Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 1

Subcommittee on Acute Exposure Guideline Levels, Committee on Toxicology, Board on Environmental Studies and Toxicology, National Research Council

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VOLUME 1

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Committee on Toxicology
Board on Environmental Studies and Toxicology
Commission of Life Sciences
National Research Council

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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 organiza

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

tions 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 November 1995, 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.

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—

[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.

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 guide

lines 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, pharmacokinetic 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 (1×1^{-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

1

Aniline[1] Acute Exposure Guideline Levels

SUMMARY

ANILINE is an aromatic amine used chiefly in the chemical industry in the manufacture of dyes, dye intermediates, rubber accelerators, antioxidants, drugs, photographic chemicals, isocyanates, herbicides, and fungicides. Production of aniline oil in 1993 was approximately 1 billion pounds. The primary effect of an acute exposure to aniline is the oxidation of the hemoglobin in red blood cells (RBCs), resulting in the formation of methemoglobin. The effect may occur following inhalation, ingestion, or dermal absorption. In conjunction with methemoglobinemia, chronic exposures or exposures to high concentrations may produce signs and symptoms of headache, paresthesia, tremor, pain, narcosis/coma, cardiac arrhythmia, and possibly death.

No reliable data on human exposures via the inhalation route were located.

[1]This document was prepared by AEGL Development Team members Robert Snyder and George Rodgers of the National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances (NAC) and Sylvia Talmadge 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).

All acute exposure guideline level (AEGL) values are based on a study in which rats were exposed to aniline at concentrations of 0, 10, 30, 50, 100, or 150 parts per million (ppm) for 8 or 12 h (Kim and Carlson 1986). The only reported effect was methemoglobin formation. The relationship between aniline concentration and methemoglobin formation appeared to be linear. Furthermore, at a constant concentration (100 ppm), the formation of methemoglobin between 3 and 8 h was basically linear, reaching an asymptote at 8 h. Based on the linear relationship between aniline concentration and methemoglobin formation and between methemoglobin formation and time at a constant aniline concentration, a linear relationship between concentration and exposure duration ($C^1 \times t = k$, where C=exposure concentration, t=exposure duration, and k=a constant) was chosen for time-scaling aniline concentrations to the appropriate AEGL exposure durations.

The AEGL-1 was based on an exposure of rats to a concentration of 100 ppm for 8 h, which resulted in elevation of methemoglobin from a control value of 1.1% (range, 0.4% to 2.1%) to 22%. A review of the published data indicates that methemoglobin levels of 15–20% in humans results in clinical cyanosis but no hypoxic symptoms. Although inhalation data for comparison purposes are not available, oral ingestion data suggest that humans may be considerably more sensitive to methemoglobin-forming chemicals than rats. Therefore, a default uncertainty factor of 10-fold was used for interspecies extrapolation (NRC 1993). Several sources also indicate that newborns may be more sensitive to methemoglobin-forming chemicals than adults. Because of the absence of specific quantitative data on sensitive human subpopulations and the fact that there are data suggesting greater susceptibility of infants, a default uncertainty factor of 10-fold was used for intraspecies extrapolation (NRC 1993). It is believed that an intraspecies uncertainty factor of 10 is protective of the general population including susceptible individuals. The default uncertainty factors of 10 for each of the interspecies and intraspecies variabilities are also supported by the small database of information and the lack of reliable human inhalation studies. The data were scaled across time using $C^1 \times t = k$ because of data indicating a linear relationship between concentration and exposure duration as related to methemoglobin formation.

The AEGL-2 was based on the same study with rats in which a concentration of 150 ppm for 8 h resulted in elevation of methemoglobin from a control value of 1.1% to 41%. This level of methemoglobin is associated with fatigue, lethargy, exertional dyspnea, and headache in humans and was considered the threshold for disabling effects. Since the same mode of action applies to AEGL-2 effects, the 150-ppm concentration was divided by a combined uncertainty factor of 100 and scaled across time using the same reasons and relationships as those used for the AEGL-1 above.

Data on concentrations of aniline inducing methemoglobin levels at the threshold for lethality were not available. Based on the fact that the relationship between the concentration of aniline and methemoglobin formation is linear, the dose-response curve from the study on which the AEGL-1 and AEGL-2 values were based was extrapolated to a concentration resulting in >70% formation of methemoglobin, the threshold for lethality. The concentration of 250 ppm for 8 h was chosen as the threshold for lethality, according to Kiese (1974) and Seger (1992). Since the same mode of action applies to AEGL-3 effects, the 250-ppm concentration was divided by a combined uncertainty factor of 100 and scaled across time using the same reasons and relationships as those used for the AEGL-1 above.

Several studies with rats support the AEGL-3 values. A 10-min exposure to aniline at 15,302 ppm resulted in no toxic effects, and a 4-h exposure at 359 ppm resulted in severe toxic effects but no deaths. Dividing these values by a total uncertainty factor of 100 and scaling across time using $C^1 \times t = k$ results in values similar to those derived from the Kim and Carlson (1986) study. Studies with repeated exposures of rats resulted in additional effects on the blood and spleen, but concentrations up to 87 ppm, 6 h/d, 5 d/w for 2 w were not disabling or life-threatening.

The derived AEGLs are listed in Table 1–1. Because aniline is absorbed through the skin in quantities sufficient to induce systemic toxicity, a skin notation was added to the summary table. The reported odor threshold for aniline ranges from 0.012 to 10 ppm. Therefore, the odor of aniline will be noticeable by most individuals at the AEGL-1 concentrations. The odor is somewhat pungent but not necessarily unpleasant.

1. INTRODUCTION

Aniline is an aromatic amine used in the manufacture of dyes, dye intermediates, rubber accelerators, and antioxidants. It has also been used as a solvent, in printing inks, and as an intermediate in the manufacture of pharmaceuticals, photographic developers, plastics, isocyanates, hydroquinones, herbicides, fungicides, and ion-exchange resins. It is produced commercially by catalytic vapor phase hydrogenation of nitrobenzene (Benya and Cornish 1994; HSDB 1996). Production of aniline oil was listed at approximately 1 billion pounds in 1993 (U.S. ITC 1994). Chemical and physical properties are listed in Table 1–2.

Aniline may be absorbed following inhalation, ingestion, and dermal exposures. The inhalation toxicity of aniline was studied in several animal species, but only one study that utilized multiple exposure concentrations for sublethal effects was located. Data from human studies lack specific details or exposures

TABLE 1–1 Summary of AEGL Values for Aniline[a]

Classification	30 min	1 h	4 h	8 h	Endpoint (Reference)
AEGL-1[b] (Nondisabling)	16 ppm (61 mg/m^3)	8.0 ppm (30 mg/m^3)	2.0 ppm (7.6 mg/m^3)	1.0 ppm (3.8 mg/m^3)	22% Methemoglobin—cyanosis (Kim and Carlson 1986)
AEGL-2 (Disabling)	24 ppm (91 mg/m^3)	12 ppm (46 mg/m^3)	3.0 ppm (11 mg/m^3)	1.5 ppm (5.7 mg/m^3)	41% Methemoglobin—lethargy (Kim and Carlson 1986)
AEGL-3 (Lethal)	40 ppm (152 mg/m^3)	20 ppm (76 mg/m^3)	5.0 ppm (19 mg/m^3)	2.5 ppm (9.5 mg/m^3)	>70% Methemoglobin—lethality (extrapolated from data of Kim and Carlson 1986)

[a]Cutaneous absorption of the neat material may occur, adding to the systemic toxicity.
[b]The aromatic, amine-like odor of aniline will be noticeable by most individuals at these concentrations.
Abbreviations: ppm, parts per million; mg/m^3, milligrams per cubic meter.

were oral or percutaneous to the liquid or an aniline dye. The primary effect of inhalation exposure to aniline vapor is the formation of methemoglobin in the RBCs. Hemolysis of the red cells and effects on the spleen occur following daily repeated or long-term exposures.

TABLE 1-2 Chemical and Physical Data

Parameter	Value	Reference
Synonyms	Benzenamine, aniline oil, phenylamine, aminobenzene, aminophen, arylamine	Budavari et al. 1996, Benya and Cornish 1994
Molecular formula	$C_{6H5}NH2$	Benya and Cornish 1994
Molecular weight	93.13	Budavari et al. 1996
CAS Registry No.	62–53–3	HSDB 1996
Physical description	Colorless oily liquid (freshly distilled); darkens on exposure to air and light	Budavari et al. 1996
Solubility in water	1 g in 28.6 mL	Budavari et al. 1996
Vapor pressure	15 mm Hg at 77°C 7.6 torr at 20°C 0.67 mm Hg at 25°C	Benya and Cornish 1994 ACGIH 1991 U.S. EPA 1987
Vapor density (air=1)	3.22	Benya and Cornish 1994
Density (water=1)	1.002 (20/4°C)	Benya and Cornish 1994
Melting point	–6.3°C	Benya and Cornish 1994
Boiling point	184–186°C	Budavari et al. 1996
Odor	aromatic amine-like pungent, oily	NIOSH 1997 U.S. EPA 1992
Odor threshold	0.012 to 10 ppm 0.5 ppm 1.0 ppm	U.S. EPA 1992 DOT 1985 Billings and Jones 1981
Conversion factors	1 ppm=3.8 mg/m^3 1 mg/m^3=0.26 ppm	ACGIH 1991

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No information on acute lethal concentrations for humans by the inhalation route was located. According to Bodansky (1951) and Kiese (1974), methemo

globin (the primary effect of inhalation exposure) levels above 85% may be lethal if treatment is not initiated. Seger (1992) cites a concentration of >70% as a potentially lethal level. Deaths of adults have occurred from ingestion, and infant deaths have occurred from absorption of aniline from diapers stenciled with ink containing aniline (Gosselin et al. 1984). Incidences of aniline intoxication in infants attributed to aniline dye through dermal exposure are numerous: (Graubarth et al. 1945; Kagan et al. 1949; Etteldorf 1951; Pickup and Eeles 1953; Ramsay and Harvey 1959; Smith 1992). In one study, most of the infants were visibly cyanotic and methemoglobin levels in these infants ranged from 30% to 60% (Etteldorf 1951). Complete recovery followed treatment with methylene blue. In a summary of these and several other reports, an overall infant mortality of 5–10% was reported (Gosselin et al. 1984).

2.2. Nonlethal Toxicity

The reported odor threshold for aniline ranges from 0.012 to 10 ppm (Table 1–2). Although the odor may be somewhat pungent, no adverse effects are predicted to occur at the odor threshold.

With increasing concentrations of aniline, exposure can cause headaches, methemoglobinemia, paresthesias, tremor, pain, narcosis/coma, cardiac arrhythmia, and possibly death (Benya and Cornish 1994). However, according to Bodansky (1951), Kiese (1974), and Seger (1992), the formation of methemoglobin concentrations of <15% are asymptomatic; methemoglobin levels exceeding 15% of the circulating blood pigment result in clinical cyanosis; and hypoxic symptoms including lethargy and semistupor are associated with serum levels of 55–60% or greater. Signs and symptoms associated with methemoglobin formation are summarized in Table 1–3.

In sampling data from 18 workplace sites provided by the Occupational Safety and Health Administration (OSHA 1997), measurable concentrations were present in 3 of 18 samples; these concentrations were 0.070, 0.14, and 0.177 ppm.

2.2.1. Experimental Studies

Two papers cited older data. However, symptoms at specific concentrations were not defined in the summary papers and details of the studies were not available. Flury and Zernik (1931) cited the following human data: a concentration of approximately 130 ppm was tolerated for 1/2 to 1 h without immediate or late sequalae and a concentration of 40–53 ppm was tolerated for 6 h without

distinct symptoms. Henderson and Haggard (1943) cited the following data: a concentration of 5 ppm was considered safe for daily exposure, concentrations of 7 to 53 ppm produced slight symptoms after several hours, and 100 to 160 ppm as the maximum concentration that could be inhaled for 1 h without serious disturbance. The statements by Henderson and Haggard were based on several studies including those of Flury and Zernik (1931).

TABLE 1–3 Signs and Symptoms Associated with Methemoglobin Concentrations in Humans

Methemoglobin Concentration (%)	Signs and Symptoms
1.1	Normal level
1–15	None
15–20	Clinical cyanosis (chocolate brown blood); no hypoxic symptoms
30	Fatigue; recovery without treatment
20–45	Anxiety, exertional dyspnea, weakness, fatigue, dizziness, lethargy, headache, syncope, tachycardia
45–55	Decreased level of consciousness
55–70, ~60	Hypoxic symptoms: semistupor, lethargy, seizures, coma, bradycardia, cardiac arrhythmias
>70	Heart failure from hypoxia, High incidence of mortality
>85	Lethal

Sources: Kiese 1974; Seger 1992.

2.2.2. Epidemiology Studies

No epidemiology studies in which exposure concentrations were measured were identified in the available literature.

2.2.3. Accidents

No accidental inhalation exposures to aniline in which concentrations were known were identified in the available literature. However, methemoglobin levels were measured after accidental exposures to liquid aniline or aromatic

nitro or amino compounds (Hamblin and Mangelsdorff 1938; Mangelsdorff 1956). In these occupational exposures, methemoglobin levels reached 50–72%; the subjects were cyanotic and complained of headache, dizziness, and weakness. In some cases, oxygen therapy was instituted and intravenous dextrose solutions were administered; in one case, methylene blue was administered intravenously. Regardless of whether or not treatment was given, the half-life of methemoglobin ranged between 3 and 10 h following cessation of exposure, and levels were below 10% in less than 20 h. No deaths occurred.

2.3. Developmental and Reproductive Effects

No developmental and reproductive toxicity data on humans concerning aniline were identified in the available literature.

2.4. Genotoxicity

In an in vitro assay with cultured human fibroblasts, aniline produced only marginal increases in sister chromatid exchanges at the highest dose tested, 10 mM; whereas two metabolites of aniline, 2-aminophenol and *N*-phenylhydroxylamine, doubled the frequency of sister chromatid exchanges at the highest tested nontoxic concentration, 0.1 mM (Wilmer et al. 1981).

2.5. Carcinogenicity

Historically, bladder tumors have been associated with exposures in the aniline dye industry. However, conclusive evidence for any one particular exposure could not be obtained in these studies since the workers were exposed to many chemicals within the same work area. For example, Case et al. (1954) investigated the incidence of bladder tumors among British workers in the chemical dye industry. In addition to aniline, the workers were exposed to other aromatic amines, including α- and β-naphthylamine, benzidine, and auramine. Although exposures could not be quantified, there was insufficient evidence to suggest that aniline was a cause of bladder cancers. More recent studies indicate that β-naphthylamine, 4-aminodiphenyl, 4-nitrodiphenyl, 4,4'-diaminodiphenyl, or *o*-toluidine may be involved in increased cancers in the dye industry (Ward et al. 1991; Benya and Cornish 1994).

On the basis of inadequate human data and sufficient animal data, U.S. EPA (1994) in their Integrated Risk Information System (IRIS) classified aniline as

B2, a probable human carcinogen. The International Agency for Research on Cancer has classified the evidence for carcinogenicity of aniline in humans as inadequate and in animals as limited (IARC 1987). Based on a high-dose feeding study with rats (NCI1978), the National Institute for Occupational Safety and Health (NIOSH 1997) considers aniline and its homologues occupational carcinogens; however, OSHA (1995) has not classified aniline as an occupational carcinogen. ACGIH (1999) categorized aniline as A3, a confirmed animal carcinogen with unknown relevance to humans. Animal feeding studies (NCI 1978; CIIT 1982) indicate that aniline may be a very weak carcinogen in male and female rats (i.e., 3,000 and 2,000 ppm dietary threshold in the two studies, respectively) but not in male or female mice. Animal studies are summarized in Section 3.5 and a quantitative cancer risk assessment is performed in Appendix A.

2.6. Summary

Human toxicity data are limited to secondary citations. Because these citations provided no experimental details, they cannot be considered reliable. Deaths have occurred from aniline ingestion and skin absorption, but doses were unknown. Reviews of the older literature indicate that a concentration of 5 ppm was considered safe for daily exposures, concentrations of 7 to 53 ppm produced slight symptoms after several hours, a concentration of 40 to 53 ppm was tolerated for 6 h without distinct symptoms, a concentration of 130 ppm may be tolerated for 0.5 to 1 h without immediate or late sequalae, and 100 to 160 ppm was the maximum concentration that could be inhaled for 1 h without serious disturbance. In studies of accidents with unknown exposure concentrations, methemoglobin levels of up to 72% were measured. Recoveries occurred with a minimum of medical intervention following cessation of exposure.

There is no conclusive evidence from studies of cancers in dye workers that aniline is the causative agent. Two known metabolites of aniline induced sister chromatid exchange in the single study with cultured human fibroblasts. No studies on possible reproductive or developmental effects in humans associated with aniline exposures were located.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Acute lethality data are summarized in Table 1–4 and discussed below.

TABLE 1–4 Summary of Acute Lethal Inhalation Data in Laboratory Animalsa

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Rat	839[b]	4 h	LC_{50}	E.I.du Pont de Nemours 1982a
Rat	478[c]	4 h	LC_{50}	E.I.du Pont de Nemours 1982a
Rat	250[d]	4 h	Approximate LC_{50}	Carpenter et al. 1949
Rat	550	8 h	82% mortality	Comstock and Oberst 1952, as cited in Oberst et al. 1956
Mouse	~175	7 h	LC_{50}	von Oettingen et al. 1947

[a]LC_{50} (lethal concentration for 50% of the animals) values were obtained 14 d post-exposure (Carpenter et al. 1949; E.I.du Pont de Nemours 1982a).
[b]Head-only exposure.
[c]Whole-body exposure.
[d]Concentrations not measured.

3.1.1. Rats

Six Sherman rats (gender not specified) were exposed to graded concentrations of aniline vapor for 4 h and observed for 14 d post-exposure (Carpenter et al. 1949). The concentration that killed approximately half of the rats (exact number not stated) was 250 ppm. Concentrations were based upon empirical calculation and were not measured. An 8-h exposure to 550 ppm killed 82% of an unreported number of rats (Comstock and Oberst 1952, as cited in Oberst et al. 1956). Methemoglobinemia was the only pathologic change cited; no further details were reported.

Groups of 10 8-w-old Crl:CD rats were exposed to various concentrations of aniline vapor/aerosol for 4 h (E.I.du Pont de Nemours 1982a). The atmospheres were generated by passing nitrogen over liquid aniline in a heated flask. The vapor/aerosol was diluted with humidified (45%) and oxygen-enriched (21%) air; the temperature of the exposure chamber was maintained at 27°C. Air samples were analyzed by gas chromatography. Two routes of exposure, head-only, using wire mesh restrainers, and whole-body, were compared to assess the significance of skin absorption and restraint on mortality. LC_{50} (lethal concentration for 50% of the animals) values for head-only and whole-body exposures were 839 ppm (95% confidence limit (CL), 802–882 ppm) and

478 ppm (95% CL, 442–540 ppm), respectively. The lower value for whole-body exposure suggests significant dermal absorption. Mortality at each exposure concentration is listed in Table 1–5.

TABLE 1–5 Mortality of Rats Exposed to Aniline via Head-Only or Whole-Body Exposures for 4 h

Head-Only Exposures		Whole-Body Exposures	
Concentration (ppm)	Mortality	Concentration	Mortality
681	0/10	359	0/10
790	2/10	400	2/10
834	5/10	453	4/10
896	8/10	530	7/10
		786	10/10

Source: E.I.du Pont de Nemours 1982a.

All deaths occurred by d 4 post-exposure. "Signs observed during exposures by both routes were similar and included cyanosis, prostration, tremors, pallor, clear to reddish-brown eye, mouth, and nasal discharges, corneal clouding, tachypnea, and hair loss" (E.I.du Pont de Nemours 1982a). The severity of the signs was generally dose-related. An initial weight loss at 24–72 h post-exposure was followed by a normal weight gain.

3.1.2. Mice

A 7-h LC_{50} for the mouse of approximately 175 ppm was reported by von Oettingen et al. (1947). Deaths occurred at all tested concentrations, which ranged from approximately 115 to 390 ppm; however, analytical determinations (both colorimetric and spectrophotometric) of calculated concentrations showed substantial variations, ranging from 49% to 81% of calculated concentrations. The discrepancy between calculated and analyzed values was probably due to condensation of aniline on the sides of the exposure chamber. The authors stated that the actual lethal values probably were within the range of the calculated and analyzed concentrations. In that case, the 7-h LC_{50} value for the mouse lies within the range of 175 to 288 ppm. Mice exposed to aniline became restless and cyanotic (ears and tails), and their eyes showed signs of irritation. Tremors, followed by convulsions and then depression, preceded death. Histologic examinations revealed hepatic fatty infiltrations.

3.2. Nonlethal Toxicity

3.2.1. Dogs

Except for cyanosis of the mucous membranes, dogs failed to show any signs of methemoglobinemia at methemoglobin concentrations of less than about 60%. At levels of 60–70% the predominant signs were salivation, ataxia and vomiting. Ataxia and vomiting occurred at 71–80% and loss of consciousness occurred at 81–90% (Bodansky 1951).

Oberst et al. (1956) exposed two male beagle dogs to aniline at 5 ppm for 6 h/d, 5 d/w for up to 26 w. Prior to daily exposure, the dogs were exercised on a treadmill for 5 min. Blood and urine analyses were performed and body weights were measured pre-exposure and weekly during exposure. Animals were observed daily for toxic signs. Aside from an increase in free chromogen content of the urine, there were no signs of exposure. Pathologic examinations at sacrifice revealed no adverse effects.

3.2.2. Rats

Kakkar et al. (1992) exposed six male Wistar rats to a single nominal concentration of 15,302 ppm for 10 min; the animals were sacrificed 24 h later. Earlier studies (not presented) had shown this to be the highest concentration tolerated without any mortality or acute toxicity. Biochemical changes in the brains of these rats suggested impairment of antioxidant defenses. No other signs of toxicity were reported. The exposure was performed under static conditions, and the measurement method was not described.

As discussed in Section 3.1.1, groups of 10 8-w-old Crl:CD rats were exposed to aniline vapor/aerosol at concentrations of 359, 400, 453, 530, or 786 ppm for 4 h (E.I.du Pont de Nemours 1982a). No deaths occurred at the lowest concentration. Signs at 359 ppm included cyanosis, tremors, lacrimation, salivation, semi-prostration, an initial body-weight loss followed by normal gain, and a reddish-brown perineal area.

Groups of five adult male Sprague-Dawley rats (200–250 g) were exposed to reagent grade aniline at concentrations of 0, 10, 30, 50, 100, or 150 ppm for 8 h/d for 5 d or 12 h/d for 4 d (Kim and Carlson 1986). Exposure concentrations were achieved by passing air through a bottle containing aniline; concentrations were monitored continuously using a gas chromotograph. Blood samples were taken for methemoglobin measurements prior to and following each daily exposure. The mean pre-exposure (control) methemoglobin level was approximately 1.1% (range of 0.4% to 1.7%). All results were presented

graphically; thus, the levels of methemoglobin following 8 or 12 h of exposure on d 1, presented in Table 1–6, are estimates read from the graphs.

Statistical analyses were not performed on the data; however, it can be seen from the data in Table 1–6 that the methemoglobin levels following exposures to 0, 10, and 30 ppm for 8 h are not different. An additional 4 h of exposure (12 h of exposure) at the higher concentrations resulted in only slightly higher methemoglobin levels.

In rats exposed at concentrations of 30 or 50 ppm for 8 h for up to 5 d, methemoglobin levels returned to control values after overnight recovery (10 ppm was identified by the authors as a no-effect level), whereas in the groups exposed at 150 ppm for 8 h or 50 or 150 ppm for 12 h for a maximum of 4 d, methemoglobin levels increased with increasing days of exposure. Hematocrit levels, measured 1 w after the start of exposure, were reduced at concentrations of ≥30 ppm. Signs of aniline intoxication either did not occur or were not reported.

Kim and Carlson (1986) also studied the formation and disappearance of methemoglobin from rat blood over time. The methemoglobin level in groups of five rats was measured at 3, 6, 8, 10, and 12 h during exposure to 100 ppm (Figure 1–1). Following exposure for 8 or 12 h, there was no difference in the maximum methemoglobin level (i.e., the increase with time begins tapering off between 6 and 8 h and reaches an asymptote at 8 h). In addition, there were no differences in the peak aniline levels in blood and fat or the rate of aniline elimination from fat and blood. The methemoglobin levels read from the original graph are approximately 10.5%, 18%, 22%, 22%, and 23% at the 3-, 6-, 8-, 10-, and 12-h exposure durations, respectively. Following 8 or 12 h of exposure, recovery was rapid as shown in the graph (Figure 1–1).

TABLE 1–6 Methemoglobin Levels in Rats Following 8 or 12 h of Exposure to Aniline

Concentration (ppm)	Methemoglobin % at 8 h[a]	Methemoglobin % at 12 h[a]
0	1.1 (0.4–1.7)	1.1 (0.4–1.7)
10	0.4–1.7	0.4–1.7
30	1.6	3.3
50	4.7	6.5
100	22	23
150	41	46

[a]Values shown represent estimates from graphic representations of the data.
Source: Kim and Carlson 1986.

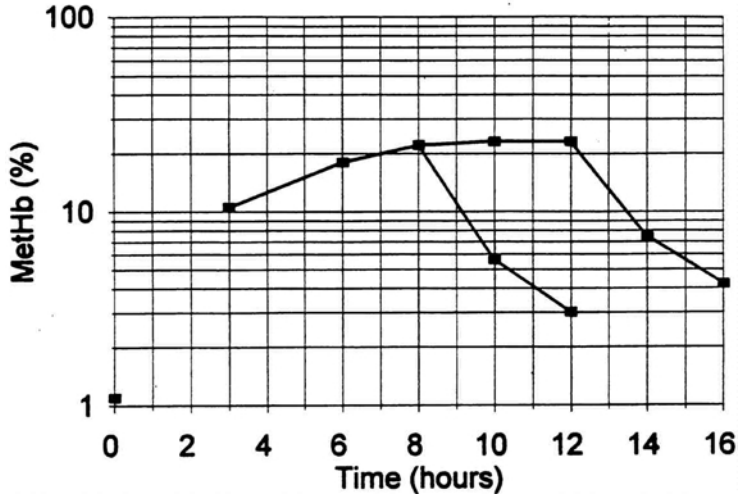

FIGURE 1–1 Formation and disappearance of methemoglobin from blood of rats exposed at 100 ppm for 8 or 12 h. Source: Modified from Kim and Carlson 1986.

In a similar study, groups of 14 male rats were exposed to aniline at concentrations of 0, 10, 30, or 90 ppm for 3, 6, or 12 h daily, 5 d/w for 2 w (Burgess et al. 1984). Methemoglobin levels were measured daily (not reported), and hematology and pathology were evaluated after the tenth exposure and after 14 d of recovery. Ten ppm was a no-effect level for all exposure durations. At 30 and 90 ppm, methemoglobin levels plateaued after four exposures (level not stated), remained at a steady-state level to the tenth day of exposure, and decreased to normal 14 d after exposure. Hemolysis (decreased erythrocyte counts, splenic congestion, and hemosiderin deposition) was seen at 30 and 90 ppm at all exposure durations after the tenth exposure (time of onset could not be determined). Hemolysis was accompanied by compensatory increases in mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCHb). After the 14-d recovery period, spleens were nearly normal, but MCV and MCHb remained elevated in the 90-ppm exposure group. The authors noted that effects were predominantly concentration, not time, dependent. Body weights and clinical signs were unaffected. The study was reported in an abstract, and no further details were available.

Groups of 16 male Crl:CD rats were placed in restraints and exposed head-

only to aniline vapor at 17, 45, or 87 ppm for 6 h/d, 5 d/w for 2 w (E.I.du Pont de Nemours 1982b; O'Neal 1982). Concentrations were generated and analyzed as in the E.I.du Pont de Nemours 1982a study. Clinical and histopathologic evaluations were made after 2 w. The 17-ppm concentration for 2 w was considered a minimal effect level —no-observed-adverse-effect level (LOAEL) —on hematologic parameters and histopathology of the spleen. Cyanosis occurred only in the group exposed at 87 ppm for 2 w.

Further details of the above study were discussed in U.S. EPA (1994). After the last exposure, methemoglobin levels were elevated in a dose-dependent manner: 17 ppm, 0% to 2.9% (no different from controls); 45 ppm, 2.2% to 5.4%; and 87 ppm, 4.2% to 23%. The animals exposed at 45 and 87 ppm were anemic with decreases in RBC counts, hemoglobin content, MCHb concentration, and hematocrit, and accompanying increases in erythropoietin foci, reticuloendothelial cell hypertrophy, and hemosiderin deposition in the spleen. The animals in the 87-ppm exposure group were judged cyanotic. In the 17-ppm exposure group, effects were limited to mild splenic congestion.

Oberst et al. (1956) exposed nine male Wistar rats to aniline at 5 ppm for 6 h/d, 5 d/w for up to 26 w. Exposed rats developed a mild hemoglobinemia (0.6%) with some blueness of the skin during w 23 of exposure. Based on the slight increase of methemoglobin content and the absence of spleen toxicity, U.S. EPA (1994) considered this concentration a free-standing no-observed-adverse-effect level (NOAEL).

Acute nonlethal studies using the rat are summarized in Table 1–7.

TABLE 1–7 Summary of Acute Sublethal Inhalation Data in Rats

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Rat	15,302	10 min	No deaths; oxidative changes in brain	Kakkar et al. 1992
Rat	359	4 h	No deaths; cyanosis, tremors, lacrimation, salivation, semi-prostration, initial weight loss followed by normal gain, reddish-brown perineal area	E.I.du Pont de Nemours 1982a
Rat	150	8 h	No deaths; 41% methemoglobin	Kim and Carlson 1986
Rat	150	12 h	No deaths; 46% methemoglobin	Kim and Carlson 1986

3.2.3. Mice

Oberst et al. (1956) exposed 20 female mice to aniline at 5 ppm for 6 h/d, 5 d/w for 20 w. Blood and urine analyses conducted prior to and during exposure and pathologic examinations made at sacrifice revealed no effects.

3.2.4 Guinea pigs

Oberst et al. (1956) exposed 10 guinea pigs to ainline at 5 ppm for 6 h/d, 5 d/w for 20 w. Blood and urine analyses conducted prior to and during exposure and pathologic examinations made at sacrifice revealed no effects.

3.3. Developmental and Reproductive Effects

No studies addressing developmental or reproductive effects following acute inhalation exposure to aniline were located. However, because effects on development and reproduction arise after systemic uptake, oral administration of aniline can be considered for evaluating potential developmental and reproductive toxicity. Aniline (administered as aniline hydrochloride) readily crosses the placental barrier in rodents (Price et al. 1985).

Price et al. (1985) administered aniline hydrochloride by gavage at doses of 10, 30, or 100 milligrams per kilogram per day (mg/kg/d) to timed-pregnant Fischer 344 (F344) rats. Intubation was on gestation d 7 through 20 (group 1) or gestation d 7 through parturition (group 2). Both a reference teratogen (hydroxyurea) and vehicle control group were included in the study protocol. All exposed females survived to scheduled termination, although signs of aniline toxicity—decreased body-weight gain, methemoglobinemia, increased relative spleen weight, decreased erythrocyte count, and hematologic changes indicative of increased hematopoietic activity—were evident in dams exposed at 100 mg/kg/d. Effects on the hematologic profile were not described for the lower doses. In group 1, maternal absolute weight gain was decreased only in the high-dose group, whereas maternal relative spleen weights were increased in all dose groups (in a dose-dependent manner); the other factors were examined only in the 100-mg/kg/d group. On d 20, fetuses from dams in group 1 exposed at 100 mg/kg/d exhibited increased relative liver weights and enhanced hematopoietic activity, but there was no evidence of embryolethality or teratogenicity. Effects in pups observed from post-natal d 0 to 60 (group 2) included transient decreased body weights (dose-related; significant only in the 100-mg/kg/d group), elevated relative liver weights (not dose related), and elevated relative spleen weights (dose-related trend, only on post-natal d 25). A statistically nonsignificant, but exposure-related, increase in the number of exposed

litters with one or more neonatal deaths was observed; the deaths were observed in conjunction with mild but persistent signs of maternal toxicity through postnatal d 30. No evidence of toxicity was observed in pups surviving to post-natal d 60. Price et al. (1985) concluded that doses of aniline that were maternally toxic but nonlethal did not present a selective risk for developmental toxicity to the fetus in the F344 rat.

3.4. Genotoxicity

Aniline and its hydrochloride were tested in standard mutagenicity, cell-transforming, and DNA-damaging tests with mixed results. Results of reverse mutagen assays using *Salmonella typhimurium* both in the presence and in the absence of an activating system and at doses of up to 2,500 microgram (μg) per plate in studies by McCann et al. (1975), Simon (1979a), and Haworth et al. (1983) were generally negative (U.S. EPA 1994). Positive responses were obtained in the two L5178Y mouse lymphoma cell mutation assays (Amacher et al. 1980; McGregor et al. 1991). Aniline was negative with and without metabolic activation in a mitotic recombination test with *Saccharomyces cerevisiae* (Simon 1979b).

An increased frequency of sister chromatid exchanges was obtained in vivo in bone-marrow cells of male Swiss mice at intraperitoneal doses of 210 and 420 mg/kg (Parodi et al. 1982, 1983) and in vitro Chinese hamster cells (Abe and Sasaki 1977), although in the latter study, no chromosomal aberrations were observed.

Aniline gave positive responses in the mouse bone-marrow micronucleus assay when administered via ingestion or intraperitoneal injection (Ashby et al. 1991; Westmoreland and Gatehouse 1991). However, the positive responses occurred only at a specific time after administration and at what the authors considered high doses (1,000 mg/kg orally and 300 mg/kg intraperitoneally).

Aniline transformed the Balb/3T3 mouse cell line at doses of 0.8 to 100 μg/mL (without a clear dose-response effect), but not the Syrian hamster embryo cells (Dunkel et al. 1981). Results were negative in DNA damage assays in *Escherichia coli* (Mamber et al. 1983) and *Bacillus subtilis* (McCarroll et al. 1981).

3.5. Carcinogenicity

The National Cancer Institute conducted a bioassay of aniline hydrochloride for possible carcinogenicity using F344 rats and $B6C3F_1$ mice (NCI 1978). Aniline hydrochloride was administered in the feed to groups of approximately

50 male and 50 female animals of each species at concentrations of 0.3% (3,000 ppm) and 0.6% (6,000 ppm) of the diet for rats and 0.6% (6,000 ppm) and 1.2% (12,000 ppm) for mice. Groups of 25 or 50 animals were used as concurrent controls. The exposure duration was 103 w; this was followed by a 5-w observation period. Hemangiosarcomas of the spleen and the combined incidence of fibrosarcomas and sarcomas (NOS (not otherwise specified)) of the spleen were each elevated ($p<0.05$) in male rats. The combined incidence of fibrosarcomas and sarcomas NOS of multiple body organs was also significant in male rats. Incidences in the 0, 3,000- and 6,000-ppm dose groups were 0/24, 1/50, and 7/50, respectively. A compound-related (but statistically nonsignificant) increase in fibrosarcomas or sarcomas NOS of either the spleen alone or multiple organs of the body cavity was observed in female rats. These incidences were statistically significant and associated with increased dietary concentrations of aniline hydrochloride. These was no evidence of compound-related carcinogenicity in mice of either sex. There were no effects on survival for either species.

In the above study, the origin of the tumors was the spleen, a rare site for F344 rats. No bladder tumors were observed. The sequence of pathologic events for this type of tumor is methemoglobinemia, splenic hemosiderosis, splenic fibrosis, splenic sarcoma, and metastatic sarcoma (Goodman et al. 1984). This sequence of events is unlikely to occur until the capacity of the erythrocyte to cope with the insult from continuous high-dose aniline exposure is exceeded (Bus and Popp 1987). Although this sequence of events is unlikely to occur with a single acute exposure, Khan et al. (1997) observed changes in the spleen of rats, including congestion of splenic blood vessels, marked expansion of red pulp, splenic weight change, increased lipid peroxidation, and malondialdehyde-protein adducts 24 h after a single high-dose oral exposure of aniline hydrochloride at 259 mg/kg.

In a second carcinogenicity study, aniline hydrochloride was administered in the diet to CD-F (F344) rats (130/sex/group) at levels of 0, 200, 600, or 2,000 ppm (CIIT 1982). There was an increased incidence of primary splenic sarcomas in male rats in the high-dose group (incidence of 31/90 compared with incidences of 0/64, 0/90, and 1/90 in the 0-, 200-, and 600-ppm groups, respectively). Stromal hyperplasia and fibrosis of the splenic red pulp also occurred in males in the high-dose group and, to a lesser extent, in females in the high-dose group. U.S. EPA (1994) notes that the stromal hyperplasia and fibrosis of the spleen may represent a precursor lesion of sarcoma.

On the basis of induction of tumors of the spleen and the body cavity in two studies with rats, U.S. EPA (1994) in their IRIS document classified aniline as B_2, a probable human carcinogen. Evidence is inadequate in humans and

sufficient in animals. Although aniline is a relatively weak carcinogen, a quantitative cancer risk assessment was performed to demonstrate that aniline does not pose a significant cancer risk at the calculated AEGLs (Appendix A).

3.6. Summary

The primary consequence of acute inhalation exposure to aniline is formation of methemoglobin. In rats exposed to aniline, formation of methemoglobin occurred rapidly after exposure, reaching a steady-state in 6 to 8 h. Methemoglobin was removed from the blood with a measurable half-life following termination of exposure. The only reported effect of 8-h exposures of rats at 30, 50, 100, or 150 ppm was the induction of methemoglobin at levels of 1.6%, 4.7%, 22%, and 41%, respectively. The concentration of 30 ppm appears to be a threshold for methemoglobin formation in the rat. No deaths occurred from a 4-h exposure at 359 ppm or a 10-min exposure at 15,302 ppm. Aniline was not a developmental toxicant at doses that were maternally toxic. No information on the reproductive toxicity of aniline was located. Results of genotoxicity tests were mixed or equivocal, most mutagenicity studies being negative. In a 2-y feeding study, daily ingestion of aniline hydrochloride produced increased sarcomas of the spleen in male and female rats but not in male or female mice. The sarcomas were of a rare type and appeared to be related to chronic administration of aniline.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Aniline is lipophilic (pK_a of 4.6) and is expected to be rapidly and completely absorbed in the small intestine (Kao et al. 1978). No information on relative bioavailability following inhalation exposure was located, but as indicated by methemoglobin formation during inhalation experiments, systemic absorption by both the inhalation and the percutaneous routes is extensive. Percutaneous absorption of aniline in hairless mice was 4.7% of the nominal applied doses (Susten et al. 1990).

Aromatic amines are initially metabolized by aromatic and *N*-hydroxylation (oxidation reactions) and *N*-acetylation. Following aromatic ring hydroxylation, the ring structure may be further conjugated with glucuronic acid or sulfate (Parkinson 1996). *N*-hydroxylation results in the potential methemoglobin-generating metabolite, phenylhydroxylamine.

Aniline is rapidly and extensively metabolized following oral administration. In the pig and sheep, approximately 30% of a 50-mg/kg dose of ^{14}C-labeled aniline was excreted in the urine, as measured by ^{14}C activity, within 3 h after administration, whereas approximately 50% of the dose was excreted in rats. Within 24 h, more than half the administered dose was excreted by pigs and sheep and 96% of the dose was excreted by rats. Fecal radioactivity was low. *N*-acetylated metabolites accounted for most of the excretion—*N*-acetyl-*p*-aminophenyl glucuronide being the primary metabolite in sheep and pig urine and *N*-acetyl-*p*-aminophenyl sulfate being the primary metabolite in the rat (Kao et al. 1978). Biologic monitoring of workers exposed to aniline showed that *p*-aminophenol constituted 15–55% of the parent compound in the urine; the *o*- and *m*-isomers were also formed (Piotrowski 1984).

4.2. Mechanism of Toxicity

Many of the aromatic amines have the ability to convert the ferrous (Fe^{+2}) iron in hemoglobin to the oxidized ferric form (Fe^{+3}), resulting in the formation of methemoglobin. Methemoglobin is unable to transport oxygen, resulting in signs and symptoms of oxygen deficiency. Aniline does not readily oxidize hemoglobin in vitro; it must be metabolized to an active form to induce methemoglobinemia (Smith 1996). Phenylhydroxylamine has been identified as the potential active metabolite, because it produces methemoglobin following administration to dogs (Kiese 1974) and in vitro (Jenkins et al. 1972). Recycling of phenylhydroxylamine may occur: following the reaction of phenylhydroxylamine and hemoglobin to form methemoglobin and nitrosobenzene, nitrosobenzene may be reduced by cell processes to regenerate phenylhydroxylamine. This process would account for the greater potency of phenylhydroxylamine compared with nitrite as a methemoglobin-generating chemical.

In an in vitro study in which phenylhydroxylamine (0.5 milligram per milliliter (mg/mL)) was added to samples of rat and human blood, blood from the human subjects produced less methemoglobin in the human subjects than in the rats (approximately 35% in human blood and 60% in rat blood) (Jenkins et al. 1972). There was no more variation in methemoglobin levels among the cells from different humans than among the cells from different rats.

4.3. Structure-Activity Relationships

As previously noted, many aromatic amines and their metabolites and derivatives are methemoglobin-generating chemicals (Smith 1996).

4.4. Other Relevant Information

In the absence of a known chemical condition such as hemoglobin M, elevated levels of methemoglobin are impossible to maintain without constant infusion of a methemoglobin-inducing chemical. Hemoglobin autoxidation occurs spontaneously in the presence of oxygen and is probably responsible for the low percent (<2%) of methemoglobin normally found in human blood and in blood of most other mammals (Smith 1996). A variety of intraerythrocytic mechanisms reduce methemoglobin to hemoglobin, the most important being methemoglobin reductase, which accounts for 95% of the reducing activity.

4.4.1. Susceptible Subpopulations

Infants are more sensitive to methemoglobin-generating chemicals than adults, as they have reduced levels of nicotine adenine dinucleotide (NADH, the cofactor (electron donor) for methemoglobin reductase) and a high concentration of fetal hemoglobin in their erythrocytes (fetal hemoglobin is more susceptible to oxidation than adult hemoglobin) (Seger 1992). NADH lacks full activity until infants are 4 mon of age. Human fetal livers are weakly capable of hydroxylating aniline by about 6 w after conception (Pelkonen and Karki 1973). Instances of cyanosis or methemoglobinemia in infants due to percutaneous absorption of aniline dyes from ink were reported in Section 2.1

In rare instances, humans may suffer from hereditary deficiencies of enzymes responsible for reducing methemoglobin. "Rare individuals" with an inherited deficiency of NADH-methemoglobin reductase have 10–50% of their circulating blood pigment in the form of methemoglobin. The effect is primarily cosmetic as these individuals have a compensatory polycythemia, although symptoms may occur during exercise. Other individuals may have a deficiency of erythrocyte NADPH-glucose-6-phosphate dehydrogenase, an enzyme responsible, via the pentose phosphate shunt, for generating an alternate source of energy for the cell; these individuals do not have elevated levels of methemoglobin, as this is a minor methemoglobin-reducing system (Kiese 1974; Smith 1996; Seger 1992). Individuals with hemoglobin M, caused by a substitution of amino acids on the hemoglobin molecule, maintain methemoglobin levels of 25–30% and are clinically cyanotic (Seger 1992).

4.4.2. Species Differences

There are large species differences in the response of hemoglobin to the administration of aniline. Differences appear to be related to the rate of metabo

lism and formation of specific metabolites as well as to the level of enzymes responsible for reducing methemoglobin (Kiese 1974; Calabrese 1991). Spicer (1950) compared the methemoglobin response in dogs, cats, and rabbits injected intravenously with aniline. Injections of 15 mg/kg of body weight produced an average methemoglobin response of 28.3% in dogs and 56.4% in cats, whereas an injection of 30 mg/kg produced a response of only 3.2% in rabbits. However, on the basis of blood volume, the response in the dog and cat were more similar, 25% and 32%, respectively, following injection of aniline at 1.1 mg/g of hemoglobin. Jenkins et al. (1972) found that an intravenous injection of 20 mg/kg to rats induced a methemoglobin level of 10.9%. For two other methemoglobin-forming chemicals, acetanilide and acetophenetidine, humans were half as susceptible as the cat and one-tenth as susceptible as the rat (Calabrese 1991).

At the low concentration used in the Oberst et al (1956) study with dogs, rats, mice, and guinea pigs (5 ppm for 6 h/d, 5 d/w), no well-defined clinical signs of intoxication occurred in any species; rats showed a slight deviation from pre-exposure methemoglobin levels (maximum, 0.6%), and dogs had an increase of chromogen in their urine, although circulating methemoglobin was not elevated. No clear species differences could be distinguished among these minor effects.

A single oral administration of aniline hydrochloride to male Sprague-Dawley rats at 2 millimole per kilogram (mmole/kg) (259 mg/kg; presumably 186 mg/kg of aniline) resulted in a peak methemoglobin level of 37% at 0.5 h following administration (Khan et al. 1997). A single oral dose of 100 mg of aniline hydrochloride (presumably about 1.0 mg of aniline/kg of body weight) to two human subjects resulted in an increase in methemoglobin content to 11% (Brodie and Axelrod 1948). In another study, oral administration of aniline at 40 mg/kg to two rats produced a mean maximum increase of 16.6% in methemoglobin within 1 to 4 h. Administration of 65 mg (presumably about 0.9 mg/kg) produced a maximum increase of 16.1% in an adult male volunteer (Jenkins et al. 1972). The maximum level in the volunteer was reached 2 h after administration and returned to normal 1 h later. The no-effect dose in 20 male and female volunteers in this study was 15 mg (0.2 mg/kg). The 20 volunteers were given an oral dose mid-morning (10 a.m.) of 5, 15, and 25 mg on successive mornings followed by treatment of some of these volunteers with 35, 45, 55, and 65 mg, whereas the rats, which were fed ad libitum, were administered a single treatment by gastric intubation. It should be noted that an intravenous dose of 40 mg/kg to rats produced a lower increase in methemoglobin (11.7%) than the oral dose (16.6%) and that the increase in methemoglobin formation in rats plateaued between oral doses of 40 and 300 mg/kg. The authors noted that the greater sensitivity may be due to differences in the extent to which aniline

is metabolized or to differences in the activities of enzymes that promote the reduction of methemoglobin.

Mier (1988) reported on the ingestion of aniline by a 4.5-y-old child weighing 16 kg. Ingestion of approximately 1 teaspoon (approximately 0.3125 mg/kg) produced a methemoglobin level of 68% by 6 h after ingestion. At this time, treatment consisted of intravenous methylene blue to which she was poorly responsive followed by blood exchange 13 h after ingestion.

Smith (1996) summarized data on the spontaneous methemoglobin reductase activity of mammalian erythrocytes. Using nitrated RBCs with glucose as a substrate, the data reflect the ratio of the activity of the species to the activity in human RBCs. Activity in rat cells and human cells ranged from 1.3 to 5.0. Activity in cells of the cat and dog was similar to that in human cells, and that of the rabbit was 3.3 to 7.5 times greater. Most studies show that the spontaneous methemoglobin reductase activity of human erythrocytes is within an order of magnitude of that of other mammals (Smith 1996).

Differential spontaneous methemoglobin reductase activity among species is not the sole determining factor for interspecies differences. The inherent sensitivity of the hemoglobin molecule to oxidation; the presence of other reducing agents, such as reduced glutathione, cysteine, and ascorbic acid; and the extent to which the methemoglobin-forming metabolite is formed and its biologic half-life are interacting factors (Calabrese 1991).

4.4.3. Concentration-Exposure Duration Relationship

No single study clearly addressed various exposure durations and concentrations or their relationship. However, the relationship between concentration of aniline and methemoglobin formation at a fixed exposure duration (8 h) is linear (Table 1–6), and although the data are limited, methemoglobin formation increased by less than a factor of 2, i.e., was linear when comparing the 3- and 6-h exposure durations at a constant concentration of 100 ppm before reaching an asymptote at 8 h (Figure 1–1). Based on the linear relationship between concentration and methemoglobin formation in the Kim and Carlson (1986) study, a value of n=1 for scaling across time was selected ($C^1 \times t = k$) for AEGL development.

As noted, during exposure to a constant concentration, the level of methemoglobin does not approach equilibrium until 6–8 h after initiation of exposure (Figure 1–1). Therefore, methemoglobin levels at the shorter exposure durations are lower than those at 8 h (e.g., the level is 10.5% at 3 h for a constant exposure to 100 ppm), and any effect used as an endpoint at 8 h may not be present at the shorter exposure duration. Because of the 6–8 h lag time before

the methemoglobin plateau (and consequential effect) is reached, the value of n=1 for scaling is considered appropriate, and a more conservative value for scaling to the shorter time periods is unnecessary.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Henderson and Haggard (1943), in citing older reports, listed 5 ppm as a maximum concentration considered safe for daily exposures but did not give the basis for their statement. No additional human data are available for the derivation of AEGL-1 values for aniline.

5.2. Animal Data Relevant to AEGL-1

Kim and Carlson (1986) exposed animals to several concentrations within the time periods relevant to development of the AEGLs. The authors also followed the increase in methemoglobin (the primary effect of aniline exposure) over time during exposure to a single concentration. Their study determined that a single 8-h exposure to a concentration of 50 ppm was a LOAEL for generation of methemoglobin in the rat (4.7%) but a NOAEL for any clinical effects. Their study also determined that a concentration of 100 ppm for 8 h resulted in a methemoglobin level of 22%. In humans, this level is characterized by clinical cyanosis but no evidence for hypoxia. Furthermore, this level is not reached in rats until completion of a full 8 h of exposure. In the study by Burgess et al. (1984), clinical signs were unaffected by exposure at 90 ppm for up to 12 h daily, 5 d/w for 2 w. Details of the study were not reported. The study by E.I. du Pont de Nemours (1982b) used head-only exposures of rats; whole-body exposures are considered more relevant to AEGL development, inasmuch as head-only exposures do not account for potential percutaneous absorption.

5.3. Derivation of AEGL-1

The concentration of 100 ppm for 8 h in the study by Kim and Carlson (1986) was used as the basis for the AEGL-1. This exposure results in a methemoglobin level of 22% but no hypoxic signs in rats. A review of the literature revealed that methemoglobin levels of 15–20% in humans results in clinical cyanosis, but no sign of clinical hypoxia (Kiese 1974; Seger 1992). Although inhalation data for comparison purposes are not available, oral

ingestion data suggest that humans may be considerably more sensitive to methemoglobin-forming chemicals than rats. Oral administration of aniline at 40 mg/kg to rats produced a maximum increase of 16.6% in methemoglobin, whereas oral administration of aniline at 0.9 mg/kg to a human volunteer produced a maximum increase of 16.1%. A 10-fold uncertainty factor is generally applied when extrapolating from valid results of studies on experimental animals to humans (NRC 1993). Thus, an uncertainty factor of 10 was used for interspecies extrapolation. Differences in sensitivity to aniline among human subpopulations are known to occur, but the extent of the differences in the general population (excluding rare inherited disorders) is unknown. Infants are more sensitive to methemoglobin-generating chemicals than adults as they have reduced levels of nicotine adenine dinucleotide (NADH, the cofactor (electron donor) for methemoglobin reductase) and a high concentration of fetal hemoglobin in their erythrocytes (fetal hemoglobin is more oxidizable than adult hemoglobin) (Seger 1992). When quantitative data on a sensitive subpopulation are lacking, a 10-fold uncertainty factor is generally applied to account for the variation in sensitivity in the human population (NRC 1993). Thus, an intraspecies uncertainty factor of 10 was applied to account for the difference in sensitivity between infants and adults. It is believed that an intraspecies uncertainty factor of 10 is protective of infants. The uncertainty factors of 10 for each of the interspecies and intraspecies variabilities are dictated by the small database and the lack of reliable human inhalation studies. The data were scaled across time using $C^1 \times t = k$ and k=480 ppm·min. (The relationship between concentration of aniline and methemoglobin formation at a fixed time (8 h) is linear.) Although an n value of 1 is not the most conservative when scaling to shorter time periods, it is believed that the total uncertainty factor of 100 is protective of human health. The calculated values are listed in Table 1–8; calculations are in Appendix B.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data relevant to the calculation of an AEGL-2 were located. Using the descriptions of Kiese (1974) and Seger (1992), concentrations of

aniline that induce methemoglobinemia levels greater than 30% (fatigue) and less than about 60% of the circulating hemoglobin (lethargy and semistupor) would be applicable to derivation of an AEGL-2.

TABLE 1–8 AEGL-1 Values for Aniline

AEGL Level	30 min	1 h	4 h	8 h
AEGL-1	16 ppm (61 mg/m^3)	8.0 ppm (30 mg/m^3)	2.0 ppm (7.6 mg/m^3)	1.0 ppm (3.8 mg/m^3)

6.2. Animal Data Relevant to AEGL-2

The study by Kim and Carlson (1986) determined that a concentration of 150 ppm for 8 h resulted in 41% methemoglobinemia. No report of clinical signs was included by these authors. According to Bodansky (1951), dogs failed to show any clinical signs at methemoglobin concentrations of less than about 60%.

6.3. Derivation of AEGL-2

The 8-h exposure at 150 ppm to rats resulted in elevation of methemoglobin to 41% with no reported clinical signs. A review of the literature revealed that methemoglobin levels of 30–45% in humans are associated with fatigue, lethargy, exertional dyspnea, and headache. These signs or symptoms were considered the threshold for disabling effects. The 8-h exposure at 150 ppm was chosen as the basis for the AEGL-2 calculations. The level of methemoglobin attained after 8 h of exposure, 41%, may produce anxiety and signs of fatigue; these signs are below the definition of the AEGL-2. Although inhalation data for comparison purposes are not available, ingestion data suggest that humans may be considerably more sensitive to methemoglobin-forming chemicals than rats. Oral administration of aniline at 40 mg/kg to rats produced a maximum increase of 16.6% in methemoglobin, whereas oral administration of 0.9 mg/kg to a human volunteer produced a maximum increase of 16.1%. A 10-fold uncertainty factor is generally applied when extrapolating from valid results of studies on experimental animals to humans (NRC 1993). Thus, an uncertainty factor of 10 was used for interspecies extrapolation. Differences in sensitivity to aniline among human subpopulations are known to occur, but the extent of the differences in the general population (excluding rare inherited disorders) is unknown. Infants are more sensitive to methemoglobin-generating chemicals than adults, as they have reduced levels of nicotine adenine dinucleotide (NADH, the cofactor (electron donor) for methemoglobin reductase) and a high concentration of fetal hemoglobin in their erythrocytes (fetal hemoglobin is more oxidizable than adult hemoglobin) (Seger 1992). When data on a sensitive subpopulation are lacking, a 10-fold uncertainty factor is generally applied to account for the variation in sensitivity among the human population (NRC 1993). Thus, an intraspecies uncertainty factor of 10 was applied to account for

the difference in sensitivity between infants and adults. It is believed that the intraspecies uncertainty factor of 10 is protective of infants. Based on the linear relationship between methemoglobin formation and aniline concentration, the data were scaled to the relevant time periods using the relationship $C^1 \times t = k$ and $k = 720$ ppm·min. Calculations are in Appendix B, and results are listed in Table 1–9.

TABLE 1–9 AEGL-2 Values for Aniline

AEGL Level	30 min	1 h	4 h	8 h
AEGL-2	24 ppm (91 mg/m^3)	12 ppm (46 mg/m^3)	3.0 ppm (11 mg/m^3)	1.5 ppm (5.7 mg/m^3)

The 8-h AEGL-2 is 1.5 ppm. Flury and Zernik (1931) cite human data in which a concentration of 40–53 ppm was tolerated for 6 h without distinct symptoms. Although of questionable reliability, their citation indicates that sensitive individuals should be protected during an 8-h exposure to 1.5 ppm.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data relevant to the calculation of an AEGL-3 were located. Using the descriptions of Bodansky (1951), Kiese (1974), and Seger (1992), concentrations of about 60% are associated with lethargy and semi-stupor, concentrations of 70% are considered the threshold for lethality, and concentrations exceeding 85% may be lethal if treatment is not initiated. Hamblin and Mangelsdorff (1938) and Mangelsdorff (1956) cite recovery of workers from methemoglobin levels up to 72% with little or no medical treatment.

7.2. Animal Data Relevant to AEGL-3

No studies resulting in a methemoglobin level relevant to the definition of the AEGL-3 were available. The study by E.I.du Pont de Nemours (1982a) with Crl:CD rats did not report methemoglobin levels but did report that no deaths occurred after exposure to a concentration of 359 ppm for 4 h. Kakkar et al. (1992) reported a 10-min no-adverse-effect concentration of 15,302 ppm. The study by Kim and Carlson (1986) with Sprague-Dawley rats did not address methemoglobin levels greater than 41%; those data showed that the methemoglobin level (after 8 h of exposure) varies directly with the concentration of

aniline. Therefore, the graph of concentration versus methemoglobin level at 8 h can be extrapolated to attain a concentration resulting in a methemoglobin level of 70–80%, the defined threshold for lethality in humans (Figure 1–2).

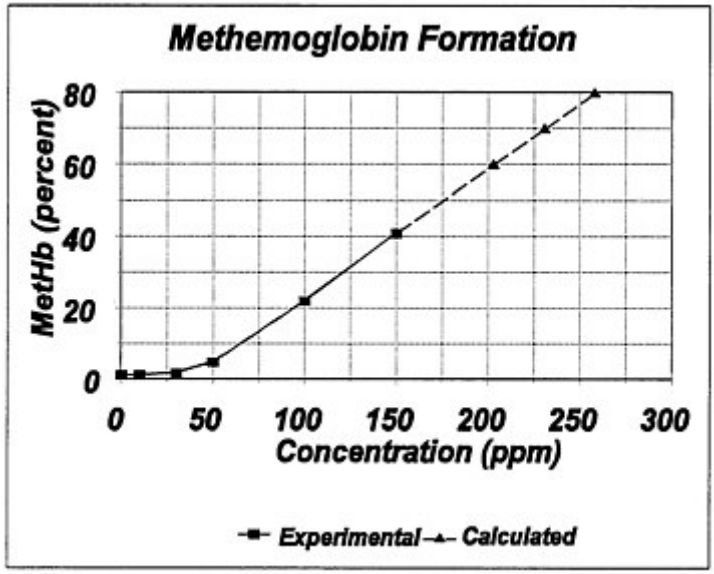

FIGURE 1–2 Measured and projected methemoglobin levels in rats exposed to aniline for 8 h. Source: Data from Kim and Carlson 1986.

7.3. Derivation of AEGL-3

An aniline concentration of 250 ppm, which is projected to result in a methemoglobin level between 70% and 80% after an 8-h exposure was identified as the basis for the AEGL-3. The same uncertainty factors and scaling procedure (the value of k in the formula $C^1 \times t = k$ is 1,200 ppm·min) as used for the AEGL-1 were applied to calculations of the AEGL-3. Calculations are in Appendix B, and values appear in Table 1–10.

The 1-h AEGL-3 value is 20 ppm and is considered safe for sensitive individuals when compared with generalizations in older references. Henderson and Haggard (1943) cited human data in which a concentration of 100 to 160 ppm was the maximum concentration that could be inhaled for 1 h without serious disturbance. The American Industrial Hygiene Association (AIHA 1955) stated that 50–100 ppm could probably be tolerated for 60 min. Two additional studies with rats support the AEGL-3 values. The 4-h exposure of rats to 359 ppm resulted in serious signs but no deaths (E.I.du Pont de Nemours 1982a). Using the combined interspecies and intraspecies uncertainty factor of

100 and extrapolating across time, the 1-h AEGL-3 value from this study would be 14 ppm. Using the same combined uncertainty factor and extrapolation across time, the 10-min concentration of 15,302 ppm in the study by Kakkar et al. (1992) results in a 1-h AEGL-3 value of 25.5 ppm. It should also be noted that 5 ppm, 6 h/d, 5 d/w for 20–26 w was a NOAEL for dogs, rats, mice and guinea pigs (Oberst et al. 1956).

TABLE 1–10 AEGL-3 Values for Aniline

AEGL Level	30 min	1 h	4 h	8 h
AEGL-3	40 ppm (152 mg/m^3)	20 ppm (76 mg/m^3)	5.0 ppm (19 mg/m^3)	2.5 ppm (9.5 mg/m^3)

TABLE 1–11 Summary and Relationship of AEGL Valuesa

	Exposure Duration			
Classification	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	16 ppm (61 mg/m^3)	8.0 ppm (30 mg/m^3)	2.0 ppm (7.6 mg/m^3)	1.0 ppm (3.8 mg/m^3)
AEGL-2 (Disabling)	24 ppm (91 mg/m^3)	12 ppm (46 mg/m^3)	3.0 ppm (11 mg/m^3)	1.5 ppm (5.7 mg/m^3)
AEGL-3 (Lethal)	40 ppm (152 mg/m^3)	20 ppm (76 mg/m^3)	5.0 ppm (19 mg/m^3)	2.5 ppm (9.5 mg/m^3)

[a]Cutaneous absorption of the neat material may occur, adding to the systemic toxicity.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity Endpoints

The AEGL values and toxicity endpoints are summarized in Table 1–11. Because aniline is absorbed through the skin, a skin notation was added to the table of values.

8.2. Comparisons with Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures are listed in Table 1–12. The American Industrial Hygiene Association (AIHA 1955) stated that 50–100 ppm could probably be tolerated for 60 min based on

a Manufacturing Chemists Association chemical safety data sheet. Because most of these standards are protective of any adverse health effect, they are comparable only to the AEGL-1 levels. The ACGIH time-weighted average (TWA) of 2 ppm is based on the slight increase in methemoglobin in rats exposed at 5 ppm for 6 h/d, 5 d/w for up to 26 w (Oberst et al. 1956) and the fact that skin absorption can contribute to aniline systemic toxicity in humans. The ACGIH Threshold Limit Value (TLV) is intended for repeated daily exposure of the healthy adult worker and is not necessarily comparable to a single 8-h exposure. However, it should be noted that both the 8-h AEGL-1 and AEGL-2 are below the 8-h ACGIH TWA, and the 8-h AEGL-3 is only slightly

TABLE 1–12 Extant Standards and Guidelines for Aniline

	Exposure Duration			
Guideline	30 min	1 h	4 h	8 h
AEGL-1	16 ppm	8 ppm	2 ppm	1 ppm
AEGL-2	24 ppm	12 ppm	3 ppm	1.5 ppm
AEGL-3	40 ppm	20 ppm	5 ppm	2.5 ppm
ERPG-1		Not derived		
ERPG-2		Not derived		
ERPG-3		Not derived		
NIOSH IDLH[a]	100 ppm			
NIOSH REL[b]				—[c]
OSHA PEL[b]				5 ppm
ACGIH TLV-TWA[d]				2 ppm[e]
MAK (German)[f]	10 ppm			2 ppm[e]
MAC (Netherlands)[g]				1 mg/m^3 [e]

[a]NIOSH 1994, 1997.

[b]NIOSH 1997.

[c]Potential occupational carcinogen; occupational exposure should be limited to the lowest feasible concentration.

[d]ACGIH 1999.

[e]Skin notation; caution against cutaneous and mucous membrane exposures (aniline and homologues).

[f]German Reasearch Association 1999.

[g]Ministry of Social Affairs and Employment 1999.

above the 8-h ACGIH TWA. The OSHA permissible exposure limit (PEL) is 5 ppm. The German and the Dutch 8-h maximum workplace concentrations are slightly lower than the 8-h AEGL-1. Emergency response planning guidelines (ERPGs) have not been derived.

The NIOSH immediately dangerous to life and health (IDLH) is based on Henderson and Haggard (1943), AIHA (1955), and von Oettingen (1941). Henderson and Haggard, in turn, is based on the animal studies of Flury and Zernik (1931). The statement by Henderson and Haggard that 100 to 160 ppm is the maximum concentration that could be inhaled for 1 h without serious disturbance appears to be the basis for the IDLH of 100 ppm. This 30-min guideline concentration is greater than the 30-min AEGL-3.

The ACGIH TLV-TWA is the time-weighted average concentration for a conventional 8-h workday and a 40-h workweek to which it is believed that nearly all workers may be repeatedly exposed, day after day, without adverse effects.

The NIOSH IDLH is defined by the NIOSH-OSHA Standard Completions Program only for the purpose of respirator selection and represents a maximum concentration from which, in the event of respiratory failure, one could escape within 30 min without experiencing any escape-impairing or irreversible health.

The OSHA PEL is a time-weighted average (8 h/d, 40 h/w).

8.3. Data Adequacy and Research Needs

Recent or definitive inhalation exposure-response data for aniline in humans are lacking. However, accidental human exposures to liquid aniline or aniline-containing dyes confirm that the primary effect is on the blood and consists of the conversion of hemoglobin to methemoglobin. Accidental human exposures also provide qualitative as well as quantitative information on symptoms and effects associated with specific blood methemoglobin concentrations. Recent animal studies which utilized reliable measurement techniques provided good concentration-response data and confirmed the primary toxicologic endpoint of methemoglobin formation. The key study was well designed, conducted and documented.

Data indicate that human infants are more sensitive to methemoglobin-generating chemicals than adults since they have reduced levels of nicotine adenine dinucleotide (NADH, the cofactor (electron donor) for methemoglobin reductase) and a high concentration of fetal hemoglobin in their erythrocytes (fetal hemoglobin is more oxidizable than adult hemoglobin). Oral exposures of humans and animals to low doses indicate that humans may be considerably more sensitive to aniline-induced methemoglobin formation than laboratory

rats. The differences in sensitivity between human infants and adults and between humans and laboratory animals are reflected in the uncertainty factor adjustments used in the development of the AEGL values. It is believed that the interspecies and intraspecies default values of 10 each for a total uncertainty factor of 100 will be protective of human health. The margin of safety of the AEGL values derived from acute animal exposures is supported by the gradual uptake/effect in the key study in that maximal methemoglobin formation was reached only after 6–8 h and by the only marginally greater effects in animal studies following repeated exposures at concentrations similar to those of the acute studies.

The available data from oral bioassays with aniline suggest that a tumorigenic response may occur following long-term, repeated high-dose exposures that cause repetitive tissue damage in the spleen as a consequence of physiologic adaptation to the chronic damage to erythrocytes (Bus and Popp 1987). The AEGL values were not based on carcinogenicity in rats, because formation of methemoglobin was a more sensitive endpoint than induction of tumors of the spleen. In addition, the endpoint of carcinogenicity was not used because the route-to-route extrapolation used in the carcinogenicity risk assessment adds additional uncertainty to the calculated values.

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Appendixes

APPENDIX A CARCINOGENICITY ASSESSMENT FOR ANILINE

No inhalation slope factor is available for aniline, and the available inhalation studies did not examine the endpoint of carcinogenicity. Based on the chronic oral administration of aniline hydrochloride to CD-F rats (CIIT 1982), U.S. EPA in its Integrated Risk Information Systems (IRIS) has estimated an oral slope factor of $5.7\times10P^{-3}$/mg/kg/d (U.S. EPA 1994). In that study, spleen tumor incidences in rats administered 0, 200, 600, or 2,000 ppm in the diet were 0/64, 0/90, 1/90, and 31/90, respectively. Aniline also has genotoxic action.

The inhalation slope factor can be estimated by dividing the oral slope factor by 70 kg and multiplying by the inhalation rate of 20 m^3/d:

Inhalation slope factor=oral slope factor×1/70 kg×20 m^3/d

$=5.7\times10^{-3}$/mg/kg/d×1/70 kg×20 m^3/d

$=1.6\times10^{-3}$/mg/m^3.

To convert to a dose or concentration of aniline that would cause an excess cancer risk of 10^{-4} (a virtually safe dose), the risk is divided by the slope factor:

dose=risk/slope

dose=(risk of 1×10^{-4})/(1.6×10^{-3} (mg/m^3)$^{-1}$)

$=6.3\times10^{-2}$ mg/m^3.

To convert a 70-y exposure to a 24-h exposure, the virtually safe dose is multiplied by the number of days in 70 yr:

24-h exposure=6.3×10^{-2} mg/m^3×25,600 d

=1,613 mg/m^3.

To adjust for uncertainties in assessing potential cancer risks for short-term exposures under the multistage model, the 24-h exposure is divided by an adjustment factor of 6 (Crump and Howe 1984).

(1,613 mg/m^3)/6=269 mg/m^3 (71 ppm).

The 24-h exposure can be converted to the shorter AEGL time points:

24-h exposure=269 mg/m^3 (71 ppm)

8-h exposure=806 mg/m^3 (212 ppm)

4-h exposure=1,613 mg/m^3 (425 ppm)
1-h exposure=6,451 mg/m^3 (1698 ppm)
30-min exposure=12,900 mg/m^3 (3395 ppm).

For 10^{-5} and 10^{-6} risk levels, the 10^{-4} values are reduced by 10-fold and 100-fold, respectively. Because the cancer risk from a short-term exposure to aniline at the AEGL concentrations is estimated to be well below 1 in 10,000, even for individuals at a sensitive age, the AEGL values are based on the more stringent requirements for methemoglobin formation.

APPENDIX B DERIVATION OF AEGL VALUES Derivation of AEGL-1

Key study:	Kim and Carlson (1986)
Toxicity endpoint:	Methemoglobin level of 22% at exposure of 100 ppm for 8 h
Scaling:	$C^1 \times t = k$, based on the linear relationship between concentration of aniline and methemoglobin formation
Uncertainty factors:	10 for interspecies 10 for intraspecies
Calculations:	100 ppm/(10×10)=1 ppm $C^1 \times t = k$ 1 ppm×480 min=480 ppm·min
30-min AEGL-1:	480 ppm·min/30 min=16 ppm
1-h AEGL-1:	480 ppm·min/60 min=8.0 ppm
4-h AEGL-1:	480 ppm·min/240 min=2.0 ppm
8-h AEGL-1:	480 ppm·min/480 min=1.0 ppm

Derivation of AEGL-2

Key study:	Kim and Carlson (1986)
Toxicity endpoint:	Methemoglobin level of 41% at exposure of 150 ppm for 8 h
Scaling:	$C^1 \times t = k$, based on the linear relationship between concentration of aniline and methemoglobin formation

Uncertainty factors:	10 for interspecies 10 for intraspecies
Calculations:	150 ppm/(10×10)=1.5 ppm $C^1 \times t = k$ 1.5 ppm×480 min=720 ppm·min
30-min AEGL-1:	720 ppm·min/30 min=24 ppm
1-h AEGL-1:	720 ppm·min/60 min=12 ppm
4-h AEGL-1:	720 ppm·min/240 min=3.0 ppm
8-h AEGL-1:	720 ppm·min/480 min=1.5 ppm

Derivation of AEGL-3

Key study:	Kim and Carlson (1986)
Toxicity endpoint:	Projected methemoglobin level of 70–80% at exposure of 250 ppm for 8 h
Scaling:	$C^1 \times t = k$, based on the linear relationship between concentration of aniline and methemoglobin formation
Uncertainty factors:	10 for interspecies 10 for intraspecies
Calculations:	250 ppm/(10×10)=2.5 ppm $C^1 \times t = k$ 2.5 ppm×480 min=1,200 ppm·min
30-min AEGL-1:	1,200 ppm·min/30 min=40 ppm
1-h AEGL-1:	1,200 ppm·min/60 min=20 ppm
4-h AEGL-1:	1,200 ppm·min/240 min=5.0 ppm
8-h AEGL-1:	1,200 ppm·min/480 min=2.5 ppm

APPENDIX C DERIVATION SUMMARY FOR ACUTE EXPOSURE GUIDELINE LEVELS FOR ANILINE (CAS No. 62–53–3)

AEGL-1 Values-Aniline

30 min	1 h	4 h	8 h
16 ppm	8.0 ppm	2.0 ppm	1.0 ppm

Key reference: Kim, Y.C., and G.P.Carlson. 1986. The effect of an unusual workshift on chemical toxicity. II. Studies on the exposure of rats to aniline. Fundam. Appl. Toxicol. 7:144–152

Test Species/Strain/Number: Adult male Sprague-Dawley rats, 5/exposure group

Exposure Route/Concentrations/Durations: Inhalation: 0–150 ppm for 8 h

Effects:	Concentration (ppm)	Methemoglobin Formation (%)[a]
	0	1.1 (0.4–1.7)
	10	1.1 (0.4–1.7)
	30	1.6
	50	4.7
	100	22
	150	41

[a]Values are estimates from data presented as graphs.

Endpoint/Concentration/Rationale: The only effect of aniline administration was formation of methemoglobin. Administration of 100 ppm for 8 h to rats resulted in elevation of methemoglobin to 22% but no hypoxic signs. A review of the literature revealed that methemoglobin levels of 15–20% in humans result in clinical cyanosis but no hypoxic symptoms. This effect was considered to be mild and reversible and, therefore, within the definition of the AEGL-1. The 8-h exposure to 100 ppm was chosen as the basis for the AEGL-1 calculations.

Uncertainty Factors/Rationale: Total uncertainty factor: 100

Interspecies: 10—A review of oral administration studies suggested that humans may be considerably more sensitive to methemoglobin formation than rats. Oral administration of aniline to rats at 40 mg/kg produced a maximum increase of 16.6% in methemoglobin, whereas oral administration of 0.9 mg/kg to a human volunteer produced a maximum increase of 16.1%.

Intraspecies: 10—Infants are more sensitive to methemoglobin-generating chemicals than adults, because they have reduced levels of nicotine adenine dinucleotide (NADH, the cofactor (electron donor) for methemoglobin reductase), and a high concentration of fetal hemoglobin in their erythrocytes (fetal hemoglobin is more oxidizable than adult hemoglobin) (Seger 1992).
Modifying Factor: Not applicable
Animal to Human Dosimetric Adjustment: Not applied; insufficient data.
Time Scaling: $C^n \times t = k$, where n=1 and k=480 ppm·min; based on the linear relationship between concentration and methemoglobin formation (Kim and Carlson 1986)
Data Adequacy: The key study was well designed, conducted, and documented. Values were presented graphically. Supporting data were sparse, probably because aniline is not a vapor at room temperature, and poisonings have involved contact with the liquid. Although human data are sparse, it is believed that a total uncertainty factor of 100 is protective of human health. Because aniline is absorbed through the skin, which increases the systemic toxicity, direct skin contact with the liquid would be additive and result in onset of adverse effects at airborne concentrations below the respective AEGL values. Therefore, direct skin contact with the liquid should be avoided.

AEGL-2 Values-Aniline

30 min	1 h	4 h	8 h
24 ppm	12 ppm	3.0 ppm	1.5 ppm

Key reference: Kim, Y.C., and G.P.Carlson. 1986. The effect of an unusual workshift on chemical toxicity. II. Studies on the exposure of rats to aniline. Fundam. Appl. Toxicol. 7:144–152

Test Species/Strain/Sex/Number: Adult male Sprague-Dawley rats, 5/exposure group

Exposure Route/Concentrations/Durations: Inhalation: 0–150 ppm for 8 h

Effects:	Concentration (ppm)	Methemoglobin Formation (%)[a]
	0	1.1 (0.4–1.7)
	10	1.1 (0.4–1.7)
	30	1.6
	50	4.7
	100	22
	150	41

[a]Values are estimates from data presented as graphs.

Endpoint/Concentration/Rationale: Administration of 150 ppm for 8 h to rats resulted in elevation of methemoglobin to 41% with no reported toxic signs. A review of the literature revealed that methemoglobin levels of 30–45% in humans are associated with fatigue, lethargy, exertional dyspnea, and headache. These signs and symptoms were considered the threshold for disabling effects. The 8-h exposure to 150 ppm was chosen as the basis for the AEGL-2 calculations.

Uncertainty Factors/Rationale: Total uncertainty factor: 100

Interspecies: 10—A review of oral administration studies suggested that humans may be considerably more sensitive to methemoglobin formation than rats. Oral administration of aniline to rats at 40 mg/kg produced a maximum increase of 16.6% in methemoglobin, whereas oral administration of 0.9 mg/kg to a human volunteer produced a maximum increase of 16.1%.

Intraspecies: 10—Infants are more sensitive to methemoglobin-generating chemicals than adults, because they have reduced levels of nicotine adenine dinucleotide (NADH, the cofactor (electron donor) for methemoglobin reductase), and a high concentration of fetal hemoglobin in their erythrocytes (fetal hemoglobin is more oxidizable than adult hemoglobin) (Seger 1992).

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applied; insufficient data
Time Scaling: $C^n \times t = k$, where n=1 and k=720 ppm·min; based on the linear relationship between concentration and methemoglobin formation (Kim and Carlson 1986)
Data Adequacy: The key study was well designed, conducted, and documented. Values were presented graphically. Supporting data were sparse, probably because aniline is not a vapor at room temperature, and poisonings have involved contact with the liquid. Although human data are sparse, it is believed that a total uncertainty factor of 100 is protective of human health. Because aniline is absorbed through the skin, which increases the systemic toxicity, direct skin contact with the liquid would be additive and result in onset of adverse effects at airborne concentrations below the respective AEGL values. Therefore, direct skin contact with the liquid should be avoided.

AEGL-3 Values-Aniline

30 min	1 h	4 h	8 h
40 ppm	20 ppm	5.0 ppm	2.5 ppm

Key reference: Kim, Y.C., and G.P.Carlson. 1986. The effect of an unusual workshift on chemical toxicity. II. Studies on the exposure of rats to aniline. Fundam. Appl. Toxicol. 7:144–152

Test Species/Strain/Sex/Number: Adult male Sprague-Dawley rats, 5/exposure group

Exposure Route/Concentrations/Durations: 0–150 ppm for 8 h

Effects:	Concentration (ppm)	Methemoglobin Formation (%)[a]
	0	1.1 (0.4–1.7)
	10	1.1 (0.4–1.7)
	30	1.6
	50	4.7
	100	22
	150	41

[a]Values are estimates from data presented as graphs.

Endpoint/Concentration/Rationale: Because the exposures did not result in effects consistent with the definition of an AEGL-3, the concentration vs percent hemoglobin formation data presented by the authors was graphed and projected to a methemoglobin level of 70–80%, which was considered the threshold for lethality in humans. This value was approximately 250 ppm. An 8-h exposure to 250 ppm was chosen as the basis for the AEGL-3 calculations.

Uncertainty Factors/Rationale: Total uncertainty factor: 100

Interspecies: 10—A review of oral administration studies suggested that humans may be considerably more sensitive to methemoglobin formation than rats. Oral administration of aniline to rats at 40 mg/kg produced a maximum increase of 16.6% in methemoglobin, whereas oral administration of 0.9 mg/kg to a human volunteer produced a maximum increase of 16.1%.

Intraspecies: 10—Infants are more sensitive to methemoglobin-generating chemicals than adults, because they have reduced levels of nicotine adenine dinucleotide (NADH, the cofactor (electron donor) for methemoglobin reductase), and a high concentration of fetal hemoglobin in their erythrocytes (fetal hemoglobin is more oxidizable than adult hemoglobin) (Seger 1992).

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applied; insufficient data
Time Scaling: $C^n \times t = k$, where n=1 and k=1,200 ppm·min; based on the linear relationship between concentration and methemoglobin formation (Kim and Carlson 1986)
Data Adequacy: The key study was well designed, conducted, and documented. Values were presented graphically. Supporting data were sparse, probably because aniline is not a vapor at room temperature and poisonings have involved contact with the liquid. Although human data are sparse, it is believed that a total uncertainty factor of 100 is protective of human health. Because aniline is absorbed through the skin, which increases the systemic toxicity, direct skin contact with the liquid would be additive and result in onset of adverse effects at airborne concentrations below the respective AEGL values. Therefore, direct skin contact with the liquid should be avoided.

2
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 than AEGLs estimated from limited anecdotal human data. The greater conser

[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).

vatism 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 AIHA1993) 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 $\mu g/m^3$ (≈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 $\mu g/m^3$ (≈0.005 ppm) were associated with urinary arsenic concentrations in excess of 50 $\mu g/L$. The investigators concluded that exposure to a 200 $\mu g/m^3$ 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

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).

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

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 B6C3F1 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

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

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

Concentration			Exposure Duration (min)	C×T (ppm·min)	Mortality	Estimated Duration (min) for 50% Mortality
mg/L	mg/m^3	ppm				
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	

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 hemato

logic 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 B6C3F1 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 (7.8×10^6/mm^3) at 1 d following exposure to arsine at 9 ppm (6.1×10^6), 11 ppm (6.2×10^6/mm^3), 15-ppm (4.0×10^6/mm^3), or 15 ppm (2.2×10^6/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 B6C3F1 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 3-6 Summary of Lethality Data For Monomethylhydrazine in Laboratory Species

Species	LC_{50} in ppm	C × T (ppm·min)	Comments	Reference
Monkey (rhesus)	1-h LC_{50}: 162	9,720	No mortality at 160 ppm; 66% mortality at 170 ppm; no time-to-death information	Haun et al. 1970
Monkey (squirrel)	15-min LC_{50}: 340 30-min LC_{50}: 145 1-h LC_{50}: 82	5,100 4,350 4,920	No deaths at 130 ppm for 1 h; 66% mortality at 150 ppm for 1 h; 100% mortality at 170 ppm for 1 h	Haun et al. 1970
Dog	15-min LC_{50}: 390 30-min LC_{50}: 195 1-h LC_{50}: 96	5,850 5,850 5,760	No deaths at 92 ppm for 1 h; 180 ppm for 30min.; and 380 ppm for 15 min.	Haun et al. 1970
Dog		4-h exposures resulting in 3,600, 5,040, or 6,960 ppm·min	No mortality at 15 ppm; 2 of 3 dogs died at 21 and 29 ppm; vomiting and convulsions noted in dogs that died	Jacobson et al. 1955
Rat	4-h LC_{50}: 74	17,760	A 4-h LC_{20} of 36 ppm (accompanied by convulsions, dyspnea, and exophthalmos) was also reported	Jacobson et al. 1955
Rat	30-min LC_{59}: 427 1-h LC_{50}: 244 120-min LC_{59}:127 240-min LC_{59}:78	12,810 14,640 15,240 18,720	Mortality within 4 h post-exposure	Haun et al. 1970
Mouse	30-min LC_{59}: 272 1-h LC_{50}: 122 2-h LC_{50}: 65 4-h LC_{50}: 65	8,160 7,320 11,040 15,600		Haun et al. 1970
Mouse	4-h LC_{50}: 56	13,440		Jacobson et al. 1955
Hamster	4-h LC_{50}: 143	34,320		Jacobson et al. 1955
Hamster	1-h LC_{50}: 991	59,460	No mortality at 460 ppm; all deaths occurred within 24 h post-exposure	MacEwen and Vernot 1975

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 Harger 1950), 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

alterations 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 (1/2 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 Elkins 1959) 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

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

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

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. Al

though the 26-ppm exposure resulted in 100% mortality within 4 d post-exposure, 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.

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.

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

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.

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/m3 (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.

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

$C^3 \times 30 \text{ min} = 0.00167 \text{ ppm}^3 \cdot \text{min}$

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 $C^3 \times t = k$

	$(0.167 \text{ ppm})^3 \times 60 \text{ min} = 0.278 \text{ ppm}^3 \cdot \text{min}$ $C^1 \times t = k$ $0.167 \text{ ppm} \times 60 \text{ min} = 10 \text{ ppm} \cdot \text{min}$
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.
30-min AEGL-2:	$C^3 \times 30 \text{ min} = 0.278 \text{ ppm}^3 \cdot \text{min}$ $C = 0.21 \text{ ppm}$
1-h AEGL-2:	$C^3 \times 60 \text{ min} = 0.278 \text{ ppm}^3 \cdot \text{min}$ $C = 0.17 \text{ ppm}$
4-h AEGL-2:	$C^1 \times 240 \text{ min} = 10 \text{ ppm} \cdot \text{min}$ $C = 0.04 \text{ ppm}$
8-h AEGL-2:	$C^1 \times 480 \text{ min} = 10 \text{ ppm} \cdot \text{min}$ $C = 0.02 \text{ ppm}$.

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 $C^3 \times t = k$ $(0.5 \text{ ppm})^3 \times 60 \text{ min} = 7.5 \text{ ppm}^3 \cdot \text{min}$ $C^1 \times t = k$ $0.5 \text{ ppm} \times 60 \text{ min} = 30 \text{ ppm} \cdot \text{min}$
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.
30-min AEGL-3:	$C^3 \times 30 \text{ min} = 7.5 \text{ ppm}^3 \cdot \text{min}$ C=0.63 ppm
1-h AEGL-3:	$C^3 \times 60 \text{ min} = 7.5 \text{ ppm}^3 \cdot \text{min}$ C=0.50 ppm
4-h AEGL-3:	$C^1 \times 240 \text{ min} = 30 \text{ ppm} \cdot \text{min}$ C=0.13 ppm
8-h AEGL-3:	$C^1 \times 480 \text{ min} = 30 \text{ ppm} \cdot \text{min}$ 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)

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

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.

3
Monomethylhydrazine[1]

Acute Exposure Guideline Levels

SUMMARY

MONOMETHYLHYDRAZINE is a clear, colorless liquid used extensively in military applications as a missile and rocket propellant, in chemical power sources, and as a solvent and chemical intermediate. Upon contact with strong oxidizers (e.g., hydrogen peroxide, nitrogen tetroxide, chlorine, fluorine) spontaneous ignition may occur.

Human volunteers exposed to monomethylhydrazine at a concentration of 90 parts per million (ppm) for 10 min reported minor ocular and nasopharyngeal irritation as the only consequence of exposure (MacEwen et al. 1970).

Toxicity data are available for multiple laboratory species including, rhesus monkeys, squirrel monkeys, beagle dogs, rats, mice and hamsters. Nonlethal toxic effects include irritation of the upper respiratory tract, hemolysis, and

[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).

histopathologic evidence of renal and hepatic toxicity. Lethal exposures are usually preceded by convulsions. Lethal toxicity varies somewhat among species. One-hour LC_{50} (lethal concentration for 50% of the animals) values of 162, 82, 96, 244, 122, and 991 ppm have been determined for rhesus monkeys, squirrel monkeys, beagle dogs, rats, mice, and hamsters, respectively. Exposure concentration-exposure duration relationships appear to follow a linear relationship, although there appears to be a critical threshold for lethality with little margin between exposures causing only minor, reversible effects, and those resulting in lethality.

In a 1-y inhalation bioassay using dogs, rats, mice, and hamsters and monomethylhydrazine concentrations of 2 ppm and 5 ppm, there was no evidence of treatment-related carcinogenicity in dogs or rats even after a 1-y post-exposure observation period. However, mice exposed at 2 ppm exhibited an increased incidence of lung tumors, nasal adenomas, nasal polyps, nasal osteomas, hemangioma, and liver adenomas and carcinomas. In hamsters exposed to monomethylhydrazine at 2 or 5 ppm, there was an increase in nasal polyps and nasal adenomas (5 ppm only), interstitial fibrosis of the kidney, and benign adrenal adenomas. Recommendation of acute exposure guideline level 1 (AEGL-1) values for monomethylhydrazine would be inappropriate. This conclusion was based on the fact that notable toxicity may occur at or below the odor threshold. Exposure concentration-exposure duration relationship for monomethylhydrazine indicated little margin between exposures producing no adverse health effect and those resulting in significant toxicity.

The AEGL-2 values were derived by a three-fold reduction of the AEGL-3 values. This approach for estimating a threshold for irreversible effects was used in the absence of exposure-response data related to irreversible or other serious long-lasting effects. It is believed that a 3-fold reduction in the estimated threshold for lethality is adequate to reach the AEGL-2 threshold level because of the steep dose-response relationship.

For AEGL-3, the 1-h LC_{50} of 82 ppm for squirrel monkeys (Haun et al. 1970) was reduced by a factor of 3 to estimate a lethality threshold (27.3 ppm). Temporal scaling to obtain time-specific AEGL values was described by $C^1 \times t = k$ (where C=exposure concentration, t=exposure duration, and k=a constant). The lethality data for the species tested indicated a near linear relationship between concentration and exposure duration (n=0.97 and 0.99 for monkeys and dogs, respectively). The derived exposure value was adjusted by a total uncertainty factor of 10.[2] An uncertainty factor of 3 was applied for

[2]Each uncertainty factor of 3 is actually the geometric mean of 10, which is 3.16; hence, 3.16×3.16=10.

interspecies variability with the following justification. One-hour LC_{50}s were determined in the monkey, dog, rat, and mouse. The LC_{50} values ranged from 82 ppm in the squirrel monkey to 244 ppm in the mouse, differing by a factor of approximately 3. The squirrel monkey data (1-h LC_{50}=82 ppm) was used to determine the AEGL-3, because this species appeared to be the most sensitive to monomethylhydrazine toxicity and because it was the species most closely related to humans. An uncertainty factor of 3 for protection of sensitive individuals was applied to reflect individual variability less than an order of magnitude. Although the mechanism of toxicity is uncertain and sensitivity among individuals may vary, the exposure-response relationship for each species tested is very steep, suggesting limited variability in physiologic response to monomethylhydrazine. Furthermore, it is likely that acute responses are, at least initially, a function of the extreme chemical reactivity of monomethylhydrazine. The interaction of the highly reactive monomethylhydrazine with tissues (e.g., pulmonary epithelium) is not likely to greatly vary among individuals.

The AEGL values reflect the steep exposure-response relationship exhibited by the toxicity data. Additional information regarding the mechanism(s) of action and metabolism of monomethylhydrazine may provide further insight into understanding and defining the threshold between nonlethal and lethal exposures.

Neither inhalation nor oral carcinogenicity slope factors were available for monomethylhydrazine. A cancer assessment based upon the carcinogenic potential of dimethylhydrazine revealed that AEGL values for a theoretical excess lifetime 10^{-4} carcinogenic risk exceeded the AEGL-3 values that were based on noncancer endpoints. Furthermore, the available data for hydrazine and its methylated derivatives suggest that the tumorigenic response observed for these compounds is the result of repeated long-term exposures causing repetitive tissue damage. Because AEGLs are applicable to rare events or single once-in-a-lifetime exposures to a limited geographic area and small population, the AEGL values based on noncarcinogenic endpoints were considered more appropriate. Table 3–1 summarizes the AEGL values for monomethylhydrazine.

TABLE 3–1 Summary of AEGL Values for Monomethylhyrazine

Classification	30 min	1 h	4 h	8 h	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	Not recommended due to inadequate data; concentration-response relationships suggest little margin between exposures causing minor effects and those resulting in serious toxicity.
AEGL-2 (Disabling)	1.8 ppm 3.4 mg/m^3	0.90 ppm 1.7 mg/m^3	0.23 ppm 0.43 mg/m^3	0.11 ppm 0.21 mg/m^3	3-fold reduction in AEGL-3.
AEGL-3 (Lethal)	5.5 ppm 10.3 mg/m^3	2.7 ppm 5.1 mg/m^3	0.68 ppm 1.3 mg/m^3	0.34 ppm 0.64 mg/m^3	1-h LC_{50} of 82 ppm reduced 3-fold to estimate a lethality threshold; uncertainty factor=10

Numeric values for AEGL-1 are not recommended, because (1) studies suggest that notable toxic effects may occur at or below the odor threshold or other modes of sensory detection, (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. The absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without any adverse effects.
Abbreviations: NR, not recommended; ppm, parts per million; mg/m^3, milligrams per cubic meter.

1. INTRODUCTION

Monomethylhydrazine is a clear, colorless liquid (Trochimowicz 1994). Upon contact with strong oxidizers (e.g., hydrogen peroxide, nitrogen tetroxide, chlorine, fluorine) spontaneous ignition may occur. It is used in military applications as a missile and rocket propellant in chemical power sources (USAF 1989), and is used also as a solvent and chemical intermediate (Trochimowicz 1994). There are are no reports of current commercial production (HSDB 1996) and, therefore, overall production may be considered sporadic (Chemical Economics Handbook 2000).

Trochimowicz (1994) provided a review of the toxicology of monomethylhydrazine. Earlier data were summarized regarding the pharmacologic and toxicologic effects of monomethylhydrazine in laboratory animals by various routes of administration, noting involvement of the central nervous system, lungs, liver, and kidneys. Monomethylhydrazine has also been the subject of previous review by the National Research Council (NRC 1985).

For derivation of AEGL values, acute exposure studies are preferentially examined. Subchronic and chronic studies generally have not been included in the data analysis for monomethylhydrazine AEGL derivation because of the great uncertainty in extrapolating such data to acute exposure scenarios. Such studies may be addressed when the data provided relate to effects following acute exposures, provide meaningful insight into understanding toxicity mechanisms, or can be used for other special considerations.

The primary physical and chemical data for monomethylhydrazine are presented in Table 3–2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No information was located regarding acute lethality to humans following inhalation exposure to monomethylhydrazine.

2.2. Nonlethal Toxicity

2.2.1. Acute Exposure Studies

A controlled human exposure study provided information regarding non-lethal effects following acute (head-only) exposure to monomethylhydrazine

(MacEwen et al. 1970). In a preliminary phase of this study, one subject was exposed at 50 ppm for 10 min and another exposed at 70 ppm for 10 min. Throughout the exposure period and during a 2-w post-exposure period, neither subject complained of adverse signs or symptoms. These subjects and five additional volunteers were then exposed to monomethylhydrazine at 90 ppm (169 mg/m^3) for 10 min. All exposures were conducted using Rochester Chambers and male volunteers (23–44 y of age) representing nonsmokers, reformed smokers, and heavy smokers. One of the seven subjects was not included in the final data compilation due to an inability to detect the odor of monomethylhydrazine at any of the exposure atmospheres. The 10-min, 90-ppm exposure (Ct=900 ppm·min) resulted in irritation of the eyes, nose, and throat but did not result in excessive lacrimation or coughing. The subjects experienced irritation ranging from faint (just perceptible, not painful) to moderate in intensity of response. Monitoring of clinical chemistry parameters for 60 d following the exposure revealed no significant findings other than 3–5% increase in Heinz body formation at d 7 that declined after 2 w. Spirometry

TABLE 3–2 Chemical and Physical Data

Parameter	Value	Reference
Synonyms	methylhydrazine, MMH	Trochimowicz et al. 1994
Chemical formula	CH_6N_2 (H_2N-NH-CH_3)	Trochimowicz et al. 1994
Molecular weight	46.07	Trochimowicz et al. 1994
CAS Registry No.	60–34–4	Trochimowicz et al. 1994
Solubility	soluble in hydrocarbons; miscible with water and low molecular weight monohydric alcohols	Trochimowicz et al. 1994
Physical state	liquid	Trochimowicz et al. 1994
Vapor density (rel to air)	1.6	Shaffer and Wands 1973
Vapor pressure	49.63 ♂ Hg at 25°C	Shaffer and Wands 1973
Specific gravity	0.874 at 25°C	Trochimowicz et al. 1994
Boiling/freezing point/ flash point	87.5°C/–52.4°C/–8.33°C	Trochimowicz et al. 1994
Odor threshold	1–3 ppm; ammonia-like or fishy odor	Shaffer and Wands 1973
Conversion factors in air	1 mg/m^3=0.53 ppm 1 ppm=1.88 mg/m^3	

tests revealed no exposure-related effects. The presence of Heinz bodies was not accompanied by anemia or reticulocytosis.

2.2.2. Epidemiologic Studies

Epidemiologic studies regarding human exposure to monomethylhydrazine were not available.

2.3. Developmental and Reproductive Toxicity

No data are available regarding the potential reproductive and developmental toxicity of monomethylhydrazine in humans.

2.4. Genotoxicity

No genotoxicity data specific for AEGL derivation were available for monomethylhydrazine.

2.5. Carcinogenicity

No data are available regarding the potential carcinogenicity of monomethylhydrazine in humans.

2.6. Summary

The human experience regarding the toxicity of acute exposures to monomethylhydrazine exposure is limited. The study by MacEwen et al. (1970) found that a 10-min exposure to monomethylhydrazine at 169 mg/m^3 (90 ppm) resulted in minor ocular and upper respiratory tract irritation.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Acute lethality studies in laboratory species are summarized in the following sections. (The LC_{50} values from these studies are summarized in Table 3–6.)

3.1.1. Nonhuman Primates

In a study by Haun et al. (1970), male and female rhesus monkeys (three to five per group, sex ratio per exposure varied) and male squirrel monkeys (two to four per exposure group) were exposed to monomethylhydrazine for 60 min (rhesus monkeys) and 15, 30, or 60 min (squirrel monkeys) (Table 3–3). For the rhesus monkeys (three males and two females), there were no deaths following a 60-min exposure to a mean concentration of 160 ppm (range, 145–170 ppm),

TABLE 3–3 Lethality in Nonhuman Primates and Dogs Following Inhalation Exposure to Monomethylhydrazine

Species	Exposure Concentration (C×T)	Mortality Ratio
	15 min	
Squirrel monkey	300 ppm (4,500 ppm·min)	1/4
	340 ppm (5,100 ppm·min)	1/2
	376 ppm (5,640 ppm·min)	3/3
Beagle dog	380 ppm (5,700 ppm·min)	0/2
	390 ppm (5,850 ppm·min)	1/2
	400 ppm (6,000 ppm·min)	3/5
	30 min	
Squirrel monkey	130 ppm (3,900 ppm·min)	0/3
	150 ppm (4,500 ppm·min)	2/3
	170 ppm (5,100 ppm·min)	2/2
Beagle dog	180 ppm (5,400 ppm·min)	0/2
	190 ppm (5,700 ppm·min)	1/3
	200 ppm (6,000 ppm·min)	2/2
	60 min	
Rhesus monkey	160 ppm (9,600 ppm·min)	0/5
	170 ppm (10,200 ppm·min)	2/3
Squirrel monkey	75 ppm (4,500 ppm·min)	0/2
	85 ppm (5,100 ppm·min)	2/4
	90 ppm (5,400 ppm·min)	2/2
Beagle dog	92 ppm (5,520 ppm·min)	0/3
	104 ppm (6,240 ppm·min)	3/3

Source: Haun et al. 1970.

but at a mean concentration of 170 ppm (range, 138–180 ppm), mortality was 2/3 (two males of two males and one female). Although no time-to-death values were reported for the rhesus monkeys, it was stated that no deaths occurred during the exposure period. A 60-min LC_{50} of 162 ppm was reported for the rhesus monkeys. For the squirrel monkeys, deaths occurred as early as 2 h post-exposure, although most deaths occurred between 10 and 24 h post-exposure. The reported 15-, 30-, and 60-min LC_{50} values for the squirrel monkeys were 340, 145, and 82 ppm, respectively. The cumulative exposure data for various exposure durations suggest a linear relationship within species.

3.1.2. Dogs

Jacobson et al. (1955) reported on the lethality of monomethylhydrazine in dogs exposed for 4 h. Groups of dogs (three per group) exposed to three different concentrations of monomethylhydrazine developed hyperactivity, salivation, vomiting, respiratory distress, and convulsions. Dogs exposed to monomethylhydrazine experienced elevated body temperatures (as high as 106°F vs 102°F for controls) immediately following exposure, but body temperatures returned to normal within 1 d after cessation of treatment. The mortality for the 15-, 21-, and 29-ppm exposure levels was 0/3, 2/3, and 2/3, respectively. This mortality data included all animals that died within 14 d of exposure and those that were terminated due to morbidity. Postmortem examination revealed pulmonary edema and hemorrhagic foci in the lungs. The latter was observed only in dogs that convulsed and was considered a secondary effect rather than a direct effect of the test substance.

The acute toxicity of monomethylhydrazine in dogs was also studied by Haun et al. (1970). Three groups of male and female beagle dogs (two to five per exposure group) were exposed to monomethylhydrazine for 15 min (380– 400 ppm), 30 min (180–200 ppm), or 60 min (92–104 ppm) (Table 3–3). Deaths occurred within 2 h following termination of the exposure. The study authors calculated 15-min, 30-min, and 1-h LC_{50} values of 390, 195, and 96 ppm, respectively.

3.1.3. Rats

Jacobson et al. (1955) assessed the lethality of monomethylhydrazine in rats (10 per exposure group; strain not specified) following a single 4-h exposure to various unspecified concentrations. An LC_{50} of 74 ppm (139 mg/m^3) was reported. Based upon the exposure-response data, an LC_{20} of ≈70 ppm (≈132

mg/m^3) can be estimated. The exposure-response curve was very steep (slope =28.5), suggesting very little variability in the response.

Haun et al. (1970) also assessed the acute lethal toxicity of rats. Groups of 10 Sprague-Dawley rats were exposed to monomethylhydrazine (30, 60, 120, or 240 ppm) for 30, 60, 120, or 240 min. Similar to the results of Jacobson et al. (1955) the exposure-response curve was steep. The study authors calculated 30-, 60-, 120-, and 240-min LC_{50} values of 427, 244, 127, and 78 ppm, respectively.

3.1.4. Mice

Acute toxicity assays using groups of 20 mice (strain not specified) exposed to various unspecified concentrations of monomethylhydrazine for 4 h were conducted by Jacobson et al. (1955). During the exposure, the mice were restless and exhibited dyspnea, convulsions, and exophthalmos. An LC_{50} of 56 ppm (105 mg/m^3) was reported. Postmortem examination of the mice revealed no significant histopathologic findings other than pulmonary edema and occasional, localized hemorrhage. The hemorrhaging was, however, considered to be secondary to the observed convulsions and not considered a direct effect of monomethylhydrazine. Based upon the exposure-response data, an LC_{20} of ≈36 ppm (≈68 mg/m^3) can be estimated. The exposure-response curve was steep (slope = 4.96), suggesting little variability in the response. Analytical concentrations of monomethylhydrazine averaged 77% of nominal, suggesting some difficulty with accurate measurement of the test material.

In a study by Haun et al. (1970), groups of 20 male ICR mice were exposed to a range of monomethylhydrazine concentrations for 30, 60, 120, or 240 min. LC_{50} values for 30, 60, 120, and 240 min were 272, 122, 92, and 65 ppm, respectively. Additional experiments in which groups of 20 mice were exposed to various monomethylhydrazine concentrations (Table 3–4) were also conducted to assure reproducibility of the mortality findings.

3.1.5. Hamsters

Jacobson et al. (1955) assessed the lethality of monomethylhydrazine in hamsters exposed for 4 h. Based on the estimated LC_{50} (143 ppm, or 270 mg/m^3), hamsters were somewhat less sensitive to inhaled monomethylhydrazine. Similar to mice and rats, the slope of the exposure-response curve was steep (2.46), suggesting little variability in the response.

In a study reported by MacEwen and Vernot (1975), groups of 10 male

Syrian golden hamsters were exposed to monomethylhydrazine at concentrations of 460, 620, 810, 910, 1,110, or 1,380 ppm for 1 h followed by a 14-d observation period. Immediate irritation of the eyes and nose followed by labored breathing and gasping were observed in all exposure groups. The onset of these signs appeared to be concentration-dependent; signs appeared more rapidly as the concentration increased. Coordination was affected, although the hamsters did not become prostrate. Convulsions were observed during the last few minutes of exposure in hamsters of the highest exposure group. These convulsions continued as long as 1 h post-exposure. Mortality ratios are shown in Table 3–5. Hamsters that died did so within 24 h post-exposure, and all survivors exhibited notable body-weight loss. A 1-h LC_{50} of 991 ppm (95% confidence interval=870–1,130 ppm) was reported based upon these data. Gross examination revealed lung and liver congestion, and concentration-related alveolar irritation. Histopathologic examination revealed concentration-related pulmonary edema and hemorrhage (observed only in hamsters exposed to the two highest concentrations). Hamsters from the highest exposure groups exhibited cuboidal atrophy, erosion and ulcerations in tracheobronchial epithe

TABLE 3–4 Mortality in Mice Following Inhalation Exposure to Monomethylhydrazine for 240 Min

Mean concentration (ppm)	Concentration range (ppm)	Mortality (no. of dead per no. of exposed)	Total Mortality
27	(10–35)	0/20	0/40
25	(23–30)	0/20	
50	(48–53)	0/20	0/40
50	(45–55)	0/20	
55	(50–58)	0/20	1/40
55	(50–58)	1/20	
63	(55–70)	5/20	7/40
60	(50–68)	2/20	
63	(48–68)	13/20	23/40
63	(58–68)	10/20	
68	(63–75)	18/20	31/40
66	(60–70)	13/20	
83	(60–113)	19/20	37/40
83	(65–88)	18/20	

Source: Haun et al. 1970.

lium. For hamsters in the lower exposure groups, only catarrhal inflammation was observed. Kidney and hepatic congestion also was noted in hamsters from all exposure levels, but the incidence and severity did not appear to be concentration related.

TABLE 3–5 Mortality in Hamsters Following Inhalation Exposure to Monomethylhydrazine for 1 H

Concentration (ppm)	Mortality Ratio	Time to Death
460	0/10	
620	2/10	18 h
810	2/10	18 h
910	2/10	2.5 h and 18 h
1,110	7/10	3 at 1 h; 4 at 17 h
1,380	9/10	6 at 3 h; 3 at 10 h

Source: MacEwen and Vernot 1975.

3.2. Nonlethal Toxicity

3.2.1. Nonhuman Primates

In the study by Haun et al. (1970), exposure of rhesus monkeys (three males and two females) to monomethylhydrazine at 160 ppm (range, 145–170 ppm) for 60 min failed to cause death. Although signs of ocular irritation were considered to represent the onset of toxicity in monkeys, the exposures for which these signs were first observed were not specified. Monkeys developed hemolysis characterized by moderate reductions in hematocrit, hemoglobin content and erythrocyte counts, and a moderate increase in reticulocytes. These hematologic changes persisted up to 4 w post-exposure. Similarly, exposure of squirrel monkeys to monomethylhydrazine at 75 ppm (two females exposed at a range of 75–80 ppm) for 60 min or at 130 ppm for 30 min (three females exposed at a range of 128–135 ppm) did not result in any deaths. These concentrations are, however, only slightly below those resulting in mortality of ≥50% (e.g., 170 ppm for 60 min in rhesus monkeys, 150 ppm for 30 min or 85 ppm for 60 min in squirrel monkeys, see Section 3.1.1). These data affirm the steep exposure-response relationship for monomethylhydrazine-induced lethality. Table 3–6 summarizes the lethality data for laboratory animals.

TABLE 3-6 Summary of Lethality Data For Monomethylhydrazine in Laboratory Species

Species	LC_{50} in ppm	C × T (ppm·min)	Comments	Reference
Monkey (rhesus)	1-h LC_{50}: 162	9,720	No mortality at 160 ppm; 66% mortality at 170 ppm; no time-to-death information	Haun et al. 1970
Monkey (squirrel)	15-min LC_{50}: 340 30-min LC_{50}: 145 1-h LC_{50}: 82	5,100 4,350 4,920	No deaths at 130 ppm for 1 h; 66% mortality at 150 ppm for 1 h; 100% mortality at 170 ppm for 1 h	Haun et al. 1970
Dog	15-min LC_{50}: 390 30-min LC_{50}: 195 1-h LC_{50}: 96	5,850 5,850 5,760	No deaths at 92 ppm for 1 h; 180 ppm for 30min.; and 380 ppm for 15 min.	Haun et al. 1970
Dog		4-h exposures resulting in 3,600, 5,040, or 6,960 ppm·min	No mortality at 15 ppm; 2 of 3 dogs died at 21 and 29 ppm; vomiting and convulsions noted in dogs that died	Jacobson et al. 1955
Rat	4-h LC_{50}: 74	17,760	A 4-h LC_{20} of 36 ppm (accompanied by convulsions, dyspnea, and exophthalmos) was also reported	Jacobson et al. 1955
Rat	30-min LC_{59}: 427 1-h LC_{50}: 244 120-min LC_{59}:127 240-min LC_{59}:78	12,810 14,640 15,240 18,720	Mortality within 4 h post-exposure	Haun et al. 1970
Mouse	30-min LC_{59}: 272 1-h LC_{50}: 122 2-h LC_{50}: 65 4-h LC_{50}: 65	8,160 7,320 11,040 15,600		Haun et al. 1970
Mouse	4-h LC_{50}: 56	13,440		Jacobson et al. 1955
Hamster	4-h LC_{50}: 143	34,320		Jacobson et al. 1955
Hamster	1-h LC_{50}: 991	59,460	No mortality at 460 ppm; all deaths occurred within 24 h post-exposure	MacEwen and Vernot 1975

3.2.2. Dogs

Jacobson et al. (1955) exposed groups of three dogs to monomethylhydrazine at concentrations of 15, 21, or 29 ppm for 4 h. Dogs exposed at 15 ppm (3,600 ppm·min) exhibited hyperactivity, retching, tremors and convulsions, and vomiting but all recovered following cessation of exposure. There was no mortality or morbidity in these animals during the 24-d post-exposure period. However, in four of the five surviving dogs (three in the 15-ppm group and one each in the 21- and 29-ppm groups), moderately severe hemolysis occurred. Intravascular hemolysis was evident in reduced erythrocyte counts, hematocrit, and hemoglobin content. These effects were persistent during d 4–8 of the post-exposure period, but recovery was noted shortly thereafter.

In the Haun et al. (1970) report, there were no deaths in three beagle dogs exposed to monomethylhydrazine at 92 ppm for 60 min (5,520 ppm·min), 180 ppm for 30 min (5,400 ppm·min), or 380 ppm for 15 min (5,700 ppm·min). Dogs in the 60-min 92-ppm exposure group exhibited intravascular hemolysis as shown by decreases in hematocrit, hemoglobin content, and erythrocyte count, and increased reticulocyte counts up to 24 d post-exposure. Additionally, one dog in the 60-min 92-ppm exposure group developed hematuria and bloody stools following the nonlethal exposure. Although no deaths occurred, these exposures appear to represent a near-lethal threshold: exposure at 140 ppm for 60 min resulted in 100% mortality (3/3), exposure at 190 ppm for 30 min produced a 33% mortality (1/3), and exposure at 390 ppm for 15 min resulted in a 50% mortality (1/2). The precision of estimating a lethality threshold based upon these values is compromised by the small sample size.

3.2.3. Rats

Data on rats were limited to assessing lethality. Definitive quantitative and qualitative information of use for AEGL-1 or AEGL-2 derivations was not available.

3.2.4. Mice

In the study by Haun et al. (1970), no deaths occurred in mice exposed to monomethylhydrazine at 50 ppm for 240 min. No additional information was provided to assess nonlethal toxicity. At slightly higher exposures (55–63 ppm), mortality was increased (1/40 and 7/40, respectively), suggesting that the 50-ppm exposures were approaching a lethality threshold.

TABLE 3–7 Developmental Effects of Monomethylhydrazine in Rats Following Intraperitoneal Administration on Gestation Days 6–15

	Dose (mg/kg)			
Parameter	0	2.5	5.0	10.0
No. of litters	13	15	15	16
Implants/litter[a]	7.8±3.6	8.8±3.4	7.3±2.5	7.6±3.4
Viable fetuses/litter[a]	6.8±4.0	7.5±3.4	6.2±2.7	6.1±3.9
No. of litters with >33% resorption	0	2	3	3
Fetal weight[a]	3.1±0.3	3.3±0.3	3.1±0.3	3.2±0.3
Incidence of abnormalities:[b]				
Gross exam	2(2)	1(1)	3(4)	2(2)
Soft-tissue exam	1(1)[c]	2(2)[d]	6(9)[d]	3(4)[e]
Skeletal exam	0(0)	1(1)	1(1)	2(2)

[a]Values are means ± standard error.

[b]Number of litters (number of fetuses in parentheses) affected.

[c]One fetus with anophthalmia and hydrocephalus.

[d]All anophthalmia or severe microphthalmia.

[e]Hydronephrosis and dilated ureter in one fetus, hydrocephalus in another, and two fetuses with anophthalmia.

Source: Keller et al. 1984.

3.3. Developmental and Reproductive Toxicity

The only available data regarding reproductive and developmental effects of monomethylhydrazine involved parenteral administration and, therefore, are of questionable relevance for AEGL derivation. Those data are discussed here to provide insight relative to monomethylhydrazine exposure.

The results of a teratogenicity assessment of monomethylhydrazine in rats was reported by Keller et al. (1984) (Table 3–7). In this study, groups of 14–18 pregnant Fischer 344 rats were given monomethylhydrazine via parenteral administration in saline (2.5, 5.0, or 10 milligrams per kilogram per day (mg/kg/d) intraperitoneally) on gestation d 6–15; controls received saline only. The pregnant rats were sacrificed on gestation d 20, and the following parameters examined: numbers and positions of implants and numbers of dead fetuses, live fetuses, and resorptions. Fetuses were examined for evidence of terata. During treatment, the rats exhibited decreased weight gain relative to controls, especially at the two highest doses, and four of eight females of the highest dose group convulsed on one or more occasions during the treatment period. The effects of monomethylhydrazine on the examined parameters were considered inconsistent, although a trend (not statistically significant) in increased resorptions with dose was observed. Although the data (increased resorptions, moder

ate increase in the incidences of eye abnormalities) suggested possible developmental toxicity, the investigators did not consider the findings definitive. Due to uncertainties regarding absorption, distribution and metabolism of monomethylhydrazine, route-to-route extrapolation for derivation of AEGLs is untenable. However, for comparative purposes, it may be noted that, based upon an adult rat body weight (0.35 kg) and ventilation rate (0.223 mg/m^3) and assuming complete absorption, the highest dose (10 mg/kg) used for 1 h in the Keller et al. (1984) study would be that received during an inhalation exposure of 128 mg/m^3 (68 ppm). This is within the range of the reported LC_{50} values for rats (Table 3–4), implying that exposures that may result in reproductive and developmental effects would also be in the range of those causing maternal lethality. This is supported by the observation in the Keller et al. (1984) study that the highest exposure produced convulsions on one or more occasions during the treatment period.

3.4. Genotoxicity

Monomethylhydrazine-induced mutagenesis was not observed in Ames *Salmonella*/microsome with activation (Matheson et al. 1978). In vivo tests in mice (dominant lethal, revertants in host-mediated assay), and dogs (micronuclei) were negative (reviewed in Trochimowicz 1994). However, in vitro chromosomal damage in human and rat tissue has been demonstrated, although in vivo liver DNA damage (as determined by DNA alkaline elution) was equivocal (reviewed in Trochimowicz 1994).

3.5. Carcinogenicity

A 1-y inhalation exposure study was reported by Kinkead et al. (1985) in which they examined the tumorigenic potential of monomethylhydrazine in dogs, rats, mice and hamsters. The experimental protocol was 6 h/d, 5 d/w with exposures of 0.02 (rats and mice only), 0.2, 2, and 5 ppm (rats and hamsters only) and followed by a 1-y observation period. There was no evidence of treatment-related carcinogenicity in dogs or rats. Mice exposed to 2 ppm exhibited an increased incidence of lung tumors, nasal adenomas, nasal polyps, nasal osteomas, hemangioma, and liver adenomas and carcinomas. At the end of the observation period, lung tumor incidences were 13/364, 17/354, 25/347, and 59/360 for the 0, 0.02, 0.2, and 2.0 ppm groups, respectively. In hamsters exposed to 2 or 5 ppm, there was an increase in nasal polyps, interstitial fibrosis of the kidney, and benign adrenal adenomas. An increase in nasal adenomas was seen in hamsters exposed to 5 ppm.

3.6. Summary

Acute lethality data for inhalation exposure to monomethylhydrazine are available for monkey, dog, rat, mouse, and hamster. Based upon the available data, hamsters appear to be the most resistant species, and the squirrel monkey and beagle dog are the most sensitive. The lethality of monomethylhydrazine appeared to follow a linear relationship for exposures up to 1 h. Most animal data focus on lethality as the toxicity endpoint with very limited exposure-response information available regarding nonlethal effects. The most significant effect reported in the acute exposure studies was the notable hemolytic response that was reversible upon cessation of exposure. However, the preponderance of the data suggest that there is little margin between exposures associated with nonlethal, reversible effects and those that result in death.

Limited animal data suggest little reproductive and developmental toxicity potential for monomethylhydrazine at doses that do not result in overt maternal intoxication.

Inhalation of monomethylhydrazine was not carcinogenic in rats or dogs, but mice exposed at 2 ppm for 1 y exhibited an increased incidence of lung tumors, nasal adenomas, nasal polyps, nasal osteomas, hemangioma, and liver adenomas and carcinomas. Hamsters exposed at 2 or 5 ppm exhibited an increased incidence in nasal polyps, interstitial fibrosis of the kidney, and benign adrenal adenomas. An increase in nasal adenomas was seen in hamsters exposed at 5 ppm.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Dost et al. (1966) reported that approximately 45% of [^{14}C]-monomethylhydrazine administered intraperitoneally (5.5 mg/kg) to rats was excreted as $^{14}CO_2$ (≈20%) or $^{14}CH_4$ (≈25%) over a 24-h period. However, at higher doses (11 and 22 mg/kg), the fraction exhaled as ^{14}C in CO_2 or CH_4 decreased. At the lowest dose, 36% of the administered ^{14}C was detected in the urine. At 11 mg/kg, urinary ^{14}C increased slightly (44%) but decreased to 19.6% at the highest dose. Generally, at the higher doses, greater amounts of ^{14}C were retained in the tissues implying a rate-limited excretion. Pinkerton et al. (1967) showed that 25–48% of monomethylhydrazine or metabolites was excreted in the urine within 48 h after intraperitoneal injection. Peak plasma concentrations occurred at 2–4 h, and the highest concentrations of monomethylhydrazine and/or metabolites were detected in muscle, liver, kidney, bladder, and pancreas of rats, mice, dogs, and monkeys.

4.2. Mechanism of Toxicity

The precise mechanism of monomethylhydrazine toxicity is uncertain. In addition to the contact irritant effects, the acute toxicity of dimethylhydrazine exposure probably involves the central nervous system as exemplified by tremors and convulsions (Shaffer and Wands 1973) and behavioral changes at sublethal doses (Streman et al. 1969). Additionally, renal and hepatic toxicity and hemolytic effects imply alternate mechanisms of toxicity.

4.3. Structure-Activity Relationships

The comparative toxicity of hydrazine, and the symmetrical and asymmetrical isomers of dimethylhydrazine were reported by Jacobson et al. (1955). Rats and mice exposed to hydrazine, and rats exposed to symmetrical dimethylhydrazine exhibited restlessness, dyspnea, and convulsions with exophthalmos. Excessive salivation, vomiting, respiratory distress, and convulsions were reported for dogs exposed to asymmetrical dimethylhydrazine as well as monomethylhydrazine. Fourteen-day mortality in three groups of dogs (three dogs per group) exposed for 4 h to asymmetrical dimethylhydrazine at concentrations of 24, 52, or 111 ppm were 0/3, 1/3, and 3/3, respectively. For rodents, estimated LC_{50} values for hydrazine, asymmetrical dimethylhydrazine, and symmetrical dimethylhydrazine are shown in Table 3–8.

Jacobson et al. (1955) noted that the toxic actions of hydrazine and its methylated derivatives were similar; all are respiratory irritants and convulsants. However, monomethylhydrazine also induced severe intravascular hemolysis in dogs.

Witkin (1956) reported intravenous (iv), intraperitoneal (i.p.), and oral LD_{50} (lethal dose for 50% of the animals) values for mice and rats, and i.v. LD_{50} values for dogs. Similar to hydrazine, the route of administration had minimal

effect on the LD_{50} within species. Generally, monomethylhydrazine and the dimethylhydrazines appeared to be somewhat more toxic in mice than was hydrazine. Results of the Witkin (1956) study showed that the asymmetrical isomer of dimethylhydrazine was less acutely toxic than hydrazine or the other hydrazine derivatives.

TABLE 3–8 Lethality (LC50) of Hydrazine and Methylated Hydrazines in Rodents

Species	Hydrazine (ppm)	Monomethylhydrazine (ppm)	Symmetrical dimethylhydrazine (ppm)	Unsymmetrical dimethylhydrazine (ppm)
Rats	570 (4 h)	74 (4 h)	280–400 (4 h)	252 (4 h)
Mouse	252 (4 h)	56 (4 h)	ND	172 (4 h)
Hamster	ND	143 (4 h)	ND	392 (4 h)

Source: Jacobson et al. 1955.

Relative to other forms of hydrazine, House (1964) reported asymmetrical dimethylhydrazine to be less toxic to monkeys, rats, and mice. Mortalities over a 90-d inhalation exposure at 0.56 ppm (0.73 mg/m^3) were 20%, 98%, and 99% for monkeys, rats, and mice, respectively.

4.4. Other Relevant Information

4.4.1. Species Variability

Based upon the available data, hamsters appear to be more resistant than other tested species to the lethal effects of acute exposure to monomethylhydrazine. Within similar exposure durations, the data expressed as concentration×time (Ct) products suggest similar response sensitivity among squirrel monkeys, dogs, and mice. Based on 1-h LC_{50} values, the rhesus monkey and rats are somewhat more resistant to the lethal effects of monomethylhydrazine but not as resistant as hamsters. Squirrel monkeys and dogs, however, appear to be more sensitive than the rodents. These comparisons suggest species variability in the range of 2- to 3-fold.

4.4.2. Unique Physicochemical Properties

Although the high reactivity of hydrazine presented substantial problems regarding accurate and consistent measurement of experimental concentrations (see Section 3), this high reactivity does not appear to reside with monomethylhydrazine.

4.4.3. Concurrent Exposure Issues

Although data analyzing the adverse effects of concurrent exposure to hydrazines and other chemicals are not available, that may be an important issue, especially for those chemicals with irritant properties. Although not as reactive as hydrazine, monomethylhydrazine is reactive with strong oxidizing agents, thereby altering its effect on physiologic systems.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

In a study by MacEwen et al. (1970) using seven adult human volunteers, 10-min exposure to monomethylhydrazine (90 ppm, or 169 mg/m^3) resulted in irritation of the eyes, nose, and throat but did not cause excessive lacrimation or coughing. Clinical chemistry parameters for 60 d following the exposure were not significantly affected; a 3–5% increase in Heinz body formation at d 7 declined after 2 w. Additionally, spirometry tests revealed no exposure-related effects.

5.2. Summary of Animal Data Relevant to AEGL-1

Nonlethal toxicity data in animals consistent with AEGL-1 effects were available for monkeys and mice (Haun et al. 1970). Squirrel monkeys exposed to monomethylhydrazine at 75 ppm for 60 min (Ct=4,500 ppm·min) or 130 ppm for 30 min (Ct=3,900 ppm·min) did not produce notable signs of toxicity. There were no notable signs of toxicity reported for mice exposed at 50 ppm for 240 min (12,000 ppm·min), although the report is vague regarding the nonlethal effects for mice.

Although the human exposure data from the MacEwen et al. (1970) study were considered for deriving AEGL-1 values, the resulting values (2 ppm, 1 ppm, 0.5 ppm, and 0.5 ppm for the 30-min, 1-h, 4-h, and 8-h AEGLS, respectively; Appendix B) were not consistent with the AEGL-2 and AEGL-3 values derived from more robust data sets from laboratory species. The AEGL-1 values based upon the human data were at or below the odor threshold and above concentrations known to cause notable irritation. Furthermore, the available data indicate that there is little difference between exposures resulting in no response and those causing lethality. Consequently, it is believed that AEGL-1 values for monomethylhydrazine cannot be recommended (Table 3–9).

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Human data were not available for deriving an AEGL based upon nonlethal, irreversible effects of monomethylhydrazine exposure.

TABLE 3–9 AEGL-1 for Monomethylhydrazine

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

NR: Numeric values for AEGL-1 are not recommended because (1) studies suggest that notable toxic effects may occur at or below the odor threshold or other modes of sensory detection, (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. The absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without any adverse effects.

6.2. Summary of Animal Data Relevant to AEGL-2

There were no definitive data that described irreversible, nonlethal effects of acute exposure to monomethylhydrazine. However, data in dogs and monkeys were available that described serious but reversible effects. Rhesus monkeys exposed to monomethylhydrazine at 160 ppm (range, 145–170 ppm; Ct=8,700– 10,200 ppm·min) for 60 min exhibited signs of ocular irritation (Haun et al. 1970). Minor hematologic alterations were detected in these monkeys up to 4 w post-exposure. Jacobson et al. (1955) reported that beagle dogs exposed for 4 h to monomethylhydrazine at 15 ppm became hyperactive and exhibited retching, tremors, convulsions, and vomiting. None of these dogs died, but a notable hemolytic response was observed. All the dogs subsequently recovered (8 d post-exposure). In the Haun et al. (1970) study, beagle dogs exposed to monomethylhydrazine at 92 ppm for 1 h or at 180 ppm for 30 min exhibited a notable hemolytic response (decreased hematocrit, hemoglobin content, erythrocyte count, and elevated reticulocyte count). These effects were reversible upon cessation of exposure. Both the Haun et al. and Jacobson et al. studies provide findings affirming the hemolytic potential of monomethylhydrazine.

6.3. Derivation of AEGL-2

Although data are available indicating genotoxic and hyperplastic responses in animals exposed to monomethylhydrazine, the proposed AEGL-2 is not based upon potential carcinogenic response. Although no U.S. EPA slope factor is currently available for monomethylhydrazine, a previously available (but currently withdrawn) inhalation slope factor for 1,1-dimethylhydrazine was used to assess carcinogenic risk associated with an acute exposure (see Appendix 3). The analysis showed that AEGLs based upon acute toxicity were more appropriate.

TABLE 3–10 AEGL-2 for Monomethylhydrazine

AEGL Level	30 min	1 h	4 h	8 h
AEGL-2	1.8 ppm 3.4 mg/m^3	0.90 ppm 1.7 mg/m^3	0.23 ppm 0.43 mg/m^3	0.11 ppm 0.21 mg/m^3

An AEGL-2 can be derived based upon hemolysis in rhesus monkeys following a 1-h exposure to monomethylhydrazine at 160 ppm (Haun et al. 1970). Although this exposure produced a hemolytic response with no mortality, it appears to be very close to the lethality threshold (see Section 7.3) and is nearly identical to the estimated 1-h LC_{50} of 162 ppm. The animal data, in total, affirm the contention of a very narrow threshold between exposure associated with lethality and those causing nonlethal, reversible effects. Data on systemic toxicity in the absence of monomethylhydrazine-induced lethality are virtually nonexistent. For these reasons, it was the consensus of the NAC/AEGL that the AEGL-2 values for monomethylhydrazine should reflect the steep exposure-response relationship known for monomethylhydrazine. This was achieved by 3-fold reduction in the AEGL-3 values. These values are affirmed by the similar values achieved using different data sets (Appendix B) and also reflect the uncertainty factors for interspecies variability (uncertainty factor=3) and intraspecies variability (uncertainty factor=3) that were applied to derive the AEGL-3 values (see Section 7.3). The AEGL-2 values are shown in Table 3– 10.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

Human data were not available for deriving an AEGL based upon lethality resulting from monomethylhydrazine exposure.

7.2. Summary of Animal Data Relevant to AEGL-3

Data on the lethality of monomethylhydrazine are available for several laboratory species (Jacobson et al. 1955; Haun et al. 1970; MacEwen and Vernot 1975). These reports provided 1-h LC_{50} values of 162, 82, 96, 244, 122, and 991 ppm for rhesus monkeys, squirrel monkeys, beagle dogs, rats, mice, and hamsters, respectively. Based on these data, the squirrel monkeys and beagle dogs appeared to be the most sensitive species. However, the rhesus

monkey may be a more appropriate model for human exposures due to greater similarities in size and respiratory tract anatomy relative to the other laboratory species.

7.3. Derivation of AEGL-3

The AEGL-3 values were derived based upon the 1-h LC_{50} value of 82 ppm reported for squirrel monkeys (Haun et al. 1970). As previously noted, there appears to be a critical and narrow threshold between an exposure that induces only minimal toxicity and one that causes death. For squirrel monkeys, 1-h exposure to a mean concentration of 82 ppm (range, 70–95 ppm) killed two of four animals. For derivation of the AEGL-3, the lethality threshold for squirrel monkeys was estimated by a 3-fold reduction of the LC_{50} (82 ppm) to obtain a value of 27.3 ppm. This estimate can be justified by the known steep exposure-response relationship for the toxic effects of monomethylhydrazine, and the fact that the resulting 27.3-ppm value represents an exposure concentration that does not produce overt toxicity in test animals.

The derived lethality threshold value of 27.3 ppm was adjusted by a total uncertainty factor of 10 (each uncertainty factor of 3 is the geometric mean of 10, which is 3.16; hence, 3.16.×3.16=10). An uncertainty factor of 3 was applied for interspecies variability with the following justification. One-hour LC_{50}s were determined in the monkey, dog, rat, and mouse. The LC_{50} values ranged from 82 ppm in the squirrel monkey to 244 ppm in the mouse, differing by a factor of approximately 3. The squirrel monkey data (1-h LC_{50}=82 ppm) was used to determine the AEGL-3, because this species appeared to be the most sensitive to monomethylhydrazine toxicity and because it was a species more closely related to humans. An uncertainty factor of 3 for protection of sensitive individuals was applied to reflect individual variability less than an order of magnitude. Although the mechanism of toxicity is uncertain and sensitivity among individuals may vary, the exposure-response relationship is very steep for each species tested, thereby suggesting limited variability in response to inhaled monomethylhydrazine. Furthermore, it is likely that acute monomethylhydrazine toxicity at least initially is a function of the extreme reactivity of monomethylhydrazine. The interaction of the highly reactive monomethylhydrazine with tissues (e.g., pulmonary epithelium) is not likely to vary greatly among individuals.

Because a regression analysis of lethality data for squirrel monkeys and dogs showed an approximately linear response (n = 0.97 and 0.99, respectively, see Appendix B), the lethality threshold estimate (27.3 ppm) was linearly scaled ($C^1 \times t=k$) to the AEGL time periods often Berge et al. (1986) (Appendix A).

TABLE 3–11 AEGL-3 for Monomethylhydrazine

AEGL Level	30 min	1 h	4 h	8 h
AEGL-3	5.5 ppm 10.3 mg/m^3	2.7 ppm 5.1 mg/m^3	0.68 ppm 1.3 mg/m^3	0.34 ppm 0.64 mg/m^3

The resulting AEGL-3 values are shown in Table 3–11. Conversion of animal exposure data to human equivalent concentrations based upon minute volume and body weight relationships was not appropriate. Such a conversion predicted that monkeys and dogs would be more sensitive than rodents, a contention that is not supported by the animal data. Furthermore, the conversion to human equivalent concentrations assumes 100% absorption of inhaled monomethylhydrazine; such absorption efficiency has not been verified.

8. SUMMARY OF PROPOSED AEGLS

8.1. AEGL Values and Toxicity Endpoints

A summary of the proposed AEGLS for monomethylhydrazine and their relationship to one another are shown in Table 3–12. For the development of AEGL values for monomethylhydrazine, toxicity endpoints specific for each of the three AEGL levels were not available, thereby necessitating the adjustment of available exposures to estimate AEGL-specific effect levels (e.g., adjustment of LC_{50} values to estimate a lethality threshold for AEGL-3). For monomethylhydrazine, an AEGL-1 was not considered to be appropriate, because notable toxicity may occur at or below the odor threshold. The AEGL-2 values were derived by reduction of the AEGL-3 values such that they would be protective of serious toxic responses yet reflect the steep exposure-response relationship known for monomethylhydrazine toxicity. The AEGL-3 was derived from data in nonhuman primates and, based on the available data, reflects a valid estimate of a lethality threshold for acute exposure to monomethylhydrazine.

An estimation of AEGLs based upon carcinogenic potential resulting from a single short-term exposure was conducted (Appendix C), and the assessment revealed that AEGLs derived from carcinogenic toxicity for a theoretical excess lifetime 10^{-4} carcinogenic risk exceeded AEGL-3 values based on noncancer endpoints. These estimates were derived from long-term exposure studies showing a tumorigenic response that is believed secondary to repeated tissue injury in mice. There are no acute inhalation exposure studies demonstrating a tumorigenic response to hydrazine or its methylated derivatives.

TABLE 3–12 Relationship of AEGL Values for Monomethylhydrazine

Classification	30 min	1 h	4 h	8 h
AEGL-1	NA	NA	NA	NA
AEGL-2	1.8 ppm	0.90 ppm	0.23 ppm	0.11 ppm
	3.84 mg/m^3	1.7 mg/m^3	0.43 mg/m^3	0.21 mg/m^3
AEGL-3	5.5 ppm	2.7 ppm	0.68 ppm	0.34 ppm
	10.3 mg/m^3	5.1 mg/m^3	1.3 mg/m^3	0.64 mg/m^3

8.2. Comparison with Other Standards and Criteria

In Table 3–13 the AEGLs are compared with existing standards and criteria. All currently available exposure standards and guidelines for monomethylhydrazine are shown.

8.3. Data Adequacy and Research Needs

Human data from controlled studies affirm that mild irritation of the eyes, nose and throat may occur following acute exposures to relatively low levels of monomethylhydrazine. Because animal studies suggest that notable toxicity may occur at or below the odor threshold or other sensory means of detection, and a narrow margin exists between exposures with no toxic response and those with significant toxicity, no AEGL-1 values were derived. However, animal data were considered appropriate for developing scientifically defensible AEGL-2 and AEGL-3 values. Lethality data were available for several animal species that permitted development of scientifically defensible AEGL-3 values. Dose-response data pertaining to serious or irreversible nonlethal effects in humans were not available, but limited data in animals suggested neurologic involvement. Available animal data also suggested that there may be little margin between nonlethal and lethal effects, and this was reflected in the uncertainty factor adjustments used in the development of the AEGL values. The available data for hydrazine and its methylated derivatives suggest that a tumorigenic response may occur following repeated long-term exposures that cause repetitive tissue damage. Because AEGLs are applicable to rare events or single once-in-a-lifetime exposures to a limited geographic area and small population, the AEGL values based on noncarcinogenic endpoints were considered to be most appropriate.

The most notable data deficiency is the absence of a well-defined exposure response relationship for monomethylhydrazine toxicity related to AEGL-2 effects. This deficiency precluded a definitive determination of the thresholds

for AEGL-2 effects and understanding of the full spectrum of effects resulting from acute exposure to this chemical. To this end, a well-designed study with a protocol defining a range of exposures that includes a maximum-tolerated exposure as well as a no-effect-level exposure would be useful in reducing areas of uncertainty that have been identified in the course of AEGL development.

TABLE 3–13 Extant Standards and Guidelines for Methylhydrazine

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1		NR	NR	NR	NR
AEGL-2		1.8 ppm	0.90 ppm	0.23 ppm	0.11 ppm
AEGL-3		5.5 ppm	2.7 ppm	0.68 ppm	0.34 ppm
ERPG-1[a]					
ERPG-2					
ERPG-3					
NRC SPEGL[b]			0.24 ppm	0.06 ppm	0.03 ppm
NRC STPL[c]	9 ppm	3 ppm	1.5 ppm		
NIOSH IDLH[d]		20 ppm			
OSHA PEL[e]	0.2 ppm				
ACGIH TLV-TWA[f]					0.01 ppm

NR: Not recommended. Numeric values for AEGL-1 are not recommended because (1) studies suggest that notable toxic effects may occur at or below the odor threshold or other modes of sensory detection, (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. The absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without any adverse effects.

[a]ERPGs (emergency response planning guidelines) are under development and review.

[b]NRC 1985; SPEGL, short-term public emergency guidance level.

[c]NRC 1996; STPL, short-term public limit.

[d]NIOSH 1994, with cancer notation; IDLH, immediately dangerous to life and health.

[e]OSHA 1993; PEL, permissible exposure limit.

[f]ACGIH 1999; TLV, Threshold Limit Value; 8-h time-weighted average (TWA) with skin notation.

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Appendixes

APPENDIX A DERIVATION OF AEGL VALUES Derivation of AEGL-1

Key study:	An AEGL-1 was considered to be inappropriate because significant irritation and possible toxic effects may occur at concentrations at or below the odor threshold and because of the exposure-response relationship exhibited by available toxicity data.

Derivation of AEGL-2

Key study:	Haun et al. 1970
Toxicity endpoint:	AEGL-2 values were based upon a 3-fold reduction in the AEGL-3 values. This estimate of a threshold for irreversible effects was justified because of the absence of exposure-response data related to irreversible or other serious, long-lasting effects and the steep dose-response relationship indicated by the data that was available on monomethylhydrazine
Uncertainty factors:	See discussion in the AEGL-3 section because the AEGL-2 is 1/3 of the AEGL-3.
Time scaling:	Not directly applicable; AEGL-2 values derived from 3-fold downward adjustment of AEGL-3 values.
30-min AEGL-2:	AEGL-3 (5.5 ppm)/3=1.8 ppm
1-h AEGL-2:	AEGL-3 (2.7 ppm)/3=0.91 ppm
4-h AEGL-2:	AEGL-3 (0.68 ppm)/3=0.23 ppm
8-h AEGL-2:	AEGL-3 (0.34 ppm)/3=0.11 ppm

Derivation of AEGL-3

Key study:	Haun et al. (1970)

Toxicity endpoint:	1-h LC_{50} of 82 ppm in female squirrel monkeys; lethality threshold estimated as a 3-fold reduction of the LC_{50} (82 ppm/3=27.3 ppm)
Uncertainty factors:	Interspecies: A factor of 3 was used. One-hour LC_{50}s were determined in the monkey, dog, rat, and mouse. The LC_{50} values ranged from 82 ppm in the squirrel monkey to 244 ppm in the mouse, differing by a factor of approximately 3. The squirrel monkey estimated threshold value of 27.3 ppm calculated above was used to determine the AEGL-3 value. Because the species used was the most sensitive to monomethylhydrazine toxicity and the most closely related to humans, an uncertainty factor of 3 is justified.
Intraspecies:	A factor of 3 was used. Although the mechanism of toxicity is uncertain and sensitivity among individuals may vary, the exposure-response relationship is steep, suggesting limited variability in the toxic response to methylhydrazine. Furthermore, it is likely that acute toxic responses are, at least initially, a function of the extreme reactivity of methylhydrazine. The interaction of the highly reactive monomethylhydrazine with tissues (e.g., pulmonary epithelium) is not likely to greatly vary among individuals.
Calculations:	27.3 ppm/10=2.73 ppm $C^1 \times t = k$ 2.73 ppm×60 min=163.8 ppm·min
Time scaling:	$C^1 \times t = k$ (ten Berge et al. 1986) $(27.3 \text{ ppm})^1 \times 60 \text{ min} = 163.8 \text{ ppm·min}$; regression analysis of the squirrel monkey lethality data suggested a near linear relationship
30-min AEGL-3:	$C^1 \times 30 \text{ min} = 163.8 \text{ ppm·min}$ **C=5.5** ppm
1-h AEGL-3:	$C^1 \times 60 \text{ min} = 163.8 \text{ ppm·min}$ **C=2.7** ppm
4-h AEGL-3:	$C^1 \times 240 \text{ min} = 163.8 \text{ ppm·min}$ **C=0.68** ppm
8-h AEGL-3:	$C^1 \times 480 \text{ min} = 163.8 \text{ ppm·min}$ C=0.34 ppm

APPENDIX B TIME SCALING CALCULATIONS FOR MONOMETHYLHYDRAZINE AEGLS

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

Two data sets of LC_{50} values for different time periods of exposure were analyzed using a linear regression analysis of the log-log transformation of a plot of C vs t to derive values of n for monomethylhydrazine.

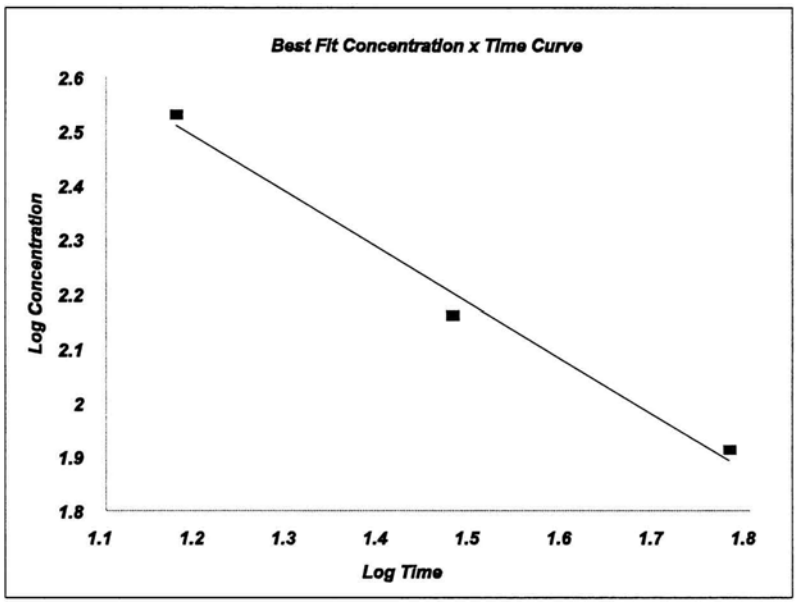
Monomethylhydrazine monkey data from Haun et al. 1970

The LC_{50} values for 15, 30, and 60 min were 340, 145, and 82 ppm, respectively.

Time	Conc.	Log Time	Log Conc.
15	340	1.1761	2.5315
30	145	1.4771	2.1614
60	82	1.7782	1.9138
n=0.97			

Calculated LC_{50} values:

Min	Conc.
30	159.30
60	78.23
240	18.87
480	9.27



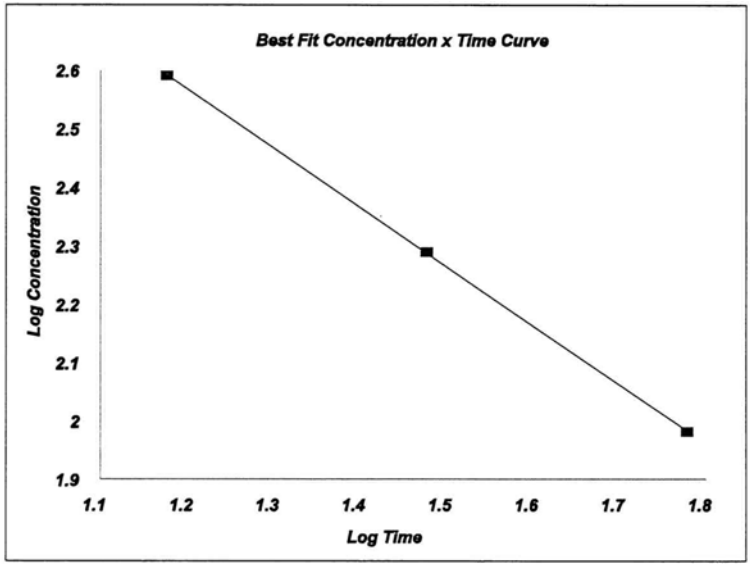
Monomethylhydrazine dog data from Haun et al. 1970

The LC_{50} values for 15, 30, and 60 min were 390, 195, and 96 ppm, respectively.

Time	Conc.	Log Time	Log Conc.
15	390	1.1761	2.5911
30	195	1.4771	2.2900
60	96	1.7782	1.9823
n=0.99			

Calculated LC_{50} values:

Min	Conc.
30	193.99
60	96.25
240	23.69
480	11.75



APPENDIX C CARCINOGENICITY ASSESSMENT FOR MONOMETHYLHYDRAZINE AEGLS

Neither an inhalation nor an oral slope factor is currently available for monomethylhydrazine. Slope factors for 1,1-dimethylhydrazine and 1,2-dimethylhydrazine were available but have been withdrawn from the U.S. EPA Integrated Risk Information System (IRIS) (U.S. EPA 1986). For a preliminary carcinogenicity assessment, the withdrawn inhalation slope factor for 1,1-dimethylhydrazine (cited in ATSDR 1994) will be used as a surrogate for monomethylhydrazine. The assessment follows previously described methodologies (NRC 1985; Henderson 1992).

The withdrawn slope factor for 1,1-dimethylhydrazine was 3.5 $(mg/kg \cdot d)^{-1}$, which, based upon a human inhalation rate of 20 m^3/d and a body weight of 70 kg, is equivalent to 1 $(mg/m^3)^{-1}$.

To convert to a level of monomethylhydrazine that would cause an excess cancer risk of 10^{-4}:

Risk of $1\times10^{-4}=(1\times10^{-4}/1)\times1$ mg/m^3$=1\times10^{-4}$ mg/m^3 (virtually safe dose).

To convert a 70-y exposure to a 24-h exposure:

24-h exposure=d×25,600

$=(1\times10^{-4}$ mg/m$^3)\times25{,}600$ d

=2.56 mg/m^3.

Adjustment to allow for uncertainties in assessing potential cancer risks for short-term exposures under the multistage model (Crump and Howe 1984):

(2.56 mg/m^3)/6=0.4 mg/m^3 (0.2 ppm).

Therefore, based upon the potential carcinogenicity of monomethylhydrazine, an acceptable 24-h exposure would be 0.4 mg/m^3 (0.2 ppm).

If the exposure is limited to a fraction (f) of a 24-h period, the fractional exposure becomes 1/f×24 h (NRC 1985).

24-h exposure=0.4 mg/m^3 (0.2 ppm)

8-h=1.2 mg/m^3 (0.5 ppm)

4-h=2.4 mg/m^3 (1 ppm)

1-h=9.6 mg/m^3 (5 ppm)

0.5-h=19.2 mg/m^3 (10 ppm)

Because the AEGLs based upon acute toxicity were equivalent to or lower than the values derived based upon potential carcinogenicity, the acute toxicity data were used for the proposed AEGLs for monomethylhydrazine. Additionally, available data on monomethylhydrazine and hydrazine suggest that long-term, repeated exposures may be necessary for tumorigenic effects. There are no data available that demonstrate a tumorigenic response following acute inhalation exposure. For 10^{-5} and 10^{-6} risk levels, the 10^{-4} values are reduced by 10-fold or 100-fold, respectively.

An alternate cancer assessment was performed using the data of Kinkead et al. (1985). In this study, mice exposed to monomethylhydrazine (0, 0.02, 0.2, or 2.0 ppm) 6 h/d, 5 d/w for 1 y followed by a 1-y observation period. At the end of the observation period, lung tumor incidences were 13/364, 17/354, 25/347, and 59/360 for the 0, 0.02, 0.2, and 2.0 ppm groups, respectively. The assessment follows previously described methodologies (NRC 1985; Henderson 1992). GLOBAL86 was used to obtain a virtually safe dose (VSD) of 2.1×10^{-6} mg/m^3.

VSD=2.1×10^{-6} mg/m^3.

To convert a 70-y exposure to a 24-h exposure:

24-h exposure=d×25,600

=(2.1×10^{-6} mg/m^3)×25,600 d

=5.4×10^{-2} mg/m^3.

Adjustment to allow for uncertainties in assessing potential cancer risks for short-term exposures under the multistage model (Crump and Howe 1984):

(5.4×10^{-2} mg/m^3)/6=0.9 mg/m^3.

Therefore, based upon the potential carcinogenicity of monomethylhydrazine, an acceptable 24-h exposure would be 0.9 mg/m^3.

If the exposure is limited to a fraction (f) of a 24-h period, the fractional exposure becomes 1/f×24 h (NRC 1985).

24-h exposure=0.9 mg/m^3 (0.5 ppm)

8-h=2.7 mg/m^3 (1 ppm)

4-h=5.4 mg/m^3 (3 ppm)

1-h=21.6 mg/m^3 (11 ppm)
0.5-h=43.2 mg/m^3 (23 ppm)

Because the AEGLs based upon acute toxicity were equivalent to or lower than the values derived based on potential carcinogenicity, the acute toxicity data were used for the proposed AEGLs for monomethylhydrazine. Additionally, available data on monomethylhydrazine and hydrazine suggest that long-term, repeated exposures may be necessary for tumorigenic effects. There are no data available that demonstrate a tumorigenic response following acute inhalation exposure. For 10^{-5} and 10^{-6} risk levels, the 10^{-4} values are reduced by 10-fold or 100-fold, respectively.

APPENDIX D DERIVATION SUMMARY FOR ACUTE EXPOSURE GUIDELINES FOR MONOMETHYLHYDRAZINE (CAS No. 60–34–4)

AEGL-1 Values-Monomethylhydrazine

30 min	1 h	4 h	8 h
Not recommended	Not recommended	Not recommended	Not recommended

Reference: Not applicable
Test Species/Strain/Number: Not applicable
Exposure Route/Concentrations/Durations: Not applicable
Effects: Not applicable
Endpoint/Concentration/Rationale: Not applicable
Uncertainty Factors/Rationale: Not applicable
Modifying Factor: Not applicable
Animal to Human Dosimetric Adjustment: Not applicable
Time Scaling: Not applicable
Data Adequacy: Both animal and human data affirm that low level exposure will cause mild irritation of the respiratory tract and that there is likely to be little margin between AEGL-1 type effects and more serious effects. Numeric values for AEGL-1 are not recommended because (1) studies suggest that notable toxic effects may occur at or below the odor threshold or other modes of sensory detection, (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. The absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without any adverse effects.

AEGL-2 Values-Monomethylhydrazine

30 min	1 h	4 h	8 h
1.8 ppm	0.90 ppm	0.23 ppm	0.11 ppm

Reference: Haun, C.C., J.D.MacEwen, E.H.Vernot, and G.F.Egan. 1970. Acute inhalation toxicity of monomethylhydrazine vapor. Am. J. Ind. Hyg. Assoc. 31:667–677

Test Species/Strain/Sex/Number: Squirrel monkeys, 2–4 males/group

Exposure Route/Concentrations/Durations: Inhalation; exposure at 300, 340, or 376 ppm for 15 min; 130, 150, or 170 ppm for 30 min; 75, 85, or 90 ppm for 60 min

Effects: Data specifically identifying serious, irreversible effects consistent with the AEGL-2 definition were not available. The lethality data are shown in the summary table for AEGL-3.

Endpoint/Concentration/Rationale: In the absence of data specifically identifying AEGL-2 endpoints, the AEGL-2 was based upon a 3-fold reduction of the AEGL-3 values for all time periods. Given the steepness of the exposure-dose curve, it is believed that a 3-fold downward adjustment would be protective against serious long-term, irreversible effects, or the inability to escape.

Uncertainty Factors/Rationale: Total uncertainty factor: 10

Interspecies: 3

Intraspecies: 3

Modifying Factor: None

Animal to Human Dosimetric Adjustment: None applied, insufficient data

Time Scaling: $C^n \times t = k$, where n=1; see discussion for AEGL-3, because AEGL-2 values were derived by 3-fold reduction of AEGL-3 values

Data Adequacy: In the absence of relevant data, the AEGL-2 values were derived by downward adjustment of the AEGL-3 values. The narrow margin between the AEGL-2 and AEGL-3 values for monomethylhydrazine reflect the steep exposure-response relationship suggested by available data. The absence of toxicologic data regarding AEGL-2 specific toxic endpoints is a notable deficiency.

AEGL-3 Values-Monomethylhydrazine

30 min	1 h	4 h	8 h
5.5 ppm	2.7 ppm	0.68 ppm	0.34 ppm

Reference: Haun, C.C., J.D.MacEwen, E.H.Vernot, and G.F.Egan. 1970. Acute inhalation toxicity of monomethylhydrazine vapor. Am. J. Ind. Hyg. Assoc. 31:667–677

Test Species/Strain/Sex/Number: Squirrel monkeys, 2–4 males/group

Exposure Route/Concentrations/Durations: Inhalation; exposure at 300, 340, or 376 ppm for 15 min; 130, 150, or 170 ppm for 30 min; 75, 85, or 90 ppm for 60 min

Effects:

Exposure	Lethality	ratio	
15 min	300 ppm	1/4	
	340 ppm	1/2	
	376 ppm	3/3	
30 min	130 ppm	0/3	
	150 ppm	2/3	
	170 ppm	2/2	
60 min	75 ppm	0/2	
	85 ppm	2/4	60-min LC_{50}=82 ppm
	90 ppm	2/2	

Endpoint/Concentration/Rationale: The 60-min LC_{50} of 82 ppm was reduced to 27.3 ppm by using a 3-fold adjustment as an estimate of the lethality threshold; the available data indicated the squirrel monkey to be the most sensitive species tested. That is a reasonable estimate of the lethality threshold, because monomethylhydrazine has a steep exposure-response curve, and data on other chemicals with similar dose response curves indicate that this approach represents a likely estimate of the threshold for lethality. For the 1-h exposure, 2/2 monkeys died at 90 ppm, 2/4 at 85 ppm, and 0/2 at 75 ppm. A similar spectrum of response is seen with the rhesus monkey and dog.

Uncertainty Factors/Rationale: Total uncertainty factor: 10

Interspecies: 3—1-h LC_{50}s were determined in the monkey, dog, rat, and mouse. The LC_{50} values ranged from 82 ppm in the squirrel monkey to 244 ppm in the mouse, differing by a factor of approximately 3. The squirrel monkey value of 82 ppm was used to determine the AEGL-3 value. Because the species used was the most sensitive to

monomethylhydrazine toxicity, and the most closely related to humans, an uncertainty factor of 3 is justified.
Intraspecies: 3—Although the mechanism of toxicity is uncertain and sensitivity among individuals may vary, the exposure-response relationship is steep, suggesting limited variability in the toxic response to monomethylhydrazine. Furthermore, it is likely that acute toxic responses are, at least initially, a function of the extreme reactivity of monomethylhydrazine. The interaction of the highly reactive monomethylhydrazine with tissues (e.g., pulmonary epithelium) is not likely to greatly vary among individuals.
Modifying Factor: None
Animal to Human Dosimetric Adjustment: None applied, insufficient data
Time Scaling: $C^n \times t = k$, where n=1 and k=163.8 ppm·min. A regression analysis of data from squirrel monkeys and dogs (Haun et al. 1970) for 15, 30, and 60-min indicated a near-linear relationship (n=0.97 and 0.99, respectively, for the monkey and dog data). It was the consensus of the National Advisory Committee to assume linearity (n=1).
Data Adequacy: Adequate lethality data were available for several species including nonhuman primates. Although the variability in response to the lethal effects of monomethylhydrazine among all species tested appeared to be relatively small (2- to 3-fold difference), the squirrel monkey appeared to be somewhat more sensitive. The AEGL values for monomethylhydrazine reflect the steep exposure-response relationship suggested by available data.

4

Dimethylhydrazine[1]

Acute Exposure Guideline Levels

SUMMARY

DIMETHYLHYDRAZINE occurs as symmetrical (1,2-dimethylhydrazine) and unsymmetrical (1,1-dimethylhydrazine) isomers. Unless otherwise specified, dimethylhydrazine refers to unsymmetrical dimethylhydrazine in this document. Both compounds are clear, colorless liquids. 1,1-Dimethylhydrazine is a component of rocket fuels and is also used as an adsorbent for acid gas, as a plant-growth control agent, and in chemical synthesis. Although it has been evaluated as a high-energy rocket fuel, commercial use of 1,2-dimethylhydrazine is limited to small quantities, and it is usually considered to be a research chemical. Because data are limited for 1,2-dimethylhydrazine, the acute exposure guideline level (AEGL) values for both isomers are based upon 1,1-dimethylhydrazine. Limited data suggest that 1,1-dimethylhydrazine may be somewhat more toxic than 1,2-dimethylhydrazine.

[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).

Data on acute exposures of humans to both isomers of dimethylhydrazine are limited to case reports of accidental exposures. Signs and symptoms of exposure include respiratory irritation, pulmonary edema, nausea, vomiting, and neurologic effects. However, definitive exposure data (concentration and duration) were unavailable for these accidents. The limited data in humans suggest that the nonlethal toxic response to acute inhalation of dimethylhydrazine is qualitatively similar to that observed in animals. No information was available regarding lethal responses in humans. In the absence of quantitative data in humans, the use of animal data is considered a credible approach for developing AEGL values.

Toxicity data of varying degrees of completeness are available for several laboratory species, including, rhesus monkeys, dogs, rats, mice, and hamsters (Weeks et al. 1963). Most of the animal studies were conducted using 1,1-dimethylhydrazine, although limited data suggest that 1,2-dimethylhydrazine exerts similar toxic effects. Minor nonlethal effects such as respiratory tract irritation appear to occur at cumulative exposures of less than 100 parts per million multiplied by hours (ppm·h). At cumulative exposures of 100 ppm·h or slightly greater than this level, more notable effects have been reported, including, muscle fasciculation, behavioral changes, tremors, and convulsions. Lethality has been demonstrated when cumulative exposures exceed these levels only slightly. The available data suggest that there is a very narrow margin between exposures resulting in no significant toxicity and those causing substantial lethality (the lethal concentration for 50% of the animals (LC_{50}) ≈ 900–2,000 ppm·h).

Developmental toxicity of dimethylhydrazines has been demonstrated in rats following parenteral administration of maternally toxic doses.

Both isomers of dimethylhydrazine have been shown to be carcinogenic in rodents following chronic oral exposure and 6-mon inhalation exposure to 1,1-dimethylhydrazine. Increased tumor incidence was observed in mice, although these findings are compromised by the contaminant exposure to dimethylnitrosamine. An increased incidence of lung tumors and hepatocellular carcinomas was also seen in rats but not in similarly exposed hamsters. The U.S. Environmental Protection Agency (U.S. EPA) inhalation slope factors are currently unavailable for dimethylhydrazine.

AEGL-1 values for dimethylhydrazine are not recommended because of inadequate data to develop health-based criteria and because the concentration-response relationship for dimethylhydrazine indicated that a very narrow margin exists between exposures producing no toxic response and those resulting in significant toxicity.

Behavioral changes and muscle fasciculations in dogs exposed for 15 min to 1,1-dimethylhydrazine at 360 ppm (Weeks et al. 1963) served as the basis for

deriving AEGL-2 values. Available lethality data in dogs and rats indicated a near linear temporal relationship (n=0.84 and 0.80 for dogs and rats, respectively). For temporal scaling ($C^1 \times t = k$) to derive values for AEGL-specific exposure durations, a linear concentration-response relationship, n=1, was used. (C=exposure concentration, t=exposure duration, and k=a constant.) This value was adjusted by an uncertainty factor of 30. An uncertainty factor of 3 for interspecies variability was applied, because the toxic response to dimethylhydrazine was similar across the species tested. This was especially true for lethality among rats, mice, dogs, and hamsters with LC_{50} values for time periods ranging from 5 min to 4 h. A comparison of LC_{50} values for the same exposure durations in these species did not vary more than 3-fold. An uncertainty factor of 10 was used for intraspecies variability. This was based primarily on the variability observed in dogs in which responses varied from one of extreme severity (vomiting, tremors, convulsions, and death) to no observable effects. Additionally, Weeks et al. (1963) indicated that dogs previously stressed by auditory stimuli may have potentiated their response to dimethylhydrazine. Based on these data, it was assumed that humans may be equally divergent in their response to dimethylhydrazine as a result of similar stresses.

The AEGL-3 values were derived from the 1-h LC_{50} (981 ppm) for 1,1-dimethylhydrazine in dogs (Weeks et al. 1963). Because of the steep slope of the dose-response curve of 1,1-dimethylhydrazine, the 1-h LC_{50} of 981 ppm was adjusted to estimate the lethality threshold of 327 ppm. An uncertainty factor of 3 for interspecies variability was applied for several reasons. The 4-h LC_{50} values for mouse, rat, and hamster differ by a factor of approximately 2 and were consistent with the dog data when extrapolated from 1 h using n=1. The more sensitive species, the dog, was used to derive the AEGL-3 values. An uncertainty factor of 10 for intraspecies variability was used since a broad spectrum of effects were seen including behavioral effects, hyperactivity, fasciculations, tremors, convulsions, and vomiting. The mechanism of toxicity is uncertain, and sensitivity among individuals may vary. Following identical exposures, the responses of the dogs varied from one of extreme severity (vomiting, tremors, convulsions, and death) to no observable effects. Temporal scaling as previously described was applied to obtain exposure values for AEGL-specific exposure periods.

Verified inhalation and oral slope factors were unavailable from U.S. EPA for dimethylhydrazine. A cancer assessment based upon the carcinogenic potential (withdrawn cancer slope factors) of dimethylhydrazine revealed that AEGL values for a theoretical excess lifetime 10^{-4} carcinogenic risk exceeded the AEGL-2 values that were based on noncancer endpoints. Because the risk for dimethylhydrazine exposure was estimated from nonverified sources and because AEGLs are applicable to rare events or single once-in-a-lifetime expo

sures to a limited geographic area and small population, the AEGL values based on noncarcinogenic endpoints were considered to be more appropriate. The derived AEGLs are listed in Table 4–1.

1. INTRODUCTION

Dimethylhydrazine occurs as 1,2-dimethylhydrazine and 1,1-dimethylhydrazine isomers. Both compounds are clear, colorless liquids (Trochimowicz 1994). 1,1-Dimethylhydrazine is a component of jet and rocket fuels and is also used as an absorbent for acid gas, as a plant-growth control agent, and as a feedstock in chemical syntheses. Although it has been evaluated as a high-energy rocket fuel, commercial use of 1,2-dimethylhydrazine is limited to small quantities, and it is usually considered to be a research chemical (Trochimowicz 1994).

Trochimowicz (1994) published a review of the toxicology of dimethylhydrazines with most of the data obtained from studies with 1,1-dimethylhydrazine. Early data on the pharmacologic and toxicologic effects of dimethylhydrazines in laboratory animals by various routes of administration were summarized and noted involvement of the central nervous system, lungs, liver, and kidneys as targets. In the 1950s, additional studies were conducted to assess the acute toxicity of various hydrazines in animals following various routes of exposure. The toxicology of dimethylhydrazines has also been reviewed by the National Research Council (NRC 1985).

For derivation of AEGL values, acute exposure studies are preferentially examined. Subchronic and chronic studies generally have not been included in the data analysis for AEGL derivation because of the great uncertainty in extrapolating such data to acute exposure scenarios. Such studies may be addressed when the data provided relate to effects following acute exposures, provide meaningful insight into understanding toxicity mechanisms, or can be used for other special considerations.

The primary physical and chemical data for dimethylhydrazines are presented in Table 4–2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No information was located regarding the acute lethality to humans following inhalation exposure to dimethylhydrazine.

TABLE 4–1 Summary of AEGL Values for 1,1- and 1,2-Dimethylhydrazines

Classification	30 min	1 h	4 h	8 h	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	Not recommended due to insufficient data; concentration-response relationships suggest little margin between exposures causing minor effects and those resulting in serious toxicity.[a]
AEGL-2 (Disabling)	6 ppm 14.7 mg/m^3	3 ppm 7.4 mg/m^3	0.75 ppm 2 mg/m^3	0.38 ppm 1 mg/m^3	Behavioral changes and muscle fasciculations in dogs exposed at 360 ppm for 15 min (Weeks et al. 1963)
AEGL-3 (Lethal)	22 ppm 54 mg/m^3	11 ppm 27 mg/m^3	2.7 ppm 6.6 mg/m^3	1.4 ppm 3.4 mg/m^3	Lethality threshold of 327 ppm for 1 h estimated from 1-h LC_{50} in dogs (Weeks et al. 1963)

Numeric values for AEGL-1 are not recommended because (1) the lack of available data, (2) data indicate that toxic effects may occur at or below the odor threshold, (3) the inadequate margin of safety that exists between the derived AEGL-1 and the AEGL-2, or (4) 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 4–2 Chemical and Physical Data for Dimethylhydrazines

Parameter	Value	Reference
Synonyms	1,1-dimethylhydrazine, unsymmetrical-dimethylhydrazine, asymmetrical-dimethylhydrazine UDMH, *N,N*-dimethylhydrazine, Dimazine; 1,2-dimethylhydrazine, symmetrical dimethylhydrazine, SDMH, *N,N′*-dimethylhydrazine	Budavari et al. 1989
Chemical formula	$(CH_3)_2N\text{-}NH_2$ (1,1-dimethylhydrazine) $CH_3\text{-}NH\text{-}NH\text{-}CH_3$ (1,2-dimethylhydrazine)	Trochimowicz et al. 1994
Molecular weight	60	U.S. EPA 1987
CAS Registry No.	57–14–7 (1,1-dimethylhydrazine) 540–73–8 (1,2-dimethylhydrazine)	Budavari et al. 1989
Physical description	liquid	U.S. EPA 1987
Solubility	soluble in water and alcohol; practically insoluble in ether	ACGIH 1996
Vapor pressure	156.8 mm Hg at 25°C (1,1-dimethylhydrazine) 69.6 mm Hg at 25°C (1,2-dimethylhydrazine)	Jacobson et al. 1955
Specific gravity	0.782 at 25°C	ACGIH 1996
Boiling/melting point/ flash point	63.9°C/–58°C/–15°C (closed cup)	Budavari et al. 1989
Odor threshold	6–14 ppm; ammonia-like odor	ACGIH 1996
Conversion factors in air	1 mg/m^3=0.41 ppm (unsymmetrical) 1 ppm=2.45 mg/m^3	Trochimowicz et al. 1994

2.2. Nonlethal Toxicity

2.2.1. Acute Exposure Case Reports

Information regarding human exposures to dimethylhydrazine are limited to a few case reports. Although case reports provide qualitative data regarding signs and symptoms of exposure, no exposure concentration data or precise exposure duration data were reported. Signs and symptoms of exposure included respiratory effects, nausea, vomiting, neurologic effects, pulmonary edema, and increased serum enzyme levels (reviewed in Trochimowicz et al. 1994).

Inhalation (approximately 90-min duration) by two workers of Aerozine-50 (a 1:1 (weight/weight) mixture of hydrazine and 1,1-dimethylhydrazine) resulted in odor detection followed by a complaint of headache, nausea, weakness, burning of the skin, tightness in the chest, and soreness of the throat by one man (Frierson et al. 1965). Pyridoxine successfully ameliorated all symptoms except the tightness in the chest; bilateral pulmonary edema, wet rales, and tachypnea were later detected upon clinical examination. Subsequent examination some weeks later revealed no hematologic, pulmonary, hepatic, or renal sequelae. The second worker, although donning an air supply upon recognition of exposure, suffered severe dyspnea that forced egress from the situation. This individual developed pulmonary edema but recovered after pyridoxine and oxygen therapy and rest. An additional four workers were exposed to high levels of Aerozine-50 (no specific concentration values available) for about 2 h experienced severe nausea and vomiting, which was also successfully treated with intravenous pyridoxine.

Shook and Cowart (1957) provided a brief report regarding two individuals exposed during an accidental spillage of 1,1-dimethylhydrazine. Although exposure concentration data were not available, it was noted that the two men were approximately 750 yards from the spill. After being exposed to the release, the men experienced choking and difficulty in breathing. Four hours later both subjects became extremely nauseated and retained the odor and taste of the chemical for an unspecified period of time. This case report also provided evidence of subclinical hepatotoxicity in a group of workers following several months of occupational exposure to low (but unspecified) concentrations of 1,1-dimethylhydrazine.

2.2.2. Epidemiologic Studies

Epidemiologic studies regarding human exposure to dimethylhydrazine were not available.

2.3. Developmental and Reproductive

No data were available regarding the potential reproductive and developmental toxicity of dimethylhydrazine in humans.

2.4. Genotoxicity

Human genotoxicity data applicable to AEGL development for dimethylhydrazine were not available.

2.5. Carcinogenicity

No data are available regarding the potential carcinogenicity of dimethylhydrazine in humans.

2.6. Summary

The human experience regarding exposure to dimethylhydrazines is limited to case reports describing severe but nonlethal effects following accidental acute exposures. There are limited data suggesting subclinical hepatotoxicity following subchronic occupational exposure to unspecified low levels of 1,1-dimethylhydrazine. No definite exposure concentrations or durations were available in these reports, and the data are not useful for quantitative derivation of AEGLs.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Acute lethality studies in laboratory species are summarized in the following sections. The LC_{50} and other lethality values from these studies are summarized in Table 4–3.

3.1.1 Nonhuman Primates

No data were available regarding lethality in nonhuman primates following acute exposures to dimethylhydrazines.

3.1.2. Dogs

Jacobson et al. (1955) reported the deaths of dogs following 4-h exposures to 1,1-dimethylhydrazine at concentrations of 24, 52, or 111 ppm (192-min exposure). Mortality was 0/3, 1/3, and 3/3 for the three exposure groups, respectively. All deaths or terminations (one dog in the high-exposure group was terminated in extremis) occurred within the first day of initiation of exposure. All three dogs in the highest exposure group exhibited vomiting, panting, and convulsions prior to death. The one dog that died in the 52-ppm group also exhibited these signs prior to death, while the two surviving dogs exhibited

TABLE 4–3 Summary of Lethality Data for Dimethylhydrazine in Laboratory Species

Species	Toxicity Value (ppm)	C×t (ppm·h)	Comments	Reference
Rat	4-h LC_{50}: 252 (1,1-DMH)	1,008		Jacobson et al. 1955
Rat	4-h: 338 (1,2-DMH)	1,352	50% mortality but not	Jacobson et al. 1955
	4-h: 285 (1,2-DMH)	1,140	statistically-derived LC_{50}	
	4-h: 210 (1,2-DMH)	840	20% mortality	
	4-h: 435 (1,2-DMH)	1,740	100% mortality	
Rat	4-h LC_{50}: 252 (1,1-DMH)	1,008	Mortality over 24 h	Weeks et al. 1963
	1-h LC_{50}: 1,410 (1,1-DMH)	1,410		
	30-min LC_{50}: 4,010 (1,1-DMH)	2,005		
	15-min LC_{50}: 8,230 (1,1-DMH)	2,058		
	5-min LC_{50}: 24,500 (1,1-DMH)	2,042		
Mouse	4-h LC_{50}: 172 (1,1-DMH)	688		Jacobson et al. 1955
Hamster	4-h LC_{50}: 392 (1,1-DMH)	1,568		
Dog	192 min: 111 (1,1-DMH)	355	100% mortality	Jacobson et al. 1955
	4-h: 52 (1,1-DMH)	208	33% mortality	
Dog	1-h LC_{50}: 981 (1,1-DMH)	981	Mortality over 24 h	Weeks et al. 1963
	15-min LC_{50}: 3,580 (1,1-DMH)	895		
	5-min LC_{50} 22,300 (1,1-DMH)	1,858		

Abbreviation: DMH: dimethylhydrazine.

nausea, panting, and incoordination, or no signs of toxicity. One dog in the low-exposure group also exhibited vomiting and convulsions but did not die. No changes were observed in hematologic values (hemoglobin level, red-blood-cell counts, leukocyte counts, prothrombin times) in any of the surviving dogs. Necropsy revealed pulmonary edema and patchy hemorrhage only in animals that had convulsions, possibly resulting from the seizures rather than direct test-article action. An LC_{50} was not estimated by the investigators.

In a study reported by Rinehart et al. (1960), three male beagle dogs were exposed to 1,1-dimethylhydrazine at 25 ppm 6 h/d, 5 d/w for 26 w. Although one dog died after the third exposure (equivalent to a Ct of 450 ppm·h), the exposure was discontinuous, making application of that result to AEGL development difficult. One of the other two dogs exhibited similar signs of toxicity without death and the other exhibited no sign of toxicity (see Section 3.2.2).

Weeks et al. (1963) studied the outcome of 1,1-dimethylhydrazine inhalation on mongrel dogs (groups of three) exposed for 5, 15, or 60 min to various concentrations. During exposure, signs of toxicity were limited to licking of the lips and nose, and vomiting. After the exposure, all dogs appeared dazed and depressed, and sharp noises induced shivering and cowering. Intermittent tonicoclonic convulsions (2–15 min duration) were observed in dogs just prior to death and in some dogs that survived. Dogs that survived appeared to be completely recovered by 48 h post-exposure, and all deaths occurred within 24 h. The LC_{50} values for the 5, 15, and 60-min exposures were 22,300, 3,580, and 981 ppm, respectively (Table 4–3). The slope of the exposure-response curve for 5-min exposures was steep (221.0, standard error (SE)=207.0); for 15 and 60 min, the slopes were 3.9 (SE=2.2) and 14.7 (SE=7.8), respectively). Because external auditory stimuli appeared to affect the response of dogs exposed to 1,1-dimethylhydrazine, additional experiments were carried out using dogs that were stressed by auditory, visual, and/or electrical stimuli. Generally, neurobehavioral responses were observed at exposure concentrations that previously had caused no response. For the 5-min exposure, one of two dogs that died was exposed to 1,1-dimethylhydrazine at 4,230 ppm. No dogs exposed for 15 min died, but tremors and vomiting occurred in two of four dogs exposed at 610 ppm, and one of three dogs exposed at 360 ppm exhibited muscle fasciculations. For the 60-min exposures, two of three dogs exposed at 400–500 ppm died, one of three dogs exposed at 200–250 ppm died, and one of four dogs exposed at 80–120 ppm exhibited slight tremors. Minimal response resulted from exposures to 1,1-dimethylhydrazine at 1,200, 400, and 100 ppm for 5, 15, and 60 min, respectively. A 1-h exposure at 96 ppm represents a no-observed-effect level for mongrel dogs. There were no gross or histopathologic changes observed in any dogs that could be attributed to exposure to the test article.

3.1.3. Rats

Jacobson et al. (1955) assessed the lethality of 1,2-dimethylhydrazine and 1,1-dimethylhydrazine in rats following a 4-h exposure. Lethality was assessed over a 14-d post-exposure variability in the response. For 1,1-dimethylhydrazine, an LC_{50} of 252 ppm was calculated, and an LC_{20} of 210 ppm (515 mg/m^3) was estimated from the exposure-response graphs in the report. The exposure-response curve was steep (slope = 8.65; SE = 2.8), suggesting very little variability among the test groups.

Preliminary studies with 1,2-dimethylhydrazine were also reported: 2/10, 5/10, and 5/5, rats died respectively, after a single 4-h exposure at 285, 338, or 435 ppm (Jacobson et al. 1955). During the exposure, the rats were restless and exhibited dyspnea, convulsions, and exophthalmos. Although an LC_{50} was not estimated, review of these data suggest that 1,2-dimethylhydrazine is somewhat less toxic under these experimental conditions in this species and strain. For 1,2-dimethylhydrazine, lethality was assessed over a 7-d period.

Weeks et al. (1963) exposed male rats (10 per group) to various concentrations of 1,1-dimethylhydrazine for periods of 5, 15, 30, 60, and 240 min. Rats exposed to 1,1-dimethylhydrazine showed signs of irritation (sneezing, eye closure, restlessness). In animals that died, deaths occurred within 24 h post-exposure and were preceded by alternating periods of tonicoclonic convulsions and depressed activity. For the 5-, 15-, 30-, 60-, and 240-min exposure periods, LC_{50} values of 24,500, 8,230, 4,010, 1,410, and 252 ppm were reported by the study authors (Table 4–3).

3.1.4. Mice

Acute toxicity assays using groups of 20 mice (strain not specified) exposed to 1,1-dimethylhydrazine for 4 h were conducted by Jacobson et al. (1955). During the exposure the mice were restless and exhibited dyspnea, convulsions, and exophthalmos. An LC_{50} of 172 ppm was reported and an LC_{20} of 140 ppm was estimated from the exposure-response curve presented by the study authors. Post-mortem examination of the mice revealed no significant histopathologic findings other than pulmonary edema and occasional, localized pulmonary hemorrhage. The hemorrhaging was, however, considered to be secondary to the observed convulsions and not a direct effect of dimethylhydrazine in those tissues. The exposure-response curve was steep (slope=8.52; SE=1.9), suggesting little variability among the test groups. Analytical concentrations of 1,1-dimethylhydrazine averaged 75% of nominal, which suggested that there were difficulties in accurately maintaining or measuring test article concentrations.

In a study reported by House (1964), groups of male ICR Swiss mice inhaled 1,1-dimethylhydrazine at a concentration of 0.56 ppm for 90 d. For the first 10 d of exposure, however, the mean concentration was 0.43 ppm (range: 0.22– 0.80 ppm). One mouse died during the first 5 d of exposure. No specific comments or observations were made for the first day of exposure. Gross and histopathologic examinations of mice exposed for the longer periods did not reveal any significant changes attributable to the treatment. Therefore, it may be inferred that 24-h exposure of mice to 1,1-dimethylhydrazine at 0.43 ppm represents a 1-d no-effect level.

3.1.5. Hamsters

The acute lethality of 1,1-dimethylhydrazine in hamsters was reported by Jacobson et al. (1955). Based on the estimated LC_{50} (392 ppm), hamsters were somewhat less sensitive than rats or mice. Similar to mice and rats, the slope of the exposure-response curve was steep (10.5; SE = 2.0), suggesting little variability in response.

3.2. Nonlethal Toxicity

3.2.1. Nonhuman Primates

In a U.S. Air Force study reported by House (1964), 10 rhesus monkeys were exposed continuously (24 h/d) to a mean concentration of 1,1-dimethylhydrazine at 0.56 ppm for 90 d (during the first 10 d, the average concentration was 0.43 ppm). Concentration excursions during the first 10 d ranged from 0.22 to 0.80 ppm. Although one monkey died at 41 d, there were no deaths or clinical signs of toxicity during the exposure period. Additionally, there were no significant alterations in clinical chemistry parameters throughout the exposure period; however, clinical data were obtained only at 30, 60, and 90 d during exposure, and no definitive observations were provided for acute exposure durations.

3.2.2. Dogs

Groups of three male beagle dogs were exposed to 1,1-dimethylhydrazine at 24 ppm for 4 h (Jacobson et al. 1955). During the exposure, one of the three dogs vomited and convulsed but recovered. The remaining dogs showed no signs of toxicity.

Exposure of three male beagle dogs to 1,1-dimethylhydrazine at 5 ppm for 6 h/d, 5 d/w for 26 w resulted in lethargy and minor body weight loss, especially after 2–3 w of exposure (Rinehart et al. 1960). There were no deaths among the test animals. There were no observations or data reported that were specific for exposures ≤24 h. In another group of dogs exposed at 25 ppm for similar durations, depression, salivation, emesis, diarrhea, ataxia, tonicoclonic convulsions, bradycardia, and fever occurred in one dog on the third day of exposure, but no signs were observed in the other dogs.

In a study reported by Weeks et al. (1963), the effects of stress on the toxic response to 1,1-dimethylhydrazine was examined. For this study, mongrel dogs were first stressed by auditory, visual, and/or electrical stimuli and subsequently subjected to varying concentrations of 1,1-dimethylhydrazine for 5, 15, or 60 min. Five-minute exposures of two dogs at concentrations as high as 1,200 ppm produced no signs of toxicity, while exposure at 1,550 ppm resulted in behavioral changes (depression), and exposure at 4,230 resulted in tremors and convulsions followed by the death (3 h post-exposure) of one of two dogs. Exposure of four dogs at 360 ppm for 15 min produced muscle fasciculations in one dog, while inhalation of 400 ppm resulted in no signs of toxicity in two dogs and mild behavioral changes in the remaining two dogs. Fifteen-minute exposure of two dogs at concentrations as high as 1,530 ppm did not result in death but produced tremors, vomiting and convulsions in both dogs; recovery was noted 24 h post-exposure. Additionally, 15-min exposure of dogs at 610 ppm produced tremors and vomiting. Exposure of five dogs to 1,1-dimethylhydrazine at 96 ppm for 60 min produced no signs of toxicity. Exposure of four dogs at 80–120 ppm for 60 min resulted in one dog experiencing slight tremors (recovery after 1 h), while 60-min exposure at 200–250 ppm resulted in slight tremors in one dog, no effects in another, and convulsions and death in a third dog.

3.2.3. Rats

House (1964) conducted 90-d continuous exposure studies of male Sprague-Dawley rats exposed to 1,1-dimethylhydrazine at average concentrations of 0.56 ppm. Mean exposure concentration over the first 10 d was 0.43 ppm. Definitive information regarding responses and biologic effects during the first day of exposure were not provided. Because laboratory data were recorded only at 30, 60, and 90 d, no inference could be made regarding potential effects of acute exposures from the House (1964) summary.

In a study reported by Rinehart et al. (1960), 30 Wistar rats were exposed for 6 h/d, 5 d/w to 1,1-dimethylhydrazine at 75 ppm for 26 w. Although no rats died during the exposure period, occasional tremors were observed. However, no time to effect was provided.

3.2.4. Mice

In the study by House (1964), groups of male ICR Swiss mice were exposed to 1,1-dimethylhydrazine (0.56 ppm) for 90 d. However, during the first 10 d of the exposure period, the mean concentration was 0.43 ppm (range: 0.22 to 0.80 ppm). Because laboratory data were recorded only at 30, 60, and 90 d, no inferences could be made regarding potential effects of acute exposures.

3.3. Developmental and Reproductive Toxicity

The only available data regarding developmental and reproductive effects of dimethylhydrazine involved parenteral administration and, therefore, are of questionable relevance for AEGL derivation. The data are included, however, to provide insight relative to dimethylhydrazine exposure.

The results of a teratogenicity assessment of 1,2-dimethylhydrazine and 1,1-dimethylhydrazine in rats were reported by Keller et al. (1984) (Tables 4–4 and 4–5). In this study, groups of 14–18 pregnant Fischer 344 (F344) rats were given 1,1-dimethylhydrazine in saline (10, 30, or 60 milligrams per kilogram per day (mg/kg/d) intraperitoneally (i.p.)) or 1,2-dimethylhydrazine in saline (2.0, 5.0, or 10 mg/kg, i.p.) on gestation d 6–15; controls received saline only. The pregnant rats were sacrificed on gestation d 20 and the following parameters examined: numbers and positions of implants, and numbers of dead fetuses, live fetuses, and resorptions. Fetuses were examined for evidence of terata.

For 1,1-dimethylhydrazine, maternal body-weight gains in the high-dose group were significantly reduced throughout the treatment period. A statistically significant reduction in mean fetal weight was observed for the 60-mg/kg group. Although not statistically significant, reductions in the numbers of implants and viable fetuses per litter were noted for the high-dose group (Table 4–4). In the high-dose group, nearly 50% of the treated dams exhibited a per litter resorption in excess of 33%, and a moderate increase in total malformation incidences.

For 1,2-dimethylhydrazine, effects on maternal body weight were inconsistent, and litter parameters were affected only in the high-dose (10 mg/kg) group (Table 4–5). There was a moderate decrease in mean viable fetuses per litter, and mean fetal weight was significantly reduced. There was a slight increase in the number of litters with 33% or more of the fetuses resorbed and a slight increase in the incidences of total malformations. The embryo toxic effects were observed at exposures that also induced maternal toxicity (body-weight loss).

TABLE 4–4 Developmental Effects of 1,1-Dimethylhydrazine in Rats Following i.p. Administration on Gestation Days 6–15

	Dose (mg/kg)			
Parameter	0	10	30	60
No. of litters	12	11	11	15
Implants/litter[a]	8.5±1.9	10.1±0.9	10.5±0.5	7.7±1.0
Viable fetuses/litter[a]	7.1±2.6	8.5±1.2	8.4±1.0	5.6±1.1
No. litters with >33% resorption	2	2	2	7
Fetal weight[a]	3.1±0.3	3.2±0.3	3.1±0.1	2.8±0.3[b]
Gross exam[c]	1 (1)	2 (2)	1 (1)	3 (3)
Soft-tissue exam	3 (3)[d,e]	1 (1)[d]	4 (4)[d]	5 (7)[f]
Skeletal exam	1 (1)[g]	1 (1)[h]	2 (2)[i]	4 (7)[j]

Note: Although no maternal lethality was reported, the developmental effects were observed at exposures that induced maternal toxicity (body-weight loss).

[a]Values are means ± SE.

[b]Significant at ≤0.05.

[c]All gross abnormalities were nanoids; one high-dose fetus also had exencephaly, shortened mandible, and agenesis of the tail.

[d]Anophthalmia and/or severe microophthalmia.

[e]One fetus had hydronephrosis.

[f]Anophthalmia or severe microophthalmia (two fetuses), agenesis of kidney (two fetuses), hydronephrosis (two fetuses), and one hydrocephalic fetus.

[g]Unossified sternebrae.

[h]Unfused ossification centers of vertebrae.

[i]Unfused ossification centers of vertebrae, 14 ribs.

[j]Fused ribs (two fetuses), 14 ribs (four fetuses), and unfused ossification centers of vertebrae (three fetuses).

Source: Keller et al. 1984.

3.4. Genotoxicity

Brusick and Matheson (1976) reported that 1,1-dimethylhydrazine failed to increase reversions in *Salmonella typhimurium* or *Saccharomyces cerevisiae* gene mutation assays with or without metabolic activation. A concentration-related response was observed in the mouse lymphoma assay (with activation). Dominant lethal tests were negative.

TABLE 4–5 Developmental Effects of 1,2-Dimethylhydrazine in Rats Following i.p. Administration on Gestation Days 6–15

	Dose (mg/kg)			
Parameter	0	2	5	10
No. of litters	12	14	14	13
Implants/litter[a]	10.2±1.1	9.8±2.8	10.2±2.0	9.8±1.8
Viable fetuses/litter[a]	9.3±2.6	9.1±3.2	9.7±1.5	6.8±4.1
No. litters with >33% resorption	1	2	0	3
Fetal weight[a]	3.2±0.3	3.2±0.1	3.1±0.2	2.8±0.2[b]
Gross exam[c]	2 (2)	0 (0)	2 (2)	5 (10)
Soft-tissue exam	1 (1)[d]	1 (1)[e]	3 (4)[e,f]	1 (2)[f]
Skeletal exam	0 (0)	0 (0)	0 (0)	3 (4)[g]

[a]Values are means±S.E.
[b]Significant at ≤0.05.
[c]All gross abnormalities were nanoids; one high-dose fetus also had exencephaly, shortened mandible, and agenesis of the tail.
[d]Anophthalmia and uterine agenesis in onr fetus.
[e]Retained testicle.
[f] Anophthalmia or severe microophthalmia.
[g]Unfused ossification centers of vertebrae and sternebrae.
Source: Keller et al. 1984.

Matheson et al. (1978) reported the results of a battery of in vivo and in vitro assays to assess the genotoxicity of 1,1-dimethylhydrazine. Included were the Ames' *Salmonella*/microsome assay, a microbial suspension assay, mutation induction at the TK locus in L5178Y mouse lymphoma cells, stimulation of UDS in WI-38 cells, and a dominant lethal assay in mice. 1,1-Dimethylhydrazine was active in all of the tests except the dominant lethal assay.

In a study using cultured L5178Y mouse lymphoma cells, Rogers and Back (1981) reported that both 1,1-dimethylhydrazine and 1,2-dimethylhydrazine induced forward mutations at the thymidine kinase level in the absence of an extraneous metabolic activation system. The investigators also noted that the two dimethylhydrazines appeared to have different modes of action under these conditions.

Parodi et al. (1981) considered 1,1-dimethylhydrazine (42 µmol/plate) to exhibit weak mutagenic activity in *Salmonella typhimurium* in streams TA 1535 and 1538 with or without metabolic activation.

In a review of 1,1-dimethylhydrazine genotoxicity, Trochimowicz et al. (1994) noted that in vitro assays using nonmammalian systems were generally positive, dominant lethal tests in rodents were negative, and in vivo tests (e.g., micronucleus assay) were equivocal. For 1,2-dimethylhydrazine, potency similar to 1,1-dimethylhydrazine and tests with intact animals provided both positive and negative results that related to the ability of the chemical to remain in contact with a specific target tissue long enough to induce genetic damage.

3.5. Carcinogenicity

Both 1,1-dimethylhydrazine and 1,2-dimethylhydrazine were carcinogenic in rodents following oral exposures. Lifetime exposure of mice to 1,1-dimethylhydrazine in drinking water (1,000 ppm) was associated with an elevated incidence of angiosarcomas, pulmonary adenomas, malignant lymphoma, kidney adenomas, and hepatomas (Toth 1973). In a 40-w gavage study, mice given 0.5 mg of 1,1-dimethylhydrazine exhibited a marginal increase in lung tumors, and rats and mice developed liver tumors following exposure to 1,1-dimethylhydrazine in drinking water for 2 y (reviewed in Trochimowicz 1994).

Inhalation studies at the U.S. Air Force Aerospace Medical Research Laboratory showed an increased tumor response (hemangiosarcomas and Kupffer cell sarcomas) in mice exposed at 5 ppm, 6 h/d, 5 d/w for 6 mon (MacEwen and Vernot 1977, and Haun 1977, reviewed in Trochimowicz 1994). Rats similarly exposed at 5 ppm exhibited increased incidences of squamous cell carcinomas of the lung and hepatocellular carcinomas. Hamsters subjected to a similar experimental protocol failed to show an increased incidence of tumors (MacEwen and Vernot 1975). It must be noted that the 1,1-dimethylhydrazine used in these studies contained 0.12% dimethylnitrosamine, which could be a significant confounder.

Inhalation slope factors of 3.5 $(mg/kg \cdot d)^{-1}$ and 3.7×10^{1} $(mg/kg \cdot d)^{-1}$ were previously available for 1,1-dimethylhydrazine and 1,2-dimethylhydrazine, respectively. Because of uncertainties regarding their development, these have been withdrawn from the U.S. EPA Integrated Risk Information System (IRIS) and, therefore, are of uncertain validity.

3.6. Summary

Inhalation lethality data are available for several laboratory species, including dogs, rats, mice, and hamsters. Most of the available data, however, were collected using 1,1-dimethylhydrazine as the test material. Independent studies and reports confirm a steep exposure-response relationship for the dimethyl

hydrazines. Cumulative exposures of ≈700–2,000 ppm·h were associated with 50% lethality. Cumulative exposures of <90 ppm·h were not associated with clinical signs of toxicity, although there is little margin between such exposures and those that induce significant toxic responses; e.g., notable but nonlethal effects have been reported for exposures of 90 ppm·h. An assessment of the limited data for dogs suggests that this species may be somewhat more sensitive than other species and that hamsters are the least sensitive. Restlessness and convulsions (tonic and clonic) are frequently associated with lethal exposures in laboratory species and most deaths tend to occur within 24 h of exposure.

Developmental toxicity of dimethylhydrazines has been demonstrated in rats following parenteral administration of maternally toxic doses during gestation. No developmental toxicity studies were available that employed inhalation.

Two oral studies in rodents demonstrated the carcinogenic potential of dimethylhydrazines. Results of an inhalation study in mice showing an increased tumor response following exposure to 1,1-dimethylhydrazine may be compromised by the contamination of the test article with dimethylnitrosamine. Both inhalation and oral slope factors for the dimethylhydrazines have been withdrawn from IRIS.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Weeks et al. (1963) reported that 80% of the 1,1-dimethylhydrazine administered via endotracheal tube to anesthetized mongrel dogs was retained in the respiratory tract. It was unclear if the retention was monitored only for the 51– 64 min duration of exposure.

Back et al. (1963) studied the absorption, distribution, and excretion of [C^{14}]-1,1-dimethylhydrazine. Various aspects of the disposition of dimethylhydrazine were measured in monkeys, dogs, cats, rabbits, or rats following intravenous or intraperitoneal administration. The doses were not specified. Based on the tissues examined, dimethylhydrazine was not preferentially concentrated or sequestered in tissues of rabbits. According to the study authors, at 2, 4, 8, 12, 18, and 24 h, plasma concentrations represented 4.18%, 2.23%, 0.17%, 0.65%, 0.85%, and 0.46% of the administered dose (i.v.). Total recovery of administered radioactivity from the rabbits never exceeded 28.3%. However, the authors noted that tissues representing the bulk of the body weight (e.g., skeletal muscle, bone, adipose tissue, and cutaneous tissue) were not examined and that these were probably substantial reservoirs for the radioactive label. Peak plasma concentrations in cats and dogs were attained at 15–60 min but varied depending on the analytical technique. Urinary excretion in cats and dogs was

dose-related; 30–50% of the administered dose was excreted by 5 h. Generally, absorption of 1,1-dimethylhydrazine is very rapid following i.p. administration and is widely distributed throughout the body. Plasma concentration did not correlate well with dose, but this may have been a function of the analytical techniques. Urinary excretion of 1,1-dimethylhydrazine was rapid, regardless of the route of administration. In cats and dogs, 30–50% of the administered dose (i.p. or i.v.) was excreted in the urine within 5 h.

Dost et al. (1966) studied the excretion of [^{14}C] 1,1-dimethylhydrazine administered i.p. to rats. Following a single (0.88 mg/kg) dose, approximately 30% of the test material was metabolized to carbon dioxide within 10 h. After injection of 20 mg/kg or 80 mg/kg, CO_2 excretion accounted for approximately 15.2% and 7%, respectively, of the administered dose. Approximately 50% of the administered dose was excreted in the urine over a 2-d period.

4.2. Mechanism of Toxicity

The precise mechanism of dimethylhydrazine toxicity is uncertain. In addition to the contact irritant effects, the acute effects of dimethylhydrazine exposure may involve the central nervous system as exemplified by tremors and convulsions (Shaffer and Wands 1973) and behavioral changes at sublethal doses (Streman et al. 1969). Back and Thomas (1963) noted that the deaths probably involve respiratory arrest and cardiovascular collapse. The central nervous system as a target is consistent with the delayed latency in response reported for dimethylhydrazine (Back and Thomas 1963). There is some evidence that 1,1-dimethylhydrazine may act as an inhibitor of glutamic acid decarboxylase, thereby adversely affecting the aminobutyric acid shunt, and could explain the latency of central-nervous-system effects (Back and Thomas 1963). Furthermore, vitamin B_6 analogues that act as coenzymes in the aminobutyric acid shunt have been shown to be effective antagonists to 1,1-dimethylhydrazine toxicity (reviewed in Back and Thomas 1963).

4.3. Structure-Activity Relationships

The toxicities of hydrazine and monomethylhydrazine and the 1,1- and 1,2-isomers of dimethylhydrazine were reported by Jacobson et al. (1955). Rats and mice exposed to hydrazine and monomethylhydrazine and rats exposed to 1,2-dimethylhydrazine exhibited restlessness, dyspnea, and convulsions with exophthalmos. Excessive salivation, vomiting, respiratory distress, and convulsions were reported for dogs exposed to 1,1-dimethylhydrazine as well as monomethylhydrazine. For rodents, estimated LC_{50} values for hydrazine,

dimethylhydrazine, and monomethylhydrazine are shown in Table 4–6. These values indicate that dimethylhydrazine was more potent than hydrazine but less potent than monomethylhydrazine.

TABLE 4–6 Lethality of Hydrazine, 1,2-Dimethylhydrazine, and Monomethylhydrazine in Rodents (LC50 in ppm)

Species	Hydrazine	Dimethylhydrazine	Monomethylhydrazine
Rat	570 (4 h)	250 (4 h)	74 (4 h)
Mouse	252 (4 h)	172 (4 h)	56 (4 h)
Hamster	ND	392 (4 h)	143 (4 h)

Source: Jacobson et al. 1955.

Hydrazine and all of its methylated derivatives appear to induce neuromuscular disorders at or near lethal doses, and all appear to be respiratory irritants. Jacobson et al. (1955) noted that the actions of hydrazine and its methylated derivatives were similar; all are respiratory irritants and convulsants. In addition, monomethylhydrazine also induced severe intravascular hemolysis in dogs.

Witkin (1956) reported intravenous (i.v.), i.p., and oral LD_{50} (lethal dose for 50% of the animals) values for mice and rats, and i.v. LD_{50} values for dogs. Similar to hydrazine, the route of administration had minimal effect on the LD_{50} within species. Generally, monomethylhydrazine and 1,2-dimethylhydrazine appeared to be somewhat more potent in mice and rats than was hydrazine. Results of this study showed that the 1,1-dimethylhydrazine was less acutely toxic than hydrazine or the other hydrazine derivatives.

Relative to other forms of hydrazine, House (1964) reported 1,1-dimethylhydrazine to be less toxic to monkeys, rats, and mice. Mortality over a 90-d inhalation exposure at 0.56 ppm (0.73 mg/m^3) was 20%, 98%, and 99% for monkeys, rats, and mice, respectively.

4.4. Other Relevant Information

4.4.1. Species Variability

Compared with other tested species, hamsters appear to be resistant to the lethal effects of acute exposure to monomethylhydrazine. Within similar exposure durations, the cumulative exposure data (exposure concentration× time) suggest similar sensitivities in response among dogs, rats, and mice. As noted by Back and Thomas (1963), death in monkeys, dogs, rats, and mice was preceded by tonicoclonic convulsions and respiratory arrest.

4.4.2. Unique Physicochemical Properties

Although the high chemical reactivity of hydrazine presented substantial problems regarding accurate and consistent measurement of experimental concentrations in earlier studies, this high reactivity does not appear to reside with the dimethylhydrazines, nor was it noted as a significant problem area in the experimental protocols.

4.4.3. Concurrent Exposure Issues

Although data analyzing the adverse effects of concurrent exposure to hydrazines and other chemicals are not available, this may be an important issue, especially for those chemicals with irritant properties. Although not as reactive as hydrazine, the dimethylhydrazines are reactive with strong oxidizing agents, thereby possibly altering effects on physiologic systems.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

Quantifiable data pertinent to AEGL-1 effects in humans were not available.

5.2. Summary of Animal Data Relevant to AEGL-1

Continuous exposure of rhesus monkeys to 1,1-dimethylhydrazine at 0.43 ppm resulted in no reported signs of toxicity during the first 30 d of a 90-d exposure period, thereby implying that this exposure caused no notable signs of toxicity (House 1964). A 4-h exposure of beagle dogs to 1,1-dimethylhydrazine at 24 ppm (Jacobson et al. 1955) and a 1-h exposure at 96 ppm (Weeks et al. 1964) resulted in no significant signs of toxicity in two of three dogs, although a third exhibited vomiting and convulsions.

5.3. Derivation of AEGL-1

The only data applicable to the AEGL-1 values are those reported by Jacobson et al. (1955) and Weeks et al. (1963) for dogs. Both the 4-h exposure to 1,1-dimethylhydrazine at 24 ppm (Jacobson et al. 1955) and the 1-h exposure

at 96 ppm (Weeks et al. 1963) resulted in cumulative exposures of 96 ppm·h that produced no significant toxic effects in two of three dogs examined, although, as previously described, notable effects were seen in one dog. However, analysis of dimethylhydrazine toxicity data in total revealed that significant toxicity may occur at or below the odor threshold. Furthermore, the available data indicate that there is an almost nonexistent margin between exposures resulting in no response and those causing lethality. Therefore, AEGL-1 values for dimethylhydrazine are not recommended (Table 4–7).

TABLE 4–7 AEGL-1 For Dimethylhydrazine

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

Numeric values for AEGL-1 are not recommended because (1) the lack of available data, (2) data indicate that toxic effects may occur at or below the odor threshold, (3) the inadequate margin of safety that exists between the derived AEGL-1 and the AEGL-2, or (4) 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.
Abbreviation: NR, not recommended.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Human data were not available for deriving AEGL-2 values based upon nonlethal, irreversible effects of dimethylhydrazine exposure.

6.2. Summary of Animal Data Relevant to AEGL-2

Exposures resulting in nonlethal, irreversible effects of dimethylhydrazine were not well defined. For most studies, responses were described in terms of no visible signs of toxicity or lethality. However, Weeks et al. (1963) described nonlethal (but reversible) effects in dogs exposed to 1,1-dimethylhydrazine at varying concentrations. In this study, dogs were exposed to 1,1-dimethylhydrazine at 1,550 ppm or 4,230 ppm for 5 min or 360, 400, or 1,530 ppm for 15 min. The highest cumulative exposures at each of two exposure periods (Ct =352–383 ppm·h) were associated with marked tremors, convulsions and death, while the lower concentration exposures at each of two periods caused behav

ioral changes and muscle fasciculations (Ct=90–129 ppm·h). Because of the steep exposure-response relationship for this chemical, concentrations more representative of a threshold for moderate but reversible toxic effects were used to represent AEGL-2 effects.

6.3. Derivation of AEGL-2

The data most applicable for derivation of AEGL-2 values were from the study reported by Weeks et al. (1963) that identified nonlethal, reversible toxic effects in dogs exposed to 1,1-dimethylhydrazine for 5 or 15 min. The exposure selected as the basis for deriving AEGL-2 values was 360 ppm for 15 min (Ct =90 ppm·h). This exposure resulted in behavioral changes and mild muscle fasciculations in dogs. Although a nearly equivalent exposure (1,550 ppm for 5 min; Ct=129 ppm·h) produced similar effects, the 15-min, 360-ppm exposure was considered more appropriate for AEGL derivation because it was more relevant to AEGL-specific exposure durations.

The 360-ppm exposure value was then adjusted by a total uncertainty factor of 30. An uncertainty factor of 3 for interspecies variability was applied for several reasons. The 4-h LC_{50} values for mouse, rat, and hamster differ by a factor of approximately 2 and were consistent with the dog data when extrapolated from 1 h using n=1. The more sensitive species, the dog, was used to derive the AEGL-3 values. The response to inhaled dimethylhydrazine was similar across the species tested. This was especially true for lethality responses (LC_{50} values for varying time periods ranging from 5 min to 4 h) among rats, mice, dogs, and hamsters. A comparison of LC_{50} values for the same exposure durations in these species did not vary more than 3-fold. An uncertainty factor of 10 was retained for intraspecies variability, however, based primarily upon the variability in the response observed in dogs. This variability was especially demonstrated in dogs wherein responses varied from one of extreme severity (vomiting, tremors, convulsions, and death) to no observable effects. Therefore, a factor of 10 was retained. A factor of 10 was also retained because the Weeks et al. (1963) results indicated that dogs that had been previously stressed (auditory stimuli) appeared to have been affected in their response to dimethylhydrazine. Based upon these data, it was assumed that humans may be equally divergent in their response to dimethylhydrazine.

The adjusted exposure value estimated to be the threshold level of AEGL-2 effects (12 ppm for 15 min) was then scaled to AEGL time frames using the $C^n \times t=k$ relationship (ten Berge et al. 1986). For relatively brief exposures (i.e., <4 h), the data for dimethylhydrazine implied a linear concentration-response relationship ($C^1 \times t=k$), which was used for AEGL derivations. LC_{50} data on

dogs and rats were available from exposures that varied from 5 to 240 min. Regression analyses of these exposure-response data indicated a near linear concentration-response relationship (n=0.84 for rats; n=0.80 for dogs). For time-scaling, a linear relationship was assumed, and a value of n=1 was selected. Temporal scaling using $C^1 \times t = k$ was then used to derive the time-specific AEGLs (Appendix A).

TABLE 4–8 AEGL-2 for Dimethylhydrazine

AEGL Level	30 min	1 h	4 h	8 h
AEGL-2	6 ppm 14.7 mg/m^3	3 ppm 7.4 mg/m^3	0.75 ppm 2 mg/m^3	0.38 ppm 1 mg/m^3

The resulting AEGL-2 values are shown in Table 4–8 and their derivations are shown in Appendix A.

7.

7.1. Summary of Human Data Relevant to AEGL-3

Human data were not available for deriving a dimethylhydrazine AEGL based upon lethality.

7.2. Summary of Animal Data Relevant to AEGL-3

Lethality data were available for several laboratory species including, dogs, rats, mice, and hamsters. Based upon the available data, dogs appeared to be the most sensitive species tested. Although LC_{50} values for various exposure periods were available for rats and dogs, and 4-h LC_{50}s were available for mice and hamsters, available data did not identify a definitive lethal threshold for inhalation exposure to dimethylhydrazine. A 30-min LC_{10} of 3,250 ppm and a 1-h LC_{10} of 1,100 ppm for 1,1-dimethylhydrazine can be estimated for rats from the exposure-response data of Weeks et al. (1963) (see Appendix D). Similarly, using the exposure-response data of Jacobson et al. (1955), a 4-h LC_{20} of 210 ppm and 140 ppm can be estimated for rats and mice, respectively. For comparison, exposure of dogs to 1,1-dimethylhydrazine at 52 ppm for 4 h resulted in 33% mortality, although this was not a statistically-derived lethality value.

7.3. Derivation of AEGL-3

For derivation of an AEGL-3 for dimethylhydrazine, it was necessary to estimate a lethality threshold. As previously indicated, the available data indicated that the dog was the most sensitive species tested, but no definitive lethality threshold values were identified for this or any other species. Although the dog appeared to be the most sensitive species, the data for dogs were compromised by the small numbers of animals used in these studies. The lethality threshold for dogs exposed to 1,1-dimethylhydrazine was estimated from the 1-h LC_{50} of 981 ppm (Weeks et al. 1963). Reducing this value 3-fold to 327 ppm results in an exposure concentration 3 times greater than the 1-h concentration (i.e., 96 ppm, Weeks et al. 1963) associated with a no-effect level in dogs. Using the available exposure-response data (Jacobson et al. 1955), a 3-fold reduction in LC_{50} values results in exposures that would not be associated with lethality. The Fowles et al. (1999) analysis of inhalation toxicity experiments revealed that for many chemicals, the ratio between the LC_{50} and the experimentally observed nonlethal level was on average a factor of approximately 2, the 90th percentile was 2.9, and the 95th percentile was 3.5.

As for AEGL-2 values, the adjusted exposure value of 327 ppm was adjusted by a total uncertainty factor of 30 (3 for interspecies variability and 10 for individual variability). An uncertainty factor of 3 was applied to account for interspecies variability because the toxic response to dimethylhydrazine (LC_{50} values) was similar across species. The 4-h LC_{50} values for mouse, rat, and hamster differ by a factor of approximately 2 and were consistent with the dog data when extrapolated from 1 h using n=1. LC_{50} values for other exposure durations (e.g., 5 min., 15 min, 30 min, and 1 h) were also similar and did not vary by more than 3-fold among the species tested. The more sensitive species, the dog, was used to derive the AEGL-3 values. An uncertainty factor of 10 was retained for intraspecies variability, and it was based primarily on the variability of response observed in dogs; this variability was demonstrated in dogs wherein responses varied from one of extreme severity (vomiting, tremors, convulsions, and death) to no observable effects. The intraspecies uncertainty factor of 10 was also retained, because in experiments by Weeks et al. (1963), dogs that had been previously stressed exhibited an enhanced response to inhaled dimethylhydrazine. Based upon these data, it was assumed that humans may be equally divergent in their response to dimethylhydrazine.

The adjusted exposure value, estimated to be the threshold for lethality (11 ppm for 15 min), was then scaled to AEGL time frames using the $C^n \times t = k$ relationship (ten Berge et al. 1986) as discussed in Section 6.3 for AEGL-2. Temporal scaling using $C^1 \times t = k$ was then used to derive the time-specific AEGLs (Appendix A).

TABLE 4–9 AEGL-3 for Dimethylhydrazine

AEGL Level	30 min	1 h	4 h	8 h
AEGL-3	22 ppm 54 mg/m^3	11 ppm 27 mg/m^3	2.7 ppm 6.6 mg/m^3	1.4 ppm 3.4 mg/m^3

The resulting AEGL-3 values are shown in Table 4–9 and their derivation shown in Appendix A.

8. SUMMARY OF PROPOSED AEGLS

8.1. AEGL Values and Toxicity Endpoints

A summary of the proposed AEGLs for dimethylhydrazine and their relationship to one another are shown in Table 4–10. No AEGL-1 values were developed because data indicated that overt toxicity may become manifest at or below the odor threshold and because the exposure-response relationship for dimethylhydrazine suggest little margin between exposures resulting in no observable effects and those producing significant toxicity. The AEGL-2 is based upon data showing only behavioral changes and moderate neuromuscular involvement, but these exposures were very close to those inducing tremors, convulsions, and death. The AEGL-3 was based upon an estimated lethality threshold because there were no data sets identifying an LC_{01} or similar threshold or near threshold value. The lethality threshold estimated from LC_{50} data represents a conservative approach to AEGL-3 derivation that was justified given the steep exposure-response relationship for dimethylhydrazine.

The derivation of AEGL values based upon potential carcinogenicity is shown in Appendix C. The assessment, following the methods of the NRC (1985), utilized an inhalation slope factor for 1,1-dimethylhydrazine. This slope factor, however, has been withdrawn from the U.S. EPA IRIS and, therefore, is of uncertain validity. Nonetheless, the assessment shows that acute toxicity is clearly more relevant as a basis for calculation of dimethylhydrazine AEGLs.

8.2. Comparison with Other Standards and Criteria

Exposure standards and guidelines for dimethylhydrazine have been established by several organizations. All currently available standards and guidelines are shown in Table 4–11.

TABLE 4–10 Comparison of AEGL Values for Dimethylhydrazine

Classification	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR
AEGL-2	6.0 ppm	3.0 ppm	0.75 ppm	0.38 ppm
	14.7 mg/m^3	7.4 mg/m^3	2 mg/m^3	1 mg/m^3
AEGL-3	22 ppm	11 ppm	2.7 ppm	1.4 ppm
	54 mg/m^3	27 mg/m^3	6.6 mg/m^3	3.4 mg/m^3

Numeric values for AEGL-1 are not recommended because (1) the lack of available data, (2) data indicate that toxic effects may occur at or below the odor threshold, (3) the inadequate margin of safety that exists between the derived AEGL-1 and the AEGL-2, or (4) 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.
Abbreviation: NR, not recommended.

Frawley (1964) provided a summary of data relevant for the derivation of emergency exposure levels (EELs) for 1,1-dimethylhydrazine. The EELs are considerably higher than the proposed AEGLs due, at least in part, to the application of a total 10-fold margin of safety and estimated no-effect (10 mg/kg) and severe-effect levels (40 mg/kg) that are higher than those used for AEGL derivation. Based upon the dog data reported by Weeks et al. (1963) that indicated a 1-h exposure at 96 ppm (235 mg/m^3) as a no-effect level, a body weight of 12.7 kg, and breathing rate of 0.179 m^3/h, the minimal no-effect dose is 3.3 mg/kg. Back and Thomas (1963) estimated that humans could tolerate 10 mg/kg (4.1 ppm) without adverse health effects. However, this estimate appears to be based upon route-to-route extrapolations and major assumptions inherent in such extrapolations make the comparisons tenuous.

8.3. Data Adequacy and Research Needs

Only qualitatively descriptive information is available regarding acute exposure of humans to dimethylhydrazines. Case reports, although lacking definitive exposure terms, indicate that acute exposure to dimethylhydrazines may cause nasal and respiratory tract irritation, breathing difficulties, and nausea. Quantitative data in animals have shown concentration-dependent effects ranging from respiratory tract irritation, pulmonary edema and neurologic effects to lethality. Because the nonlethal effects in humans and animals are qualitatively similar, the animal data were considered relevant and appropriate for development of AEGL values.

TABLE 4–11 Extant Standards and Guidelines for Dimethylhydrazine

	Exposure Duration			
Guideline	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	NR	NR	NR	NR
AEGL-2 (Disabling)	6 ppm	3 ppm	0.75 ppm	0.38 ppm
AEGL-3 (Lethal)	22 ppm	11 ppm	2.7 ppm	1.4 ppm
NRC EEL[a]	100 ppm	50 ppm		
NIOSH IDLH[b]	15 ppm (REL: 0.06 ppm, 120-min.ceiling)			
OSHA PEL[c]				0.5 ppm
ACGIH TLV-TWA[d]				0.05 ppm (0.01 ppm proposed)

Numeric values for AEGL-1 are not recommended because (1) the lack of available data, (2) data indicate that toxic effects may occur at or below the odor threshold, (3) the inadequate margin of safety that exists between the derived AEGL-1 and the AEGL-2, or (4) 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]NRC 1985.

[b]NIOSH 1994.

[c]OSHA 1993.

[d]ACGIH 1999, 8-h TWA with skin notation.

Abbreviations: NR, Not recommended; EEL, emergency exposure levels; IDLH, immediately dangerous to life and health; PEL, permissible exposure limit; TLV-TWA, Threshold Limit Value-time-weighted average.

The most notable database deficiencies were the absence of quantitative exposure data regarding the human experience, the absence of a well-defined exposure-response curve relationship in animals, and understanding of individual variability in response to inhaled dimethylhydrazines.

Because the theoretical excess lifetime cancer risk for dimethylhydrazines was estimated from nonverified potency estimates and because AEGLs are applicable to rare events or single, once-in-a-lifetime exposures in a limited geographic area with a small population, the AEGL values based on noncarcinogenic endpoints were considered to be more appropriate.

Critical research needs include definition of thresholds for adverse health effects and how these thresholds vary with exposure concentration and duration. Such data would be valuable for affirming AEGL values. Additionally, the mode of dimethylhydrazine toxicity is not fully understood and, therefore, research providing insight into the underlying mechanism(s) of dimethylhydrazine toxicity would reduce current uncertainties in quantitative health risk issues.

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Appendixes

APPENDIX A

DERIVATION OF AEGL VALUES

Derivation of AEGL-1

Key study:	None. An AEGL-1 was not recommended because of inadequate data for developing health-based criteria and because exposure-response relationships suggest little margin between exposures resulting in no observable adverse effects and those producing significant toxicity. The absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

Derivation of AEGL-2

Key study:	Weeks et al. 1963
Toxicity endpoint:	Dogs exposed to 1,1-dimethylhydrazine at 360 ppm for 15 min exhibited behavioral changes and muscle fasciculations
Uncertainty factors:	An uncertainty factor of 3 for interspecies variability was applied because the toxic response to dimethylhydrazine was similar across the species tested. This was especially true for lethality responses (LC_{50} values for varying time periods ranging from 5 min to 4 h) among rats, mice, dogs, and hamsters. A comparison of LC_{50} values for the same exposure durations in these species did not vary more than 3-fold. An uncertainty factor of 10 was retained for intraspecies variability (protection of sensitive populations). A broad spectrum of effects were seen that included behavioral effects, hyperactivity, fasciculations, tremors, convulsions, and vomiting. The mechanism of toxicity is uncertain and sensitivity among individuals regarding these effects may vary. Following identical exposures, the responses of the dogs varied from one of extreme severity (vomiting, tremors, convulsions, and death) to no observable effects. A

	factor of 10 was also retained because experiments by Weeks et al. (1963) indicated that dogs that had been previously stressed (auditory stimuli) were more sensitive to the adverse effects of dimethylhydrazine.
Calculations:	360 ppm/30=12 ppm $C^1 \times t = k$ 12 ppm×15 min=180 ppm·min
Time scaling:	$C^1 \times t = k$ (ten Berge et al. 1986) $(12 \text{ ppm})^1 \times 15 \text{ min} = 180 \text{ ppm·min}$ LC_{50} data were available for 5-, 15-, 30-, 60-, and 240-min exposures in rats and 5, 15, and 60 min in dogs. Exposure-response data indicated a near linear concentration-response relationship (n=0.84 for rats; n=0.80 for dogs). For time-scaling, a linear relationship was assumed and a value of n =1 was selected.
30-min AEGL-2:	$C^1 \times 30 \text{ min} = 180 \text{ ppm·min}$ C=6 ppm
1-h AEGL-2:	$C^1 \times 60 \text{ min} = 180 \text{ ppm·min}$ C=3 ppm
4-h AEGL-2:	$C^1 \times 240 \text{ min} = 180 \text{ ppm·min}$ C=0.75 ppm
8-h AEGL-2:	$C^1 \times 480 \text{ min} = 180 \text{ ppm-min}$ C=0.38 ppm

Derivation of AEGL-3

Key study:	Weeks et al. 1963
Toxicity endpoint:	1-h LC_{50} of 981 ppm in dogs reduced by a factor of three to 327 ppm as an estimate of a lethality threshold. Weeks et al. (1963) provided data showing that 15-min exposure of dogs at 36–400 ppm produced only minor, reversible effects (behavioral changes and mild muscle fasciculations)
Uncertainty factors:	An uncertainty factor of 3 for interspecies variability was applied because the toxic response to dimethylhydrazine

	was similar across the species tested. This was especially true for lethality responses (LC_{50} values for varying time periods ranging from 5 min to 4 h) among rats, mice, dogs, and hamsters. A comparison of LC_{50} values for the same exposure durations in these species did not vary more than 3-fold. An uncertainty factor of 10 was retained for intraspecies variability (protection of sensitive populations). A broad spectrum of effects were seen that included behavioral effects, hyperactivity, fasciculations, tremors, convulsions, and vomiting. The mechanism of toxicity is uncertain and sensitivity among individuals regarding these effects may vary. Following identical exposures, the responses of the dogs varied from one of extreme severity (vomiting, tremors, convulsions, and death) to no observable effects. A factor of 10 was also retained because experiments by Weeks et al. (1963) indicated that dogs that had been previously stressed (auditory stimuli) were more sensitive to the adverse effects of dimethylhydrazine.
Calculations:	327 ppm/30=10.9 ppm $C^1 \times t = k$ 11.9 ppm×60 min=654 ppm-min
Time scaling:	$C^1 \times t = k$ (ten Berge et al. 1986) 11.9 ppm^1×60 min=654 ppm-min LC_{50} data were available for 5, 15, 30, 60, and 240-min exposures in rats and 5, 15, and 60 min in dogs. Exposure-response data indicated a near linear concentration-response relationship (n=0.84 for rats, n=0.80 for dogs). For time-scaling, a linear relationship was assumed and a value of n =1 was selected.
30-min AEGL-2:	$C^1 \times 30$ min=654 ppm·min C=22 ppm
1-h AEGL-2:	$C^1 \times 60$ min=654 ppm·min C=11 ppm
4-h AEGL-2:	$C^1 \times 240$ min=654 ppm-min C=2.7 ppm
8-h AEGL-2:	$C^1 \times 480$ min=654 ppm-min C=1.4 ppm

APPENDIX B

TIME SCALING CALCULATIONS FOR DIMETHYLHYDRAZINE AEGLS

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

Two data sets of LC_{50} values for different time periods of exposure were analyzed using a linear regression analysis of the log-log transformation of a plot of C vs t to derive values of n for dimethylhydrazine.

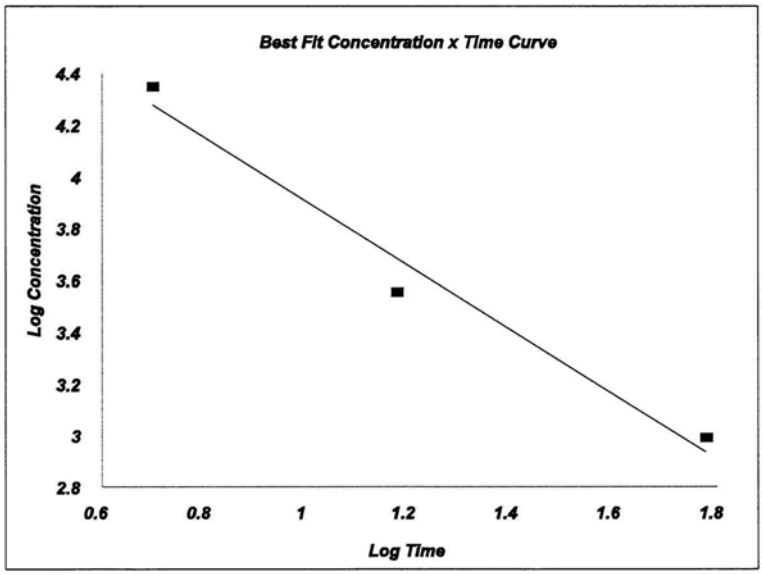
Dimethylhydrazine dog data from Weeks et al. 1963

The LC_{50} values for 5-, 15-, and 60-min exposures were 22,300, 3,580, and 981 ppm, respectively.

Time	Concentration	Log Time	Log Concentration
5	22,300	0.6990	4.3483
15	3,580	1.1761	3.5539
60	981	1.7782	2.9917
n=0.8			

Calculated LC_{50} values:

Min	Concentration
30	2036.15
60	860.12
240	153.48
480	64.83



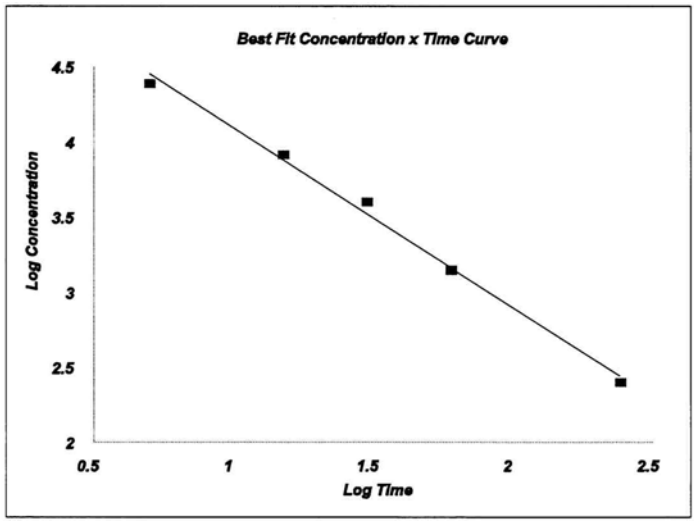
Dimethylhydrazine rat data from Weeks et al. 1963

The LC_{50} values for 5-, 15-, 30-, 60-, and 240-min exposures were 24,500, 8,230, 4,010, 1,410, and 252 ppm, respectively.

Time	Concentration	Log Time	Log Concentration
5	24,500	0.6990	4.3892
15	8,230	1.1761	3.9154
60	4,010	1.4771	3.6031
240	252	2.3802	2.4014
n=0.84			

Calculated LC_{50} values:

Min	Concentration
30	3,323.28
60	1,449.93
240	276.00
480	120.42



APPENDIX C

CARCINOGENICITY ASSESSMENT OF DIMETHYLHYDRAZINE

Slope factors for 1,1-dimethylhydrazine and 1,2-dimethylhydrazine were available but have been withdrawn from the U.S. EPA Integrated Risk Information System (IRIS) (U.S. EPA1986). For a preliminary carcinogenicity assessment, the withdrawn inhalation slope factor for 1,1-dimethylhydrazine (cited in ATSDR 1994) will be used. The assessment follows previously described methodologies (NRC 1985; Henderson 1992).

The withdrawn slope factor for 1,1-dimethylhydrazine was 3.5 $(mg/kg \cdot d)^{-1}$, which, based upon a human inhalation rate of 20 m^3/d and a body weight of 70 kg, is equivalent to 1 $(mg/m^3)^{-1}$.

To convert to a level of monomethylhydrazine that would cause a theoretical excess cancer risk of 10^{-4}:

Risk of $1\times 10^{-4}=(1\times 10^{-4}/1)\times 1\ mg/m^3=1\times 10^{-4}\ mg/m^3$

(virtually safe dose)

To convert a 70-y exposure to a 24-h exposure:

24-h exposure=d×25,600

$=(1\times 10^{-4}\ mg/m^3)\times 25{,}600$ d

$=2.56\ mg/m^3$

To account for uncertainty regarding the variability in the stage of the cancer process at which monomethylhydrazine or its metabolites may act, a multistage factor of 6 is applied (Crump and Howe 1984):

$(2.56\ mg/m^3)/6=0.43\ mg/m^3$ (0.18 ppm)

Therefore, based upon the potential carcinogenicity of monomethylhydrazine, an acceptable 24-h exposure would be 0.9 mg/m^3 (0.5 ppm).

If the exposure is limited to a fraction (f) of a 24-h period, the fractional exposure becomes 1/f×24 h (NRC 1985).

24-h exposure=0.43 mg/m^3 (0.18 ppm)

8-h=1.3 mg/m^3 (0.5 ppm)

4-h=2.6 mg/m^3 (1.1 ppm)

1-h=10.3 mg/m^3 (4.2 ppm)

0.5h=20.6 mg/m^3 (8.5 ppm)

Because the AEGL-2 values based upon acute toxicity were equivalent to or lower than the 10^{-4} risk values derived based on potential carcinogenicity, the acute toxicity data were used for the AEGLs for dimethylhydrazine. For 10^{-5} and 10^{-6} risk levels, the 10^{-4} values are reduced by 10-fold or 100-fold, respectively.

APPENDIX D

DERIVATION SUMMARY FOR ACUTE EXPOSURE GUIDELINE LEVELS FOR DIMETHYLHYDRAZINE (CAS No. 57–14–7; 1,1-Dimethylhydrazine) (CAS No. 540–73–8; 1,2-Dimethylhydrazine)

AEGL-1 Values			
30 min	1 h	4 h	8 h
Not recommended	Not recommended	Not recommended	Not recommended

Reference: Not applicable.
Test Species/Strain/Number: Not applicable
Exposure Route/Concentrations/Durations: Not applicable
Effects: Not applicable
Endpoint/Concentration/Rationale: Not applicable
Uncertainty Factors/Rationale: Not applicable
Modifying Factor: Not applicable
Animal to Human Dosimetric Adjustment: Not applicable
Time Scaling: Not applicable
Data Adequacy: Numeric values for AEGL-1 are not recommended because (1) data are not available, (2) data indicate that toxic effects may occur at or below the odor threshold, (3) an inadequate margin of safety exists between the derived AEGL-1 and the AEGL-2, or (4) 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

30 min	1 h	4 h	8 h
6.0 ppm	3.0 ppm	0.75 ppm	0.38 ppm

Reference: Weeks, M.H., G.C.Maxey, M.E.Sicks, and E.A.Greene. 1963. Vapor toxicity on UDMH in rats and dogs from short exposures. Am. Ind. Hyg. Assoc. J. 24:137–143

Test Species/Strain/Sex/Number: mongrel dogs, 2–4/group, sex not specified

Exposure Route/Concentrations/Durations: Inhalation; 1,200–4,230 ppm for 5 min; 360, 400, or 1,530 ppm for 15 min; 80–250 ppm for 60 min

Effects:

Exposure (15 min)	Effect
360 ppm	muscle fasciculations in 1 of 4 dogs (determinant for AEGL-2)
400 ppm	behavioral changes in 2 of 4 dogs
1,530 ppm	tremors, convulsions, vomiting in 2 of 2 dogs

Endpoint/Concentration/Rationale: 15-min exposure at 360 ppm considered a threshold for potentially irreversible effects or effects that would impair escape. At this exposure, muscle fasciculations were observed in 1 of 4 exposed dogs, and at 400 ppm, behavioral changes were observed.

Uncertainty Factors/Rationale: Total uncertainty factor: 30

Interspecies: 3—The toxic response to dimethylhydrazine (LC_{50} values) was similar across species. The 4-h LC_{50} values for mouse, rat, and hamster differ by a factor of approximately 2 and were consistent with the dog data when extrapolated from 1 h using n=1. The more sensitive species, the dog, was used to derive the AEGL-2 values.

Intraspecies: 10—A broad spectrum of effects were seen, including behavioral effects, hyperactivity, fasciculations, tremors, convulsions, and vomiting. The mechanism of toxicity is uncertain and sensitivity among individuals regarding these effects may vary. This variability was especially demonstrated in dogs wherein responses varied from one of extreme severity (vomiting, tremors, convulsions, and death) to no observable effects. Therefore, a factor of 10 was retained. A factor of 10 was also retained because experiments by Weeks et al. (1963) indicated that dogs had been previously stressed (auditory stimuli), which may have affected their response to dimethylhydrazine. Based upon these data, it was assumed that humans may be equally divergent in their response to dimethylhydrazine.

Modifying Factor: None
Animal to Human Dosimetric Adjustment: None applied, insufficient data
Time Scaling: $C^n \times t = k$, where n=1 and k=180 ppm·min; LC_{50} data were available for 5-, 15-, 30-, 60-, and 240-min exposures in rats and 5-, 15-, and 60-min in dogs. Exposure-response data indicated a near linear concentration-response relationship (n=0.84 for rats; n=0.80 for dogs). For time-scaling, a linear relationship was assumed and a value where n= 1 was selected.
Data Adequacy: Information regarding the human experience for acute inhalation exposure to dimethylhydrazine are limited to qualitatively case reports indicating nasal and respiratory tract irritation, breathing difficulties, and nausea. Data in animals have shown concentration-dependent effects ranging from respiratory tract irritation, pulmonary edema and neurologic effects to lethality. Because the nonlethal effects in humans and animals are qualitatively similar, the animal data were considered relevant and appropriate for development of AEGL values. The AEGL values for dimethylhydrazine reflect the steep exposure-response relationship suggested by available data.

AEGL-3 Values

30 min	1 h	4 h	8 h
22 ppm	11 ppm	2.7 ppm	1.4 ppm

Reference: Weeks, M.H., G.C.Maxey, M.E.Sicks, and E.A.Greene. 1963. Vapor toxicity of UDMH in rats and dogs from short exposures. Am. Ind. Hyg. Assoc. J. 24:137–143

Test Species/Strain/Sex/Number: mongrel dogs, 3–4/group; sex not specified

Exposure Route/Concentrations/Durations: Inhalation; exposure to various concentrations (80–22,300 ppm) for 5, 15, or 60 min

Effects:

1-h LC_{50}	981 ppm (reduction by 1/3 was basis for AEGL-3 derivation)
15-min LC_{50}	3,580 ppm
5-min LC_{50}	22,300 ppm

Endpoint/Concentration/Rationale: 1-h LC_{50} (981 ppm) reduced by 1/3 was considered an estimate of the lethality threshold (327 ppm). Based on the available exposure-response data for this chemical (Jacobson et al. 1955), a 3-fold reduction in LC_{50} values results in exposures that would not be associated with lethality.

Uncertainty Factors/Rationale: Total uncertainty factor: 30

Interspecies: 3—The toxic response to dimethylhydrazine (LC_{50} values) was similar across species. The 4-h LC_{50} values for mouse, rat, and hamster differ by a factor of approximately 2 and were consistent with the dog data when extrapolated from 1 h using n=1. The more sensitive species, the dog, was used to derive the AEGL-3 values.

Intraspecies: 10—A broad spectrum of effects were seen, including behavioral effects, hyperactivity, fasciculations, tremors, convulsions, and vomiting. The mechanism of toxicity is uncertain, and sensitivity among individuals regarding these effects may vary. This variability was especially demonstrated in dogs wherein responses varied from one of extreme severity (vomiting, tremors, convulsions, and death) to no observable effects. Therefore, a factor of 10 was used. A factor of 10-fold was also used because experiments by Weeks et al. (1963) indicated that dogs previously stressed by auditory stimuli may have a potentiated response to dimethylhydrazine. Based upon these data, it was assumed that humans may be equally divergent in their response to dimethylhydrazine subsequent to similar stresses.

Modifying Factor: None
Animal to Human Dosimetric Adjustment: None applied, insufficient data
Time Scaling: $C^n \times t = k$, where n=1 and k=654 ppm-min; LC_{50} data were available for 5-, 15-, 30-, 60-, and 240-min exposures in rats and 5-, 15-, and 60-min in dogs. Exposure-response data indicated a near linear concentration-response relationship (n=0.84 for rats; n=0.80 for dogs). For time-scaling, a linear relationship was assumed and a value where n= 1 was selected by the National Advisory Committee.
Data Adequacy: Information regarding the lethality of dimethylhydrazine in humans were not available. Lethality data for several animal species allowed for a defensible development of the AEGL-3 values but uncertainties remain regarding individual variability in the toxic response to dimethylhydrazines.