM)

Parameter	Value	Reference
Molecular formula	$C_6H_4(AsCl)(NH)C_6H_4$	Salem et al., 2001
Molecular weight	277.59	Salem et al., 2001
Physical state	crystalline powder	USACHPPM, 1996
Color	light green to yellow	USACHPPM, 1996
Solubility	insoluble in water (0.0064 g/100 g); slightly soluble in some solvents (13.03 g/100 g acetone)	USACHPPM, 1006
Vapor pressure	$2x10^{-13}$ mm Hg @20EC	Macy, 1931
Density (air = 1)	1.65@20EC (solid); negligible (vapor)	USACHPPM, 1996
Melting point	195EC	Salem et al., 2001
Boiling point	410EC	USACHPPM, 1996
Flammability limits	-	

TABLE 3. Chemical And Physical Data for Diphenylchloroarsine (DA)

Parameter	Value	Reference
Molecular formula	$C_{12}H_{10}AsCl$	
Molecular weight	264.5	Macy, 1931
Physical state	crystalline powder	
Color	colorless	Lewis, 1997
Solubility	-	
Vapor pressure	0.0005 mm Hg @ 20 EC 0.0007 mm Hg @ 25 EC	Macy, 1931
Density (air = 1)	-	
Melting point	333 EC	Trammell, 1992
Boiling point	-	
Flammability limits	-	

TABLE 4. Chemical And Physical Data for Ethyldichloroarsine (ED)

Parameter	Value	Reference
Molecular formula	$C_2H_5AsCl_2$	
Molecular weight	174.89	Lewis, 1997
Physical state	liquid	Lewis, 1997
Color	colorless	Lewis, 1997
Solubility	soluble in alcohol, benzene, ether	Lewis, 1997
Vapor pressure	2.29 mm Hg @ 21.5 EC	Lewis, 1997
Density (air = 1)	1.74 @ 14 EC	Lewis, 1997
Melting point	-65 EC	Lewis, 1997
Boiling point	156 EC	Sullivan and Krieger, 1992
Flammability limits	-	

TABLE 5. Chemical And Physical Data for Methyldichloroarsine (MD)

Parameter	Value	Reference
Molecular formula	CH_3AsCl_2	
Molecular weight	160.90	Macy, 1931
Physical state	liquid	Macy, 1931
Color	-	
Solubility	-	
Vapor pressure	7.59 mm Hg @20EC 10.19 mm Hg @25EC	Macy, 1931
Density (air = 1)	1.559	NDRC, 1946
Melting point	42.5 EC	NDRC, 1946
Boiling point	132.5 EC	NDRC, 1946
Flammability limits	-	

TABLE 6. Chemical And Physical Data for Phenyldichloroarsine (PD)

Parameter	Value	Reference
Molecular formula	$C_6H_5AsCl_2$	
Molecular weight	222.93	Lide and Milne (1994)
Physical state	liquid	Lewis, 1997
Color	colorless	
Solubility	soluble in acetone, benzene, ether; insoluble in water	HSDB 2004
Vapor pressure	0.0036 @ 45 EC	Salem et al., 2001
Density (air = 1)	7.7 (no temp. specified)	Lewis, 1997
Melting point	-	
Boiling point	255 EC	Lide (Ed), 2000
Flammability limits	-	

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Adamsite (DM)

An LCt_{50} of 11,000 mg · min/m^3 has been estimated for humans (Owens et al., 1967). The death of an individual following inhalation of DM was also reported by Owens et al. (1967). The exposure concentration was estimated at 1,130 to 2,260 mg/m^3 and the exposure duration was equivocal (5 minutes by one source and 30 minutes by another). Postmortem findings in this individual and in an individual killed following an accidental exposure to an unspecified high concentration of DM in a confined space were severe damage to the airways and lungs.

Diphenylchloroarsine (DA)

Agent DA is a sternutator and vomiting agent (Beebe, 1924; Prentiss, 1937). Acute lethality data for humans is limited. Prentiss (1937) reported 15,000 mg • min/m^3 as a lethal concentration for a 10-minute exposure but the value is not verifiable. Based upon data in CWS (1944), NDRC (1946) estimated that the human LCt_{50} would be greater than 10,000 mg • min/m^3 and that, due to the non-persistence of DA vapor clouds, deaths from DA would occur only under very unusual circumstances.

Ethyldichloroarsine (ED)

A median lethal dose (MLD_{50}) of 3000 to 5000 mg • min/m^3 has been cited (Sullivan and Krieger, 1992). No details are available regarding the development of this value.

Methyldichloroarsine (MD)

No data were available regarding lethality of humans exposed to methyldichloroarsine.

Phenyldichloroarsine (PD)

A median lethal dose (MLD_{50}) of 2,600 mg • min/m^3 has been cited (Sullivan and Krieger, 1992) but information is unavailable regarding the origin of this value.

2.2. Nonlethal Toxicity

2.2.1. Case Reports/Individual Studies

Adamsite (DM)

Macy (1932) reported an odor detection threshold of 2.5 mg/m^3. No additional information regarding exposure conditions was available.

Nonlethal effects of DM exposure in humans have been characterized as coughing and sneezing, acute pain in the nose and sinuses, irritation of the nasopharyngeal region, tightness and pain in the chest, and ocular effects (burning and tearing, blepharospasm, and conjunctival injection) (Gongwer et al., 1958; Owens et al., 1967; WHO, 1970; Ballantyne, 1977; FM 8-285, 1995). Punte et al. (1962) reported slight burning of the nose and throat in laboratory personnel while they were conducting animal experiments with DM. Exposure to DM also exhibits latency in effects and a propensity for prolonged systemic involvement (Sidell, 1997). Latency periods are brief (several minutes). Systemic effects including headache, depression, gastrointestinal disorders (nausea, vomiting, abdominal cramps, diarrhea), and chills which may last for several hours. Specific exposure-response data in humans are limited.

Some studies conducted prior to 1921 attempted to determine tolerance levels of humans exposed to low levels of DM for brief periods (<1 min to ~15 min). Subsequent evaluation of these studies found serious deficiencies in test atmosphere generation and concentration determinations (Craighill and Folkoff, 1922).

An early study by Lawson and Temple (1922) provided preliminary information regarding the response of human subjects to ocular and inhalation exposure to DM. Symptoms of exposure were more pronounced after exposure than during exposure, and the severity was directly related to the concentration of DM. At lower concentrations, the effects were negligible but the highest concentrations tested resulted in severe distress for 2-3 hours. Signs and symptoms during exposure included nasal and throat irritation followed by discomfort in the chest and coughing. After exposure burning and tightness of the chest occurred along with a persistent rasping cough, burning sensation in the nose and throat and general depression. It was reported that the severity of these effects peaked at about 10 minutes post exposure. Based upon the responses of four to five volunteers, the investigators estimated average tolerance levels for various concentration-time exposures (Table 7).

Table 7. Response of Human Volunteers to Inhalation of DM[a]

Concentration	Exposure Duration	Ct	Effect
0.53 mg/m^3	6.5 min	3.3 mg • min/m^3	average tolerance of 5 male subjects
0.276 mg/m^3	11.1 min	3.1 mg • min/m^3	average tolerance of 4 male subjects
0.275 mg/m^3	11.2 min	3.1 mg • min/m^3	average tolerance of 5 male subjects
0.133 mg/m^3	60 min	7 mg • min/m^3	average tolerance of 2 male subjects
0.141 mg/m^3	60 min	8 mg • min/m^3	average tolerance of 1 male
0.201 mg/m^3	25.97 min	5 mg • min/m^3	average tolerance of 4 male subjects
0.97 mg/m^3	3.92 min	4 mg • min/m^3	average tolerance of 5 male subjects
1.01 mg/m^3	3.92 min	4 mg • min/m^3	average tolerance of 7 male subjects
2.22 mg/m^3	2.8 min	6 mg • min/m^3	average tolerance of 5 male subjects
6.00 mg/m^3	2.05 min	12.3 mg • min/m^3	average tolerance of 6 male subjects
14.0 mg/m^3	1.28 min	18 mg • min/m^3	average tolerance of 10 male subjects
22.3 mg/m^3	0.93 min	24 mg • min/m^3	average tolerance of 6 male subjects
45.0 mg/m^3	0.77 min	59 mg • min/m^3	average tolerance of 7 male subjects
61.4 mg/m^3	0.68 min	90 mg • min/m^3	average tolerance of 6 male subjects

[a] These exposures were the subjectively determined maximum tolerated exposure.
Lawson and Temple, 1922.

The Lawson and Temple (1922) study was also evaluated by Craighill and Folkoff (1922) and was considered to be carefully and accurately conducted with only minimal error in concentration determination. Using the data from the Lawson and Temple, Craighill and Folkoff (1922) determined intolerable concentrations for specific exposure durations somewhat different from the experimental periods reported by Lawson and Temple (Table 8). These were simply based upon calculating concentrations from a Ct vs time plot of the Lawson and temple data.

Table 8. Estimation of Intolerable Exposure Concentrations for Adamsite (DM)

Exposure Concentration		Exposure Time (min)
mg/L	mg/m^3	
0.0490	49	0.75
0.0255	22.5	1
0.0058	5.8	2
0.0022	2.2	3
0.0010	2.0	4
0.00072	0.78	5
0.00030	0.30	10
0.00023	0.23	15
0.00019	0.19	20
0.00017	0.17	30
0.00014	0.14	60

Craighill and Folkoff, 1922

Additional tolerance and minimum effect exposures were reported by investigators at Aberdeen proving Ground (Craighill and Folkoff, 1922; Beebe, 1924; Kibler, 1942; CWS, 1944). These exposure-effect estimates are summarized in Table 9.

Table 9. Response of Human Volunteers to Inhalation of DM

Concentration	Exposure Duration	Ct	Effect
0.1 mg/m^3	1 min	0.1 mg @ min/m^3	lowest detectable concentration (cited by Beebe, 1924)
0.3 mg/m^3	3 min	0.9 mg @ min/m^3	lacrymation (cited by Beebe, 1924)
117 mg/m^3	0.85 min	100 mg @ min/m^3	intolerable (cited by Beebe, 1924)
0.23 mg/m^3	15 min	3.45 mg @ min/m^3	lowest intolerable concentration (cited by Craighill and Folkoff, 1922)
0.72 mg/m^3	5 min	3.6 mg @ min/m^3	lowest intolerable concentration (cited by Craighill and Folkoff, 1922)
22 mg/m^3	1 min	22 mg @ min/m^3	lowest intolerable concentration (cited by Craighill and Folkoff, 1922)
0.22 mg/m^3	1 min	0.22 mg @ min/m^3	throat irritation (cited by Kibler, 1942)
2 mg/m^3	2 min	4 mg @ min/m^3	minimum harassment (cited by Kibler, 1942)
2.2 mg/m^3	3 min	6.6 mg @ min/m^3	intolerable (cited by Kibler, 1942)
8 mg/m^3	0.5 min	4 mg @ min/m^3	minimum harassment (cited by Kibler, 1942)
0.38 mg/m^3	1 min	0.38 mg @ min/m^3	lowest concentration for throat irritation (cited by CWS, 1944)
0.5 mg/m^3	1 min	0.5 mg @ min/m^3	lowest concentration for lower respiratory tract irritation (cited by CWS, 1944)

Gongwer et al. (1958) conducted a series of investigations in which human volunteers were exposed to DM under varying regimens. These studies were conducted in accordance with principles, policies, and rules established at that time regarding human volunteer subjects. The subjects were screened to avoid inclusion of individuals with histories of allergies, or pulmonary pathology. The human exposures occurred in two phases. The first phase (30-second duration) involved subjects utilizing a face mask and breathing DM from a 200 L dynamic flow chamber. The mask allowed for exposure of the eyes, nose, and mouth. The second exposure protocol (120-second exposure) was whole-body exposure in a 20 m^3 chamber. For both exposure protocols, the subjects were instructed to remove themselves from exposure when, in their judgement, the exposure became intolerable. The subjects were not allowed to maintain exposure beyond a preset limit (not specified) regardless of their tolerance threshold. Samples of the test atmospheres were analyzed during each exposure to determine actual tolerance level for each subject. Details regarding analytical techniques were not provided. Airway resistance of the subjects was determined before and after whole-body exposures. Effects of DM were qualitatively characterized by an initial burning sensation in the airways which, upon removal from DM exposure and exposure to fresh air, were accentuated and accompanied by salivation, severe coughing and sneezing. These

responses persisted for up to two hours. One severe reaction, lasting 20-25 minutes, included face flushing, trembling, profuse sweating, severe chest pain, and uncontrollable coughing. Full recovery in this individual took several hours. The results of the Gongwer et al. (1958) study on DM are summarized in Table 10. In estimating the relative safety of various tested agents, Gongwer et al. (1958) considered 1,000 mg • min/m^3 as a minimum lethal Ct for humans and estimated the effective 1-minute Ct_{50} for humans at >100 mg • min/m^3.

Table 10. Results of Tolerance Studies on Human Volunteers Exposed to DM.

Concentration (mg/m^3) Minimum	Maximum	Response Ratio for Intolerance
30-Second Exposure (face mask)		
2	10	0/10
11	20	0/11
21	50	0/4
51	100	0/1
101	360	-
120-Second Exposure (whole body)		
2	10	0/10
11	20	1/11
21	50	0/4
51	100	1/1
101	360	-

Gongwer et al., 1958.

Quantitative estimates of exposures considered intolerable (22-92 mg/m^3 for 1-minute duration) were reported by McNamara et al. (1969). McNamara et al. (1969) also noted that, under experimental conditions, exposure to 22-220 mg/m^3 for one minute would likely be intolerable to 50% of the population. A threshold of 1 mg/m^3 for unspecified irritation was reported by Owens et al. (1967). More specifically, Owens et al. (1967) estimated threshold exposures of 0.38, 0.5, and 0.75 mg/m^3 for irritation of the throat, lower respiratory tract and initiation of the cough reflex, respectively. DM is often functionally classified as a sternutator (inducing sneezing) and vomiting agent. However, the specific exposure necessary to induce vomiting is uncertain (Sidell, 1997). Owens et al. (1967) reported on results of early studies (1922-1958) showing that exposure of human volunteers (number not specified) to cumulative exposures of 4.6 to 144 mg · min/m^3 resulted in less than 10% incidence for nausea. The nausea threshold for exposure to DM was estimated by Ballantyne (1977) to be ~370 mg · min/m^3.

In experiments conducted at Edgewood Arsenal, 67 individuals were exposed to DM (Owens et al., 1967). The subjects were exposed to DM in aerosol chambers. Individuals were masked upon entry and the masks apparently removed at specified times and for specified durations. Subjects in the earlier set of tests received one to five exposures to DM over one or two days while subjects in the later experiments received only one exposure each. Specific exposure concentration and duration data for the

complete array of experiments, however, are incomplete. One test exposure of 14 subjects in the earlier study involved cumulative exposures of 7.1 to 100 mg • min/m^3; exposure times for eight of the subjects ranged from 1 minute to 4 minutes and 28 seconds. In the later experiments where there was only one exposure per subject, cumulative exposures ranged from 7.1 to 236 mg • min/m^3 with exposure times ranging from 45 seconds to 10 min, respectively.

The most prevalent effects were respiratory tract irritation (burning sensation in the airways, dysphonia, choking, coughing, sneezing, and dyspnea) and nausea. Occurring less frequently were anorexia, retching, headache, dizziness, lacrimation, salivation, and increased urination. Less frequently occurring effects included rhinorrhea, wheezing, conjunctivitis and diaphoresis. Blood differential counts and urinalysis revealed no abnormalities at seven days post exposure and the aforementioned effects were not persistent. Longer-term follow-up of these subjects was not indicated.

Diphenylchloroarsine (DA)

Odor detection thresholds of 0.3 mg/m^3 (War Dept. 1942) and 0.5 mg/m^3 have been reported (Dept. Army and Air Force, 1952).

The most prevalent effects of DA are severe irritation of the eyes, nose, and throat (NDRC, 1946). Diphenylchloroarsine is generally considered to be primarily a sternutatory agent.

Macy (1931)cited irritation thresholds in humans of 1.5 mg/m^3 (nose irritation) and 2.5 mg/m^3 (throat irritation) for 3-minute exposures. No further details were available.

Prentiss (1937) summarized the effects of inhaled DA but did not relate these effects to any specific exposures. In addition to sensory irritation, neuromuscular effects including motor disturbances, irregular gait, swaying, and inability to walk were noted. Prentiss also stated these effects were often accompanied by severe pain in the joints and limbs. Exposure to non-specified "very high concentrations" reportedly resulted in giddiness, faintness, and unconsciousness of several hours duration.

In an effort to assess the physiological versus psychological effects of agent DA, studies were conducted in which groups of military personnel (numbers not specified in the review of this study) were exposed to either DA or to harmless smoke (Porton Report, 1942; reviewed in NDRC, 1946). In theses studies, the volunteers in each group were exposed to DA (0.266 mg/L) or the harmless smoke for two minutes after which their performance through an assault corse was evaluated. Two-thirds of the group exposed to DA were unaffected while the remaining third exhibited a decrease in performance and 7% were unable to complete the course. No further details were available in the NDRC review of this study.

Ethyldichloroarsine (ED)

Ethyl dichloroarsine reportedly has a biting, fruit-like and very irritating odor (Sullivan and Krieger, 1992; HSDB 2004). No information is available regarding odor threshold or detection limits.

Sullivan and Krieger (1992) reported 5-10 mg • min/m^3 as a median temporarily incapacitating (ICt_{50}) exposure but no details regarding the development of this value were available.

Methyldichloroarsine (MD)

No definitive data were available regarding nonlethal responses of humans to methyldichloroarsine inhalation exposures. Macy (1931) cited and odor threshold of 0.8 mg/m^3 and a nasal irritation threshold of 0.9 mg/m^3 (no exposure duration). No additional information was available.

Phenyldichloroarsine (PD)

Sullivan and Krieger (1992) state that DA is odorless. A median incapacitating (ICt_{50}) doses for vomiting (16 mg • min/m^3) and dermal blistering (1800 mg • min/m^3) have been cited (Sullivan and Krieger, 1992) but no details are available regarding the development of these values.

2.2.2. Epidemiology Studies

Epidemiologic studies regarding human exposure to the title chloroarsines were not found in the available literature.

2.2.3. Other

Adamsite (DM)

Adamsite is generally considered odorless (Salem et al., 2001), although Sim (1971) describes an odor similar to that of burning fireworks. The odor characteristics or lack thereof and the latency in effects may potentially result in delay in donning protective measures in exposure situations, thereby resulting in injury that could have been prevented.

2.3. Developmental/Reproductive Effects

No human developmental/reproductive toxicity data concerning the chloroarsines were found in the available literature.

2.4. Genotoxicity

No human genotoxicity data on the title chloroarsines were found in the available literature.

2.5. Carcinogenicity

No data were found in the available literature regarding the carcinogenic potential of the chlroarsenical agents in humans.

2.6. Summary

Information regarding human lethality from exposure to chloroarsenicals are limited to an incompletely characterized accident report for DM, and human lethal exposure estimates derived from animal data. The response of human volunteer subjects to low level exposures (<90 mg • min/m^3) of DM for short durations (<1 minute to 60 minutes) provided estimates of tolerance thresholds determined by ocular and respiratory tract irritation. Latency in effects was also verified along with full recovery. NDRC (1946) estimated the human LCt_{50} for agents DA and DM to be greater than 10 mg • min/L based upon available data. NDRC further noted that, due to the nonpersistent nature of the aerosol clouds from these agents, human deaths from exposure to the arsenical smokes would be unlikely except under very unusual conditions. Additional information from various sources also indicated irritation as a primary effect but quantitative information was limited to estimated odor thresholds and nonverifiable estimates of incapacitating exposures.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Monkeys

Adamsite (DM)

Striker et al. (1967a) exposed groups of 10 monkeys (*Macaca mulatta*) to DM aerosols (from No. 113 grenades) for 3 minutes (855 mg/m^3), 5 minutes (1,708 mg/m^3), or 11 minutes (2,615 mg/m^3) (Table 11). Two monkeys from each group were terminated and examined at 12 hours and 24 hours, and at 3, 7, and 30 days after the exposures. No deaths occurred at the low or mid dose but eight monkeys in the high-exposure group died within 24 hours, another was sacrificed at 24 hours, and the 10th died on day 29. The monkey terminated for examination at 24 hours post exposure exhibited early bronchopneumonia, pulmonary edema, emphysema, ulceration of the trachea and bronchi and visceral congestion.

Table 11. Effects of Acute Exposure of Monkeys to Adamsite (DM) Aerosols.

Exposure Concentration (mg/m^3)	Exposure Duration (min)	Ct (mg•min/m^3)	Effects
855	3	2565	superficial tracheitis, edema of trachea and bronchial mucosa in one monkey at 12 hrs post exposure; no other effects noted for any monkeys at any examination time.
1708	5	8540	At 12 hrs bronchorrhea, focal pulmonary edema and congestion in 2 monkeys At 24 hrs, more pronounced edema and congestion (incidence not specified); membranous tracheitis and focal pulmonary hemorrhage in one monkey At 72 hrs, no edema or congestion At 7 days, emphysema and atelectasis in one monkey; no findings in 2nd monkey At 30 days, emphysema and atelectasis in one monkey; extensive early pneumonia in 2nd monkey
2615	11	28,765	8 monkeys died within 24 hrs At 24 hrs, one monkey terminated exhibited bronchial and pulmonary damage, and visceral congestion At 29 days, last monkey died; exhibited similar lesions as above.

Striker et al., 1967a.

Owens et al. (1967) conducted studies with monkeys, dogs, and guinea pigs which provided lethal response data (Table 12). The DM aerosols were generated from a No. 113 grenade. Data for monkeys from two different 10-day exposure regimens (11,609 mg•min/m^3 per day and 17,302 mg•min/m^3 per day) are summarized in Table 12. Both of these exposures were below the LCt_{50}.

Table 12. Lethal Response in Monkeys Exposed to Adamsite (DM) Aerosol.	
Exposure	**Mortality fraction**
11,609 mg•min/m^3 per day	5/8
17,302 mg•min/m^3/day	8/8

Owens et al., 1967.

The lethality of agent DM (dispersed in 10% acetone solution) in monkeys was examined by McNamara et al. (1969). For these experiments agent DM was dispersed in a 10% acetone solution. Exposure and time-to-death data for these experiments are shown in Table 13. The time-to-death varied as much as nine-fold within some exposure regimens.

Table 13. Lethality in Monkeys Following Acute Inhalation Exposure to Adamsite (DM)				
Exposure concentration (mg/m^3)	**Exposure duration (min)**	**Mortality ratio**	**Time-to-death (hrs)**	**LCt_{50}[a] (mg•min/m^3)**
296	135	6/6	28, 43, 149, 190 (2), 248	40,000
214	117	6/6	43, 47, 67, 148, 235, 307	25,085
219	95	4/6	42, 65, 238, 286	20,800
209	80	3/6	192, 278, 350	16,700
279	46	0/6	-	12,555
297	20	0/6	-	5,040

[a] Reported as Bliss-calculated value
Numbers in parenthesis are number of deaths at that time.
McNamara et al., 1969.

Diphenylchloroarsine (DA)
No data were available regarding the lethal toxicity of DA in monkeys.

Ethyldichloroarsine (ED)
No data were available regarding the lethal toxicity of ED in monkeys.

Methyldichloroarsine (MD)
No data were available regarding the lethal toxicity of MD in monkeys.

Phenyldichloroarsine (PD)
No data were available regarding the lethal toxicity of PD in monkeys.

3.1.2. Dogs

Adamsite (DM)

Craighill and Folkoff (1922) analyzed data from previously conducted studies with dogs. In these experiments, 26 dogs were exposed for 30 minutes to various concentrations of DM (0.40- 1.01 mg/L, analytical; equivalent to 400 - 1010 mg/m^3). No details were available regarding the analytical techniques used to determine the concentrations; analytical values tended to be lower than nominal values. Results of this study are shown in Table 14. It was concluded that a 30-minute exposure to 0.40-0.62 mg/L (400-620 mg/m^3) was the lowest concentration causing death within 12 days while exposure to 0.65 mg/L (650 mg/m^3) would result in death within 48 hours. An evaluation of this study by Craighill and Folkoff found it to be a carefully conducted set of experiments but that analytical and nominal concentrations often did not closely correspond.

Table 14. Acute Lethality of Dogs Following 30-Minute Inhalation Exposure to Adamsite (DM)[a]

Concentration (mg/m^3)	Percent Lethality	Remarks
900	100	both dead at 18 hrs
920	100	dead at 12 and 48 hrs
1010	50	one dead at 4 days, second killed at 12 days
810	50	one dead at 12 hrs, second killed at 15 days
600	50	one dead at 50 hrs, second killed at 12 days
300	100	one dead at 48 hrs, second dead at 3 days
800	50	one dead at 48 hrs, second discharged after 12 days
600	50	one dead at 14 days, second killed after 14 days
530 (nominal)	50	one dead at 7 days, second discharged at 9 days
700	50	one dead at 10 days, second discharged at 12 days
400	50	one dead at 12 days, second discharged at 14 days
140	0	one killed after 9 days second discharged at 9 days
110	0	both discharged at 9 days

[a] Two dogs per exposure concentration.
Ransom and Bogart as cited in Craighill and Folkoff, 1922.

Lethality data for dogs from the Owens et al. (1967) studies are shown in Table15. These experiments also utilized DM aerosols from No. 113 grenades and two different 10-day exposure regimens (11,609 mg•min/m^3 per day and 17,302 mg•min/m^3 per day). Dogs were notably less responsive than the monkeys and guinea pigs.

Table 15. Lethal Response in Dogs Exposed to Adamsite (DM) Aerosol.

Exposure	Mortality fraction
11,609 mg•min/m^3 per day	1/8
17,302 mg•min/m^3/day	2/8

Owens et al., 1967.

McNamara et al. (1969) reported LCt_{50} values for dogs exposed to DM in 10% acetone (Table 16). Time-to-death varied as much as 6-fold for any given Ct product.

Table 16. Lethality in Dogs Following Acute Inhalation Exposure to Adamsite (DM)

Exposure concentration (mg/m^3)	Exposure duration (min)	Mortality ratio	Time-to-death (hrs)
209	110	6/6	10, 16, 17, 35(3)
279	45	4/6	18. 20, 42, 116
206	44	5/6	63, 86, 278, 136, 356
297	20	1/6	305
212	14	0/6	-

Numbers in parenthesis are number of deaths at that time.
McNamara et al., 1969.

Diphenylchloroarsine (DA)

Dog lethality data were reported by MMW (1918). These data are shown in Table 17. The value of these data is limited by the small numbers of dogs tested and the spurious results. Details regarding the experiments were not available.

Table 17. Lethality in Dogs Exposed to DA at Varying Exposure Regimens

Exposure concentration (mg/m^3)	Exposure duration (min)	Cumulative exposure ($mg•min/m^3$)	Response
236	-	7080	1 of 2 dead
1180	10	11,800	0 of 2 dead
590	30	17,700	3 of 4 dead
295	60	17,700	1 of 2 dead
1180	30	35,400	0 of 1 dead

MMW(1918)

Ethyldichloroarsine (ED)

No data were available regarding the lethal toxicity of ED in dogs.

Methyldichloroarsine (MD)

A study was conducted in which a total of 116 dogs (11-30 per exposure group; age, gender, breed not specified) were exposed to MD at average concentrations of 846±90 (21 dogs), 377±74 (26 dogs), 160±38 (28 dogs), 59±18 (30 dogs), or 33±4 mg/m^3 (11 dogs) for durations of 7.5, 15, 30, 60, or 120 minutes, respectively (Allen et al., 1922). The MD was 98.5% pure and test atmospheres were generated by electric pumps passing a constant flow of air through a mixing bulb with the test article. Concentrations were nominally estimated by flow rate, chamber volumes, and loss of test article. During the exposures, dogs responded with eye blinking and sneezing within 1 minute and lasting throughout the exposure. As exposure continued, the dogs exhibited lachrymation, nasal discharge, salivation, vomiting, and excitability (longer exposures were characterized by depression following the excitation). Immediately following the exposure, the dogs were lethargic and most exhibited a frothy, oral discharge and labored, erratic breathing. Latency in effects was observed, especially for the more serious effects leading to death. Twenty eight percent of the deaths occurred within 24 hours of exposure, and 48% occurred at 24-48 hours post exposure. Only 6% of deaths occurred after 100 hours of exposure although some possibly treatment-related deaths (pneumonia) occurred as late as six weeks after exposure. Pathological/toxicological findings were categorized into three groups based upon the overall clinical observations, severity of respiratory tract damage and systemic involvement. Generally, the most critical effects were tracheo-bronchial/pulmonary damage which often led to death. Mortality ratios for the 7.5, 15, 30, 60, and 120-minute exposure groups were 13/21 (14%), 17/26 (59%), 20/28 (71%), 20/30 (67%) and 9/11 (82%). Cumulative exposure products (Ct) for the test groups were 6345, 5655, 9600, 3540, and 3960 $mg•min/m^3$. Allen et al. (1922) reported the following LC_{50} values: 815 mg/m^3 (7.5 min), 303 mg/m^3 (15 min), 125 mg/m^3 (30 min), 47 mg/m^3 (60 min), and 31 mg/m^3 (120 min). Exposure duration rather than concentration appeared to have been more instrumental in determining the severity of the toxic response.

Phenyldichloroarsine (PD)

No data were available regarding the lethal toxicity of PD in dogs.

3.1.3. Rats

Adamsite (DM)

Gongwer et al. (1958) reported LCt_{50} and minimum lethal exposures for several species including rats. In these experiments exposure durations ranged from 15 to 60 minutes and exposure concentrations ranged from 50 to 4000 mg/m^3. Airborne concentrations were determined by periodic sampling of the exposure chambers. No further details were provided regarding experimental protocols or study conduct. The LCt_{50} for rats (neither strain nor gender specified) was 3000 mg • min/m^3 and the minimum lethal exposure was 1200 mg • min/m^3.

Punte et al. (1962) conducted inhalation studies to assess the toxicity of DM in several animal species including rats. In these experiments, groups of 24 adult male rats were exposed in 200 L dynamic exposure chambers (800 L/min airflow) to aerosols of DM for 5 to 90 minutes. The aerosols were generated by passing dry air or nitrogen through an aspirator to which was attached a flask of agent kept 10-15 EC above its melting point. Mass median aerodynamic diameter was determined. The rats were observed for 14 days following exposure at which time survivors were killed for histopathological examination. Upon exposure, the rats immediately became hyperactive followed by signs of nasal and ocular irritation within one minute. At 5-15 minutes, the rats became lethargic and exhibited labored breathing the latter persisting up to two hours after exposure. An LCt_{50} of 3700 mg • min/m^3 was determined by the method of Bliss. Necropsy of dead and sacrificed rats revealed tracheal hyperemia, pulmonary congestion and edema, and pneumonia. Most deaths occurred at days 2 and 3 and no deaths occurred after day 6. The specific exposure regimens were not specified, and there were no pathological findings in rats exposed to 500 mg • min/m^3.

Lethality data for rats are summarized in Table 18 (McNamara et al., 1969). Rats exhibited considerable variability in time-to-death.

Table 18. Lethality in Rats Following Acute Inhalation Exposure to Adamsite (DM)

Exposure concentration (mg/m^3)	Exposure duration (min)	Mortality ratio	Time-to-death (hrs)
223	273	20/20	4, 8, 20(4), 47(5), 71, 95(2), 118(2), 124, 147(2), 168
296	135	20/20	1(2), 47(12), 120(10), 190(4), 216(2)
214	117	18/20	29, 110(12), 134, 158, 211(3)
216	91	14/20	68(3), 140(3), 146, 148, 166(6)
209	80	1/20	11
279	45	1/20	21
297	20	0/20	-

Numbers in parenthesis are number of deaths at that time.
McNamara et al., 1969.

Diphenylchloroarsine (DA)

Lethality in rats exposed to DA (MMW, 1918) are summarized in Table 19. No experimental details are available regarding these data. The limited data suggest that at an equivalent cumulative exposure (i.e., 17,700 mg • min/m^3) exposure duration appears to be a greater determinant of lethal response than does exposure concentration.

Table 19. Lethality in Rats Exposed to DA at Varying Exposure Regimens

Exposure concentration (mg/m^3)	Exposure duration (min)	Cumulative exposure (mg•min/m^3)	Response
236	30	7080	0 of 4 dead
118	60	7080	0 of 4 dead
295	30	8850	1 of 2 dead
1180	15	17,700	0 of 4 dead
590	30	17,700	2 of 6 dead
295	60	17,700	2 of 2 dead
2361	10	23,610	3 of 4 dead
1180	30	35,400	5 of 8 dead

MMW(1918)

Ethyldichloroarsine (ED)

No data were available regarding the lethal toxicity of ED in rats.

Methyldichloroarsine (MD)

No data were available regarding the lethal toxicity of MD in rats.

Phenydichloroarsine (PD)

No data were available regarding the lethal toxicity of PD in rats.

3.1.4. Mice

Adamsite (DM)

Gongwer et al. (1958) reported an LCt_{50} for mice (neither strain nor gender were specified) of 30,000 mg • min/m^3 and a minimum lethal exposure of 1000 mg • min/m^3. No further details were provided

In the Punte et al. (1962) study (§3.1.3.), groups of 42 adult male mice (20-30 g) were exposed in 200 L dynamic exposure chambers (800 L/min airflow) to aerosols of DM for 5 to 90 minutes. The mice were observed for 14 days following exposure at which time survivors were killed for histopathological examination. The response of the mice was reportedly similar to that of the rats (initial hyperactivity followed by nasal and ocular irritation within one minute and lethargy and labored breathing at 5-15 minutes that persisted up to two hours after exposure). An LCt_{50} of 22,400 mg • min/m^3 was determined by the method of Bliss. An estimated dose (LC_{50}) of DM, based upon respiratory parameters, body weight, estimated retention of agent and the LCt_{50} determination was 17.9 mg/kg. Necropsy of dead and

sacrificed mice revealed tracheal hyperemia, pulmonary congestion and edema, and pneumonia; findings similar to those in the rats. Most deaths occurred at days 2, 3, and 6 but some occurred at 9 days and beyond.

Diphenylchloroarsine (DA)

Lethality data for mice exposed to DA are limited (Table 20). Most of the data are from secondary sources and, therefore, not verifiable. Information on analytical techniques was not available.

Table 20. Lethality in Mice Exposed to DA for 10 Minutes at Varying Concentrations

Exposure concentration (mg/m^3)	Exposure duration (min)	Cumulative exposure ($mg•min/m^3$)	Response/Reference
298	10	2980	LC_{lo} (cited by CWS, 1944)
690		6900	LC_{50} (EATR, 1933)
853		8530	LC_{50} (cited by CWS, 1944)
1300		13,000	LC_{50} (cited by Kibler, 1942)

Ethyldichloroarsine (ED)

A mouse LCt_{50} value of 1.555 mg • min/L was reported by Hutchens et al. (1943). In these experiments, mice were exposed (whole body) for 10 minutes and observed for 10 days. To avoid complications resulting from varying degrees of moisture in the animals' fur, the mice were exposed to low humidity air (20-30%) for one hour prior to being exposed to the test article. The ethyl dichloroarsine atmosphere was generated by passing the chemical through dry nitrogen at 25-30 EC.

An LCt_{50} of 3.4 mg • min/L (nominal) was also reported in EATR (1941).

Methyldichloroarsine (MD)

The effects of humidity on the toxicity of MD in mice was reported by Wells (1924). The study was conducted in response to concerns regarding the fact that MD readily hydrolyzed to the more toxic methyl arsenious oxide and, therefore would become more toxic with increasing relative humidity. In this study, mice (gender, strain, age not specified) were exposed for 10 minutes to MD at varying concentrations at varying relative humidity (RH). Twelve groups of five mice were exposed to 0.450 to 0.840 mg/L (450 - 850 mg/m^3) at 37-50% RH, 15 groups of five mice were exposed to 0.17 to 1.01 mg MD/L (170 - 1010 mg/m^3) at 17-21% RH, 13 groups of five mice were exposed to 0.20 to 1.94 mg MD/L (200 - 1940 mg/m^3) at 78-92% RH, and 20 groups of five mice were exposed to 170 to 1010 mg MD/L (1.70 - 1.01 mg/m^3) at 69-72% RH. The resulting 10-minute LC_{50} values for the four groups are summarized in Table 21. Lethality thresholds (10-min LC_{01}) values were also calculated using the method of Litchfield and Wilcoxon (1949). Wells concluded that as humidity increased, the increased hydrolysis resulted in increased toxicity. However, as humidity continued to increase, the more toxic hydrolysis product became less available for inhalation due to increasing particle agglomeration effectively reducing toxic potential.

Table 21. Effect of Relative Humidity on Lethality of MD in Mice Exposed for 10 Minutes.

Relative Humidity	No. Mice per Group	10-min LC_{50}	10-min LC_{01} [a]
17-21%	15	930 mg/m^3	-
37-50%	12	560 mg/m^3	257 mg/m^3
69-72%	20	680 mg/m^3	68 mg/m^3
83-92%	13	1,940 mg/m^3	163 mg/m^3

Wells, 1924

[a] Calculated using method of Litchfield and Wilcoxon (1949)

Phenyldichloroarsine (PD)

Mouse LCt_{50} values of 3.3-3.4 mg/L (nominal) and 3.7 mg/L (nominal) were reviewed by NDRC (1946). These values were developed from 10-minute exposures with a 10-day observation period. No further details were provided in NDRC (1946). The NDRC review was apparently based upon studies by Skipper et al. (1942) in which seven groups of 20 mice (age, body weight, gender not specified) were exposed to PD for 10 minutes and observed for 10 days. The exposure concentrations were determined as the quotient of loss of PD (expressed in mg) from a source bath divided by the product of flow rate (L/min) x time (min). Nominal concentrations of PD were 0.10, 0.10, 0.22, 0.27, 0.45, 0.48, and 0.53 mg/L (equivalent to 100, 100, 220, 270, 450, 480, and 530 mg/m^3). Mortality rates and time of death are shown in Table 22. Most deaths occurred within 24 hours of exposure. Under the conditions of this study, the investigators estimated the median lethal concentration of PD in mice to be 0.33±0.08 mg/L (330±80 mg/m^3).

Table 22. Mortality in Mice Exposed for 10 Minutes to Phenyldichloroarsine.

Exp. No.	Conc (mg/m^3)	Daily cumulative deaths										Mortality (%)
		1	2	3	4	5	6	7	8	9	10	
1	100	0	0	0	1	1	1	1	1	1	1	5
5	100	0	0	0	0	0	0	0	0	0	0	0
7	220	0	1	2	2	2	2	2	2	2	2	10
6	270	0	0	0	0	0	0	0	0	0	0	0
2	450	9	13	14	15	15	15	15	15	15	15	75
3	480	11	11	11	11	11	11	11	11	11	11	55
4	530	17	18	18	18	19	19	19	19	19	19	95

Skipper et al., 1942.

3.1.5. Rabbits

Adamsite (DM)

Lethality data for rabbits (McNamara et al., 1969) were summarized by NRC 1984). A 100% mortality was observed for a Ct of 20,900 mg @ min/m^3 (279 mg/m^3 for 75 minutes) and 66% mortality at 8050 mg @ min/m^3 (268 mg/m^3 for 30 minutes) based upon experiments with groups of six rabbits.

Diphenylchloroarsine (DA)

MMW (1918) provides the only information regarding lethality of DA in rabbits (Table 23). Details regarding experimental protocol were not available for review. The data suggest that, for the exposure regimens tested, the lethality threshold may be approximated by a Ct of about 17,000 mg • min/m^3.

Table 23. Lethality in Rabbits Exposed to DA at Varying Exposure Regimens

Exposure concentration (mg/m^3)	Exposure duration (min)	Cumulative exposure ($mg•min/m^3$)	Response
236	30	7080	0/2 dead
118	60	7080	0/2 dead
1180	15	17,700	0/2 dead
590	30	17,700	1/4 dead
295	60	17,700	0/2 dead
2361	10	23,610	0/2 dead
1180	30	35,400	2/6 dead

MMW(1918)

Ethyldichloroarsine (ED)

No data were available regarding the lethality of ED in rabbits.

Methyldichloroarsine (MD)

No data were available regarding the lethality of MD in rabbits.

Phenyldichloroarsine (PD)

No data were available regarding the lethality of PD in rabbits.

3.1.6. Guinea Pigs

Adamsite (DM)

Gongwer et al. (1958) reported an LCt_{50} for guinea pigs (neither strain nor gender were specified) of 8500 mg • min/m^3 and a minimum lethal exposure of 3500 mg • min/m^3. No further details were provided.

In the Punte et al. (1962) study (see §3.1.3. for details regarding methodologies), 56 male guinea pigs (300 g) were exposed in 200 L dynamic exposure chambers (800 L/min airflow) to aerosols of DM for 5 to 90 minutes. As for the rats and mice, the guinea pigs were observed for 14 days following exposure at which time survivors were killed for histopathological examination. The response was reportedly similar to that of the rats and mice (initial hyperactivity followed by nasal and ocular irritation within one minute and lethargy and labored breathing at 5-15 minutes that persisted up to two hours after exposure. An LCt_{50} of 7,900 mg • min/m^3 was determined by the method of Bliss. An estimated dose (LC_{50}) of DM, based upon respiratory parameters, body weight, estimated retention of agent and the LCt_{50} determination was 2.4 mg/kg. Necropsy of dead and sacrificed mice revealed tracheal hyperemia, pulmonary congestion and edema, and pneumonia; findings similar to those in the rats. Lethality rate in the guinea pigs was greatest during the first 3 day of exposure but continued at a lower frequency thorough day 9.

Lethal response data (McNamara et al., 1969) for guinea pigs are summarized in Table 24.

Table 24. Lethality in Guinea Pigs Following Acute Inhalation Exposure to Adamsite (DM)

Exposure concentration (mg/m^3)	Exposure duration (min)	Mortality ratio	Time-to-death (hrs)
209	80	17/20	11(6), 17, 35(7), 42, 64, 96
279	45	19/20	19(14), 26(2), 528(2), 552
297	20	11/20	16(8), 21(2), 40
212	14	8/20	14, 16, 38(5), 70
220	5	1/20	230

Numbers in parenthesis are number of deaths at that time.
McNamara et al., 1969.

Diphenylchloroarsine (DA)

Lethality data (MMW 1918) for guinea pigs exposed to DA are summarized in Table 25. The exposure regimens were similar to those used for other species (dogs, rats, mice, rabbits, cats) but the lethal response appeared to be greater for the guinea pigs. Similar to the experiments with other species, however, the MMW data are compromised by low numbers of animals and uncertainties regarding protocols and analytical techniques.

Table 25. Lethality in Guinea Pigs Exposed to DA at Varying Exposure Regimens

Exposure concentration (mg/m^3)	Exposure duration (min)	Cumulative exposure ($mg \cdot min/m^3$)	Response
118	30	3540	1/4 dead
236	30	7080	2/2 dead
118	60	7080	3/4 dead
590	15	8850	1/2 dead
295	30	8850	1/2 dead
1180	15	17,700	2/2 dead
590	30	17,700	3/4 dead
295	60	17,700	2/2/ dead
2361	10	23,610	2/2 dead

MMW(1918)

Ethyldichloroarsine (ED)

No data were available regarding the lethality of ED in guinea pigs.

Methyldichloroarsine (MD)

No data were available regarding the lethality of MD in guinea pigs.

Phenyldichloroarsine (PD)

No data were available regarding the lethality of PD in guinea pigs.

3.1.7. Swine

Adamsite (DM)

Lethality data for swine reported by McNamara et al. (1969) are summarized in Table 26.

Table 26. Lethality in Swine Following Acute Inhalation Exposure to Adamsite (DM)

Exposure concentration (mg/m^3)	Exposure duration (min)	Mortality ratio	Time-to-death (hrs)
223	273	3/6	5.5, 20, 167
210	198	2/6	4, 335
227	132	2/6	47(2)
216	91	1/6	42
206	48	0/6	-

Numbers in parenthesis are number of deaths at that time.
McNamara et al., 1969.

Diphenylchloroarsine (DA)

No data were available regarding the lethality of DA in pigs.

Ethyldichloroarsine (ED)

No data were available regarding the lethality of ED in pigs.

Methyldichloroarsine (MD)

No data were available regarding the lethality of MD in pigs.

Phenyldichloroarsine (PD)

No data were available regarding the lethality of PD in pigs.

3.1.8. Goat

Adamsite (DM)

Lethality data for goats reported by McNamara et al. (1969) are summarized in Table 27. Goats exhibited considerable variability (up to 28-fold) in time-to-death.

Table 27. Lethality in Goats Following Acute Inhalation Exposure to Adamsite (DM)

Exposure concentration (mg/m^3)	Exposure duration (min)	Mortality ratio	Time-to-death (hrs)
210	198	6/6	4, 16(2), 72, 77, 113
227	132	6/6	22(2), 71, 95, 240, 552
216	91	4/6	18, 90, 198, ?
233	42	3/6	20(2), 239
230	22	0/6	-

Numbers in parenthesis are number of deaths at that time.
McNamara et al., 1969.

Diphenylchloroarsine (DA)

No data were available regarding the lethality of DA in goats.

Ethyldichloroarsine (ED)

No data were available regarding the lethality of ED in goats.

Methyldichloroarsine (MD)

No data were available regarding the lethality of MD in goats.

Phenyldichloroarsine (PD)

No data were available regarding the lethality of PD in goats.

3.1.9. Cat

Adamsite (DM)

No data were available regarding the lethality of MD in cats.

Diphenylchloroarsine (DA)

MMW (1918) also conducted experiments using cats exposed to DA (Table 28). The exposure regimens were similar to those used for other species. Lethal response data for cats were generally inconsistent. Similar to the experiments with other species, the MMW data are compromised by low numbers of animals and uncertainties regarding protocols and analytical techniques.

Table 28. Lethality in Cats Exposed to DA at Varying Exposure Regimens

Exposure concentration (mg/m^3)	Exposure duration (min)	Cumulative exposure ($mg•min/m^3$)	Response
236	30	7080	0/2 dead
118	60	7080	0/4 dead
590	15	8850	0/2 dead
1180	15	17,700	1/2 dead
590	30	17,700	2/4 dead
295	60	17,700	0/2 dead
1180	30	35,400	0/4 dead

MMW(1918)

Ethyldichloroarsine (ED)
No data were available regarding the lethality of ED in cats.

Methyldichloroarsine (MD)
No data were available regarding the lethality of MD in cats.

Phenyldichloroarsine (PD)
No data were available regarding the lethality of PD in cats.

3.2. Nonlethal Toxicity

3.2.1. Monkeys

Adamsite (DM)
In the previously described (§3.3.3.) study by Punte et al. (1962), there were no pathological findings in rats exposed to DM aerosols at 500 mg • min/m^3. Although specific exposure regimens were not provided, exposure durations were for 5 to 90 minutes. Signs of initial exposure included immediate hyperactivity followed by lethargy and signs of nasal and ocular irritation. Signs of irritation generally subsided within 5 to 10 minutes. There was a 14-day post exposure observation period whereupon the rats were killed for pathological examination.

Striker et al. (1967a) exposed 30 monkeys (*Macaca mulatta*) to DM aerosols from No. 113 grenades. Exposure durations were 3, 5, and 11 minutes with average exposure concentrations of 855, 1708, 2615 mg/m^3, respectively (Table 29). At 12 and 24 hours, and 3, 7, and 30 days following the exposure, the animals were killed and examined. The investigators concluded that pulmonary edema was the most significant health effect resulting from the acute exposures.

Table 29. Effects of Acute Exposure of Monkeys to Adamsite (DM) Aerosols.

Exposure Concentration (mg/m^3)	Exposure Duration min	Ct ($mg \cdot min/m^3$)	Effects
855	3	2565	superficial tracheitis, edema of trachea and bronchial mucosa in one monkey at 12 hrs post exposure; no other effects noted for any monkeys at any examination time.
1708	5	8540	At 12 hrs bronchorrhea, focal pulmonary edema and congestion in 2 monkeys At 24 hrs, more pronounced edema and congestion (incidence not specified); membranous tracheitis and focal pulmonary hemorrhage in one monkey At 72 hrs, no edema or congestion At 7 days, emphysema and atelectasis in one monkey; no findings in 2nd monkey At 30 days, emphysema and atelectasis in one monkey; extensive early pneumonia in 2nd monkey
2615	11	28,765	8 monkeys died within 24 hrs At 24 hrs, one monkey terminated exhibited bronchial and pulmonary damage, and visceral congestion At 29 days, last monkey died; exhibited similar lesions as above.

Striker et al., 1967a.

Striker et al. (1967b) also conducted experiments to evaluate response severity at low DM concentrations for long durations versus high concentrations for short durations. The low exposure studies were conducted in response to concerns regarding the previously conducted (Striker et al., 1967a) high-exposure studies. These concerns focused on variability in delivered dose due to breath holding by the monkeys in the presence of a noxious material such as DM, subsequent removal of the agent by maximal protective responses (bronchospasm, coughing, gaging, etc.), and because the monkeys used in the experiments had pre-existing emphysema and atelectasis. The low-exposure study used groups of five monkeys (*Macaca mulatta*) exposed to various exposure/time combinations (Table 30). Aerosols of DM were generated from an M6A1 grenade. Controls were held similarly but not exposed to DM. Chest x-rays were taken immediately before exposure and at 2, 6, 12, 24, and 72 hrs, and at 7 and 30 days post exposure. One monkey from each exposure group was terminated by overdosing with intravenously injected sodium pentobarbital at 12 hrs, 24 hrs, 72 hrs, 1 week or 30 days post exposure. Controls were terminated at 1 week and 30 days. The results of these experiments are summarized in Table 7. Most signs and symptoms dissipated within several hours to one day after exposure. The investigators concluded that, under the conditions of this study, exposure to lower concentrations (~100 mg/m^3) for longer durations resulted in greater severity of effect than did exposure to higher concentrations (~300 mg/m^3) for shorter durations.

Table 30. Effects of Exposure Concentration and Duration on Response Severity in Monkeys to Inhaled Adamsite (DM)

Concentration (mg/m^3)	Duration (min)	Ct ($mg \cdot min/m^3$)	Effects
291	2	582	Modest hyperactivity during exposure, blinking. Slight pulmonary congestion with greater severity at 1 week and 30 days post exposure
291	10	2910	Modest hyperactivity during exposure, blinking. Focal pulmonary edema and bronchorrhea at 12 hrs; edema cleared at 24 hrs but bronchorrhea/bronchitis persisted to 30 days
272	20	5440	Modest hyperactivity during exposure, blinking, depression, vomiting. Focal pulmonary edema and bronchorrhea of greater severity than at 2910 $mg \cdot min/m^3$
330	40	13,200	Conjunctival congestion, depression, oral and nasal discharges, vomiting, dyspnea. Similar pathological findings as for 5440
99	2	198	Mild blinking. Pulmonary edema, congestion, bronchorrhea observed at 72 hrs was cleared at 1 week;
108	12	1296	Blinking. Pulmonary edema, congestion, bronchorrhea persisted to 30 days
77	60	4620	Tearing, blinking, depression, rapid respiration, gasping, trace oral and nasal discharges. Labored breathing, pulmonary edema, congestion, bronchorrhea marked at 72 hrs but resolved at days 7 and 30

Striker et al. 1967b.

Diphenylchloroarsine (DA)

No data were available regarding the nonlethal effects of DA in animal species.

Ethyldichloroarsine (ED)

No data were available regarding the nonlethal effects of ED in animal species.

Methyldichloroarsine (MD)

No data were available regarding the nonlethal effects of MD in animal species.

Phenyldichloroarsine (PD)

No data were available regarding the nonlethal effects of PD in animal species.

3.3. Developmental/Reproductive Effects

No data were available regarding developmental toxicity of the chloroarsine compounds.

3.4. Genotoxicity

No data were available regarding the genotoxicity of the chloroarsine compounds.

3.5. Carcinogenicity

Assessment of potential carcinogenicity of the chloroarsine agents is limited. The U.S. EPA (1988) found no human or animal data with which to calculate a potency factor for agent PD (phenyl dichloroarsine) and classified it as a Group D chemical.

3.6. Summary

Animal lethality data for the arsenical agents are often compromised by incomplete exposure terms, absence of analytically determined concentrations, and a general lack of experiment descriptions. Some values are reported only in terms of cumulative exposures that lack concentration or duration terms with which the Ct products were derived. The most extensive animal data focus primarily on DM and DA. Striker et al. (1967a,b) conducted studies with monkeys which provided detailed information regarding respiratory pathology and lethality following brief (3-11 minutes) exposures. The lethal response of dogs following 10-minute exposure to DM was reported by Craighill and Folkoff (1922). Gongwer et al. (1958) reported on lethal responses of rats and mice and estimated the LCt_{50} for these. Additional lethality data for DM are also available for several animal species, much of which come from studies conducted by Owens et al. (1967) and reported by McNamara et al. (1969). The data from these and other reports have also been previously reviewed by the NRC (1984). The more definitive quantitative data for DM are summarized in Table 31. Toxicity data for diphenylchloroarsine (DA) originate primarily with MMW (1918) and reports cited by Kibler (1942), CWS (1944), and EATR (1933). Although these reports provided lethality data in multiple species (dogs, rats, mice, rabbits and guinea pigs), there are no data on nonlethal effects, thereby precluding evaluation of a definitive exposure-response relationship. The lethal response of dogs to MD was well characterized by Allen et al. (1922) who derived LC_{50} values of 815, 303, 125, 47, and 31 mg/m^3 for 7.5, 15, 30, 60, and 120-minute exposure durations, respectively. Allen et al. (1922) also provided information affirming the irritant effects of MD, involvement of the respiratory tract, and latency in the manifestation of some effects. Wells (1924) studied the effect of humidity on the lethal toxicity of MD in mice and reported 10-minute LC_{50} value ranging from 560 to 1940 mg/m^3 depending on humidity. Data for ED and PD were very limited.

Table 31. Data Summary for Animal Toxicity for DM.

Species	Exposure Duration	Toxicity value	Response	Reference
Monkey	3 min	2565 mg• min/m^3 (855 mg/m^3)	nonlethal, mild effects	Striker et al., 1967a
Monkey	3 min	8540 mg• min/m^3 (1708 mg/m^3)	severe, nonlethal effects	Striker et al., 1967a
Monkey	3 min	28,765 mg• min/m^3 (2615 mg/m^3)	100 % lethality over 30 days	Striker et al., 1967a
Monkey	60 min	4620 mg • min/m^3 (77 mg/m^3 for 60 min)	severe effects with recovery at 7-30 days	Striker et al., 1967b
Monkey	10 min	2910 mg• min/m^3 (291 mg/m^3 for 10 min)	moderate, nonpersistent effects	Striker et al., 1967b
Monkey	80 min	16,700 mg• min/m^3	50% lethality	McNamara et al., 1969
Dog	30 min	400-620 mg/m^3	lowest exposure not causing death within 12-days	Craighill and Folkoff, 1922
Dog	30 min	650 mg/m^3	lowest exposure not causing death within 48 hrs	Craighill and Folkoff, 1922
Rat	15-60 min	3000 mg• min/m^3	LCt_{50}	Gongwer et al., 1958
Rat	15-60 min	1200 mg• min/m^3	est. minimum lethal exposure	Gongwer et al., 1958
Rat	-	3700 mg• min/m^3	LCt_{50}	Punte, 1962
Mouse	-	1,000 mg• min/m^3	est. minimum lethal exposure	Gongwer et al., 1958
Mouse	-	22,400 mg• min/m^3	LCt_{50}	Gongwer et al., 1958
Rabbit	30-60 min	17,000 mg• min/m^3	estimated lethality threshold	MMW, 1918
Rabbit	30 min	8050 mg• min/m^3	66% lethality	McNamara, et al., 1969
Guinea pig	20 min	297 mg/m^3	- 50% lethality	McNamara et al., 1969
Guinea pig	5 min	220 mg/m^3	5% lethality	McNamara et al., 1969

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

4.2. Mechanism of Toxicity

Generally, arsenicals such as PD, ED, and MD react with endogenous thiol groups. O'Connor et al. (1986) studied the binding of agent PD to mouse erythrocytes and human hemoglobin, and their associated thiol-containing SH-molecules. The investigators found that PD penetrated erythrocytes and reacted with an intracellular component (most likely glutathione). Castro (1968) reported than DM exhibited anticholinesterase activity which could, in part, explain its lacrimatory effect. Roberts et al. (1967) reported that DM directly affected gastric activity but noted that lethality involved the respiratory tract. This latter observation is consistent with that reported for monkeys exposed to DM (Striker et al., 1967a; 1967b).

4.3. Structure-Activity Relationships

NRDC (1946) and Savit (1945) noted that the dichloroarsines are generally more effective vesicants than are monochloroarsines. It was postulated that the addition of a single chlorine atom on the terminal carbon of a normal aliphatic substituent in a dichloroarsine or the inclusion of a branched chain substituent reduces vesicant potency. Mouse acute lethality data suggested that most of the dichloroarsines exhibit similar toxicity (NDRC, 1946).

In reviewing efficacy of the dichloroarsines for military applications (especially relevant to lewisite), the Chemical Warfare Service (CWS, 1944) concluded that only MD, ED, and PD have toxic-vesicant potential similar to that of lewisite. Although irritating to the eyes at low concentrations (based upon experiments utilizing direct ocular application of liquid to rabbit eyes), MD is rapidly hydrolyzed resulting in low effectiveness as a vesicant agent. ED was evaluated similar to MD. PD generally exhibited systemic and vesicant toxicity similar to lewisite but was shown to easily hydrolyze.

4.4. Other Relevant Information

4.4.1. Species Variability

It is unlikely that the mode of action *per se* would vary greatly among species. Available data indicate species variability but it is uncertain to what degree the variability can be attributed to varying sensitivities, dosimetric variabilities, or variabilities in experimental protocols and techniques.

4.4.2. Concentration-Exposure Duration Relationship

In the absence of response data for AEGL-specific exposure durations, exposure values are scaled to AEGL time frames using the concentration-time relationship given by the equation $C^n \times t = k$, where C = concentration, t = time, and k is a constant. The values of the exponent n generally are in the range of 1-3.5, and "should always be derived empirically from acute inhalation toxicity experiments, in which both the concentration and exposure period are variables" (ten Berge et al., 1986). For adamsite (DM) and methyldichloroarsine (MD), exposure-response data were available with which to empirically derive the respective exponents (n) of 0. 71 and 0.82, respectively. These derivations are presented in Appendix B.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Adamsite (DM)

Human data regarding tolerance to DM exposure were available were available in older reports. Lawson and Temple (1922) reported average tolerances of 1 to 10 human volunteers to various DM exposure regimens. Severity of effects ranged from negligible (nasal and throat irritation) to severe distress for 2

to 3 hours (burning and tightness in the chest, persistent rasping cough, burning sensation in the upper respiratory tract, depression) and were reportedly directly related to concentration. The more severe effects exhibited a latency period of 10 minutes. Exposure durations ranged from 0.68 to 60 minutes, exposure concentrations ranged from 0.133 to 61.4 mg/m^3, and Ct products ranged from 3.1 to 90 mg • min/m^3. The more severe effects are clearly inappropriate for AEGL-1 development. Additional reports on responses of human volunteers also assessed tolerance thresholds (see Table 9, Section 2.2.1).

Gongwer et al. (1958) conducted tests with human volunteers to determine tolerance levels to 30-second and 120-second DM exposures. The responses to the DM exposure were qualitatively similar to the more severe responses reported by previous investigators (i.e., ocular and respiratory tract irritation of varying severities but of greater severity than that consistent with AEGL-1 definition). In all cases, full recovery from all effects was achieved. For the 30 second exposures, a Ct of 50 mg • min/m^3 failed to produce a response in any of the subjects. For the 120-second exposure group, a response rate of 0 to 10% was observed at 20 to 100 mg • min/m^3. Although full recovery was reported for these subjects, the responses were of greater severity than that encompassed by the AEGL-1 definition.

Ethyldichloroarsine (ED)
No information was located regarding AEGL-1 type effects following human exposure to ED.

Methyldichloroarsine (MD)
Information regarding human exposure to MD were limited to an odor threshold of 0.8 mg/m^3 and nasal irritation threshold of 0.9 mg/m^3 cited by Macy (1931).

Phenyldichloroarsine (PD)
No information was located regarding AEGL-1 type effects following human exposure to PD.

Diphenylchloroarsine (DA)
Non verifiable odor thresholds of 0.3 mg/m^3 (War Dept., 1942) and 0.5 mg/m^3 (Depts. of Army and Air Force, 1952) have been reported. Macy (1931) estimated nasal and throat irritation thresholds of 1.5 and 2.5 mg/m^3 for 3-minute exposures but the data and rationale for these is not available.

5.2. Animal Data Relevant to AEGL-1

Adamsite (DM)
There were no relevant animal data for deriving an AEGL-1 for DM.

Ethyldichloroarsine (ED)
No animal data were available regarding AEGL-1 type effects following exposure to ED.

Methyldichloroarsine (MD)
Animal data were unavailable with which to develop AEGL-1 values for MD.

Phenyldichloroarsine (PD)
Animal data were unavailable with which to develop AEGL-1 values for PD.

Diphenylchloroarsine (DA)
There were no relevant animal data for deriving an AEGL-1 for DA.

5.3. Derivation of AEGL-1

Adamsite (DM)

Tolerance data for human volunteer subjects reported by Lawson and Temple (1922) and analyzed by Craighill and Folkoff (1922) was selected for development of AEGL-1 values. These data indicated a 60-minute exposure to 0.14 mg/m^3 to be a tolerance limit. Because a tolerance limit is considered to exceed the effects severity as described for AEGL-1, this exposure was reduced threefold (0.047 mg/m^3) as an estimate of an appropriate point-of-departure for AEGL-1 development.

An assessment by ten Berge et al. (1986) of LC_{50} data for certain chemicals revealed chemical-specific relationships between exposure concentration and exposure duration that were often exponential. This relationship can be expressed by the equation $C^n \times t = k$, where n represents a chemical specific, and even a toxic endpoint-specific, exponent. The relationship described by this equation is basically the form of a linear regression analysis of the log-log transformation of a plot of concentration (C) vs time (t). Available data suggest that exposure duration may be more relevant than exposure concentration with respect to DM. Analysis of human tolerance limits for DM based on average response of 1 to 6 volunteer subjects. (Lawson and Temple,1922; Craighill and Folkoff, 1922) resulted in an empirically-derived exponent (n) of 0.71 (see Appendix B).

Uncertainty factor application was limited to 3 for individual variability. Qualitatively, the human response to DM is well characterized but uncertainty exists regarding a precise threshold for minor irritation. As previously explained, the concentrations selected as point-of-departures were downwardly adjusted to estimate an exposure producing a less severe response. Therefore, there were no additional uncertainty adjustments. The resulting AEGL-1 values are shown in Table 32 and their derivation summarized in Appendix A.

TABLE 32. AEGL-1 Values For Adamsite (DM)

Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	0.20 mg/m^3	0.041 mg/m^3	0.016 mg/m^3	0.0022 mg/m^3	0.00083 mg/m^3

Ethyldichloroarsine (ED)

Data were unavailable with which to develop AEGL-1 values for ED (Table 33).

Table 33. AEGL-1 Values For Ethyldichloroarsine (ED)

Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]

NR: Not recommended.

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

Methyldichloroarsine (MD)

Data were unavailable with which to develop AEGL-1 values for MD. The available data were not considered sufficient to support development of AEGL-1 value by extrapolation from AEGL-2 values or other data. Therefore, AEGL-1 values are not recommended (Table 34).

Table 34. AEGL-1 Values For Methyldichloroarsine (MD)

Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]

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

Phenyldichloroarsine (PD)

Data were unavailable with which to develop AEGL-1 values for PD (Table 35).

Table 35. AEGL-1 Values For Phenyldichloroarsine (PD)

Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]

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

Diphenylchloroarsine (DA)

Data were unavailable with which to develop AEGL-1 values for DA. The overall data on DA were not considered sufficient to support development of AEGL-1 value by extrapolation from other data or exposure values. Therefore, AEGL-1 values are not recommended (Table 36).

Table 36. AEGL-1 Values For Diphenylchloroarsine (DA)

Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]

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

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

Adamsite (DM)

Nonlethal response of humans to DM are characterized by nasopharyngeal irritation resulting in coughing and sneezing, respiratory difficulties, and ocular irritation. Qualitative data relevant to the derivation of the AEGL-2 are available from early studies (Lawson and Temple, 1922) in which average tolerance was determined for groups of 1-10 human volunteers were exposed to DM at varying concentrations (3.1 - 61.4 mg/m^3) and durations (0.68 - 60 minutes); Ct products ranged from 3.1 to 90 mg • min/m^3. Qualitatively, the responses of the volunteers showed that the primary effects of DM under these exposure conditions were nasopharyngeal irritation, respiratory discomfort (chest tightness, coughing) and depression. Latency (~10 minutes) in peak response was also noted. The exposure concentrations used in these human volunteer studies appear to be nominal values. The reports lack information regarding generation of exposure atmospheres and analytical determinations.

Ethyldichloroarsine (ED)

There were no definitive human data regarding AEGL-2 type effects following exposure to ED. Sullivan and Krieger (1992) reported an ICt_{50} (temporarily incapacitating concentration) of 5-10 mg • min/m^3 for an unspecified time frame. No further information was provide regarding the derivation of this value.

Methyldichloroarsine (MD)

No human data were available relevant to AEGL-2 development.

Phenyldichloroarsine (PD)

Sullivan and Krieger (1992) reported human ICt_{50} (temporarily incapacitating concentration) values of 16 mg • min/m^3 for vomiting and 1800 mg • min/m^3 for blistering. No exposure times were specified and no additional information was provided regarding the derivation of these values.

Diphenylchloroarsine (DA)
No human data were available relevant to AEGL-2 development.

6.2. Animal Data Relevant to AEGL-2

Adamsite (DM)
Most of the animal studies with DM focused on lethality and provided only limited quantitative information regarding nonlethal responses. Although lower exposures in some animal lethality studies often failed to illicit a lethal response, most provided no details regarding the exposures that did not cause death. In more recent studies, Striker et al., (1967a, b) reported on the responses of monkeys exposed for 2 to 60-minutes to varying concentrations of DM. Responses included behavioral effects, respiratory effects (irritation, congestion, pulmonary and tracheal edema) and ocular irritation (blinking, conjunctival irritation). For one aspect of the study (Striker, 1967a), monkeys were killed at 12 or 24 hours, or at 3, 7 or 30 days post exposure for gross pathology evaluations. The necropsy findings of tracheal, bronchial and pulmonary edema were consistent with the observed clinical responses. With the exception of the highest exposure (2615 mg/m^3 for 11 minutes), necropsy examinations at the aforementioned termination times indicated recovery from pulmonary damage following exposure to DM.

Ethyldichloroarsine (ED)
There were no animal data regarding nonlethal effects following exposure to ED.

Methyldichloroarsine (MD)
No definitive information was available regarding nonlethal effects of MD in animals.

Phenyldichloroarsine (PD)
No definitive information was available regarding nonlethal effects of PD in animals.

Diphenylchloroarsine (DA)
No animal data were available for AEGL-2 development. Lethality studies provided no information about the toxic response for those exposures which were not lethal.

6.3. Derivation of AEGL-2

Adamsite (DM)
AEGL-2 values were developed based upon data reported by Striker et al. (1967b) for monkeys exposed to DM at various concentration-time regimens and exhibiting various physiological/behavioral responses (hyperactivity, blinking, nasopharyngeal irritation, ocular irritation) and gross pathological effects (tracheal, bronchial and pulmonary edema). Necropsy findings at 12, 24, or 72 hours, or 1 or 30 days post exposure indicated sequential resolution of DM-induced pulmonary damage for all exposure groups. Although exposure durations were all 60 minutes or less, some exposure durations (10 and 60 minutes) coincided with AEGL-specific time points. The response of monkeys exposed to 291 mg DM/m^3 for 10 minutes served as the basis for the 10- and 30-minute AEGL-2 values and response to 77 mg DM/m^3 for 60 minutes was utilized for developing the 1-, 4-, and 8-hr AEGL-2 values. Time scaling was performed using an empirically-derived *n* of 0.71 as described for AEGL-1 development. Qualitative evaluation of the responses of humans and animals to DM indicate that the range of effects is

a function of severity of irritation and subsequent damage to respiratory tract epithelium. Therefore, it is assumed that the exposure time relationship may be similar across the effect continuum for DM.

A total uncertainty factor adjustment of 30 was applied in development of the AEGL-2 values. This included an intraspecies adjustment of 3 to account for individual variability in response to a direct-acting irritant. Agent DM appears to damage epithelial tissue with which it comes in contact subsequently resulting respiratory tract injury. This process is supported by clinical observations in humans and animals and by pathological findings in animals exposed to sufficiently high concentrations of DM. An interspecies uncertainty factor of 10 was applied because available data suggest notable variability among the species tested. Data from a study with nonhuman primates (i.e.,cynomolgus monkey, *Macaca mulatta*) was used for developing the AEGL-2 and, while not the most sensitive species based upon review of the available data, it was considered more appropriate due to greater similarities in respiratory anatomy and physiology than other species. However, early studies with human volunteer subjects indicated very low tolerance to DM at low concentrations for very short durations which would preclude reduction of uncertainty in animal-to-human extrapolation

The AEGL-2 values for DM are shown in Table 37 and their derivation summarized in Appendix A

Table 37. AEGL-2 Values For Adamsite (DM)

Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	9.7 mg/m^3	6.8 mg/m^3	2.6 mg/m^3	0.36 mg/m^3	0.14 mg/m^3

Diphenylchloroarsine (DA)

Toxicity data were not available with which to develop AEGL-2 values. The lethality studies in dogs, rats, mice, rabbits, and cats did not characterize nonlethal toxic responses. Consistent with previously reported AEGL procedures and methodologies (NRC, 2001), the AEGL-2 for DA were estimated as a three-fold reduction of the AEGL-3 values (Table 38).

Table 38. AEGL-2 Values For Diphenylchloroarsine (DA)

Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	1.1 mg/m^3	0.79 mg/m^3	0.39 mg/m^3	0.098 mg/m^3	0.049 mg/m^3

Ethyldichloroarsine (ED)

Toxicity data were not available with which to develop AEGL-2 values. Consistent with previously reported AEGL procedures and methodologies (NRC, 2001), the AEGL-2 values (10-minute, 30-minute, and 1-hour values only) for MD were estimated as a three-fold reduction of the AEGL-3 values (Table 39).

Table 39. AEGL-2 Values For Ethyldichloroarsine (ED)

Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	0.17 mg/m^3	0.057 mg/m^3	0.029 mg/m^3	NR	NR

Methyldichloroarsine (MD)

Toxicity data for MD were limited to lethality studies in dogs (Allen et al., 1922) and mice (Wells, 1924). Consistent with previously reported AEGL procedures and methodologies (NRC, 2001), the AEGL-2 values for MD were estimated as a three-fold reduction of the AEGL-3 values. The resulting AEGL-2 values for MD are shown in Table 40.

Table 40. AEGL-2 Values For Methyldichloroarsine (MD)

Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	0.63 mg/m^3	0.14 mg/m^3	0.053 mg/m^3	0.015 mg/m^3	0.0063 mg/m^3

Phenyldichloroarsine (PD)

Toxicity data were not available with which to develop AEGL-2 values for PD. Consistent with previously reported AEGL procedures and methodologies (NRC, 2001), the AEGL-2 values (10-minute, 30-minute, and 1-hour values only) for PD were estimated as a three-fold reduction of the AEGL-3 values (Table 41).

Table 41. AEGL-2 Values For Phenyldichloroarsine (PD)

Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	0.37 mg/m^3	0.12 mg/m^3	0.061 mg/m^3	NR	NR

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

Adamsite (DM)

Information regarding human deaths from DM inhalation exposures is limited to two poorly characterized accident case reports and an LCt_{50} estimated from animal data (Owens et al., 1967). The accident report involved an individual exposed to an estimated concentration of 1130 to 2260 mg/m^3 (Owens et al., 1967). The exposure duration for this incident is uncertain (5-30 minutes). Another report described recorded a human fatality following exposure to an unknown high concentration of DM in a confined space. Although not providing quantitatively useful information, postmortem findings from these cases verified severe pulmonary and airway damage similar to that observed in laboratory species exposed to lethal concentrations of DM.

Diphenylchloroarsine (DA)

Prentiss (1937) reported 15,000 mg • min/m^3 as a lethal concentration for a 10-minute exposure but the value is not verifiable. Based upon data in CWS (1944), NDRC (1946) estimated that the human LCt_{50} would be greater than 10,000 mg • min/m^3 and that, due to the non-persistence of DA vapor clouds, deaths from DA would occur only under very unique circumstances. There were no human data available for development of AEGL-3 values for DA.

Ethyldichloroarsine (ED)

Human lethality data for ED are limited to a median lethal dose (MLD_{50}) of 3,000 to 5,000 mg • min/m^3 reported by Sullivan and Krieger (1992). A Ct product (ICt_{50}) of 5-10 mg • min/m^3 for temporary incapacitation was also reported by Sullivan and Krieger (1992). Neither exposure duration nor other qualifying information was provided regarding these values.

Methyldichloroarsine (MD)

No information was available regarding lethality in humans exposed to MD.

Phenyldichloroarsine (PD)

Information regarding lethality in humans exposed to PD is limited to an MLD_{50} of 2,600 mg/m^3 cited by Sullivan and Krieger (1992). There were no details provided regarding the derivation of this value and, therefore, it was not verifiable.

7.2. Animal Data Relevant to AEGL-3

Adamsite (DM)

Lethality data of varying quality are available for monkeys, dogs, rats, mice, rabbits, guinea pigs, cats, pigs, and goats. Many of the data are from older studies for which precision of exposure concentration determinations is uncertain. There is considerable variability in lethal response data among the species tested. Much of this variability can be attributed to varying experimental protocols, generation of test atmospheres, and determination of test atmosphere concentrations. Consequently, determination of a definitive exposure-response relationship for this chemical is difficult. Animal data do, however, suggest that lethality is a function of pulmonary damage similar to many irritant chemicals which damage epithelial tissue. Striker et al. (1967a) reported both lethal and non-lethal responses in monkeys exposed to DM aerosols for 3, 5 or 11 minutes. Gross pathology findings were also provided in this study.

Diphenylchloroarsine (DA)

Animal data relevant to AEGL-3 development were limited to older lethality studies in multiple species (§3.1.2) reported in MMW (1918). These data are limited to overall percent lethality responses at various exposure concentrations (~118 to 2300 mg/m^3) and durations (10 to 60 minutes). The data for dogs is very inconsistent and, therefore, considered unreliable. The data for rats, mice and cats indicate that cumulative exposures #7080 mg • min/m^3 did not result in lethality. Both rat and rabbit data showed no deaths at exposures of 236 mg/m^3 for 30 minutes and 118 mg/m^3 for 60 minutes. An estimated 10-minute LC_{50} of 690 mg/m^3 for mice was cited by EATR (1933) and a mouse 10-minute LC_{lo} of 298 mg/m^3 reported by CWS (1944).

Ethyldichloroarsine (ED)

The only animal data available for ED were the 10-minute LCt_{50} of 1555 mg • min/m^3 for mice (Hutchens et al., 1943) and a mouse LCt_{50} of 3400 mg • min/m^3 for which no time frame was specified (EATR, 1941). The former was reported for an experiment in which mice were exposed (whole body) in a low humidity atmosphere and observed for 10 days.

Methyldichloroarsine (MD)

Two studies provided lethality data for MD. Allen et al. (1922) provided LC_{50} values of 815, 303, 125, 47, and 31 mg/m^3 for dogs exposed to MD for 7.5, 15, 30, 60, or 120 minutes. Wells (1924) examined the effects of humidity and subsequent hydrolysis on the lethal response of mice exposed to MD for 10 minutes. Resulting LC_{50} values were 930, 560, 680, and 1940 mg/m^3 with increasing humidity.

Phenyldichloroarsine (PD)

The only animal data available for PD was a mouse 10-minute LC_{50} of 330±80 mg/m^3 from a study by Skipper et al. (1942) in which groups of 20 mice were exposed to varying concentrations for 10 minutes and observed for lethality for 10 days.

7.3. Derivation of AEGL-3

Adamsite (DM)

No one study utilized exposure periods consistent with the range of AEGL time periods. Striker et al. (1967a) provided data involving both lethal and nonlethal responses of monkeys (10/group) exposed to DM aerosols for 3, 5, or 11 minutes. The exposure resulting in serious but nonlethal effects (1708 mg/m^3 for 5 minutes) was considered appropriate as a point-of-departure for developing AEGL-3 values for 10 minutes. Extrapolation of this exposure/duration value to 30-minute and greater time periods was tenable and, therefore, not used for development of the remaining AEGL-3 values. The 30-minute, 1, 4, and 8-hour AEGL-3 values, were also based upon a nonlethal exposure of monkeys (279 mg/m^3 for 46 minutes) reported by McNamara et al. (1969). These exposures resulted in Ct products of 986.36 and 2,506.89 mg•min/m^3 with which to develop the AEGL-3 values for 10-minute values and 30-minute and greater values, respectively.

Time scaling was performed using the empirically-derived exponent (n) of 0.71. Because lethality studies in multiple species indicated irritation and subsequent damage to respiratory tract epithelium to be a prominent underlying mode of action, it was assumed that the exposure time relationship would be similar across the effect continuum for DM. As for AEGL-2 development, uncertainty factor adjustment consisted of 10 for interspecies variability due to uncertainties in extrapolating from animal lethality to exposures resulting in human deaths. An uncertainty factor of 3 was applied to account for individual variability in response to a direct-acting irritant. The AEGL-3 values for DM are shown in Table 42 and their derivation in Appendix A.

Table 42. AEGL-3 Values for Adamiste (DM)

Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	21 mg/m^3	17 mg/m^3	6.4 mg/m^3	0.91 mg/m^3	0.34 mg/m^3

Diphenylchloroarsine (DA)

The AEGL-3 values for DA were based upon the rat data reported by MMW (1918). These data are supported by similar findings in rabbits and cats (MMW,1918). For both rats, rabbits and cats, 30-minute exposure to 236 mg/m^3 and 60 minute exposure to 118 mg/m^3 did not result in the death of any of the animals (4 rats and rabbits/group, 2 to 4 cats/group). The 30-minute exposure value was used as the point-of-departure for the 10 and 30-minute AEGL-3 values for DA, while the 60-minute data point was used for developing the 1-, 4-, and 8-hour AEGL-3 values for DA. An empirically-derived value for the exponent, n, in the equation $C^n \times t = k$ could not be developed. Consistent with AEGL methodologies (NRC, 2001), an n of 1 was used in extrapolating from the 60-minute experimental exposure period to the 4 and 8 hour AEGL-3 time periods, and an n of 3 was used for extrapolating from the 30-minute experimental period to the 10-minute AEGL-3 exposure.

Uncertainty factor adjustment consisted of 10 for interspecies variability due to uncertainties in extrapolating from animal lethality to exposures resulting in human deaths. A default uncertainty factor of 10 was retained to account for individual variability in response due to lack of data regarding individual variability in the toxic response to DA.. The resulting AEGL-3 values for DA are shown in Table 43 and their derivation shown in Appendix A.

Table 43. AEGL-3 Values for Diphenylchloroarsine (DA)

Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	3.4 mg/m^3	2.4 mg/m^3	1.2 mg/m^3	0.30 mg/m^3	0.15 mg/m^3

Ethyldichloroarsine (ED)

The only data that could be considered for AEGL-3 development was that of Hutchens et al. (1943) identifying a mouse 10-minute LCt_{50} of 1555.5 mg • min/m^3 (equivalent to a 10-minute LC_{50} of 155.5 mg/m^3). AEGL-3 values for 10 and 30 minutes, and 1 hour could be developed based on a lethality threshold estimated as a 3-fold reduction of this LC_{50} (i.e., 51.8 mg/m^3). Assuming similarity in activity to other dichloroarsines, uncertainty factors of 10 for interspecies variability (uncertainties in extrapolating from animal lethality to exposures resulting in human deaths) and 10 (insufficient data for determining individual variability in the toxic response to ED). Time scaling from the 10-minute experimental time point to the 30- and 60-minute AEGL-3 time frames utilized a default *n* of 1 (NRC, 2001). Limited data and uncertainties in extrapolating to exposure durations 24-fold and 48-fold greater than the 10-minute experimental time frame, preclude development of the 4-hour and 8-hour AEGL-3 values. The AEGL-3 values for ED are shown in Table 44 and their derivation summarized in Appendix A.

Table 44. AEGL-3 Values for Ethyldichloroarsine (ED)

Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	0.52 mg/m^3	0.17 mg/m^3	0.086 mg/m^3	NR[a]	NR[a]

[a]NR: Not recommended; 10-minute experimental data point is insufficient to support extrapolation to 4-hour and 8-hour exposure durations.

Methyldichloroarsine (MD)

The AEGL-3 values for MD were developed using the multiple time-point dog lethality data provided by Allen et al. (1922). The study appeared to be well conducted and adequately described. Allen et al. (1922) reported LC_{50} values for 7.5, 15, 30, 60, and 120-minute exposure durations (815, 303, 125, 47, and 31 mg/m^3, respectively), two of which (those for 30 and 60 minutes) are AEGL-specific time frames and were used as such. The 7.5-minute value served as the basis for the 10-minute AEGL-3 while the 120-minute LC_{50} was used as the basis for the 4-hr and 8-hr AEGL-3 values. These LC_{50} values were decreased 3-fold as an estimate of the lethality threshold (NRC, 2001).

Time scaling was performed using the empirically-derived exponent (*n*) of 0.82 from multiple time-point dog LC_{50} values of Allen et al. (1922). Uncertainty factor adjustment consisted of 10 for interspecies variability due to uncertainties in extrapolating from animal lethality to exposures resulting in human deaths. An uncertainty factor of 10 accounted for uncertainties regarding individual variability in the toxic response to MD. The AEGL-3 values for MD are shown in Table 45 and their derivation in Appendix A.

Table 45. AEGL-3 Values for Methyldichloroarsine (MD)

Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	1.9 mg/m^3	0.42 mg/m^3	0.16 mg/m^3	0.044 mg/m^3	0.019 mg/m^3

Phenyldichloroarsine (PD)

AEGL-3 values for PD may be developed using a 3-fold reduction of the mouse 10-minute LC_{50} of 330 mg/m^3 reported by Skipper et al. (1942) as an estimate of a lethality threshold (NRC, 2001). The resulting point-of-departure is 110 mg/m^3. Because no data were available with which to empirically derive an exponent for $C^n \times t = k$, a default of $n = 1$ was used for scaling from the 10-minute experimental value to longer AEGL-specific time periods. Due to the limited data and the uncertainties regarding extrapolation to exposure durations that are 24-fold and 48-fold greater than the 10-minute experimental time frame, the 4-hour and 8-hour AEGL-3 values are not recommended. Assuming similarity in activity to other dichloroarsines, uncertainty factors of 10 for interspecies variability (uncertainties in extrapolating from animal lethality to exposures resulting in human deaths) and 10 for intraspecific variability (insufficient data with which to assess individual variation in the toxic response to PD) were applied. The AEGL-3 values for PD are shown in Table 46 and their derivation summarized in Appendix A.

Table 46. AEGL-3 Values for Phenyldichloroarsine (PD)

Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	1.1 mg/m^3	0.37 mg/m^3	0.18 mg/m^3	NR[a]	NR[a]

[a]NR: Not recommended; 10-minute experimental data point is insufficient to support extrapolation to 4-hour and 8-hour exposure durations.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

The AEGL values for the chloroarsenical agents are summarized in Table 47. All of the chloroarsenicals are irritants exerting their effect primarily on ocular and respiratory targets. Both animal data and human experience information affirm a similar mode of action for these compounds. Lethality data of varying quality were available for all of the chloroarsenicals of concern, with some having data in multiple species including nonhuman primates. Results of early studies using human volunteer subjects provided valuable information regarding the irritant effects of DM (adamsite) at low exposure concentrations for brief periods. The characterization of nonlethal responses for some of the agents, however, was less well defined and precluded development of AEGL-1 and AEGL-2 values for DA, ED, and PD, and necessitated default procedures for developing AEGL-2 values as a 3-fold reduction of AEGL-3 values for MD. Similar to most irritants, the chloroarsenicals likely exhibit exposure time-response relationships that are near linear or possibly somewhat more dependent on time (i. e., $C^n \times t = k$, where $n \neq 1$); this is verified to some extent by empirically-derived n values <1).

Table 47. Summary/Relationship of AEGL Values (mg/m^3)

Classification	10-min	30-min	1-hr	4-hr	8-hr
Adamsite (DM)					
AEGL-1 (Nondisabling)	0.20 mg/m^3	0.041mg/m^3	0.016 mg/m^3	0.0022 mg/m^3	0.00083 mg/m^3
AEGL-2 (Disabling)	9.7 mg/m^3	6.8 mg/m^3	2.6 mg/m^3	0.36 mg/m^3	0.14 mg/m^3
AEGL-3 (Lethal)	21 mg/m^3	17 mg/m^3	6.4 mg/m^3	0.91 mg/m^3	0.34 mg/m^3
Diphenylchloroarsine (DA)					
AEGL-1 (Nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2 (Disabling)	1.1 mg/m^3	0.79 mg/m^3	0.39 mg/m^3	0.098 mg/m^3	0.049 mg/m^3
AEGL-3 (Lethal)	3.4 mg/m^3	2.4 mg/m^3	1.2 mg/m^3	0.30 mg/m^3	0.15 mg/m^3
Ethyldichloroarsine (ED)					
AEGL-1 (Nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2 (Disabling)	0.17 mg/m^3	0.057 mg/m^3	0.029 mg/m^3	NR[b]	NR[b]
AEGL-3 (Lethal)	0.52 mg/m^3	0.17 mg/m^3	0.086 mg/m^3	NR[c]	NR[c]
Methyldichloroarsine (MD)					
AEGL-1 (Nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2 (Disabling)	0.63 mg/m^3	0.14 mg/m^3	0.053 mg/m^3	0.015 mg/m^3	0.0063 mg/m^3
AEGL-3 (Lethal)	1.9 mg/m^3	0.42 mg/m^3	0.16 mg/m^3	0.044 mg/m^3	0.019 mg/m^3
Phenyldichloroarsine (PD)					
AEGL-1 (Nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2 (Disabling)	0.37 mg/m^3	0.12 mg/m^3	0.061 mg/m^3	NR[a]	NR[a]
AEGL-3 (Lethal)	1.1 mg/m^3	0.37 mg/m^3	0.18 mg/m^3	NR[c]	NR[c]

NR: Not recommended; insufficient data.

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

[b] Absence of an AEGL-2 does not imply that exposure below the AEGL-3 is without severe and possibly irreversible adverse effects.

[a] 10-minute experimental data point is insufficient to support extrapolation to 4-hour and 8-hour exposure durations.

8.2. Comparisons with Other Standards and Guidelines

There are no typical standards or guidance levels currently available for the title chloroarsenicals. Based upon results from inhalation experiments in animals (rat, mouse, guinea pig), and body weight and respiratory parameters, Punte et al. (1962) estimated a tentative safe airborne concentration of 100 mg · min/m^3 for a 5-minute exposure to DM. Available standards and guidelines are summarized in Table 48.

Table 48. Extant Standards and Guidelines for Adamsite (DM), Ethyldichloroarsine (ED), Methyldichloroarsine (MD), Phenyldichloroasrine (PD), and Diphenylchloroarsine (DA).

Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
Adamsite (DM)					
AEGL-1	0.20 mg/m^3	0.041 mg/m^3	0.016 mg/m^3	0.0022 mg/m^3	0.00083 mg/m^3
AEGL-2	9.7 mg/m^3	6.8 mg/m^3	2.6 mg/m^3	0.36 mg/m^3	0.14 mg/m^3
AEGL-3	21 mg/m^3	17 mg/m^3	6.4 mg/m^3	0.91 mg/m^3	0.34 mg/m^3
Diphenylchloroarsine (DA)					
AEGL-1	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2	1.1. mg/m^3	0.79 mg/m^3	0.39 mg/m^3	0.098 mg/m^3	0.049 mg/m^3
AEGL-3	3.4 mg/m^3	2.4 mg/m^3	1.2 mg/m^3	0.30 mg/m^3	0.15 mg/m^3
Ethyldichloroarsine (ED)					
AEGL-1	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2	0.17 mg/m^3	0.057 mg/m^3	0.029 mg/m^3	NR[a]	NR[a]
AEGL-3	0.52 mg/m^3	0.17 mg/m^3	0.086 mg/m^3	NR[a]	NR[a]
Methyldichloroarsine (MD)					
AEGL-1	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2	0.63 mg/m^3	0.14 mg/m^3	0.053 mg/m^3	0.015 mg/m^3	0.0063 mg/m^3
AEGL-3	1.9 mg/m^3	0.42 mg/m^3	0.16 mg/m^3	0.044 mg/m^3	0.019 mg/m^3
Phenyldichloroarsine (PD)					
AEGL-1	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2	0.37 mg/m^3	0.12 mg/m^3	0.061 mg/m^3	NR[a]	NR[a]
AEGL-3	1.1 mg/m^3	0.37 mg/m^3	0.18 mg/m^3	NR[a]	NR[a]
ERPG-1 (AIHA)[b]	-	-	-	-	-
ERPG-2 (AIHA)	-	-	-	-	-
ERPG-3 (AIHA)	-	-	-	-	-
PEL-TWA (OSHA)[c]	-	-	-	-	-
IDLH (NIOSH)[d]	-	-	-	-	-
REL-TWA (NIOSH)[e]	-	-	-	-	-
TLV-TWA (ACGIH)[f]	-	-	-	-	-
MAK (Germany)[g]	-	-	-	-	-
MAC[h] (the Netherlands)	-	-	-	-	-

[a] **NR**: Not Recommended. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects, and absence of an AEGL-2 does not imply that exposure below the AEGL-3 is without severe and possibly irreversible adverse effects. Absence of 4- and 8-hour AEGL-3 due to insufficient data for time extrapolation.

[b]**ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association (AIHA 1996)**
The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.
The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects.
fifth the LC_{50} in mice and rats exposed for 4 hours.

[c]**OSHA PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits - Time Weighted Average)** (OSHA 1996) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[d]**IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** (NIOSH 1994; 1999) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

[e]**NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** (NIOSH 1999) is defined analogous to the ACGIH-TLV-TWA.

[f]**ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH 1991; 2000)
is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[g]**MAK (Maximale Argeitsplatzkonzentration [Maximum Workplace Concentration])** (Deutsche Forschungsgemeinschaft [German Research Association] 1999)
is defined analogous to the ACGIH-TLV-TWA.

[h]**MAC (Maximaal Aanvaaarde Concentratie [Maximal Accepted Concentration])** (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000)
is defined analogous to the ACGIH-TLV-TWA.

8.3. Data Adequacy and Research Needs

The overall data set for agent DM includes information on multiple species, including human volunteer subjects. Details regarding the quantitation of exposure atmospheres in the older reports are lacking but overall the data appear to exhibit some continuity. Experiments with laboratory species have traditionally focused on estimating a lethality threshold or identifying a specific response rate for lethality. Although data and observations have affirmed that the eyes and respiratory tract are the primary targets for low level exposures to the chloroarsenicals, quantitative exposure-response data for these endpoints are limited or lacking, especially for the more obscure agents such as DA, ED, MD, and PD. Such data would ameliorate the current deficiency in development of AEGL-1 and AEGL-2 values.

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APPENDIX A
Derivation of AEGL Values

Derivation of AEGL-1 for Adamsite (DM)

Key studies: Craighill and Folkoff (1922) analyzed data from (Lawson and Temple, 1922) indicating a 60-minute exposure to 0.14 mg/m^3 to be a tolerance limit for human volunteer subjects.

Critical effect: Subjectively determined tolerance limit of 0.14 mg/m^3 in human volunteer subjects (Craighill and Folkoff, 1922; Lawson and Temple, 1922) following 60-minute exposure.

NOTE: The effects described by Craighill and Folkoff (1922)/Lawson and Temple, 1922) are of greater severity (i.e., a tolerance limit) than would be considered consistent with the definition of AEGL-1. Therefore, the exposure concentration was reduced three-fold to 0.047 mg/m^3 to approximate an exposure resulting in effects of less severity and more consistent with those associated with AEGL-1.

Time scaling: Analysis of human tolerance limits for DM based on average response of 1 to 6 volunteer subjects. (Lawson and Temple,1922; Craighill and Folkoff, 1922) resulted in an empirically-derived exponent (n) of 0.71 (see Appendix B) for use in the equation $C^n \times t = k$.

Uncertainty factors: Uncertainty factor application was limited to 3 for individual variability. Qualitatively, the human response to DM is well characterized but uncertainty exists regarding a precise threshold for minor irritation. As previously explained, the concentrations selected as point-of-departures were downwardly adjusted to estimate an exposure producing a less severe response. Therefore, there were no additional uncertainty adjustments.

Calculations: $(0.047\ mg/m^3)^{0.71} \times 60\ min = 6.81\ mg - min/m^3$

10-minute AEGL-1

$C^{0.71} \times 10\ min = 6.81\ mg - min/m^3$
$C^{0.71} = 0.68\ mg/m^3$
$C = 0.58\ mg/m^3$
UF application: $0.58\ mg/m^3/3 = 0.19\ mg/m^3$ rounded to $0.20\ mg/m^3$

30-minute AEGL-1

$C^{0.71} \times 30\ min = 6.81\ mg - min/m^3$
$C^{0.71} = 0.227\ mg/m^3$
$C = 0.124\ mg/m^3$
UF application: $0.124\ mg/m^3/3 = 0.041\ mg/m^3$

1-hour AEGL-1

$C^{0.71} \times 60\ min = 6.81\ mg - min/m^3$
$C^{0.71} = 0.11\ mg/m^3$
$C = 0.047\ mg/m^3$
UF application: $0.047\ mg/m^3/3 = 0.016\ mg/m^3$

4-hour AEGL-1

$C^{0.71}$ x 240 min = 6.81 mg - min/m^3

$C^{0.71}$ = 0.028 mg/m^3

C = 0.0066 mg/m^3

UF application: 0.0066 mg/m^3/3 = 0.0022 mg/m^3

8-hour AEGL-1

$C^{0.71}$ x 480 min = 6.81 mg - min/m^3

$C^{0.71}$ = 0.014 mg/m^3

C = 0.0025 mg/m^3

UF application: 0.0025 mg/m^3/3 = 0.00083 mg/m^3

Derivation of AEGL-2 for Adamsite (DM)

Key study: Striker et al. (1967b) reported nonlethal effects in monkeys (*Macaca mulatta*) exposed to DM.

Critical effect: Nasopharyngeal and ocular irritation; gross pathology characterized by tracheal and bronchial damage and pulmonary edema. Effects resolved within one month post-exposure. Responses of monkeys following 10-minute exposure to 291 mg/m^3 or 60-minute exposure to 77 mg/m^3 were used as starting points for AEGL-2 development.

Time scaling: Analysis of human tolerance limits for DM based on average response of 1 to 6 volunteer subjects. (Lawson and Temple,1922; Craighill and Folkoff, 1922) resulted in an empirically-derived exponent (n) of 0.71 (see Appendix B) for use in the equation $C^n \times t = k$. The continuum of effects observed for DM appear to be the result of a similar mode of action (irritation and subsequent injury to epithelial tissue) and, therefore, time scaling was the same for all AEGL tiers.

Uncertainty factors: A total uncertainty factor adjustment of 30 was applied including an intraspecies adjustment of 3 to account for individual variability in response to a direct-acting irritant. Agent DM appears to damage epithelial tissue with which it contacts subsequently resulting in respiratory tract injury. This process is supported by clinical observations in humans and animals and by pathological findings in animals exposed to sufficiently high concentrations of DM. An interspecies uncertainty factor of 10 was applied because available data suggest notable variability among the species tested.

Calculations: For 10-minute AEGL-2:

$(291\ mg/m^3)^{0.71} \times 10\ minutes = 561.52\ mg - min/m^3$

For 30-minute, 1-hr, 4-hr and 8-hr AEGL-2:

$(77\ mg/m^3)^{0.71} \times 60\ minutes = 1{,}310.88\ mg - min/m^3$

<u>10-minute AEGL-2</u>

$C^{0.71} \times 10\ min = 561.52\ mg - min/m^3$

$C^{0.71} = 56.15\ mg/m^3$

$C = 291.0\ mg/m^3$

UF application: $291.0\ mg/m^3/30 = 9.7\ mg/m^3$

<u>30-minute AEGL-2</u>

$C^{0.71} \times 30\ min = 1{,}310.88\ mg - min/m^3$

$C^{0.71} = 43.7\ mg/m^3$

$C = 204.4\ mg/m^3$

UF application: $204.4 mg/m^3/30 = 6.8\ mg/m^3$

<u>1-hour AEGL-2</u>

$C^{0.71} \times 60\ min = 1{,}310.88\ mg - min/m^3$

$C^{0.71} = 21.85\ mg/m^3$

$C = 77.0\ mg/m^3$

UF application: $77.0\ mg/m^3/30 = 2.6\ mg/m^3$

4-hour AEGL-2

$C^{0.71}$ x 240 min = 1,310.88 mg - min/m^3

$C^{0.71}$ = 5.46 mg/m^3

C = 10.93 mg/m^3

UF application: 10.93 mg/m^3/30 = 0.36 mg/m^3

8-hour AEGL-1

$C^{0.71}$ x 480 min = 1,310.88 mg - min/m^3

$C^{0.71}$ = 2.73 mg/m^3

C = 4.12 mg/m^3

UF application: 4.12 mg/m^3/30 = 0.14 mg/m^3

Derivation of AEGL-3 for Adamsite (DM)

Key study: Striker et al. (1967a) reported that monkeys (*Macaca mulatta*) exposed to DM at a concentration of 1708 mg/m^3 for 5 minutes exhibited emphysema and persistent pneumonia but no lethality.
McNamara et al., 1969 reported a highest nonlethal exposure of 279 mg/m^3 for 46 minutes (12,834 mg-min/m^3). Striker et al. (1967b) reported that exposure of monkeys to DM at a concentration of 330 mg/m^3 for 40 minutes was not lethal but resulted in severe pulmonary effects.

Critical effect: severe but reversible pulmonary damage; no lethality

Scaling: Analysis of human tolerance limits for DM based on average response of 1 to 6 volunteer subjects. (Lawson and Temple,1922; Craighill and Folkoff, 1922) resulted in an empirically-derived exponent (n) of 0.71 (see Appendix B) for use in the equation $C^n \times t = k$. The continuum of effects observed for DM appear to be the result of a similar mode of action (irritation and subsequent injury to epithelial tissue) and, therefore, time scaling was the same for all AEGL tiers.

Uncertainty factors: A total uncertainty factor adjustment of 30 was applied including an intraspecies adjustment of 3 to account for individual variability in response to a direct-acting irritant. Agent DM appears to damage epithelial tissue with which it contacts subsequently resulting in respiratory tract injury. This process is supported by clinical observations in humans and animals and by pathological findings in animals exposed to sufficiently high concentrations of DM. An interspecies uncertainty factor of 10 was applied because available data suggest notable variability among the species tested.

Calculations: For 10-minute AEGL-3:

$(1708 \text{ mg/m}^3)^{0.71} \times 5 \text{ minutes} = 986.36 \text{ mg-min/m}^3$

For 30-min., 1-hr, 4-hr, and 8-hr ASEGL-3:

$(279 \text{ mg/m}^3)^{0.71} \times 46 \text{ minutes} = 2{,}506.89 \text{ mg-min/m}^3$

<u>10-minute AEGL-3</u>

$C^{0.71} \times 10 \text{ min} = 986.36 \text{ mg - min/m}^3$
$C^{0.71} = 98.6 \text{ mg/m}^3$
$C = 643.43 \text{ mg/m}^3$
UF application: $643.43 \text{ mg/m}^3/30 = 21 \text{ mg/m}^3$

<u>30-minute AEGL-3</u>

$C^{0.71} \times 30 \text{ min} = 2{,}506.89 \text{ mg - min/m}^3$
$C^{0.71} = 83.56 \text{ mg/m}^3$
$C = 509.38 \text{ mg/m}^3$
UF application: $509.38 \text{ mg/m}^3/30 = 17 \text{ mg/m}^3$

<u>1-hour AEGL-3</u>

$C^{0.71} \times 60 \text{ min} = 2{,}506.89 \text{ mg - min/m}^3$
$C^{0.71} = 41.78 \text{ mg/m}^3$
$C = 191.90 \text{ mg/m}^3$
UF application: $191.90 \text{ mg/m}^3/30 = 6.4 \text{ mg/m}^3$

4-hour AEGL-3

$C^{0.71}$ x 240 min = 2,506.89 mg - min/m^3

$C^{0.71}$ = 10.45 mg/m^3

C = 27.23 mg/m^3

UF application: 27.23 mg/m^3/30 = 0.91 mg/m^3

8-hour AEGL-3

$C^{0.71}$ x 480 min = 2,506.89 mg - min/m^3

$C^{0.71}$ = 5.22 mg/m^3

C = 10.26 mg/m^3

UF application: 10.26 mg/m^3/30 = 0.34 mg/m^3

Derivation of AEGL-1 for Diphenylchloroarsine (DA)

Data were not available with which to develop AEGL-1 values for DA and, therefore, none are recommended. Furthermore, data were unavailable with which to characterize the exposure-response curve for DA making extrapolation from DM or other chloroarsines tenuous and uncertain.

Derivation of AEGL-2 for Diphenylchloroarsine (DA)

Toxicity data were not available with which to develop AEGL-2 values. The lethality studies in dogs, rats, mice, rabbits, and cats did not characterize nonlethal toxic responses. Consistent with AEGL procedures and methodologies (NRC 2001), the AEGL-2 values for DA were estimated as one third of the AEGL-3 values.

Derivation of AEGL-3 for Diphenylchloroarsine (DA)

Key study: MMW (1918) reported no lethality in rats, rabbits, or cats following 30-minute exposure to 236 mg DA/m^3 or 60-minute exposure to 118 mg DA/m^3. A 30-minute exposure to 295 mg DA/m^3 resulted in the death of one of two rats while neither of two cats exposed for 15-minutes to 590 mg/m^3 died and neither of two rabbits exposed to 1180 mg/m^3 for 15 minutes died.

Critical effect: The aforementioned 30-minute and 60-minute exposures were considered an estimate of the lethality threshold.

Time scaling: An empirically-derived value for the exponent, *n*, in the equation $C^n \times t = k$ could not be developed. Consistent with AEGL methodologies (NRC, 2001), an *n* of 1 was used in extrapolating from the 60-minute experimental exposure period to the 4 and 8 hour AEGL-3 time periods, and an *n* of 3 was used for extrapolating from the 30-minute experimental period to the 10-minute AEGL-3 exposure.

Uncertainty factors: Uncertainty factor adjustment consisted of 10 for interspecies variability due to uncertainties in extrapolating from animal lethality to exposures resulting in human deaths. Due to insufficient data with which to assess individual variability in the toxic response to DA, an uncertainty factor of 10 was retained for intraspecies variability.

Calculations: For the 10 and 30-minute AEGL-3:

$(236 \text{ mg/m}^3)^3 \times 30 \text{ minutes} = 394{,}432{,}768 \text{ mg - min}^3/\text{m}^3$

For the 1-hr, 4-hr, and 8-hr AEGL-3:

$(118 \text{ mg/m}^3)^1 \times 60 \text{ minutes} = 7080 \text{ mg - min/m}^3$

<u>10-minute AEGL-3</u>

$C^3 \times 10 \text{ min} = 394{,}327{,}680 \text{ mg - min/m}^3$

$C^3 = 39{,}432{,}768 \text{ mg/m}^3$

$C = 340.37 \text{ mg/m}^3$

UF/MF application: $340.37 \text{ mg/m}^3/100 = 3.4 \text{ mg/m}^3$

30-minute AEGL-3

$C^3 \times 30$ min = 394,327,680 mg - min/m^3

C^3 = 13,144,256 mg/m^3

C = 235.99 mg/m^3

UF/MF application: 235.99 mg/m^3/100 = 2.4 mg/m^3

60-minute AEGL-3

$C^1 \times 60$ min = 7080 mg - min/m^3

C^1 = 118 mg/m^3

UF/MF application: 118 mg/m^3/100 = 1.2 mg/m^3

240-minute AEGL-3

$C^1 \times 240$ min = 7080 mg - min/m^3

C^1 = 29.5 mg/m^3

UF/MF application: 29.5 mg/m^3/100 = 0.30 mg/m^3

480-minute AEGL-3

$C^1 \times 480$ min = 7080 mg - min/m^3

C^1 = 14.75 mg/m^3

UF/MF application: 14.75 mg/m^3/100 = 0.15 mg/m^3

Derivation of AEGL-1 for Ethyldichloroarsine (ED)

Data were not available with which to develop AEGL-1 values for ED and, therefore, none are recommended. Furthermore, data were unavailable with which to characterize the exposure-response curve for ED making extrapolation from DM or other chloroarsines tenuous and uncertain.

Derivation of AEGL-2 for Ethyldichloroarsine (ED)

Toxicity data were not available with which to develop AEGL-2 values. The lethality studies in dogs, rats, mice, rabbits, and cats did not characterize nonlethal toxic responses. Consistent with AEGL procedures and methodologies (NRC 2001), the AEGL-2 values for ED were estimated as one third of the AEGL-3 values.

Derivation of AEGL-3 for Ethyldichloroarsine (ED)

Key study:	Hutchens et al. (1943) reported a 10-minute LCt_{50} of 1,555 mg - min/m^3 for mice equivalent to a 10-minute LC_{50} of 155.5 mg/m^3.
Critical effect:	Lethality threshold for mice estimated as a three-fold reduction of the LCt_{50} (NRC 2001): 155.5 mg/m^3 ÷ 3 = 51.8 mg/m^3.
Time scaling:	An empirically-derived value for the exponent, *n*, in the equation $C^n \times t = k$ could not be developed. Consistent with AEGL methodologies (NRC, 2001), an *n* of 1 was used in extrapolating from the 10-minute experimental exposure period to the 30-minute and 60-minute AEGL-3 time periods. The longer duration AEGL-2 values for ED are not recommended.
Uncertainty factors:	Uncertainty factor adjustment consisted of 10 for interspecies variability due to uncertainties in extrapolating from animal lethality to exposures resulting in human deaths. An uncertainty factor of 10 was applied due to insufficient data with which to assess the individual variability in the toxic response to ED.
Calculations:	$(51.8 \text{ mg/m}^3)^1 \times 10 \text{ minutes} = 518 \text{ mg - min/m}^3$
<u>10-minute AEGL-3</u>	$C^1 \times 10 \text{ min} = 518 \text{ mg - min/m}^3$ $C^1 = 51.8 \text{ mg/m}^3$ UF application: 51.8 mg/m^3/100 = 0.52 mg/m^3

30-minute AEGL-3 C^1 x 30 min = 518 mg - min/m^3
C^1 = 17.2 mg/m^3
UF application: 17.2 mg/m^3/100 = 0.17 mg/m^3

60-minute AEGL-3 C^1 x 60 min = 518 mg - min/m^3
C^1 = 8.63 mg/m^3
UF application: 8.63 mg/m^3/100 = 0.086 mg/m^3

The cumulative exposures (~8.6 mg - min/m^3) resulting from the above AEGL-2 values are similar to the human ICt_{50} range of 5 -10 mg - min/m^3 reported by Sullivan and Kreiger (1992).

240-minute AEGL-3 Not recommended due to uncertainties in extrapolating from a 10-minute to a 240-minute exposure time.

480-minute AEGL-3 Not recommended due to uncertainties in extrapolating from a 10-minute to a 480-minute exposure time.

Derivation of AEGL-1 for Methyldichloroarsine (MD)

Data were not available with which to develop AEGL-1 values for MD and, therefore, none are recommended. It is currently not possible to characterize the exposure-response curve for ED, thus making extrapolation from other chloroarsines tenuous and uncertain.

Derivation of AEGL-2 for Methyldichloroarsine (MD)

Data consistent with AEGL-2 type effects were unavailable with which to develop AEGL-2 values for MD. Consistent with AEGL procedures and methodologies (NRC 2001), the AEGL-2 values for MD were estimated as one third of the AEGL-3 values.

Derivation of AEGL-3 for Methyldichloroarsine (MD)

Key study: A lethality study in dogs exposed to MD for 7.5, 15, 30, 60, or 120 minutes Allen et al. (1922) served as the basis for developing the AEGL-3 values for MD.

Critical effect: Lethality threshold estimated as a three-fold reduction (NRC 2001)of various time-specific LC_{50} values for dogs reported by Allen et al. (1922). The LC_{50} values were 815, 303, 125, 47, and 31 mg/m^3 for dogs exposed to MD for 7.5, 15, 30, 60, or 120 minutes, respectively. These were reduced 3-fold to 271.6, 101, 41.7, 15.7, and 10.3 mg/m^3, respectively

Time scaling: Time scaling was used to develop the 10-minute, 4-hour and 8-hour AEGL-3 values for MD. Time scaling was performed using the empirically-derived exponent (n) of 0.82 derived from multiple time-point dog LC_{50} values of Allen et al. (1922) and applied to the time scaling equation, $C^n \times t = k$ (ten Berge et al. 1986). (see Appendix B)

Uncertainty factors: Uncertainty factor adjustment consisted of 10 for interspecies variability due to uncertainties in extrapolating from animal lethality to exposures resulting in human deaths. In the absence of sufficient data, an uncertainty factor of 10 was applied to account for individual variability in the toxic response to MD.

Calculations: For the 10-minute AEGL-3:

$(271.6\ mg/m^3)^{0.82} \times 7.5\ minutes = 742.8\ mg - min/m^3$

For the 30-minute AEGL-3:

$(41.7\ mg/m^3)^{0.82} \times 30\ minutes = 639.2\ mg - min/m^3$

For the 1-hr AEGL-3:

$(15.7\ mg/m^3)^{0.82} \times 60\ minutes = 573.8\ mg - min/m^3$

For the 4-hour and 8-hour AEGL-3:

$(10.3\ mg/m^3)^{0.82} \times 120\ minutes = 812.3\ mg - min/m^3$

<u>10-minute AEGL-3</u>

$C^{0.82} \times 10\ min = 742.8\ mg - min/m^3$

$C^{0.82} = 74.2\ mg/m^3$

$C = 191.2$

UF application: $191.2\ mg/m^3/100 = 1.9\ mg/m^3$

30-minute AEGL-3

$C^{0.82}$ x 30 min = 639.2 mg - min/m^3
$C^{0.82}$ = 21.3 mg/m^3
C = 41.7 mg/m^3
UF/MF application: 41.7 mg/m^3/100 = 0.42 mg/m^3

60-minute AEGL-3

$C^{0.82}$ x 60 min = 573.8 mg - min/m^3
$C^{0.82}$ = 9.56 mg/m^3
C = 15.7
UF application: 15.7 mg/m^3/100 = 0.16 mg/m^3

240-minute AEGL-3

$C^{0.82}$ x 240 min = 812.3 mg - min/m^3
$C^{0.82}$ = 3.38 mg/m^3
C = 4.42
UF application: 4.42mg/m^3/100 = 0.044 mg/m^3

480-minute AEGL-3

$C^{0.82}$ x 480 min = 812.3 mg - min/m^3
$C^{0.82}$ = 1.69 mg/m^3
C = 1.89
UF application: 1.89 mg/m^3/100 = 0.019 mg/m^3

Derivation of AEGL-1 for Phenyldichloroarsine (PD)

Data were not available with which to develop AEGL-1 values for PD and, therefore, none are recommended. Furthermore, data were unavailable with which to characterize the exposure-response curve for PD making extrapolation from DM or other chloroarsines tenuous and uncertain.

Derivation of AEGL-2 for Phenyldichloroarsine (PD)

Toxicity data were not available with which to develop AEGL-2 values for PD. Consistent with AEGL procedures and methodologies (NRC 2001), the AEGL-2 values for PD were estimated as one third of the AEGL-3 values.

Derivation of AEGL-3 for Phenyldichloroarsine (PD)

Key study:	Skipper et al. (1942) reported a 10-minute LC_{50} of 330 mg/m^3 based upon mortality in groups of 20 mice over a 10-day post exposure observation period.
Critical effect:	Lethality threshold based upon a one-third reduction of the 10-min LC_{50} (330 $mg/m^3 \div 3 = 110$ mg/m^3 as per AEGL procedures and methodologies (NRC 2001).
Time scaling:	An empirically-derived value for the exponent, *n*, in the equation $C^n \times t = k$ could not be developed. Consistent with AEGL methodologies (NRC, 2001), an *n* of 1 was used in extrapolating from the 10-minute experimental exposure period to the 30-minute and 60-minute AEGL-3 time periods. The longer duration AEGL-3 values for PD are not recommended.
Uncertainty factors:	Uncertainty factor adjustment consisted of 10 for interspecies variability due to uncertainties in extrapolating from animal lethality to exposures resulting in human deaths. Due to data deficiencies, an uncertainty factor of 10 was retained to account for individual variability in response to a direct-acting irritant.
Calculations:	$(110 mg/m^3)^1 \times 10$ minutes = 1,100 mg - min/m^3
<u>10-minute AEGL-3</u>	$C^1 \times 10$ min = 1,100 mg - min/m^3
	$C^1 = 110$ mg/m^3
	UF/MF application: 110 $mg/m^3/100 = 1.1$ mg/m^3

30-minute AEGL-3	C^1 x 30 min = 1,100 mg - min/m^3 C^1 = 36.67 mg/m^3 UF/MF application: 36.67 mg/m^3/100 = 0.37 mg/m^3
60-minute AEGL-3	C^1 x 60 min = 1100 mg - min/m^3 C^1 = 18.3 mg/m^3 UF/MF application: 18.3 mg/m^3/100 = 0.18 mg/m^3
240-minute AEGL-3	Not recommended due to uncertainties in extrapolating from a 10-minute to a 240-minute exposure time.
480-minute AEGL-3	Not recommended due to uncertainties in extrapolating from a 10-minute to a 480-minute exposure time.

APPENDIX B
Time Scaling Calculations

The relationship between dose and time for any given chemical is a function of the physical and chemical properties of the substance and the unique toxicological and pharmacological properties of the individual substance. Historically, the relationship according to Haber (1924), commonly called Haber's Law (NRC, 1993) or Haber's Rule (i.e., $C \times t = k$, where C = exposure concentration, t = exposure duration, and k = a constant) has been used to relate exposure concentration and duration to effect (Rinehart and Hatch, 1964). This concept states that exposure concentration and exposure duration may be reciprocally adjusted to maintain a cumulative exposure constant (k) and that this cumulative exposure constant will always reflect a specific quantitative and qualitative response. This inverse relationship of concentration and time may be valid when the toxic response to a chemical is equally dependent upon the concentration and the exposure duration. However, an assessment by ten Berge et al. (1986) of LC_{50} data for certain chemicals revealed chemical-specific relationships between exposure concentration and exposure duration that were often exponential. This relationship can be expressed by the equation $C^n \times t = k$, where n represents a chemical specific, and even a toxic endpoint specific, exponent. The relationship described by this equation is basically the form of a linear regression analysis of the log-log transformation of a plot of C vs t ten Berge et al. (1986) examined the airborne concentration (C) and short-term exposure duration (t) relationship relative to death for approximately 20 chemicals and found that the empirically derived value of n ranged from 0.8 to 3.5 among this group of chemicals. Hence, these workers showed that the value of the exponent (n) in the equation $C^n \times t = k$ quantitatively defines the relationship between exposure concentration and exposure duration for a given chemical and for a specific health effect endpoint. Haber's Rule is the special case where $n = 1$. As the value of n increases, the plot of concentration vs time yields a progressive decrease in the slope of the curve.

Data were available for deriving a chemical-specific exponent (n) for adamsite (DM) and methyldichloroarsine (MD). These derivations are presented in this appendix.

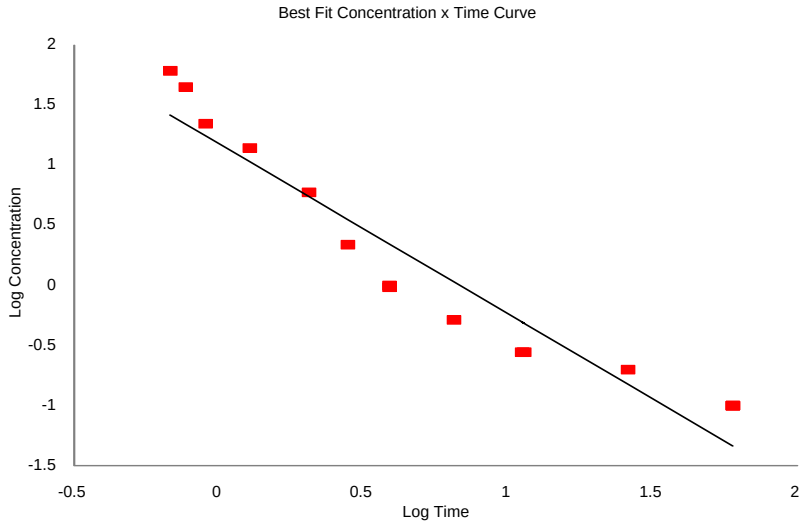
Adamsite (DM)

Human tolerance limits for adamsite (DM) based on average response of 1 to 6 volunteer subjects. (Lawson and Temple,1922; Craighill and Folkoff, 1922).

Time	Conc.	Log Time	Log Conc.
0.68	61.4	-0.1675	1.7882
0.77	45	-0.1135	1.6532
0.9	22.3	-0.0458	1.3483
1.28	14	0.1072	1.1461
2.05	6	0.3118	0.7782
2.8	2.2	0.4472	0.3424
3.9	1	0.5911	0.0000
3.9	0.97	0.5911	-0.0132
6.5	0.52	0.8129	-0.2840
11.4	0.28	1.0569	-0.5528
11.2	0.28	1.0492	-0.5528
26	0.2	1.4150	-0.6990
60	0.1	1.7782	-1.0000
60	0.1	1.7782	-1.0000

Regression Output:	
Intercept	1.1830
Slope	-1.4157
R Squared	0.9185
Correlation	-0.9584
Degrees of Freedom	12
Observations	14

n = 0.71
k = 6.85



Methyldichloroarsine (MD)

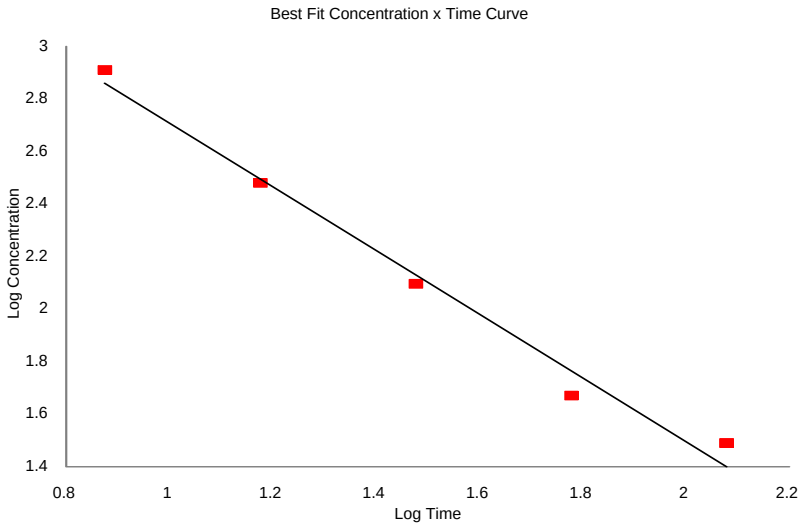
Lethality in dogs (11-30 per group) exposed to MD (Allen et al., 1922)

Time	Conc.	Log Time	Log Conc.
7.5	815	0.8751	2.9112
15	303	1.1761	2.4814
30	125	1.4771	2.0969
60	47	1.7782	1.6721
120	31	2.0792	1.4914

Regression Output:	
Intercept	3.9211
Slope	-1.2122
R Squared	0.9846
Correlation	-0.9923
Degrees of Freedom	3
Observations	5

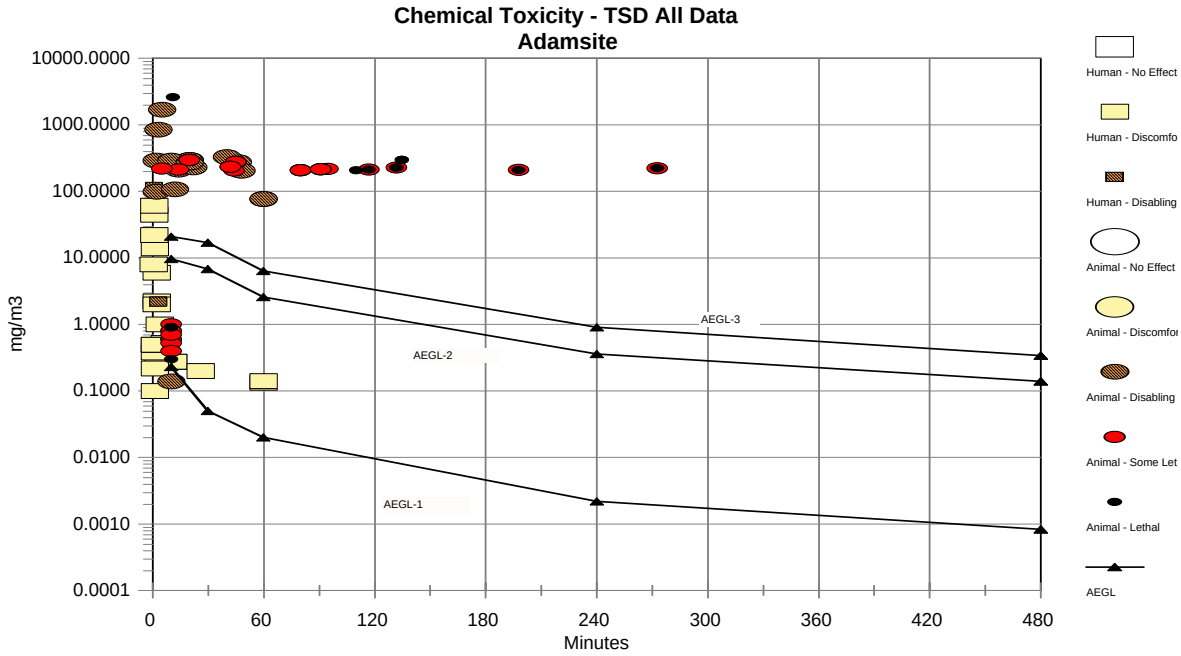
n = 0.82

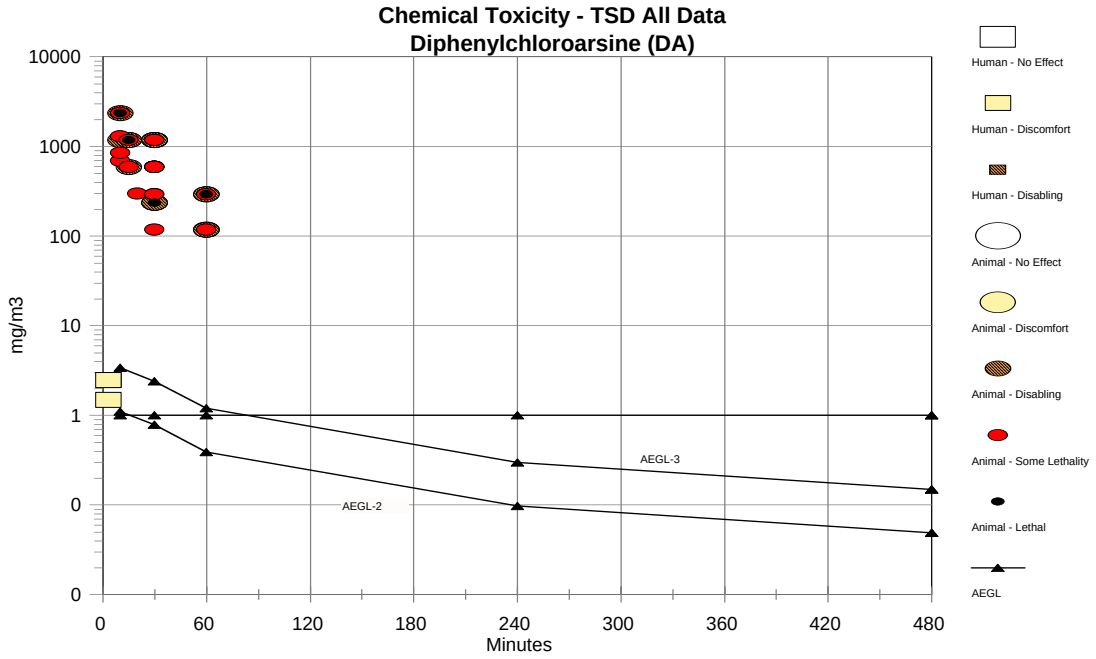
k = 1717.19

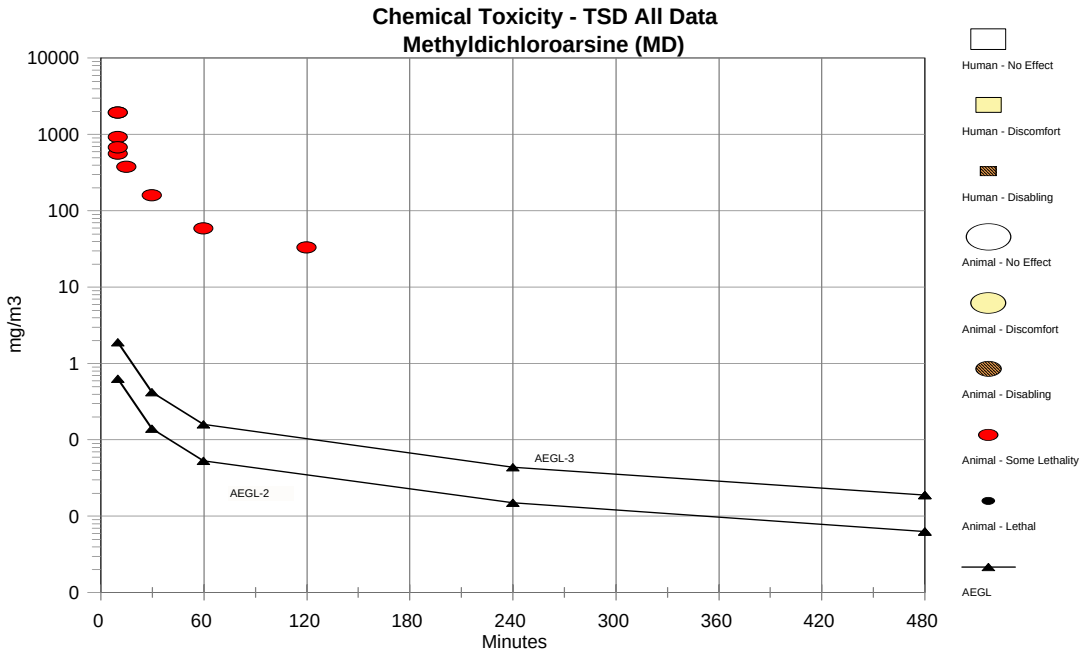


APPENDIX C
Category Plots

A useful way to evaluate the AEGL values in context of existing empirical data is presented in Figures 1 and 2. For these plots, the toxic response data were categorized by severity. The severity categories fit into definitions of the AEGL health effects: no effects, discomfort, disabling, some lethality (an experimental concentration at which some of the animals died), and lethal (100% mortality). The spectrum of effects are, of course, chemical-specific, and the exposures often span an order of magnitude or more. Therefore, exposure concentrations are plotted on a log scale. The category plots display the AEGL values along with the existing acute toxicity data which have been categorized by severity. From these plots, the relationship of the AEGL values can be viewed with respect to available data.


Chemical Toxicity - TSD All Data
Adamsite
mg/m3
10000.0000
1000.0000
100.0000
10.0000
1.0000
0.1000
0.0100
0.0010
0.0001
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
AEGL-1
Human - No Effect
Human - Discomfo
Human - Disabling
Animal - No Effect
Animal - Discomfor
Animal - Disabling
Animal - Some Let
Animal - Lethal
AEGL


Chemical Toxicity - TSD All Data
Diphenylchloroarsine (DA)
mg/m3
10000
1000
100
10
1
0
0
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 - Some Lethality
Animal - Lethal
AEGL


Chemical Toxicity - TSD All Data
Methyldichloroarsine (MD)
mg/m3
10000
1000
100
10
1
0
0
0
Minutes
0
60
120
180
240
300
360
420
480
AEGL-2
AEGL-3
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL

APPENDIX D
Derivation Summary Tables

ACUTE EXPOSURE GUIDELINE LEVELS FOR ADAMSITE (DM) DERIVATION SUMMARY

AEGL-1 VALUES FOR ADAMSITE (DM)				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
0.20 mg/m^3	**0.041 mg/m^3**	**0.016 mg/m^3**	**0.0022 mg/m^3**	**0.00083 mg/m^3**

References:
Craighill, M.D., Folkoff, C.M. 1922. A digest of reports concerning the toxic effect of diphenylaminechloroarsine on man and laboratory animals. EA-CD-145, Edgewood Arsenal, Aberdeen Proving Ground, MD. April 1922. Unclassified, Limited Distribution Report.

Test Species/Strain/Number: 1 to 10 human volunteers per exposure; males

Exposure Route/Concentrations/Durations: inhalation

Effects: Subjectively determined tolerance limit for ocular and nasopharyngeal irritation: 0.14 mg/m^3 for 60-minute exposure.

Endpoint/Concentration/Rationale: Tolerance limit for ocular and nasopharyngeal irritation (0.14 mg/m^3 for 60-minute exposure) was reduced 3-fold as an estimate for AEGL-1 severity effects rather than a tolerance limit resulting in a point0of-departure of 0.047 mg/m^3.

Uncertainty Factors/Rationale: Uncertainty factor application was limited to 3 for individual variability. Qualitatively, the human response to DM is well characterized but uncertainty exists regarding a precise threshold for minor irritation. As previously explained, the concentrations selected as point-of-departures were downwardly adjusted to estimate an exposure producing a less severe response. Therefore, there were no additional uncertainty adjustments.

Modifying Factor: None were applied.

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: Analysis of human tolerance limits for DM based on average response of 1 to 6 volunteer subjects. (Lawson and Temple,1922; Craighill and Folkoff, 1922) resulted in an empirically-derived exponent (n) of 0.71 (see Appendix B) for use in the equation $C^n \times t = k$.

Data Adequacy: The human response to low-level exposures to DM are well characterized based upon controlled exposure studies. The critical effects thresholds are consistent with the know activity of DM and represent a valid basis for AEGL-1 development.

AEGL-2 VALUES FOR ADAMSITE (DM)				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
9.7 mg/m^3	**6.8 mg/m^3**	**2.6 mg/m^3**	**0.36 mg/m^3**	**0.14 mg/m^3**

Reference:
Striker, G.E., Streett, C.S., Ford, D.F., Herman, L.H., Helland, D.R. 1967b. A clinicopathological study of the effects of riot control agents on monkeys. V. Low concentrations of diphenylaminochloroarsine (DM) or o-chlorobenzylidine malononitrite (CS) for extended periods. U.S. Army Medical Research Laboratory, Edgewood Arsenal, MD. Technical report 4072. Unclassified, Limited Distribution Report.

Test Species/Strain/Sex/Number: monkey (*Macaca mulatta*)/gender not specified/5

Exposure Route/Concentrations/Durations: inhalation; exposures concentrations ranged from 77-330 mg/m^3 exposure durations ranged from 2-60 minutes; specific Ct values for 7 exposure groups were 582, 2910, 5440, 13,200, 198, 1296, and 4692 mg-min/m^3

Effects: Nasopharyngeal and ocular irritation; gross pathology characterized by tracheal and bronchial damage and pulmonary edema. Effects resolved within one month post-exposure. Responses of monkeys following 10-minute exposure to 291 mg/m^3 or 60-minute exposure to 77 mg/m^3 were used as starting points for AEGL-2 development.

Endpoint/Concentration/Rationale: Responses of monkeys following 10-minute exposure to 291 mg/m^3 or 60-minute exposure to 77 mg/m^3 were used as starting points for AEGL-2 development.

Uncertainty Factors/Rationale:
Total uncertainty factor: 30
Interspecies: A factor of 10 was applied because available data suggest notable variability among the species tested.
Intraspecies: A factor of 3 was applied to account for individual variability in response to a direct-acting irritant. Agent DM appears to damage epithelial tissue with which it contacts subsequently resulting in respiratory tract injury. This process is supported by clinical observations in humans and animals and by pathological findings in animals exposed to sufficiently high concentrations of DM.

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling:
Analysis of human tolerance limits for DM based on average response of 1 to 6 volunteer subjects. (Lawson and Temple,1922; Craighill and Folkoff, 1922) resulted in an empirically-derived exponent (n) of 0.71 (see Appendix B) for use in the equation $C^n \times t = k$. The continuum of effects observed for DM appear to be the result of a similar mode of action (irritation and subsequent injury to epithelial tissue) and, therefore, time scaling was the same for all AEGL tiers.

Data Adequacy: The critical effect is consistent with AEGL-2 severity. The toxic response was qualitatively similar to that expected in humans and its severity verified by gross pathology correlates.

AEGL-3 VALUES FOR ADAMSITE (DM)

10 minutes	30 minutes	1 hour	4 hours	8 hours
21 mg/m^3	17 mg/m^3	6.4 mg/m^3	0.91 mg/m^3	0.34 mg/m^3

Reference:

Striker, G.E., Streett, C.S., Ford, D.F., Herman, L.H., Helland, D.R. 1967a. A clinicopathological study of the effects of riot control agents on monkeys. III. Diphenylaminochloroarsine (DM) grenade. U.S. Army Medical Research Laboratory, Edgewood Arsenal, MD. Technical report 4070. (Cited in NRC, 1984).

Striker, G.E., Streett, C.S., Ford, D.F., Herman, L.H., Helland, D.R. 1967b. A clinicopathological study of the effects of riot control agents on monkeys. V. Low concentrations of diphenylaminochloroarsine (DM) or o-chlorobenzylidine malononitrile (CS) for extended periods. U.S. Army Medical Research Laboratory, Edgewood Arsenal, MD. Technical report 4072. Unclassified, Limited Distribution Report.

McNamara, B.P., Owens, E.J., Weimer, J.T., Ballard, T.A., Vocci, F.J. 1969. Toxicology of riot control chemicals - CS, CN, and DM. U.S. Army Medical Research Laboratory, Edgewood Arsenal, MD. Technical report EATR 4309. (Cited in NRC, 1984).

Test Species/Strain/Sex/Number: groups of 5-10 monkeys (*Macaca mulatta*)/gender not specified

Effects:

McNamara et al. 1969:

Conc. (mg/m^3)	Duration (min)	Response
296	135	6 of 6 dead
214	117	6 of 6 dead
219	95	4 of 6 dead
209	80	3 of 6 dead
279	46	no lethality
297	20	no lethality

Striker et al., 1947a

Conc. (mg/m^3)	Duration (min)	Response
1708	5	Emphysema and pulmonary edema up to 30 days
2615	11	8 of 10 dead at 24 hrs

Striker et al., 1947b

Conc. (mg/m^3)	Duration (min)	Response
330	40	Ocular irritation, nausea, vomiting, dyspnea, pulmonary edema

Endpoint/Concentration/Rationale:

Exposure of monkeys to1708 mg DM/m^3 for 5 minutes produced emphysema and persistent pneumonia but no lethality (McNamara et al., 1969) and served as the point-of-departure for the 10-min. AEGL-3.

Highest nonlethal exposure of 279 mg/m^3 for 46 minutes (McNamara et al., 1969) served as the point-of-departure for the 30-min, 1-, 4-, and 8-hr AEGL-3.

Striker et al. (1967b) reported that exposure of monkeys to DM at a concentration of 330 mg/m^3 for 40 minutes was not lethal but resulted in severe pulmonary effects.

Uncertainty Factors/Rationale: A total uncertainty factor adjustment of 30 was applied. Intraspecies: adjustment of 3 to account for individual variability in response to a direct-acting irritant. Agent DM appears to damage epithelial tissue with which it contacts subsequently resulting in respiratory tract injury. This process is supported by clinical observations in humans and animals and by pathological findings in animals exposed to sufficiently high concentrations of DM. Interspecies: an uncertainty factor of 10 was applied because available data suggest notable variability among the species tested
Modifying Factor: Not applicable
Animal to Human Dosimetric Adjustment: Not applicable
Time Scaling: Analysis of human tolerance limits for DM based on average response of 1 to 6 volunteer subjects. (Lawson and Temple,1922; Craighill and Folkoff, 1922) resulted in an empirically-derived exponent (n) of 0.71 (see Appendix B) for use in the equation $C^n \times t = k$. The continuum of effects observed for DM appear to be the result of a similar mode of action (irritation and subsequent injury to epithelial tissue) and, therefore, time scaling was the same for all AEGL tiers.
Data Adequacy: Exposure/response data identifying effects consistent with an AEGL-3 point-of-departure were available from studies using nonhuman primates. The critical effects were consistent with the continuum of toxic responses know for agent DM.

ACUTE EXPOSURE GUIDELINE LEVELS FOR DIPHENYLCHLOROARSINE (DA) DERIVATION SUMMARY

AEGL-1 VALUES FOR DIPHENYLCHLOROARSINE (DA)				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
Not recommended	**Not recommended**	**Not recommended**	**Not recommended**	**Not recommended**

Reference: Not applicable

Test Species/Strain/Number: Not applicable

Exposure Route/Concentrations/Durations: Not applicable

Effects: Not applicable

Endpoint/Concentration/Rationale: Not applicable

Uncertainty Factors/Rationale: Not applicable

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: Not applicable

Data Adequacy: Not applicable

AEGL-2 VALUES FOR DIPHENYLCHLOROARSINE (DA)				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
1.1 mg/m^3	**0.79 mg/m^3**	**0.39 mg/m^3**	**0.098 mg/m^3**	**0.049 mg/m^3**
Reference: Toxicity data were not available with which to develop AEGL-2 values. The lethality studies in dogs, rats, mice, rabbits, and cats did not characterize nonlethal toxic responses. Consistent with AEGL procedures and methodologies (NRC 2001), the AEGL-2 values for DA were estimated as one third of the AEGL-3 values. Not applicable				
Test Species/Strain/Sex/Number: See AEGL-3 Summary Table				
Exposure Route/Concentrations/Durations: See AEGL-3 Summary Table				
Effects: See AEGL-3 Summary Table				
Endpoint/Concentration/Rationale: One-third reduction of AEGL-3 values				
Uncertainty Factors/Rationale: See AEGL-3 Summary Table				
Modifying Factor: None				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: See AEGL-3 Summary Table				
Data Adequacy: Data were insufficient for development of AEGL-2. Consistent with AEGL procedures and methodologies (NRC 2001), the AEGL-2 values for DA were estimated as one third of the AEGL-3 values. Not applicable				

AEGL-3 VALUES FOR DIPHENYLCHLOROARSINE (DA)				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
3.4 mg/m^3	**2.4 mg/m^3**	**1.2 mg/m^3**	**0.30 mg/m^3**	**0.15 mg/m^3**

Reference:
MMW (Ministry of Munitions of War, Chemical Warfare Dept.). 1918. Report upon certain gases and vapours and their physiological effects. England. Unclassified, Limited Distribution Report.

Test Species/Strain/Sex/Number: 2-8 animals per exposure group depending on species tested

Exposure Route/Concentrations/Durations: inhalation/118-2361 mg/m^3/10-60 min.

Effects: Lethality assessed following varying concentration/time exposures for the concentration and time ranges note above.

Endpoint/Concentration/Rationale:
No lethality was observed fro rats, rabbits, or cats following 30-minute exposure to 236 mg DA/m^3 or 60-minute exposure to 118 mg DA/m^3. A 30-minute exposure to 295 mg DA/m^3 resulted in the death of one of two rats while neither of two cats exposed for 15-minutes to 590 mg/m^3 died and neither of two rabbits exposed to 1180 mg/m^3 for 15 minutes died. The aforementioned 30-minute and 60-minute exposures were considered an estimate of the lethality threshold.

Uncertainty Factors/Rationale:
Total uncertainty factor: 100
Interspecies: A default factor of 10 was retained to account for uncertainties in extrapolating from animal lethality to exposures resulting in human deaths.
Intraspecies: Due to insufficient data with which to assess individual variability in the toxic response to DA, an uncertainty factor of 10 was also retained for intraspecies variability.

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling:
An empirically-derived value for the exponent, *n*, in the equation $C^n \times t = k$ could not be developed. Consistent with AEGL methodologies (NRC, 2001), an *n* of 1 was used in extrapolating from the 60-minute experimental exposure period to the 4 and 8 hour AEGL-3 time periods, and an *n* of 3 was used for extrapolating from the 30-minute experimental period to the 10-minute AEGL-3 exposure.

Data Adequacy: Details regarding experimental protocols and results of the key studies were lacking. However, the studies were reviewed in credible sources and data represented several species. Exposure durations in the studies were representative of AEGL time frames.

ACUTE EXPOSURE GUIDELINE LEVELS FOR ETHYLDICHLOROARSINE (ED) DERIVATION SUMMARY

AEGL-1 VALUES FOR ETHYLDICHLOROARSINE (ED)				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
Not recommended	**Not recommended**	**Not recommended**	**Not recommended**	**Not recommended**
Reference: Not applicable				
Test Species/Strain/Number: Not applicable				
Exposure Route/Concentrations/Durations: Not applicable				
Effects: Not applicable				
Endpoint/Concentration/Rationale: Not applicable				
Uncertainty Factors/Rationale: Not applicable				
Modifying Factor: Not applicable				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: Not applicable				
Data Adequacy: Not applicable				

AEGL-2 VALUES FOR ETHYLDICHLOROARSINE (ED)				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
0.17 mg/m^3	**0.057 mg/m^3**	**0.029 mg/m^3**	**Not recommended**	**Not recommended**
Reference: Data were unavailable with which to develop AEGL-2 values for ED. Consistent with AEGL procedures and methodologies (NRC 2001), the AEGL-2 values for ED were estimated as one third of the AEGL-3 values.				
Test Species/Strain/Sex/Number: See AEGL-3 Summary Table				
Exposure Route/Concentrations/Durations: See AEGL-3 Summary Table				
Effects: See AEGL Summary Table				
Endpoint/Concentration/Rationale: One third reduction of AEGL-3				
Uncertainty Factors/Rationale: See AEGL-3 Summary Table				
Modifying Factor: Not applicable				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: See AEGL-3 Summary Table				
Data Adequacy: Insufficient for directly developing AEGL-2 values.				

AEGL-3 VALUES FOR ETHYLDICHLOROARSINE (ED)				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
0.52 mg/m^3	**0.17 mg/m^3**	**0.086 mg/m^3**	**Not recommended**	**Not recommended**

Reference:
Hutchens, J.O., Doyle, W.L., Merrill, R., Glass, H.G., Lushbaugh. 1943. A comparison of the lethal effects of several dichloroarsines on mice exposed to the vapors at low relative humidity. Univ. Chicago Toxicity Laboratory. February 16, 1943. Office of Scientific Research and Development Report 1199. (Cited in NDRC 1946).

Test Species/Strain/Sex/Number: mouse; strain, gender and number not specified

Exposure Route/Concentrations/Durations: whole-body inhalation exposure; 10-minute duration

Effects: Reported LCt_{50} of 1,555.5 mg-min/m^3

Endpoint/Concentration/Rationale
The reported LCt_{50} of 1,555.5 mg-min/m^3 (equivalent to 155 mg/m^3 for a 10-min exposure) was reduced threefold as an estimate of the lethality threshold as per AEGL development Standing Operating Procedures (NRC, 2001). The resulting point-of-departure was 51.8 mg/m^3

Uncertainty Factors/Rationale:
Total uncertainty factor: 100
Interspecies: Uncertainty factor adjustment consisted of 10 for interspecies variability due to uncertainties in extrapolating from animal lethality to exposures resulting in human deaths.
Intraspecies: A default uncertainty factor of 10 was retained due to insufficient data with which to assess the individual variability in the toxic response to ED.

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: An empirically-derived value for the exponent, *n*, in the equation $C^n \times t = k$ could not be developed. Consistent with AEGL methodologies (NRC, 2001), an *n* of 1 was used in extrapolating from the 10-minute experimental exposure period to the 30-minute and 60-minute AEGL-3 time periods. The longer duration AEGL-2 values for ED are not recommended.

Data Adequacy: AEGL-3 values for 4 and 8 hours were not recommended due to uncertainty involved in extrapolating from a 10-minute experimental exposure period. The cumulative exposure (- 5.2 mg - min/m^3) resulting from the above AEGL-2 values are at the lower range the human ICt_{50} range of 5 - 10 mg - min/m^3 reported by Sullivan and Kreiger (1992).

ACUTE EXPOSURE GUIDELINE LEVELS FOR METHYLDICHLOROARSINE (MD) DERIVATION SUMMARY

AEGL-1 VALUES FOR METHYLDICHLOROARSINE (MD)				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
Not recommended	**Not recommended**	**Not recommended**	**Not recommended**	**Not recommended**
Reference: Not applicable				
Test Species/Strain/Number: Not applicable				
Exposure Route/Concentrations/Durations: Not applicable				
Effects: Not applicable				
Endpoint/Concentration/Rationale: Not applicable				
Uncertainty Factors/Rationale: Not applicable				
Modifying Factor: Not applicable				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: Not applicable				
Data Adequacy: Not applicable				

AEGL-2 VALUES FOR METHYLDICHLOROARSINE (MD)				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
0.63 mg/m^3	**0.14 mg/m^3**	**0.053 mg/m^3**	**0.015 mg/m^3**	**0.0063 mg/m^3**
Reference: Data were unavailable with which to develop AEGL-2 values for MD. Consistent with AEGL procedures and methodologies (NRC 2001), the AEGL-2 values for MD were estimated as one third of the AEGL-3 values.				
Test Species/Strain/Sex/Number: See AEGL-3 Summary Table				
Exposure Route/Concentrations/Durations: See AEGL-3 Summary Table				
Effects: See AEGL-3 Summary Table				
Endpoint/Concentration/Rationale: AEGL-2 values estimated as one third of the AEGL-3 values				
Uncertainty Factors/Rationale: See AEGL-3 Summary Table				
Modifying Factor: Not applicable				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: See AEGL-3 Summary Table				
Data Adequacy: Exposure-response data consistent with AEGL-2 severity effects were unavailable.				

AEGL-3 VALUES FOR METHYLDICHLOROARSINE (MD)				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
1.9 mg/m^3	**0.42 mg/m^3**	**0.16 mg/m^3**	**0.044 mg/m^3**	**0.019 mg/m^3**

Reference:
Allen, M.S., Kuhn, H.A., Vedder, E.B. 1922. Minimum lethal concentrations and pathology of methyldichloroarsine. Report No. E.A.M.R.D. 4. War Dept., Chemical Warfare Service, Edgewood Arsenal, Edgewood, MD. 27 December 1922. Unclassified, Limited Distribution Report.

Test Species/Strain/Sex/Number: dogs (11-30 per exposure group); age, gender and breed not specified

Exposure Route/Concentrations/Durations: inhalation/846, 377, 160, 59, 33 mg/m^3 for 7.5, 15, 30, 60, or 120 min, respectively.

Effects:
Mortality ratios for the 7.5, 15, 30, 60, and 120-minute exposure groups were 13/21 (14%), 17/26 (59%), 20/28 (71%), 20/30 (67%) and 9/11 (82%).
Cumulative exposure products (Ct) for the test groups were 6345, 5655, 9600, 3540, and 3960 mg•min/m^3.
LC_{50} values: 815 mg/m^3 (7.5 min), 303 mg/m^3 (15 min), 125 mg/m^3 (30 min), 47 mg/m^3 (60 min), and 31 mg/m^3 (120 min).

Endpoint/Concentration/Rationale:
Lethality threshold estimated as a three-fold reduction (NRC 2001) of various time-specific LC_{50} values for dogs reported by Allen et al. (1922). The LC_{50} values were 815, 303, 125, 47, and 31 mg/m^3 for dogs exposed to MD for 7.5, 15, 30, 60, or 120 minutes, respectively. These were reduced 3-fold to 271.6, 101, 41.7, 15.7, and 10.3 mg/m^3, respectively

Uncertainty Factors/Rationale:
Total uncertainty factor: 100
Interspecies: Uncertainty factor adjustment consisted of 10 for interspecies variability due to uncertainties in extrapolating from animal lethality to exposures resulting in human deaths.
Intraspecies: In the absence of sufficient data, a default uncertainty factor of 10 was retained to account for individual variability in the toxic response to MD.

Modifying Factor: None applied

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling:
Time scaling was used to develop the 10-minute, 4-hour and 8-hour AEGL-3 values for MD. Time scaling was performed using the empirically-derived exponent (n) of 0.82 derived from multiple time-point dog LC_{50} values of Allen et al. (1922) and applied to the time scaling equation, $C^n \times t = k$ (ten Berge et al. 1986). (see Appendix B)

Data Adequacy: Lethality data were available for dogs and rats and for several exposure concentration/time combinations. Dogs appeared to be the most sensitive species although comparisons were difficult due to variations in exposure conditions (e.g., humidity) on lethality.

ACUTE EXPOSURE GUIDELINE LEVELS FOR PHENYLDICHLOROARSINE (PD) DERIVATION SUMMARY

AEGL-1 VALUES FOR PHENYLDICHLOROARSINE (PD)				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
Not recommended	**Not recommended**	**Not recommended**	**Not recommended**	**Not recommended**
Reference:Not applicable				
Test Species/Strain/Number: Not applicable				
Exposure Route/Concentrations/Durations: Not applicable				
Effects: Not applicable				
Endpoint/Concentration/Rationale: Not applicable				
Uncertainty Factors/Rationale: Not applicable				
Modifying Factor: Not applicable				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: Not applicable				
Data Adequacy:				

AEGL-2 VALUES FOR PHENYLDICHLOROARSINE (PD)				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
0.37 mg/m^3	**0.12 mg/m^3**	**0.061 mg/m^3**	**Not recommended**	**Not recommended**
Reference: Data were unavailable with which to develop AEGL-2 values for PD. Consistent with AEGL procedures and methodologies (NRC 2001), the AEGL-2 values for PD were estimated as one third of the AEGL-3 values.				
Test Species/Strain/Sex/Number: See AEGL-3 Summary Table				
Exposure Route/Concentrations/Durations: See AEGL-3 Summary Table				
Effects: See AEGL-3 Summary Table				
Endpoint/Concentration/Rationale: AEGL-2 values estimated as one third of the AEGL-3 values				
Uncertainty Factors/Rationale: See AEGL-3 Summary Table				
Modifying Factor: Not applicable				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: See AEGL-3 Summary Table				
Data Adequacy: Exposure-response data consistent with AEGL-2 severity effects were unavailable.				

AEGL-3 VALUES FOR PHENYLDICHLOROARSINE (PD)				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
1.1 mg/m^3	**0.37 mg/m^3**	**0.18 mg/m^3**	**Not recommended**	**Not recommended**

Reference:
Skipper, H.E., Silver, S.D., Bowden, E., Hunt, C. M. 1942. Phenyldichloroarsine: Median lethal concentration for mice; 10-min exposure. Project A 10.2 T.D.M.R. 380. May 25, 1942. Unclassified, Limited Distribution Report.

Test Species/Strain/Sex/Number: mouse (age, strain, and gender not specified)/20 per group

Exposure Route/Concentrations/Durations: inhalation/exposure concentrations of 100 (2 groups), 220, 270, 450, 480, and 530 mg/m^3/10-min. exposure/10-day observation period

Effects:

Concentration (mg/m^3)	Mortality (%)
100	5
100	0
220	10
270	0
450	75
480	55
530	95

deaths generally occurred within 24 hrs post exposure

Endpoint/Concentration/Rationale:
Investigator-reported LC_{50} was 300±80 mg/m^3. Following AEGL methodologies (NRC, 2001), an lethality threshold of 110 mg/m^3, estimated as a 3-fold reduction of the LC_{50} was used as the point-of-departure for AEGL03 development.

Uncertainty Factors/Rationale:
Total uncertainty factor:
Interspecies: A default factor of 10 was retained for interspecies variability due to uncertainties in extrapolating from animal lethality to exposures resulting in human deaths.
Intraspecies: A default of 10 was retained to account for individual variability in response to a direct-acting irritant.

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling:
An empirically-derived value for the exponent, *n*, in the equation $C^n \times t = k$ could not be developed. Consistent with AEGL methodologies (NRC, 2001), an *n* of 1 was used in extrapolating from the 10-minute experimental exposure period to the 30-minute and 60-minute AEGL-3 time periods. The longer duration AEGL-3 values for PD are not recommended.

Data Adequacy: Data regarding the lethal response of animals to phenyldichloroarsine are limited to only one study in a single species utilizing a very short exposure duration. There is no information regarding human lethality following inhalation exposure to phenyldichloroarsine.