Acute Exposure Guideline Levels for Selected Airborne Chemicals

Volume 1

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Preface

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

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

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

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

from the private sector—has developed acute exposure guideline levels (AEGLs) for approximately 80 EHSs.

In 1998, EPA and DOD requested that the NRC independently review the AEGLs developed by NAC. In response to that request, the NRC organized within its Committee on Toxicology the Subcommittee on Acute Exposure Guideline Levels, which prepared this report. This report is the first volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*. It reviews the appropriateness of the AEGLs for four chemicals for their scientific validity, completeness, and consistency with the NRC guideline reports.

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report: Gary Carolson, Purdue University; Charles Feigley, University of South Carolina, Charleston; and Ralph Kodell, National Center for Toxicological Research.

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

The subcommittee gratefully acknowledges the valuable assistance provided by the following persons: Roger Garrett, Paul Tobin, and Ernest Falke (all from EPA); George Rusch (Honeywell, Inc.); Po Yung Lu, Sylvia Talmage, Robert Young, and Sylvia Milanez (all from Oak Ridge National Laboratory), and Karl Rozman (University of Kansas Medical Center). Aida Neel was the project assistant. Ruth Crossgrove edited the report. We are grateful to James J. Reisa, director of the Board on Environmental Studies and Toxicology (BEST), and David Policansky, associate director of BEST, for their helpful comments. The subcommittee particularly acknowledges Kulbir Bakshi, project director for the subcommittee, for bringing the report to completion. Finally, we would like to

thank all members of the subcommittee for their expertise and dedicated effort throughout the development of this report.

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

Bailus Walker, *Chair*
Committee on Toxicology

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

Introduction

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

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

As a first step in assisting the LEPCs, EPA identified approximately 400 EHSs largely on the basis of their "immediately dangerous to life and health" (IDLH) values developed by the National Institute for Occupational Safety and Health in experimental animals. Although several public and private groups, such as the Occupational Safety and Health Administration and the American

Conference of Governmental Industrial Hygienists, have established exposure limits for some substances and some exposures (e.g., workplace or ambient air quality), these limits are not easily or directly translated into emergency exposure limits for exposures at high levels but of short duration, usually less than 1 h, and only once in a lifetime for the general population, which includes infants, children, the elderly, and persons with diseases, such as asthma, heart disease, or lung disease.

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

In November1995, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC[1]) was established to identify, review, and interpret relevant toxicologic and other scientific data and to develop acute exposure guideline levels (AEGLs) for high-priority, acutely toxic chemicals. The NRC's previous name for acute exposure levels—community emergency exposure levels (CEELs)—was replaced by the term AEGLs to reflect the broad application of these values to planning, response, and prevention in the community, the workplace, transportation, the military, and the remediation of Superfund sites.

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[1]NAC is composed of members from EPA, DOD, many other federal and state agencies, industry, academia, and other organizations. The roster of NAC is shown on page 9.

AEGLs represent threshold exposure limits (exposure levels below which adverse health effects are not likely to occur) for the general public and are applicable to emergency exposures ranging from 10 min to 8 h. Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 min, 30 min, 1 h, 4 h, and 8 h) and are distinguished by varying degrees of severity of toxic effects.

The three AEGLs are defined as follows:

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

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

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

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

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

For substances that affect several organ systems or have multiple effects, all endpoints—including reproductive (in both sexes), developmental, neurotoxic, respiratory, and other organ-related effects—are evaluated, the most important or most sensitive effect receiving the greatest attention. For carcinogenic chemicals, theoretical excess carcinogenic risk is estimated, and the AEGLs corresponding to carcinogenic risks of 1 in 10,000 (1×10^{-4}), 1 in 100,000 (1×10^{-5}), and 1 in 1,000,000 (1×10^{-6}) exposed persons are estimated.

REVIEW OF AEGL REPORTS

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

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

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

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

This report is the first volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*. AEGL documents for four chemicals—aniline, arsine, monomethylhydrazine, and dimethyl hydrazine—are published as an appendix to this report. The subcommittee concludes that the AEGLs developed in those documents are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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Appendix

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Arsine[1]
Acute Exposure Guideline Levels

SUMMARY

ARSINE is a colorless gas used in the semiconductor industry. Arsine also is used in mining and manufacturing processes involving arsenicals and paints and herbicides containing arsenicals.

Arsine is extremely toxic and a potent hemolytic agent, ultimately causing death via renal failure. Numerous human case reports are available, but these reports lack definitive quantitative exposure data. The reports, however, affirm the extreme toxicity and latency period for the toxic effects of arsine in humans.

Exposure-response data from animal studies were used to derive acute exposure guideline level (AEGL) values for arsine. AEGL values derived with animal data which had complete exposure data were more scientifically valid

[1]This document was prepared by AEGL Development Team member Richard Thomas of the National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances (NAC) and Robert Young of the Oak Ridge National Laboratory. The NAC reviewed and revised the document, which was then reviewed by the National Research Council (NRC) Subcommittee on Acute Exposure Guideline Levels. The NRC subcommittee concludes that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NAC and are consistent with the NRC guidelines reports (NRC 1993; NRC in press).

than AEGLs estimated from limited anecdotal human data. The greater conservatism afforded by the animal data is justified by the incomplete and often equivocal data for human exposures, the documented extreme toxicity of arsine, and the known latency involved in arsine-induced lethality. The AEGL values for the various exposure periods of concern (0.5, 1, 4, and 8 h) were scaled from the experimental exposure duration using exponential scaling ($C^n \times t = k$, where C = exposure concentration, t = exposure duration, and k = a constant). Data were unavailable to empirically derive a scaling factor (n) for arsine. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived exponent (n), temporal scaling was performed using n = 3, when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation.

Based upon the available data, derivation of AEGL-1 values was considered inappropriate. The continuum of arsine-induced toxicity does not appear to include effects consistent with the AEGL-1 definition. The available human and animal data affirm that there is a very narrow margin between exposures that result in little or no signs or symptoms of toxicity and those that result in lethality. The mechanism of arsine toxicity (hemolysis that results in renal failure and death), and the fact that toxicity in humans and animals has been reported at concentrations at or below odor detection levels (!0.5 parts per million (ppm)) also support such a conclusion. The use of analytical detection limits (0.01 to 0.05 ppm) was considered as a basis for AEGL-1 values but was considered to be inconsistent with the AEGL-1 definition.

The AEGL-2 values were based upon exposures that did not result in significant alterations in hematologic parameters in mice exposed to arsine for 1 h (Peterson and Bhattacharyya 1985). Uncertainty factor application included 10-fold interspecies variability because of uncertainties regarding species-specific sensitivity to arsine-induced hemolysis. The 10-min LC_{50} (lethal concentration for 50% of the animals) value for the monkey was approximately 60% of the rat value and one-third the rabbit value. A less sensitive species, the rat, was used to calculate the AEGL levels because the data exhibited clear exposure-response relationships and the reduced hematocrit can be considered a sensitive indicator of arsine toxicity. Uncertainty regarding intraspecies variability was limited to a factor of 3-fold, because the hemolytic response is likely to occur to a similar extent and with similar susceptibility in most individuals. This was based on the assumption that physiologic parameters (such as absorption, distribution and metabolism of arsine, as well as renal responses and the structure of the erythrocyte and its response to arsine) would not vary among individuals of the same

species by an order of magnitude. Additionally, individual variability (i.e., variability in erythrocyte structure/function or response of the kidney to hemolysis) is not likely to have a significant impact on any of the proposed subcellular mechanisms of arsine toxicity. The steep exposure-response curves from animal data also affirm the limited variability in response. Furthermore, the AEGL-2 values were developed using an exposure resulting in no significant hemolysis in mice exposed to arsine at 5 ppm for 1 h, and, therefore, additional reduction of the values was unwarranted.

Arsine data were not available to determine a concentration-exposure time relationship. The concentration-exposure time relationship for many irritant and systemically acting vapors may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of chemical-specific data, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation.

The AEGL-3 values were based upon lethality and hemolysis in mice exposed to arsine for 1 h (Peterson and Bhattacharyya 1985). A 1-h exposure at 15 ppm resulted in significant hemolysis, and a 1-h exposure at 26 ppm produced 100% lethality. A total uncertainty factor of 30 was applied, as was done for AEGL-2 values using identical rationale. Because the AEGL-3 values were developed based upon an exposure producing hemolysis but no lethality in mice, no further reduction in the values was warranted. The derivation of AEGL-3 values using limited data in monkeys affirmed the values derived based upon the mouse data. Although the human experience was of qualitative value, the absence of definitive verifiable exposure terms severely limited its utility as a valid quantitative measure for AEGL-3 development.

Time scaling for AEGL-3 development was performed as previously described for the AEGL-2 tier.

The three AEGL exposure levels reflect the narrow range between exposures resulting in minor effects and those producing lethality. The approach used in the development of AEGLs for arsine was justified by the confirmed steep dose-response curve, the induction of hemolysis by arsine at extremely low concentrations, and the potential of hemolysis to progress to life-threatening renal failure. It is also noted that all of the AEGL values are near or below the odor threshold for arsine. A summary of AEGL values for arsine is shown in Table 2-1.

TABLE 2-1 Summary of AEGL Values for Arsine

Classification	30 min	1 h	4 h	8 h	Endpoint (Reference)
AEGL-1 (Non-disabling)	NR[a]	NR	NR	NR	Not recommended due to steep dose-response relationship, mechanism of toxicity, and because toxicity occurs at or below the odor threshold
AEGL-2 (Disabling)	0.21 ppm 0.7 mg/m^3	0.17 ppm 0.5 mg/m^3	0.04 ppm 0.1 mg/m^3	0.02 ppm 0.06 mg/m^3	Absence of significant hematologic alterations in mice consistent with the known continuum of arsine toxicity (Peterson and Bhattacharyya 1985)
AEGL-3 (Lethal)	0.63 ppm 2.0 mg/m^3	0.50 ppm 1.6 mg/m^3	0.13 ppm 0.4 mg/m^3	0.06 ppm 0.2 mg/m^3	Estimated threshold for lethality in mice (Peterson and Bhattacharyya 1985)

Numeric values for AEGL-1 are not recommended because (1) data are not available, (2) an inadequate margin of safety exists between the derived AEGL-1 and the AEGL-2, or (3) the derived AEGL-1 is greater than the AEGL-2. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

Abbreviations: NR, not recommended, ppm, parts per million; mg/m^3, milligrams per cubic meter.

TABLE 2-2 Chemical and Physical Data

Parameter	Value	Reference
Synonyms	arsenic trihydride; hydrogen arsenide; arsenious trihydride; arsenic hydride; arsenic hydrid; arsineuretted hydrogen	Budavari et al. 1989; AIHA 1993; Hesdorffer et al. 1986
Chemical formula	AsH_3	Budavari et al. 1989
Molecular weight	77.93	Budavari et al. 1989
CAS Registry No.	7784-42-1	Budavari et al. 1989
Physical state	gas	Budavari et al. 1989
Solubility in water	20% at 20°C	AIHA 1993
Vapor pressure	14.95 atm @ 21.1°C	Braker and Mossman 1980
Density	2.695 g/cm^3	USAF 1990
Melting/boiling/flash point	-117°/-55°C/ND	Budavari et al. 1989
Odor threshold	0.5 ppm; garlic-like odor	NAPCA 1969
Conversion factors in air	1 mg/m^3 = 0.31 ppm 1 ppm = 3.19 mg/m^3	AIHA 1993

1. INTRODUCTION

Arsine is an extremely toxic, colorless gas used extensively in the semiconductor industry. Arsine also is used in mining and manufacturing processes involving arsenicals and in paints and herbicides containing arsenicals (Risk and Fuortes 1991). Annual production has been estimated at over 10,000 pounds and is likely increasing with greater use in the semiconductor industry (U.S. EPA 1980). The physical and chemical data for arsine are shown in Table 2-2.

2. HUMAN TOXICITY DATA

Human data for arsine are compromised by deficiencies in exposure concentration and duration data and by concurrent exposures to other materials. It has been reported that exposure to 3-100 ppm for several hours may result in slight

symptoms, and exposure to 16-30 ppm arsine for 0.5-1 h is dangerous (Coles et al. 1969). These estimates, however, reflect uncertainties in the human data and are not necessarily consistent with all the available data. The odor threshold for arsine ranges from 0.5 to 1 ppm. The clinical aspects of arsine poisoning have been reviewed by Fowler and Weissberg (1974) and Dreisbach (1983).

2.1. Acute Lethality

Human LC_{lo} values of 25 ppm (30 min) and 300 ppm (5 min) have been reported (RTECS 1986). Henderson and Haggard (1943) (as cited in AIHA 1993) noted that exposure of humans to arsine at 250 ppm for 30 min was fatal.

Early reports, summarized by Flury and Zernik (1931), provided the following anecdotal information regarding human responses to arsine exposure: immediately fatal following exposure at 1,530 ppm (no duration specified), fatal within 30 min following exposure at 250 ppm, immediately fatal following exposure at 15.5 ppm for 30-60 min, dangerous to life following exposure at 6.25 ppm for 30-60 min. Contrary to the above estimates, the following were also reported in Flury and Zernik (1931): no immediate or delayed effects following exposure at 6.25 ppm for 30-60 min, no symptoms following 6-h exposure at 3.1 ppm.

2.1.1. Case Reports

Case reports are available regarding lethal effects of acute exposure to arsine (Pinto et al. 1950; Morse and Setterlind 1950; Hesdorffer et al. 1986). However, no definitive quantitative exposure data accompany these reports. Signs and symptoms varied depending on the exposure situation but usually included abdominal and muscle pain, nausea and diarrhea, hematuria, and oliguria. Delayed lethality, common in arsine poisoning, varied considerably.

Levinsky et al. (1970) reported on three men exposed to an unknown concentration of arsine for an estimated, 2, 3, and 15 min. Signs and symptoms of exposure (malaise, headache, abdominal pain, chills, nausea, vomiting, oliguria/anuria, hematuria, bronze skin color) developed within 1-2 h. All three individuals required extensive medical intervention to save their lives. Clinical findings were indicative of massive hemolysis and repeated blood exchange transfusions were necessary for the survival of these individuals.

Pinto (1976) also reported similar characteristics regarding acute arsine poisoning. Although, an exposure concentration was unavailable, exposure to newly formed arsine for less than 1 h resulted in severe (likely fatal without

medical intervention of exchange transfusion) signs and symptoms, including abdominal pain, chest pain, and hematuria within hours of exposure. A successive reduction in hematocrit (42.2 to 27.7) and hemoglobin (14.1 to 9.6 g %) occurred within 3 d. Cardiac involvement indicative of left ventricular ischemia was detected within 1 d of exposure.

2.2. Nonlethal Toxicity

Human TC_{lo} values of 3 ppm (no duration specified) and 325 micrograms per cubic meter ($\mu g/m^3$) (0.1 ppm) (no duration specified) have been reported (RTECS 1987). Henderson and Haggard (1943) (as cited in AIHA 1993) noted that exposure of humans to arsine at 3-10 ppm for a few hours may result in signs and symptoms of poisoning. Similar to the data set for acute lethality, most information on nonlethal effects of arsine exposure in humans are case reports representing exposure estimates.

2.2.1. Case Reports

Numerous cases of arsine poisoning have been reported (Elkins and Fahy 1967; DePalma 1969). However, these reports lack definitive exposure concentration data and usually lack exposure duration data as well. Some of the more recent and complete reports involving nonlethal consequences are described in the following section. These reports do not provide quantitative data suitable for AEGL derivations, but they do provide valuable insight into the nature and progression of arsine poisoning in humans. In most cases, the severity of the effects was usually sufficient to necessitate medical intervention to prevent lethality. Some of the more prominent reports and those with the best descriptive data have been summarized, but the overview is by no means exhaustive.

Three cases of arsine poisoning were reported by DePalma (1969). One day after exposure, the blood arsenic levels were 0.66, 0.25 and 2.2 milligram per liter (mg/L). Hemoglobin levels at 1 d after exposure were 5.9, 7.8, and 11.7 grams per deciliter (g/dL) but tended to fluctuate considerably over several weeks. Although no quantitative exposure data were provided, the case reports serve to identify the hemolysis, abdominal pain and tenderness, hematuria, nausea and vomiting that appears to be characteristic signs and symptoms of acute arsine poisoning. Additionally, the case reports attest to the prolonged nature of arsine-induced toxicity; recovery frequently requires many weeks even with medical intervention.

A case of oliguric renal failure following acute exposure to arsine was

reported by Uldall et al. (1970). The concentration of arsine was not available, but the duration of exposure was approximately 7 h. Within hours of the exposure, the subject experienced episodic hot and cold sensation, abdominal pain and cramping, hematuria, and confusion. On admission to the hospital (3 d post-exposure), the subject was disoriented, abdominal pain had increased, and his skin was discolored (yellowish-brown), and mucous membranes were pale. Hemoglobin was 6.1 g/dL, hematocrit was 18%, and urine samples contained protein and erythrocytes and erythrocyte casts. The victim required peritoneal dialysis and considerable medical intervention prior to a long-term moderate recovery. Two additional workers were also exposed in a similar fashion but for only 1 h. Hemoglobin values for these individuals (admitted to the hospital 3 and 4 d post-exposure) was 8.9 and 12 g/dL, respectively, and hematocrit was 27% and 36%, respectively. Both exhibited hematuria and mild proteinuria, and both recovered without sequelae.

A case report of acute arsine poisoning in which a 27-y-old man was exposed to arsine during chemical manufacturing was reported by Pinto (1976). The subject was exposed to arsine as a result of arsine production via a reaction between a galvanized bucket and an arsenic-containing sulfuric acid solution. The exposure (duration not specified) produced toxic effects characterized by abdominal cramping, thoracic discomfort, and hematuria. Over the next week, the patient's hematocrit declined from 42.5 to 27.1 and hemoglobin dropped from 14.1 to 9.5 g/dL even with medical intervention (blood transfusions and mannitol diuresis). Nine hours after exposure, blood arsenic was 159 µg/dL and urinary arsenic was 1862 µg/L.

Kleinfeld (1980) reported a case of arsine poisoning in a 31-y-old man. The exposure to arsine occurred from a leaking canister thought to be empty. The exposure duration was estimated to be 1-2 min, but no actual or estimated arsine concentrations were available. The victim presented with hematuria. On hospital admission, no intact erythrocytes were present in the urine, hematocrit was 43%, and hemoglobin was 9.8 g/dL. The hematocrit dropped to as low as 18%, the correction of which required one unit of packed cells. Based upon the exposure history and the subject's note of a "garlicky" odor, the diagnosis was arsine-induced hemolytic anemia. Urinary arsenic was 7.2 mg/L on admission and 0.1 mg/L 4 d later. The patient was subsequently discharged.

The occupational exposure of five workers to arsine was reported by Phoon et al. (1984). All cases involved hematuria and, except for one patient, abdominal pain and jaundice. One worker was exposed for approximately 1 3/4 h, while the others were exposed for approximately 2 1/4 h. The latency in appearance of toxic effects was unusually short (. 3 h). The following day, the arsine level in the workers' breathing zone was 0.055 mg/m^3 (0.017 ppm), although no processing of arsenic-containing material was taking place at the

time of measurement. It was hypothesized by the report authors that the arsine concentration at the time of exposure was much higher, thus accounting for the very short latency period.

Mora et al. (1992) reported on two cases of acute arsine poisoning in workers shoveling scories at a ferrous metal foundry. One case involved acute hemolysis followed by acute renal failure requiring dialysis, and the other involved acute hemolysis and cytolytic hepatitis; a definitive etiology for the hepatitis was not found but was thought to be possibly related to the arsine exposure. Arsine levels were subsequently found to be at or below the ACGIH Threshold Limit Value (TLV) (0.05 ppm) during dry conditions but increased to 60 ppm when water was added to the scories. It was not known if the exposures occurred during wet or dry conditions.

Data from case reports indicated that there is usually a 1- to 24-h delay between exposure and onset of signs and symptoms of poisoning. Additionally, hematologic parameters (e.g., hemoglobin, hematocrit levels) appear to be progressively affected for several days after the exposure. Hence although the exposure is acute, the most serious adverse effect may be delayed by several hours or days.

Bulmer et al. (1940) (as cited in Elkins 1959) reported on eight workers in a gold extraction plant who were exposed to arsine for up to 8 mon. During this period, major medical findings were jaundice and anemia. Based upon urinary arsine levels (0.7- 4 mg/L), a 50% absorption factor, and an inhalation rate of 5 m^3/8 h, the arsine concentration was estimated at 0.12 ppm. It was suggested that a maximum allowable concentration of 0.05 ppm would not be unreasonable. The estimation of exposure levels provides some insight into arsine toxicity in humans but it is unclear if the effects observed were the result of long-term, repeated exposure or would have been observed after a single exposure.

2.2.2. Epidemiologic Studies

Landrigan et al. (1982) conducted an epidemiologic survey to evaluate occupational exposure to arsine in a lead-acid battery manufacturing plant. Arsine concentrations ranged from nondetectable to 49 µg/m^3 (. 0.02 ppm) in 177 breathing zone samples. A high correlation was found between urinary arsenic concentration and arsine exposure ($r = 0.84$; $p = 0.0001$ for an n of 47). Additionally, arsine levels above 15.6 µg/m^3 (. 0.005 ppm) were associated with urinary arsenic concentrations in excess of 50 µg/L. The investigators concluded that exposure to a 200 µg/m^3 arsine exposure standard would not prevent chronic increased absorption of trivalent arsenic.

2.3. Developmental and Reproductive Toxicity

No definitive, quantitative data were available regarding the potential reproductive and developmental toxicity of arsine in humans.

2.4. Genotoxicity

Genotoxicity data relevant to the derivation of AEGLs for arsine were not available.

2.5. Carcinogenicity

Although some forms of inorganic arsenic are considered known human carcinogens, there are no data available regarding the carcinogenic potential of arsine or its conversion to carcinogenic forms. The extreme acute toxicity of arsine gas precludes the relevance of carcinogenic potential for acute exposures. Therefore, a carcinogenicity assessment based upon elemental equivalence has not been carried out.

2.6. Summary

Numerous case reports are available regarding the lethal and nonlethal toxicity of arsine in humans, but definitive exposure concentration or duration data are lacking. Although the case reports are of limited use for quantitative estimates of exposure limits, they do provide qualitative information about the nature of arsine poisoning in humans. Some estimated human toxicity values are available and are summarized in Table 2-3.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Acute lethality data for several laboratory species are summarized in the following sections. Lethal concentrations for various species are shown in Table 2-4. Cumulative exposures ($C \times t$) exhibit notable variability even within species.

TABLE 2-3 Acute Toxicity Values for Arsine Poisoning in Humans

Estimated Toxicity Value	C × t (ppm"min)	Comments	Reference
30-min LC_{lo}: 25 ppm	750	Fatal within 30 min	RTECS 1987
5-min LC_{lo}: 300 ppm	1,500		RTECS 1987
30-min LC_{lo}: 250 ppm	7,500		Henderson and Haggard 1943 (as cited in AIHA 1993)
30-min LC_{lo}: 250 ppm	7,500		Flury and Zernik 1931
30 to 60-min LC_{lo}: 15.5 ppm	465-930		Flury and Zernik 1931
30 to 60-min LC_{lo}: 6.25 ppm	188-375	"Dangerous to life"[a]	Flury and Zernik 1931
6-h NOAEL: 3.1 ppm	19	No symptoms reported following this 6-h exposure	Flury and Zernik 1931

[a]Flury and Zernik (1931) also reported no immediate or delayed effects in a human exposed at 6.25 ppm for 30-60 min.
Abbreviation: NOAEL, no-observed-adverse-effect level.

3.1.1. Nonhuman Primates

A 30-min LC_{50} of 250 mg/m^3 for monkeys was reported by RTECS (1987). Effects included hemolysis without anemia and abnormal erythrocytes.

Kensler et al. (1946) exposed three monkeys (species not specified) to arsine at a concentration of 0.45 mg/L (450 mg/m^3 or 140 ppm) for 15 min. One monkey died in 24 h and exhibited marked intravascular hemolysis and hematuria.

Delayed lethality (3 d post-exposure) in a monkey exposed to arsine at approximately 190,000 ppm for 1 h was reported by Joachimoglu (1924) (as cited in Flury and Zernik 1931). Four hours after the exposure, the monkey was vomiting and hematuria was evident.

3.1.2. Dogs

Dubitski (1911) (as cited in Flury and Zernik 1931) noted that the dog was similar to the cat regarding arsine toxicity. Exposure to 10 ppm was without

TABLE 2-4 Acute Lethality of Arsine in Laboratory Species

Species	Lethal Concentration in ppm [mg/m^3]	C × T (ppm'min)	Reference
Monkey	10-min LC_{50}: 78 [250]	780	RTECS 1987
Monkey	15-min LC_{lo}: 140 [450]	2,100	Kensler et al. 1946
Rat	30-min LC_{50}: 250 [798]	7,500	IRDC 1985
Rat	1-h LC_{50}: 178 [568]	10,680	IRDC 1985
Rat	4-h LC_{50}: 45 [144]	10,800	IRDC 1985
Rat	10-min LC_{50} 121 [390]	1,210	RTECS 1987
Rat	4-h LC_{50} 42.6 [135]	10,224	Craig and Frye 1988
Rat	10-min LC_{50}: 202 [650]	2,020	RTECS 1987
Mouse	1-h: 26 ppm [83]; 100% mortality	1,560	Peterson and Bhattacharyya 1985
Rabbit	10-min LC_{50}: 202 [650]	2,020	RTECS 1987
Dog	10-min LC_{50}: 109 [350]	1,090	RTECS 1987
Mouse	50-min LC_{50}: 31 [100]	5,450	Levvy 1948
Mouse	24-h LC_{50}: 8 [25]	11,520	Levvy 1948

observable effects but exposure to 100 ppm was noted as being "quickly dangerous." Exposure durations were not specified but were assumed to be 1 h as for the cat experiments (Section 3.1.3).

3.1.3. Cats

Dubitski (1911) (as cited in Flury and Zernik 1931) provided data on the acute lethality of arsine in cats, noting the following for 1-h exposures: no observable signs of toxicity following exposure to 43-50 ppm, sick with recovery following exposure to 50-100 ppm, and death (12-40 h post-exposure) following exposure to 120-290 ppm.

3.1.4 Rats

Several LC_{50} values for arsine are listed in RTECS (1987) for rats (Table 2-4). Several inhalation studies evaluating lethality are also available and are summarized in the following paragraphs.

Fowler et al. (1989) reported a 100% mortality in male and female Fischer 344 (F344) rats exposed to arsine at concentrations above 10 ppm, 6 h/d over 4 d. However, rats survived 28-d (6 h/d) exposures to 5 ppm and exhibited no mortality or overt signs of toxicity. The study authors noted the sharp threshold between tolerated and lethal exposures to arsine.

Craig and Frye (1988) reported a 4-h LC_{50} values for Sprague-Dawley rats. The 4-h LC_{50} for males, females, and both sexes combined were 46.8 ppm, 38.9 ppm, and 42.6 ppm, respectively. Groups of five male and five female rats were exposed to concentrations of 25.2, 35.1, 44, 54.4, or 63.5 ppm. At 54.4 ppm four of five males and five of five females died. At 63.5 ppm, all rats of both sexes died. At 25.2 ppm there was no mortality. At 35.1 ppm mortality was 2/5 in females and 0/5 in males.

The International Research and Development Corporation (IRDC 1985) also conducted acute lethality studies on male and female Sprague-Dawley rats to determine 0.5-h, 1.0-h, and 4.0-h LC_{50} values. For all experiments, groups of 10 male and 10 female rats were used, and there was a 14-d post-exposure observation period. For determining the 0.5-h LC_{50}, rats were exposed to concentrations of 97, 170, 200, 260 (two groups), 350, or 400 ppm. The 0.5-h LC_{50} (sexes combined) was 250 ppm. There were no deaths in male rats exposed at 97, 170, or 200 ppm and no deaths in females exposed at 97 ppm. All male rats exposed at 400 ppm died and all female rats exposed at 350 or 400 ppm died. In the 1-h LC_{50} experiments, rats were exposed to arsine concentrations of 120, 160, 190, or 220 (two groups) ppm. The 1-h LC_{50} was 178 ppm (sexes combined). No males and two females died at the lowest exposure, although rats in all exposure groups exhibited pale ears, and red/brown material around the nose. A 60% and 70% mortality occurred in each group of males exposed to the highest concentration (220 ppm); the mortality in females exposed at 220 ppm was 90% and 100%. In the 4-h exposure studies, rats were exposed to arsine at concentrations of 24, 27, 36, 46, 56, or 110 ppm. The 4-h LC_{50} (sexes combined) was 45 ppm. No males died at 24, 27, or 36 ppm, but mortality was 100% at 110 ppm. For female rats, there was no mortality at 24 or 27 ppm, but mortality at 46, 56, or 110 ppm was 100%, 90%, and 100%, respectively. Rats in most exposure groups exhibited pale ears. Additional signs included pale feet and eyes, especially in exposures $37 ppm, although these signs were noted for female rats in the lowest exposure groups.

3.1.5. Mice

Early studies in mice indicated that the following exposure conditions resulted in lethality: 900 ppm for 20-30 min, 400 ppm for 45 min, 300 ppm for

15 min (2 h post-exposure), 150-300 ppm for 1 h, 100 ppm for 15 min (7 h post-exposure), and 30-60 ppm for 2-4 h (Flury and Zernik 1931).

Levvy (1948) studied acute arsine toxicity in mice. In this study, groups of 30 inbred mice (15 males and 15 females; 25-30 g) were exposed by inhalation (whole-body) to arsine at concentrations of 2.5, 1.0, 0.50, 0.25, 0.10, or 0.025 mg/L (six mice only) for periods ranging from 0.33 min to 30 h. The results of this experiment are shown in Table 2-5. The average time-to-death was 4 d. Hemoglobinemia was noted for many of the mice exposed at 8 ppm (0.025 mg/L), indicating that even at the lowest exposure, effects characteristic of arsine poisoning were observed. It was not specified whether an assessment of this effect was made for mice in the other exposure groups. It was noted that, for concentrations at or below 155 ppm, the relationship between arsine concentration and duration of exposure for 50% mortality was consistent with $C^2 \times t = k$.

The effects of acute inhalation exposure of mice ($B6C3F_1$/Anl) to arsine were reported by Peterson and Bhattacharyya (1985). Although the study focused on assessing hematologic responses, specifically hematocrit, numbers of erythrocytes, leukocytes and reticulocytes, and erythrocyte fragility, lethality occurred in the high-exposure group. A 100% mortality was noted for groups of eight female $B6C3F_1$ mice exposed to arsine for 1 h at a concentration of 26 ppm (three died immediately following exposure, and the remaining five died within 4 d. At 24 h post-exposure, there was a significant exposure-related decrease (21.7% relative to sham-exposed controls) in hematocrit values of the 26-ppm exposure group. Mice in this group subsequently died within 4 d following exposure.

Similar to the results of studies in rats, female $B6C3F_1$ mice exposed to arsine at concentrations above 10 ppm, 6 h/d over 4 d exhibited a 100% mortality (Fowler et al. 1989).

3.2. Nonlethal Toxicity

3.2.1. Nonhuman Primates

In a study by Kensler et al. (1946), three monkeys were exposed by inhalation to arsine at a concentration of 0.45 mg/L (450 mg/m^3 or 140 ppm) for 15 min. Although one monkey died in 24 h, one remaining monkey survived without treatment; another was treated with 2,3-dimercaptopropyl ethyl ether. The surviving monkey that was not treated could "scarcely raise himself from the floor of his cage from the 2nd to the 7th days." The erythrocyte count of this monkey decreased to 65% of pre-treatment level in 24 h, and by d 3-4 decreased to approximately 20% prior to recovery. The monkey treated with

TABLE 2-5 Acute Inhalation Toxicity in Mice Exposed to Arsine (Levvy 1948)

Concentration			Exposure Duration	C × T		Estimated Duration (min)
mg/L	mg/m^3	ppm	(min)	(ppm"min)	Mortality	for 50% Mortality
2.5	2,500	775	0.50	388	93	0.40
			0.33	257	20	
1.0	1,000	310	1.25	388	57	1.18
			0.83	257	13	
0.50	500	155	10	1,550	100	2.4
			5	775	93	
			2.5	388	57	
			1.7	264	0	
0.25	250	78	15	1,170	70	12
			9	702	33	
0.10	100	31	70	2,170	100	50
			50	1,550	50	
0.025	25	8	900	7,200	0	1,440
			1,080	8,640	0	
			1,260	10,000	50	
			1,440	11,520	50	
			1,620	12,960	50	
			1,800	14,400	100	

2,3-dimercaptopropyl ethyl ether did not exhibit the rate or magnitude of erythrocyte reduction observed in the untreated monkey.

3.2.2. Rats

Blair et al. (1990a) conducted experiments to evaluate interspecies variability in the toxic effects of arsine. In addition to hamsters and mice, this study assessed the toxic effects of subchronic exposure (14, 28, or 90 d) of F344 rats to arsine. Rats were exposed 6 h/d for 14 or 28 consecutive days, or for 6 h/d for 5 consecutive days per week for 13 w. Exposure concentrations were 0.5, 2.5, or 5.0 ppm for the 14- and 28-d exposures and 0.025, 0.5, or 2.5 ppm for the 90-d exposure. Rats exposed at the two highest concentrations exhibited significant increases in relative liver weight and relative spleen weight. Relative spleen weight was also significantly increased in the 0.5-ppm group (except 14-d females). Packed cell volume also was significantly decreased in the 0.5-, 2.5-, and 5.0-ppm groups (except 14-d females). Some alterations in hematologic

values were observed but only for rats in the 90-d exposure group. This report focuses on arsine-induced effects following 14-, 28-, and 90-d exposures, the duration of which would not allow for valid extrapolation to durations relevant to AEGLs.

Male and female F344 rats exposed to arsine at 5 ppm, 6 h/d for 28 d exhibited no mortality or overt signs of toxicity (Fowler et al. 1989). However, there was a 100% mortality within 4 d of exposure to 10 ppm, thereby demonstrating a sharp delimitation and very narrow margin between lethal and nonlethal exposure concentrations.

3.2.3. Mice

The results of nonlethal effects in mice following acute inhalation exposure to arsine were reported by Peterson and Bhattacharyya (1985). The study focused on assessing hematologic responses, specifically hematocrit levels, numbers of erythrocytes, leukocytes and reticulocytes, and erythrocyte fragility. In this study, groups of eight female B6C3F_1 mice were exposed to arsine for 1 h at concentrations of 0, 5, 9, 11, 15, or 26 ppm. Exposure to 26 ppm resulted in the death of three of eight mice shortly after the exposure. The remaining five mice died within 4 d. Blood samples were taken from mice of the other exposure groups at 1, 5, and 11 d following the 1-h exposure. At 24 h post-exposure, there was a significant exposure-related decrease in hematocrit values following exposure to $9 ppm; 80.2%, 79.7%, 61.4%, and 21.7% of sham-exposed controls for the 5-, 9-, 11-, 15-, and 26-ppm groups, respectively. At 5 d post-exposure, hematocrit values for the 9-, 11-, and 15-ppm groups had increased but were still significantly lower than those for controls. The number of erythrocytes was also significantly decreased relative to sham-exposed controls ($7.8 \times 10^6/mm^3$) at 1 d following exposure to arsine at 9 ppm (6.1×10^6), 11 ppm ($6.2 \times 10^6/mm^3$), 15-ppm ($4.0 \times 10^6/mm^3$), or 15 ppm ($2.2 \times 10^6/mm^3$). By 11 d post-exposure, erythrocyte numbers exhibited notable recovery to near normal values. At 5 d post-exposure, significant reticulocytosis was observed in mice exposed to arsine at $9 ppm. This condition was ameliorated by 11 d post-exposure. Transient leukocytosis was noted for 9- and 15-ppm groups 1 d after exposure, and erythrocyte osmotic fragility was altered in the 15- and 26-ppm groups 1 d after exposure. Generally, this study showed that a hemolytic response occurs rapidly in mice exposed to arsine at concentrations $9 ppm and that the margin between the no-effect level (5 ppm) and a lethal concentration (26 ppm) is less than 10-fold in mice.

Female B6C3F_1 mice exposed to arsine at 5 ppm, 6 h/d for 28 d exhibited no mortality or overt signs of toxicity (Fowler et al. 1989). However, there was a 100% mortality within 4 d of exposure to 10 ppm, thereby demonstrating a

sharp threshold between lethal and nonlethal exposures.

As part of the aforementioned short-term exposure study by Fowler et al. (1989), an assessment of immune function was also conducted (Rosenthal et al. 1989). In the Rosenthal et al. (1989) study, female B6C3F_1 mice (18-22 g, 6-8 w of age) were exposed to arsine at 0.5, 2.5, or 5.0 ppm, 6 h/d for 14 d; controls were exposed to clean air. All mice survived through the exposure period. Briefly, alterations in splenic cell populations (i.e., increase in rubricytes and decrease in percentage of lymphocytes) suggested the spleen as a target for short-term arsine exposure. These cell population changes were considered to be the result of the hemolytic effects of arsine. An impairment of immune function, possibly the result of cellular redistribution, was noted. The relevance of these findings to human exposure is that they occurred at concentrations only 10-fold higher than the current TLV of 0.05 ppm (see Table 2-11).

The hematopoietic effects of arsine exposure in mice was investigated by Hong et al. (1989). In this study, female B6C3F_1 mice (12/group) were exposed to arsine at concentrations of 0, 0.5, 2.5, or 5.0 ppm, 6 h/d for 14 d. Additional groups of mice were also exposed at 0, 0.025, 0.5, or 2.5 ppm, 6 h/d, 5 d/w for 12 w. Following the 14-d exposure, there was a significant exposure concentration-related decrease in erythrocyte count, hemoglobin, and hematocrit levels. These alterations returned to normal by 3 w after exposure. At 2 d post-exposure, there was a significant increase in absolute spleen weight (35%, 102%, and 236%, for the 0.5-, 2.5-, and 5.0-ppm groups, respectively) and relative spleen weight (38%, 97%, and 236% for the 0.5-, 2.5-, and 5.0-ppm groups, respectively) in the arsine-exposed mice. At 24 d post-exposure, the absolute spleen weight returned to normal in the 0.5-ppm group only, and the relative spleen weight remained significantly elevated.

As previously described in Section 3.2.2, Blair et al. (1990a) conducted experiments to evaluate interspecies variability in the toxic effects of arsine. In addition to subchronic exposure studies in rats and hamsters, this study assessed the toxic effects on female B6C3F_1 mice following exposure to arsine (0.025, 0.5, 2.5, or 5.0 ppm) for 6 h/d for 1 d or 14 consecutive days, or for 6 h/day, 5 consecutive days per week for 13 w. Relative spleen weight and packed cell volume were assessed at termination of exposure and after 1, 2, 4, and 7 d of recovery. At 2, 4, and 7 d post-exposure, the 5.0-ppm arsine exposure group exhibited significantly increased relative spleen weight relative to sham-exposed controls. Packed cell volume was also significantly decreased in the 2.5-ppm group at 2, 4, and 7 d of recovery and in the 5.0-ppm group throughout the 7-d recovery period. Experiments were also conducted wherein mice were exposed for 14 or 90 d. It is significant that the results of this study suggest that a single exposure (0.5 ppm) to 10 times the ACGIH TLV (0.05 ppm) resulted in no significant hematopoietic damage but that repeated exposure to one-half the TLV for 13 w produced significant hematopoietic effects.

3.2.4. Hamsters

Groups of 16 male and 16 female Syrian golden hamsters were exposed to arsine at 0, 0.5, 2.5, or 5.0 ppm, 6 h/d, 5 d/w for 28 d (Blair et al. 1990a). Relative liver weight, relative spleen weight, packed cell volume, and whole-blood aminolevulinic acid dehydratase (ALAD) activity were examined at 3 and 4 d post-exposure. Minor changes in relative liver weight occurred, and significant increases in relative spleen weight were observed for the 2.5- and 5.0-ppm groups. Minor decreases in packed cell volumes were noted for the 5.0-ppm group at both post-exposure times. ALAD activity was significantly increased at 3 d post-exposure. The increased ALAD activity is indicative of a red-blood-cell (RBC) regenerative process and is considered a compensatory response.

3.3. Developmental/Reproductive Toxicity

3.3.1. Rats

The developmental toxicity of arsine in rats was investigated by Morrissey et al. (1990). Groups (28-29) of pregnant F344 rats were exposed (whole-body exposure) to arsine at concentrations of 0, 0.025, 0.5, or 2.5 ppm (0, 0.08, 1.6, or 8 mg/m^3) for 6 h/d on gestation d 6 through 15. Measures were assessed for all litters (number of corpora lutea per litter, percent pre-implantation, and percent post-implantation) and live litters (number of live fetuses per litter, average fetal body weight per litter, and percent fetuses malformed per litter). With the exception of an increase in average fetal body weight in the highest exposure group, no significant treatment-related effects were detected. High-dose dams exhibited significant decreases in RBC count, hemoglobin content, hematocrit level, and mean corpuscular hemoglobin concentration, and significant increases in white-blood-cell count, mean corpuscular volume, mean corpuscular hemoglobin, and platelet counts. At 2.5 ppm, maternal spleen size was increased and an exposure-related increase in anemia was noted. In conclusion, there were no significant arsine-related development effects in the presence of mild maternal toxicity.

3.3.2. Mice

Morrissey et al. (1990) also conducted experiments to assess the developmental toxicity of arsine in mice. Groups (24-25) of pregnant Swiss (CD-1) mice were exposed to arsine at concentrations of 0, 0.025, 0.5, or 2.5 ppm (0, 0.08, 1.6, or 8 mg/m^3) for 6 h/d on gestation d 6 through 15. Developmental measures

for all litters included number of implantation sites per litter, percent resorptions per litter, and percent litters with resorptions. Assessments for live litters included the number of live fetuses per litter, average fetal body weight per litter, and percent fetuses malformed per litter. Maternal spleen weights (relative and absolute) were significantly increased in the 2.5-ppm group. No treatment-related developmental effects were observed.

3.4. Genotoxicity

No data regarding the genotoxicity of arsine in animals were available.

3.5. Carcinogenicity

There are no data suggesting a carcinogenic potential for arsine in animals. Inorganic arsenic has been associated with skin and pulmonary tumors (IARC 1987; U.S. EPA 1987). The National Institute for Occupational Safety and Health (NIOSH) has recommended that all inorganic arsenicals, including arsine, be considered a potential human carcinogen. However, the extreme acute toxicity of arsine and the absence of carcinogenicity and genotoxicity data for arsine would preclude these endpoints as valid for AEGL consideration.

3.6. Summary

The nonlethal effects of acute exposure of laboratory species to arsine are summarized in Table 2-6. Many of the effects observed appear to occur from one to several days following cessation of exposure and, to some extent, increase in severity as post-exposure time increases. This is consistent with clinical observations for human poisonings with arsine.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

There are no definitive data regarding the metabolism of arsine. Based upon proposed mechanisms of action and the known interaction with RBCs and hemoglobin, metabolism per se may of limited importance relative to acute exposures to arsine. Delayed toxicity and lethality are observed in both humans and animals following acute exposure to arsine, and it is known that increased

TABLE 2-6 Nonlethal Effects of Acute Arsine Exposure in Animals

Species	Exposure (ppm) Duration (hr)	C × t (ppm"min)	Effect[a]	Reference
Monkey	140 (15 min)	2,100	Extreme disability (inability to maintain normal posture) at 2-7 d post-exposure	Kensler et al. 1946
Mouse	0.5 (6 h)	180	No effect on spleen weight or packed cell volume	Blair et al. 1990a
Mouse	2.5 (6 h)	900	Slight decrease in packed cell volume (females only)	Blair et al. 1990a
Mouse	5.0 (6 h)	1,800	Statistically significant increase in relative spleen weight and decrease in packed cell volume	Blair et al. 1990a
Mouse	5 (1 h)	300	Minor hematologic alterations (reduced erythrocyte count)	Peterson and Bhattacharyya 1985
Mouse	9 (1 h)	540	Minor hematologic alterations (reduced erythrocyte count, decreased hematocrit, increased reticulocyte count)	Peterson and Bhattacharyya 1985
Mouse	11 (1 h)	660	Significant reduction (20% of control) in erythrocytes and hematocrit, significant increase in reticulocytes and leukocytes	Peterson and Bhattacharyya 1985
Mouse	15 (1 h)	900	Significant reduction (40-50% of control) in erythrocytes and hematocrit, significant increase in reticulocytes and leukocytes	Peterson and Bhattacharyya 1985
Mouse	26 (1 h)	1,560	Significant reduction (20-30% of control) in erythrocytes and hematocrit, significant increase in reticulocytes and leukocytes[b]	Peterson and Bhattacharyya 1985

[a]Some effects observed at post-exposure periods of varying duration, see text for details.
[b]Data from five surviving mice (38% mortality) all of which died within days after exposure.

damage occurs even after cessation of exposure. It is not known if such damage is a function of arsine metabolites or a continuation of sequential subcellular processes resulting in increased hematologic effects and renal failure.

Urinary arsenic is routinely evaluated in victims of arsine poisoning. Urine arsenic in unexposed people is <50 µg/L (Landrigan et al. 1982). These authors reported that 15.6 µg of arsine/m^3 is associated with urinary arsenic of 50 µg/L. Other studies of urinary arsenic levels have also been reported, but the post-exposure time of measurement varies considerably, and there are no corresponding exposure correlates. Urinary arsenic levels in humans poisoned by arsine include 3.08 mg/L (Spolyar and Harger1950), 1.14 mg/L, and 2.25 mg As/L (Elkins and Fahy 1967); 20 mg/L, 220 mg/L (24 h post-exposure) (Uldall et al. 1970), 130 mg/L, 175 mg/L (Uldall et al. 1970), and 0.43 mg As/L (24 h post-exposure) (De Palma 1969)

Blood arsenic levels are also routinely evaluated but also lack exposure correlates and vary as to post-exposure assessment: 0.6 mg/L (2 d post-exposure; Hesdorffer et al. 1986), 0.66 mg/L, 0.25 mg/L, and 2.2 mg/L (1 d post-exposure, De Palma 1969).

4.2. Mechanism of Toxicity

It is well documented that exposure to arsine causes intravascular hemolysis resulting in anemia and acute oliguric renal failure (Fowler and Weissberg 1974; Landrigan et al. 1982). However, the underlying mechanism by which arsine causes these effects is not fully understood. Several investigators have noted that hemoglobin is a primary subcellular target for arsine (Klimecki and Carter 1995; Hatlelid et al. 1996), and several mechanisms of arsine-induced hemolysis have also been proposed: (1) formation of colloidal arsenic within the erythrocyte (Labes 1926; Heubner 1935), (2) arsine-induced formation of hydrogen peroxide (Jung 1947), (3) inhibition of catalase (Lasch 1958), and (4) inhibition of NA^+/K^+ -ATPase (Levinsky et al. 1970). More recently, Blair et al. (1990b) noted increased levels of circulating methemoglobin and decreased reduced glutathione levels in erythrocytes of mice exposed to arsine, and hypothesized that oxidative stress may be a key mechanism in arsine toxicity.

The hemolytic potential of arsine is considerable. Arsine at 0.1-0.5 mM may cause significant hemolysis (Hatelid et al. 1995; Pernis and Magistretti 1960). Inhalation exposure of mice to arsine at 9 ppm for only 1 h resulted in a statistically significant decrease in hematocrit levels at 24 h to 11 d after exposure (Peterson and Bhattacharyya 1985). The practical significance of this finding is demonstrated by a simple calculation provided by Klimecki and Carter (1995) showing an arsine concentration of 0.26 mM resulting from a 4-h exposure to arsine at a concentration of 30 ppm. This calculation assumed a minute alveolar

volume of 5.25 L/min, a circulatory volume of 5 L, and an arsine density and molecular weight of 2.696 g/L and 77.95, respectively.

Of additional concern regarding acute exposures to arsine is the fact that human case reports indicate that serious health effects (e.g., renal failure) resulting from arsine exposure may be delayed for several hours or several days. Legge (1916) noted an interval of 6-36 h between the arsine exposure and the appearance of RBC destruction. Latency is also indicated by data from laboratory species that show hematopoietic effects of arsine persisting after exposure has ceased (Hong et al. 1989; Blair et al. 1990a). Based upon clinical chemistry and hematologic parameters, effects of severe arsine poisoning may last for weeks and months after exposure even following medical intervention (Levinsky et al. 1970).

4.3. Structure-Activity Relationships

There are no structure-activity relationships applicable to estimating acute exposure limits for arsine. The nature and rapidity of its toxicity are notably different from other inorganic arsenic compounds.

4.4. Other Relevant Information

Delayed neurologic and psychiatric disorders following acute arsine exposures have been reported (Frank 1976). Exposure concentrations were not provided, but duration of exposure ranged from 10 to 90 min. Within hours after the exposures, characteristic signs of arsine poisoning (e.g., hemolysis and hematuria) were observed. Polyneuropathies and neuropsychiatric syndromes were detected at 1-36 mon after the acute exposures to arsine.

4.4.1. Species Variability

No significant differences in arsine-induced toxicity were observed among F344 rats, B6C3F_1 mice, and Syrian golden hamsters subjected to various exposure regimens (Blair et al. 1990a). In this inhalation study, mice were exposed to arsine for 6 h/d for 1 d or 4 consecutive days or for 6 h/d, 5 consecutive days per week for 13 w. Rats were exposed 6 h/d for 14 or 28 consecutive days, or for 6 h/d for 5 consecutive days per week for 13 w. Hamsters were exposed 6 h/d for 5 consecutive days each week for 4 w. Exposure concentrations were 0.5, 2.5, or 5.0 ppm except for the 13-w exposures where concentrations were reduced to 0.025, 0.5, or 2.5 ppm. The investigators assessed alter-

ations in various parameters of the hematopoietic system (e.g., spleen weight, extramedullary splenic hematopoiesis, hematocrit, hematology profiles, etc.) and found the effects to be similar among the species tested. In comparing the effects resulting from the various exposure regimens, it was noted that the 1-d 0.5 ppm (10 times the ACGIH TLV) exposure failed to produce significant effects on the hematopoietic system but that repeated exposure to 0.025 ppm (½ the ACGIH TLV) caused significant anemia.

4.4.2. Unique Physicochemical Properties

The uniqueness of arsine revolves primarily around its accidental formation (need for nascent hydrogen) resulting in relatively unexpected exposures.

4.4.3. Concurrent Exposure Issues

Exposure to arsine usually occurs in occupational settings that often involve concurrent exposures to other metal vapors and solvents. It is assumed that concurrent exposure with other chemicals, the toxicity of which targets the erythrocyte or renal function, would increase the severity of the response to arsine.

5. DATA ANALYSIS AND PROPOSED AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

For derivation of an AEGL-1, human data are limited to equivocal anecdotal information reported by Flury and Zernik (1931) and Coles et al. (1969). These include a 6-h NOAEL of 3.1 ppm and a 1-h NOAEL of 6.25 ppm, equivalent to cumulative exposures of 1,116 and 375 ppm"min, respectively (Flury and Zernik 1931). Coles et al. (1969) estimated that humans could be exposed at 3-100 ppm for several hours with the occurrence of only slight symptoms. However, these data are not consistent with similar or lower exposures resulting in lethality (see Table 2-3). Numerous case reports are available documenting effects of varying severity following acute exposures of humans to arsine, but these reports lack definitive exposure data. Although human data are considered to be inadequate for derivation of AEGL-1 values for arsine, the available data do provide valuable qualitative insight into the signs and symptoms of arsine-induced toxicity and the oftentimes delayed nature of this toxicity.

5.2. Summary of Animal Data Relevant to AEGL-1

Acute toxicity data are available for several animal species but earlier reports often lacked details regarding experimental protocol and results. Most studies involved longer-term exposures (e.g., 14 d to 12 w or longer) but some provided data for exposure durations within the scope of AEGL concern. Data showing relatively inconsequential effects of acute exposure to arsine were available for mice (Peterson and Bhattacharyya 1985; Blair et al. 1990a). Results of these studies showed that cumulative exposures of 180-540 ppm"min resulted in minor alterations in hematologic parameters (e.g., packed cell volume, hematocrit level, erythrocyte count; see Table 2-6). Slightly higher cumulative exposures (660-1,800 ppm"min) resulted in more severe changes in the same parameters. The parameters evaluated in these studies are appropriate endpoints for assessing arsine toxicity. Although some of the observed changes were statistically significant, they may be more appropriately considered compensatory responses (e.g., minor increase in spleen weight) and not necessarily indicative of a biologically significant toxic response (minor reduction in erythrocyte count or decreased hematocrit).

5.3. Derivation of AEGL-1

For comparative purposes, AEGL-1 values were initially derived using two data sets (Blair et al. 1990a; Flury and Zernick 1931). These included a 6-h NOAEL of 0.5 ppm for mice (Blair et al. 1990a) and the estimated 1-h NOAEL of 6.25 ppm for humans reported by Flury and Zernik (1931).

The values calculated using the data (6-h NOAEL of 0.5 ppm in mice) from Blair et al. (1990a) were initially selected to estimate the AEGL-1. For AEGL-1 derivation, an uncertainty factor of 30 was applied to this value to account for intraspecies variability and interspecies extrapolation. The uncertainty factor of 10 for interspecies variability was chosen to account for the uncertainties in distribution kinetics and susceptibility to subsequent renal failure among different species. The uncertainty factor of 3 for intraspecies variability was applied because of the extreme toxicity of arsine and because the mechanism of toxicity (hemolysis and subsequent renal failure) is not likely to vary greatly among individuals. The basis for this assumption was that physiologic parameters (e.g., absorption, distribution, metabolism, structure of the erythrocyte and its response to arsine, and renal responses) would not vary among individuals of the same species to such an extent that the response severity to arsine would be altered by an order of magnitude. It is unlikely that individual variability (i.e., variability in erythrocyte structure/function or response of the kidney to

hemolysis) would have a significant impact on any of the proposed subcellular mechanisms of arsine toxicity.

Exponential scaling ($C^n \times t = k$; ten Berge et al.1986) was used to derive the other exposure duration-specific values. The concentration exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In lieu of a definitive data set allowing empirical derivation of the exponent (n), temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation. The human data from the earlier reports appears to be equivocal and unverifiable. Although of some qualitative value, the human experience information was not considered of sufficient quality for quantitative applications.

The calculations for the AEGL-1 values initially derived are shown in Appendix A. However, because of the extreme toxicity of arsine and the steep dose-response indicated by the available data, the derivation of AEGL-1 values for arsine was considered inappropriate. The available human and animal toxicity data indicate that there is little margin between exposures that produce little or no toxicity and those that result in lethality and, therefore, do not justify the derivation of a safe exposure level that meets the AEGL-1 definition. This is further supported by reports of toxicity in humans and animals at concentrations similar to or below odor detection levels (- 0.5 ppm) and where hemolysis, the mechanism of toxicity, may rapidly progress to renal failure. The decision also was based on the known toxicity of arsine, the latency in development and expression of toxicity even after removal from exposure, and the possible progression of hemolysis to life-threatening renal failure. The continuum of arsine-induced toxicity does not appear to include effects consistent with the AEGL-1 definition. The use of detection limits (0.01 to 0.05 ppm; (OSHA 1999)) was considered to be inconsistent with the AEGL-1 definition. The AEGL-1 values for arsine are shown in Table 2-7.

TABLE 2-7 AEGL-1 for Arsine

AEGL Level	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR

NR: Not recommended. Numeric values for AEGL-1 are not recommended, because (1) data are not available, (2) an inadequate margin of safety exists between the derived AEGL-1 and the AEGL-2, or (3) the derived AEGL-1 is greater than the AEGL-2. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

6. DATA ANALYSIS AND PROPOSED AEGL-2

6.1. Human Data Relevant to AEGL-2

Several reports identified nonlethal effects in humans acutely exposed to arsine. These reports, however, lacked definitive exposure data but verified hematologic disorders leading to renal failure as critical effects of arsine exposure. Bulmer et al. (1940) (as cited in Elkins1959) reconstructed an exposure incident at a gold extraction facility and estimated that subchronic (up to 8 mon) exposure to 0.12 ppm arsine resulted in jaundice and anemia (see Section 2.2.1). The lack of definitive exposure data for humans necessitates the use of animal data for quantitative estimation of AEGL values. Derivation of AEGL-2 values based upon limited human data (Flury and Zernik 1931) was considered but rejected because the data were poorly documented and inconsistent with other data showing lethality at lower cumulative exposures.

6.2. Animal Data Relevant to AEGL-2

Consistent with the human responses to arsine exposure, observations in several animal species (rats, mice, and hamsters) indicated hematologic involvement. Cumulative exposures of 540-1,800 ppm"min produced decreases in hematocrit levels, RBC counts, packed cell volumes, and increases in absolute and relative spleen weights (consistent with erythrocyte damage). For acute exposures, the exposure-response curve is steep; generally less than a 10-fold difference between no-effect and lethality exposures.

6.3. Derivation of AEGL-2

Although several data sets were available to derive AEGL-2 values, the 1-h exposure data from the mouse study by Peterson and Bhattacharyya (1985) provided the most sound basis.

The 1-h no-observed-effect level (NOEL) of 5 ppm represented a no-effect exposure level for mice, and 11 ppm represented a lowest-observed-adverse-effect level (LOAEL) based upon altered hematologic parameters in mice that were reversible at 5 d post-exposure. At 15 ppm, the effects on hematocrit levels, packed cell volume, and RBC count were more severe but were approaching reversibility at 11 d. The use of what might appear to be a conservative NOEL in the derivation of AEGL-2 is justified by the documented latency in the expression of severe toxicity in humans even after removal from exposure

and the potential for hemolysis to rapidly progress to life-threatening renal failure. Furthermore, the steep exposure-response curve for arsine (1-h exposure of mice to 26 ppm resulted in 100% lethality within 4 d, but exposure to 15 ppm resulted in nothing more than severe but reversible hematologic changes (Peterson and Bhattacharyya 1985)) justifies the approach used for derivation of the AEGL-2.

Data from mice were used to calculate the AEGL levels because these data exhibited a good exposure response relationship, and the endpoint of decreased hematocrit levels can be considered a sensitive indicator of arsine toxicity. For AEGL-2 derivation, an uncertainty factor of 30 was applied to the 1-h NOAEL of 5.0 ppm to account for intraspecies variability and interspecies extrapolation. A factor of 10 was applied for interspecies variability. The 10-min LC_{50} value for the monkey was about 60% of the rat value and one-third the rabbit value, thereby demonstrating interspecies variability. Additionally, the human experience data lacked sufficient quantitative exposure terms to allow for a definitive assessment of the animal-to-human variability. An uncertainty factor of 3-fold was used to account for intraspecies variability. Since the hemolytic response is likely to occur to a similar extent and with similar susceptibility in most individuals following exposure to extremely low arsine concentrations. The physiologic parameters (e.g., absorption, distribution, metabolism, structure of the erythrocyte and its response to arsine, and renal responses) would not vary among individuals of the same species to such an extent that the severity in response to arsine would be altered by an order of magnitude. Also it is unlikely that individual variability (i.e., variability in erythrocyte structure/function or response of the kidney to hemolysis) would have a significant impact on any of the proposed subcellular mechanisms of arsine toxicity. Only a twofold reduction in dosage is used to account for variability in sensitivity to the hemolytic response to some antimalarial drugs such as primaquine (Kellermeyer et al.,1962; Webster 1985). The steep exposure-response curves from animal data also affirm the limited variability in response and would appear to argue for no further reduction in the AEGL values. Finally, the AEGL-2 values were developed using a conservative estimate of a toxic response (no significant indication of hemolysis in mice exposed to arsine at 5 ppm for 1 h) and additional reduction of the values would seem unwarranted. The AEGL-2 values are shown in Table 2-8 and their derivations shown in Appendix A.

Exponential scaling ($C^n \times t = k$; ten Berge et al.1986) was used to derive the other exposure duration-specific values. The concentration exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In lieu of a definitive data set allowing empirical derivation of the exponent n, temporal scaling was performed, using n = 3 when extrapolating to

TABLE 2-8 AEGL-2 for Arsine

AEGL Level	30 min	1 h	4 h	8 h
AEGL-2	0.21 ppm 0.7 mg/m^3	0.17 ppm 0.5 mg/m^3	0.04 ppm 0.1 mg/m^3	0.03 ppm 0.1 mg/m^3

shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation.

7. DATA ANALYSIS AND PROPOSED AEGL-3

7.1. Human Data Relevant to AEGL-3

There are numerous case reports of human lethality resulting from acute exposure to arsine. Although these reports verify the extreme toxicity of arsine, with the erythrocyte as the primary target, and the propensity for delayed lethality due to renal failure, valid exposure data are lacking. Human lethality has been documented for cumulative exposures ranging from 375 to 7,500 ppm"min. Although an AEGL-3 could be derived based upon the human experience (Flury and Zernick 1931; Henderson and Haggard 1943, as cited in AIHA 1993), the resulting values are higher than those using animal data and are compromised by uncertainties regarding validity of exposure terms. More important, however, is the fact that the human data appear to be equivocal and lack verification.

7.2. Summary of Animal Data Relevant to AEGL-3

Lethality data are available for several animal species including rats, mice, monkeys, dogs, and cats. Cumulative exposures producing lethality range from 525 to 11,520 ppm"min, with the highest value representing a 24-h exposure to only 8 ppm.

7.3. Derivation of AEGL-3

The most definitive data set for deriving AEGL-3 values is that of Peterson and Bhattacharyya (1985), which provides exposure response data for mice exposed to arsine for 1 h at concentrations of 0, 5, 9, 11, 15, or 26 ppm. Although the 26-ppm exposure resulted in 100% mortality within 4 d post-expo-

sure, the 15-ppm exposure produced significant, hematologic changes. Therefore, these data affirm the steep exposure-response curve for arsine and provide a basis for a lethality threshold.

Although several data sets could be used to derive AEGL-3 values, the 1-h exposure data from the mouse study by Peterson and Bhattacharyya (1985) provided the most sound basis and were selected to derive AEGL-3 values. Due to the steep concentration-response curve for arsine, the 15-ppm exposure (where there was no lethality) was considered an estimate of the lethality threshold. An uncertainty factor of 30-fold was applied to account for interspecies extrapolation (10-fold) and intraspecies variability (3-fold) (see Section 6.3).

As described in Section 6.3, exponential scaling ($C^n \times t = k$; ten Berge et al.1986) was used to derive exposure duration-specific values.

The AEGL-3 values are shown in Table 2-9 and their derivations shown in Appendix A.

8. SUMMARY OF PROPOSED AEGLS

8.1. AEGL Values and Toxicity Endpoints

The data used to derive exposure values for the various AEGL tiers are consistent with respect to the known target (erythrocytes) and effects (hemolysis and alteration of hematologic parameters resulting in renal failure and death) of arsine. The relationship among the three tiers of proposed AEGLs reflects the steep exposure-response relationship and extreme toxicity documented for arsine. It is apparent from the AEGL values that it is difficult to quantitatively differentiate a lethal exposure from one that produces serious but nonlethal effects. This lack of quantitative discrimination is also reflected in the overall database for arsine where there does not appear to be a well-defined exposure threshold between irreversible, nonlethal effects and lethality. It must also be noted that the reported odor threshold (0.5 ppm) is above the proposed AEGL-2 values. The approach used in the selection of the exposure concentrations and

TABLE 2-9 AEGL-3 for Arsine

AEGL Level	30 min	1 h	4 h	8 h
AEGL-3	0.63 ppm 2.0 mg/m^3	0.5 ppm 1.6 mg/m^3	0.13 ppm 0.4 mg/m^3	0.06 ppm 0.2 mg/m^3

the respective determinants for AEGL-2 (absence of significant hemolysis) and AEGL-3 (absence of lethal response) along the continuum of arsine toxicity and the approach employed for time scaling are considered sufficient for AEGLs that are protective of human health. Selection of uncertainty factors (10-fold for interspecies variability and 3-fold for protection of sensitive populations) are also considered sufficient for protection of human health.

A relational comparison of AEGL values for arsine is made in Table 2-10.

8.2. Comparison with Other Standards and Criteria

All currently available standards and guidelines are shown in Table 2-11. Emergency exposure limits (EELs) and continuous exposure limits (CELs) were previously derived by the Committee on Toxicology (reported in NRC 1984). Additionally, ACGIH TLV values, emergency response planning guideline (ERPG) values, NIOSH immediately dangerous to life and health (IDLH) values, and Dutch maximum allowable concentration (MAC) values have been published. Currently, no German MAK values are available. The AEGL values are consistent with, albeit somewhat lower, than currently established guidelines. The absence of AEGL-1 values is also consistent with the AIHA ERPG decision not to recommend ERPG-1 values.

8.3. Data Adequacy and Research Needs

The human experience is defined by only qualitative data. These data, however, affirm the extreme toxicity of arsine and the characteristic latency

TABLE 2-10 Relational Comparison of AEGL Values for Arsine

Classification	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	NR	NR	NR	NR
AEGL-2 (Disabling)	0.21 ppm	0.17 ppm	0.04 ppm	0.02 ppm
AEGL-3 (Lethal)	0.63 ppm	0.50 ppm	0.13 ppm	0.06 ppm

NR: Not recommended. Numeric values for AEGL-1 are not recommended because (1) data are not available, (2) an inadequate margin of safety exists between the derived AEGL-1 and the AEGL-2, or (3) the derived AEGL-1 is greater than the AEGL-2. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

TABLE 2-11 Extant Standards and Guidelines for Arsine

Guideline	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	NR	NR	NR	NR
AEGL-2 (Disabling)	0.21 ppm	0.17 ppm	0.04 ppm	0.02 ppm
AEGL-3 (Lethal)	0.63 ppm	0.50 ppm	0.13 ppm	0.06 ppm
ERPG-1[a]		NR		
ERPG-2[a]		0.5 ppm		
ERPG-3[a]		1.5 ppm		
NRC CEL[b]		1 ppm		0.05 ppm
NRC EEL[b]		1 ppm		
NIOSH[c]	3 ppm			
ACGIH TLV-TWA[d]				0.05 ppm
MAC (Netherlands)[e]				0.2 mg/m^3 (0.06 ppm)

NR: Not recommended. Numeric values for AEGL-1 are not recommended because (1) data are not available, (2) an inadequate margin of safety exists between the derived AEGL-1 and the AEGL-2, or (3) the derived AEGL-1 is greater than the AEGL-2. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.
[a]AIHA 1993.
[b]NRC 1984.
[c]NIOSH 1997, a 15-min recommended exposure limit (REL) of 0.002 mg/m^3 (0.0006 ppm) is also listed.
[d]ACGIH 1999, 8-h time-weighted average (TWA) (impending change to 0.002 ppm proposed).
[e]Ministry of Social Affairs and Employment 1999.

period prior to renal failure. Quantitative animal data are available from several well-conducted peer-reviewed studies that demonstrate a toxic response similar to that observed for humans. There are no exposure-response data consistent with AEGL-1 level effects. This is likely a function of the progression of arsine-induced toxicity from essentially no observable effects to those effects indicative of a lethal response, and the consequent steep exposure-response relationship.

The inappropriateness of AEGL-1 values is affirmed by the steep dose-response for arsine and the inability, based upon available data, to imply a safe

exposure level for this chemical. The validity of AEGL-2 values that are markedly different from AEGL-3 values would be questionable because of the steep exposure-response curve for arsine. Additional data would be useful in providing greater precision in identifying thresholds between nonlethal and lethal exposures that may cause immediate or delayed lethality. The relatively low values of the proposed AEGLs reflect the steep exposure-concentration response for arsine-induced toxicity. Although based upon animal data, the values appear to be consistent with limited human exposure information to the extent that they offer a margin of safety.

As for most chemical hazard evaluations, the greatest data deficiency is the lack of definitive human exposure values. The animal data are adequate for demonstrating the extreme toxicity of arsine and the fact that there is little margin between exposures resulting in mild, reversible effects and lethality. There are no exposure-response data consistent with AEGL-1 level effects. This is likely a function of the rapid progression of arsine-induced toxicity from essentially no observable effects to that of a lethal response and the consequent steep exposure-response relationship. Additionally, studies addressing exposure concentration-duration relationships would allow for more precise temporal extrapolation for the development of AEGL values of varying exposure time durations.

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Appendixes

APPENDIX A
DERIVATION OF AEGL VALUES

Derivation of AEGL-1

Key study: Blair et al. (1990a). Male and female $B6C3F_1$ mice exposed to arsine at 0.5 ppm for 6 h exhibited no change in relative spleen weights or hematologic parameters and exhibited no overt signs of toxicity.

Uncertainty factors: An uncertainty factor of 10 was used for interspecies variability to account for possible variability in arsine-induced hemolysis and progression to renal effects.
An uncertainty factor of 3 was used for intraspecies variability assuming limited individual variability in hemolytic response (described more fully under AEGL-2 and AEGL-3).

Calculations: 0.5 ppm/30 = 0.0167 ppm
$C^3 \times t = k$
$(0.0167 \text{ ppm})^3 \times 30 \text{ min} = 0.00167 \text{ ppm}^3\text{"min}$

Time scaling: $C^n \times t = k$; data were unavailable for empirical derivation of a scaling factor. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of chemical-specific data, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation.

NOTE: The following analysis served as an initial estimate for the AEGL-1. However, it is believed that it is not appropriate to derive AEGL-1 values for arsine because of the steep dose-response and the inability of available data to justify an exposure that would result in little or no toxic effect.

30-min AEGL-1: $C^3 \times 30 \text{ min} = 0.00167 \text{ ppm}^3\text{"min}$

C = 0.04 ppm

1-h AEGL-1: $C^3 \times 60$ min = 0.00167 ppm^3"min

C = 0.03 ppm

4-h AEGL-1: $C^3 \times 240$ min = 0.00167 ppm^3"min

C = 0. 02 ppm

8-h AEGL-1: $C^3 \times 480$ min = 0.00167 ppm^3"min

C = 0.01 ppm.

Derivation of AEGL-2

Key study: Peterson and Bhattacharyya (1985). NOAEL of 5 ppm based upon absence of hematologic changes in mice following 1-h exposure. At 15 ppm, hematologic changes were significant, and at 26 ppm there was 100% mortality.

Uncertainty factors: An uncertainty factor of 10 was used for interspecies variability to account for possible variability in arsine-induced hemolysis and progression to renal effects. Uncertainty regarding intraspecies variability was limited to 3, because the hemolytic response is likely to occur to a similar extent and with similar susceptibility in most individuals. This was based on the consideration that physiologic parameters (e.g., absorption, distribution, metabolism, structure of the erythrocyte and its response to arsine, and renal responses) are not likely to vary among individuals of the same species to such an extent that the response severity to arsine would be altered by an order of magnitude. Individual variability (i.e., variability in erythrocyte structure/function or response of the kidney to hemolysis) would not likely have a significant impact on any of the proposed subcellular mechanisms of arsine toxicity. The steep exposure-response relationships from animal data also affirm the limited variability in response. Because of the forgoing considerations and the fact that the AEGL-2 values were developed from a data point showing no significant indication of hemolysis in mice exposed for 1 h to arsine at 5 ppm, the additional reduction of the values would seem unwarranted.

Calculations: 5 ppm/30 = 0.167 ppm
$C^3 \times t = k$
$(0.167 \text{ ppm})^3 \times 60 \text{ min} = 0.278 \text{ ppm}^3\text{"min}$

$C^1 \times t = k$
$0.167 \text{ ppm} \times 60 \text{ min} = 10 \text{ ppm"min}$

Time scaling: $C^n \times t = k$; data were unavailable for empirical derivation of a scaling factor. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of chemical-specific data, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation.

30-min AEGL-2: $C^3 \times 30 \text{ min} = 0.278 \text{ ppm}^3\text{"min}$
C = 0.21 ppm
1-h AEGL-2: $C^3 \times 60 \text{ min} = 0.278 \text{ ppm}^3\text{"min}$
C = 0.17 ppm
4-h AEGL-2: $C^1 \times 240 \text{ min} = 10 \text{ ppm"min}$
C = 0.04 ppm
8-h AEGL-2: $C^1 \times 480 \text{ min} = 10 \text{ ppm"min}$
C = 0.02 ppm.

Derivation of AEGL-3

Key study: Peterson and Bhattacharyya (1985), based upon an estimate of a lethality threshold (15 ppm) in mice exposed for 1 h. Hematologic changes were significant at 15 ppm, and at 26 ppm there was 100% mortality.

Uncertainty factors: An uncertainty factor of 10 was retained for interspecies variability to account for possible variability in arsine-induced hemolysis and progression to renal effects. An uncertainty factor for intraspecies variability of 3 was used, because the hemolytic response is likely to occur to a similar

extent and with similar susceptibility in most individuals. This was based on the consideration that physiologic parameters (e.g., absorption, distribution, metabolism, structure of the erythrocyte and its response to arsine, and renal responses) would not vary among individuals of the same species to such an extent that the response severity to arsine would be altered by an order of magnitude. Individual variability (i.e., variability in erythrocyte structure/function or response of the kidney to hemolysis) is not likely to have a significant impact on any of the proposed subcellular mechanisms of arsine toxicity. The steep exposure-response relationships from animal data also affirm the limited variability in response. Because of the aforementioned considerations and the fact that the AEGL-3 values were developed based on a nonlethal toxic response (hemolysis in the absence of lethality), any additional reduction of the values would seem unwarranted.

Calculations: 15 ppm/30 = 0.5 ppm

$C^3 \times t = k$

$(0.5 \text{ ppm})^3 \times 60 \text{ min} = 7.5 \text{ ppm}^3\text{"min}$

$C^1 \times t = k$

$0.5 \text{ ppm} \times 60 \text{ min} = 30 \text{ ppm"min}$

Time scaling: $C^n \times t = k$; data were unavailable for empirical derivation of a scaling factor. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of chemical-specific data, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation.

30-min AEGL-3: $C^3 \times 30 \text{ min} = 7.5 \text{ ppm}^3\text{"min}$

$C = 0.63$ ppm

1-h AEGL-3: $C^3 \times 60 \text{ min} = 7.5 \text{ ppm}^3\text{"min}$

$C = 0.50$ ppm

4-h AEGL-3: $C^1 \times 240 \text{ min} = 30 \text{ ppm"min}$

$C = 0.13$ ppm

8-h AEGL-3: $C^1 \times 480$ min = 30 ppm"min
C = 0.06 ppm.

APPENDIX B

TIME SCALING CALCULATIONS FOR ARSINE

Data were unavailable to empirically derive a scaling factor (n) for arsine. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived exponent (n), and to obtain AEGL values, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation.

APPENDIX C

DERIVATION SUMMARY FOR ACUTE EXPOSURE GUIDELINES FOR ARSINE (CAS No. 7784-42-1)

AEGL-1 Values - Arsine			
30 min	1 h	4 h	8 h
Not recommended	Not recommended	Not recommended	Not recommended
Reference: The available human and animal data indicate that there is very little margin between seemingly inconsequential exposures and lethal exposures. The mechanism of arsine toxicity (hemolysis and subsequent renal failure) and the fact that toxicity has been demonstrated at or below the odor threshold justify the inappropriateness of AEGL-1 values for any exposure period.			
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 (1)			
Animal to Human Dosimetric Adjustment: Not applicable			
Time Scaling: Not applicable			
Data Adequacy: Numeric values for AEGL-1 are not recommended, because (1) data are not available, (2) an inadequate margin of safety exists between the derived AEGL-1 and the AEGL-2, or (3) the derived AEGL-1 is greater than the AEGL-2. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.			

AEGL-2 Values - Arsine			
30 min	1 h	4 h	8 h
0.21 ppm	0.17 ppm	0.04 ppm	0.02 ppm
Reference: Peterson, D.P., and M.H. Bhattacharyya. 1985. Hematological responses to arsine exposure: quantitation of exposure response in mice. Fundam. Appl. Toxicol. 5: 499-505			
Test Species/Strain/Sex/Number: Female B6C3F_1 mice, 8/group			
Exposure Route/Concentrations/Durations: Inhalation: 0, 5, 9, 11, 15, or 26 ppm for 1 h			
Effects: hematocrit level (as % of controls) 5 ppm no significant effects (determinant for AEGL-2) 9 ppm 80.2 % 11 ppm 79.7% 15 ppm 61.4% 26 ppm 21.7% (100% mortality at 4 d post-exposure)			
Endpoint/Concentration/Rationale: 5 ppm for 1 h considered as a no-observed-effect level (NOEL) for decreased hematocrit levels. A NOEL was used because of an extremely steep dose-response curve and the fact that the ultimate toxic effect, renal failure, is delayed for several days.			
Uncertainty Factors/Rationale: Total uncertainty factor: 30 Interspecies: 10 - The 10-min LC_{50} value for the monkey was about 60% of the rat value and one-third the rabbit value. The mouse data were used to calculate the AEGL levels, because the data exhibited a good exposure-response relationship and the endpoint of decreased hematocrit levels can be considered a sensitive indicator of arsine toxicity. In addition, arsine has an extremely steep dose-response relationship, allowing little margin in exposure between no effects and lethality. Intraspecies: 3 - An uncertainty factor of 3-fold was used, because the hemolytic response is likely to occur to a similar extent and with similar susceptibility in most individuals. This was based on the consideration that physiologic parameters (e.g., absorption, distribution, metabolism, structure of the erythrocyte and its response to arsine, and renal responses) are not likely to vary among individuals of the same species to such an extent that the response severity to arsine would be altered by an order of magnitude. Individual variability (i.e., variability in erythrocyte structure/function or response of the kidney to hemolysis) *(Continued)*			

also is not likely have a significant impact on any of the proposed subcellular mechanisms of arsine toxicity. The steep exposure-response curves derived from animal data also affirm the limited variability in response. Because of these considerations and the fact that the AEGL-2 values were developed using a toxic response indicative of no significant hemolysis in mice exposed for 1 h to arsine at 5 ppm, an additional reduction of the values would seem unwarranted.
Modifying Factor: Not applicable
Animal to Human Dosimetric Adjustment: None applied, insufficient data
Time Scaling: $C^n \times t = k$, where n = 1 or 3. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation.
Data Adequacy: The study was considered adequate for AEGL-2 derivation. It was carefully designed and performed, used adequate numbers of animals, used an appropriate exposure regimen, and identified an endpoint consistent with the AEGL-2 definition and with the known effects of arsine.

AEGL-3 Values - Arsine			
30 min	1 h	4 h	8 h
0.63 ppm	0.50 ppm	0.13 ppm	0.06 ppm

Reference: Peterson, D.P., and M.H. Bhattacharyya. 1985. Hematological responses to arsine exposure: quantitation of exposure response in mice. Fundam. Appl. Toxicol. 5: 499-505

Test Species/Strain/Sex/Number: Female $B6C3F_1$ mice, 8/group

Exposure Route/Concentrations/Durations: Inhalation: 0, 5, 9, 11, 15, or 26 ppm for 1 h

Effects: hematocrit level (as % of controls) and lethality

5 ppm	no significant effects
9 ppm	80.2 % (no mortality)
11 ppm	79.7% (no mortality)
15 ppm	61.4% (no mortality) (determinant for AEGL-3)
26 ppm	21.7% (3/8 immediately following exposures; 100% mortality at 4 d post-exposure)

Endpoint/Concentration/Rationale: 15 ppm for 1 h induced a significant decrease in hematocrit levels that may be approaching a degree of hemolysis that can lead to renal failure. Given the steepness of the dose-response relationship this is justified as an estimate of the lethality threshold. An exposure of 26 ppm for 1 h resulted in 100% lethality.

Uncertainty Factors/Rationale: Total uncertainty factor: 30

Interspecies: 10 - The 10-min LC_{50} value for the monkey was about 60% of the rat value and one-third the rabbit value. The mouse data were used to calculate the AEGL levels, because the data exhibited a good exposure-response relationship curve, and the endpoint of decreased hematocrit levels can be considered a sensitive indicator of arsine toxicity. In addition, arsine has an extremely steep dose-response relationship giving little margin between no effects and lethality.

Intraspecies: 3 - Uncertainty regarding intraspecies variability was limited to 3, because the hemolytic response is likely to occur to a similar extent and with similar susceptibility in most individuals. This was based on the consideration that physiologic parameters (e.g., absorption, distribution, metabolism, structure of the erythrocyte and its

(Continued)

response to arsine, and renal responses) are not likely to vary among individuals of the same species to such an extent that the response severity to arsine would be altered by an order of magnitude. Individual variability (i.e., variability in erythrocyte structure/function or response of the kidney to hemolysis) also is not likely to have a significant impact on any of the proposed subcellular mechanisms of arsine toxicity. The steep exposure-response curves derived from animal data also affirm the limited variability in response. Because of these considerations and the fact that the AEGL-2 values were developed using a toxic response indicative of no significant hemolysis in mice exposed for 1 h to arsine at 5 ppm, additional reduction of the values would seem unwarranted.

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: None applied, insufficient data

Time Scaling: $C^n \times t = k$, where n = 1 or 3. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation.

Data Adequacy: The study was considered adequate for AEGL-3 derivation. It was carefully designed and performed, used adequate numbers of animals, used an appropriate exposure regimen, and identified an endpoint consistent with AEGL-3 definition and with the known effects of arsine. The available data indicate that the exposure-response relationship for arsine is very steep, thereby justifying the approach taken to derive the AEGL-3 values.