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

Commission of Life Sciences

National Research Council

NATIONAL ACADEMY PRESS
Washington, DC

NATIONAL ACADEMY PRESS 2101 Constitution Ave., N.W. Washington, D.C. 20418

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This project was supported by Contract Nos. DAMD17-89-C-9086 and DAMD17-99-C-9049 between the National Academy of Sciences and the U.S. Army. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

International Standard Book Number 0-309-07294-8

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National Academy Press
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Preface

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

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

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

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

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

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

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

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

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

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

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

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

Introduction

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

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

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

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

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

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

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

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

The three AEGLs are defined as follows:

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

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

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

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

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

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

REVIEW OF AEGL REPORTS

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

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

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

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

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

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Appendix

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

[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).

monkeys, squirrel monkeys, beagle dogs, rats, mice and hamsters. Nonlethal toxic effects include irritation of the upper respiratory tract, hemolysis, and 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 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.

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

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 nonlethal effects following acute (head-only) exposure to monomethylhydrazine

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	

(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

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

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.

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 3-5 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.

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.

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.

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-

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.

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

TABLE 3-8 Lethality (LC_{50}) of Hydrazine and Methylated Hydrazines in Rodents

Species	Hydrazine (ppm)	Monomethyl-hydrazine (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.

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.

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.

5.3. Derivation of AEGL-1

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 using the methods of ten 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 3.84 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
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

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

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.

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.

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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 monomethyl-hydrazine

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)
$(27.3 \text{ ppm})^1 \times 60 \text{ min} = 163.8$ ppm"min; regression analysis of the squirrel monkey lethality data suggested a near linear relationship

30-min AEGL-3: $C^1 \times 30 \text{ min} = 163.8$ ppm"min
C = 5.5 ppm

1-h AEGL-3: $C^1 \times 60 \text{ min} = 163.8$ ppm"min
C = 2.7 ppm

4-h AEGL-3: $C^1 \times 240 \text{ min} = 163.8$ ppm"min
C = 0.68 ppm

8-h AEGL-3: $C^1 \times 480 \text{ min} = 163.8$ 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.

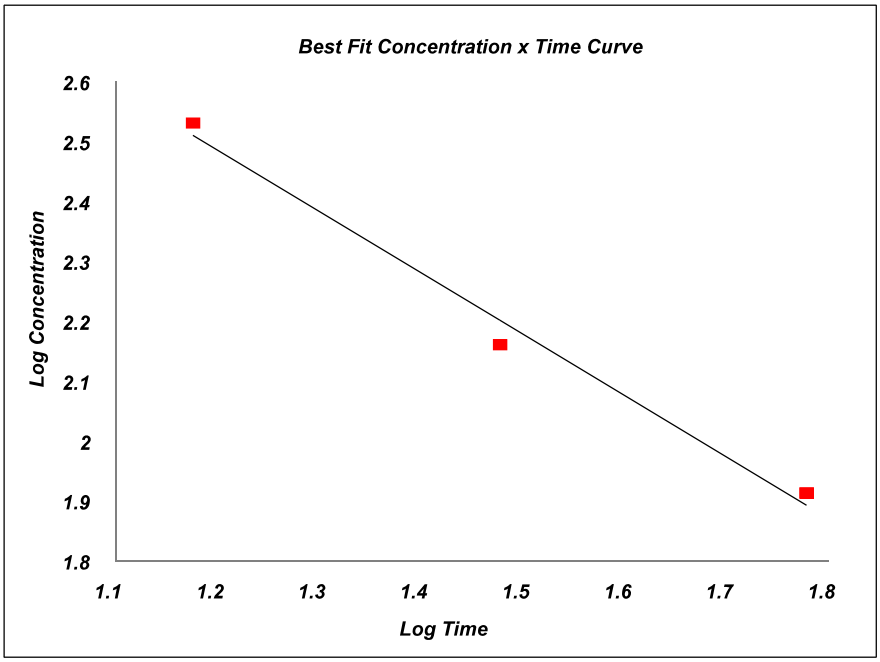
Time	Conc.	Log Time	Log Conc.
15	340	1.1761	2.5315
30	145	1.4771	2.1614
60	82	1.7782	1.9138

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



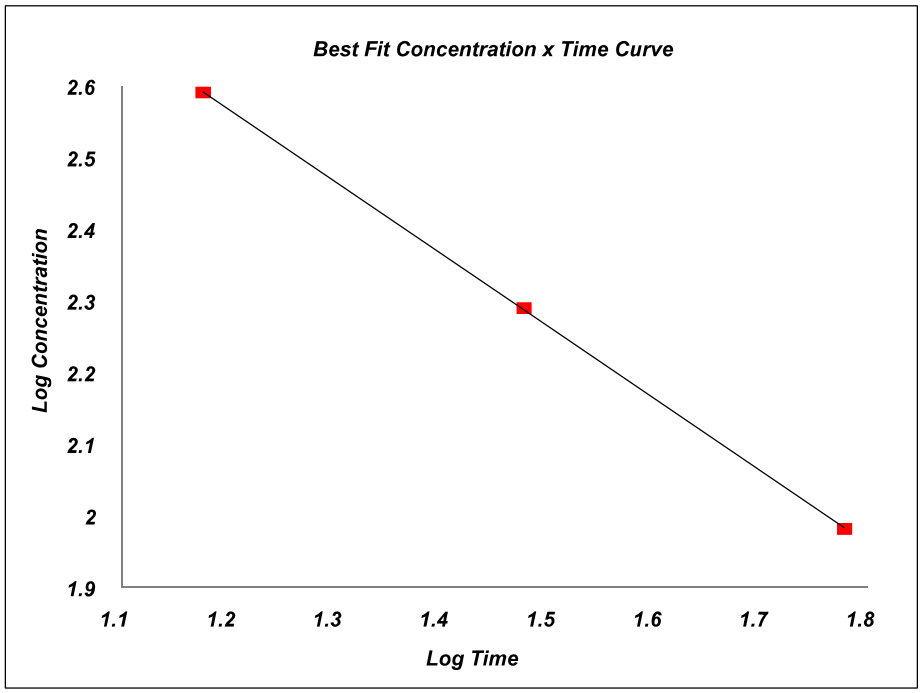
The LC_{50} values for 15, 30, and 60 min were 390, 195, and 96 ppm, respectively.

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 $(mg/kg"d)^{-1}$, 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}:

$$\text{Risk of } 1 \times 10^{-4} = (1 \times 10^{-4}/1) \times 1 \text{ mg/m}^3 = 1 \times 10^{-4} \text{ mg/m}^3$$
(virtually safe dose).

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

$$\begin{aligned} \text{24-h exposure} &= \text{d} \times 25{,}600 \\ &= (1 \times 10^{-4} \text{ mg/m}^3) \times 25{,}600 \text{ d} \\ &= 2.56 \text{ mg/m}^3. \end{aligned}$$

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

$$(2.56 \text{ mg/m}^3)/6 = 0.4 \text{ mg/m}^3 \text{ (0.2 ppm)}.$$

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 $1/f \times 24$ 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
= $(2.1 \times 10^{-6}$ mg/m$^3) \times 25{,}600$ 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):

$(5.4 \times 10^{-2}$ 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

(Continued)

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.