Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 8

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

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Preface

Extremely hazardous substances (EHSs)[2] can be released accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars and trucks transporting EHSs. Workers and residents 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 or intentional releases by terrorists. 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) in 1991 requested that the National Research Council (NRC) 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. Subsequently, *Standard Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Substances* was published in 2001, providing updated procedures, methodologies, and other guidelines used by the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances and the Committee on Acute Exposure Guideline Levels (AEGLs) in developing the AEGL values.

Using the 1993 and 2001 NRC guidelines reports, the NAC—consisting of members from EPA, the Department of Defense (DOD), the Department of Energy (DOE), the Department of Transportation (DOT), other federal and state governments, the chemical industry, academia, and other organizations from the private sector—has developed AEGLs for approximately 200 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 (COT) the Committee on Acute Exposure Guideline Levels, which prepared this report. This report is the eighth volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*. It

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

reviews the AEGLs for acrolein, carbon monoxide, 1,2-dichloroethene, ethylenimine, fluorine, hydrazine, peracetic acid, propylenimine, and sulfur dioxide for scientific accuracy, completeness, and consistency with the NRC guideline reports.

The committee's review of the AEGL documents involved both oral and written presentations to the committee by the NAC authors of the documents. The committee examined the draft documents and provided comments and recommendations for how they could be improved in a series of interim reports. The authors revised the draft AEGL documents based on the advice in the interim reports and presented them for reexamination by the committee as many times as necessary until the committee was satisfied that the AEGLs were scientifically justified and consistent with the 1993 and 2001 NRC guideline reports. After these determinations have been made for an AEGL document, it is published as an appendix in a volume such as this one.

The 10 interim reports of the committee that led to this report were reviewed in draft form by individuals selected 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 the ten committee interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for acrolein (fourteenth interim report, 2006), carbon monoxide (ninth, eleventh, thirteenth, and sixteenth interim reports, 2003, 2004, 2005, and 2009, respectively), dichloroethene (third, eleventh, thirteenth, fourteenth, and sixteenth interim reports, 2000, 2004, 2005, 2006, and 2009 respectively), ethylenimine (fifth, ninth, tenth, twelfth, and fourteenth interim reports, 2001, 2003, 2004, 2005, and 2006 respectively), fluorine (second, eleventh, and thirteenth interim reports, 2000, 2004, and 2006 respectively), hydrazine (second, tenth, twelfth, and fourteenth interim reports, 2000, 2004, 2005, and 2006 respectively), peracetic acid (fourteenth interim report, 2006), propylenimine (fifth, ninth, tenth, twelfth, and fourteenth interim reports, 2001, 2003, 2005, and 2006 respectively), and sulfur dioxide (thirteenth and fourteenth interim reports, 2005 and 2006 respectively): Deepak Bhalla (Wayne State University), Joseph Borzelleca (Virginia Commonwealth University), Charles Feigley (University of South Carolina), David Gaylor (Gaylor & Associates), Sidney Green (Howard University), A. Wallace Hayes (Harvard School of Public Health), Rogene F. Henderson (Lovelace Respiratory Research Institute), Sam Kacew (University of Ottawa), Nancy Kerkvliet (Oregon State University), Charles R. Reinhardt (DuPont Haskell Laboratory [retired]), Andrew G. Salmon (California Environmental Protection Agency), and Bernard M. Wagner (New York University Medical Center).

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 this volume before its release. The review of the interim report completed in 2005 was overseen by Sidney Green, Jr. (Howard University). The review of the interim report completed in 2006 was overseen by Robert A. Goyer, professor emeritus, University of Western Ontario. Appointed by the NRC, they were responsible for making certain that an independent examination of the interim reports were 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 committee gratefully acknowledges the valuable assistance provided by the following persons: Iris A. Camacho, Ernest Falke, Marquea D. King, and Paul Tobin (all from EPA); George Rusch (Honeywell, Inc.). The committee acknowledges James J. Reisa, director of the Board on Environmental Studies and Toxicology, and Susan Martel, Senior Program Officer for Toxicology, for their helpful guidance. Kulbir Bakshi, project director for his work in this project, and Raymond Wassel for bringing the report to completion. Other staff members who contributed to this effort are Keegan Sawyer (associate program officer), Ruth Crossgrove (senior editor), Radiah Rose (manager, Editorial Projects), Mirsada Karalic-Loncarevic (manager, Technical Information Center), Aida Neel (program associate), and Korin Thompson (project assistant). Finally, we would like to thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

Donald E. Gardner, *Chair*
Committee on Acute Exposure
Guideline Levels

Contents

National Research Council Committee Review of Acute Exposure Guideline Levels of Selected Airborne Chemicals

This report is the eighth volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*.

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, or what steps to take in an 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 that the U.S. Environmental Protection Agency (EPA) identify extremely hazardous substances (EHSs) and, in cooperation with the Federal Emergency Management Agency and the U.S. Department of Transportation, 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 that the Agency for Toxic Substances and Disease Registry (ATSDR) 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 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 hour (h), and only once in a lifetime for the general population, which includes infants (from birth to 3 years (y) of age), children, the elderly, and persons with diseases, such as asthma or heart 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 U.S. Department of Defense (DOD) and the National Aeronautics and Space Administration (NASA) (NRC 1968, 1972, 1984a,b,c,d, 1985a,b, 1986a, 1987, 1988, 1994, 1996a,b, 2000a, 2002a, 2007a, 2008a). COT has also published guidelines for developing emergency exposure guidance levels for military personnel and for astronauts (NRC 1986b, 1992, 2000b). Because of COT's experience in recommending emergency exposure levels for short-term exposures, in 1991 EPA and ATSDR 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 the data, and how to present the results.

In November 1995, the National Advisory Committee (NAC)[1] for Acute Exposure Guideline Levels for Hazardous Substances 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 minutes (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

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

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 adverse 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 adverse 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 idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

As described in *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993) and the NRC guidelines report *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals* (NRC 2001a), the first step in establishing AEGLs for a chemical is to collect and review all relevant published and unpublished information. 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 in 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 for 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, data from the most sensitive animal species are used. Uncertainty factors are commonly used when animal data are used to estimate 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 end points (including reproductive [in both genders], developmental, neurotoxic, respiratory, and other organ-related effects) are evaluated, the most important or most sensitive effect receiving the greatest attention. For carcinogenic chemicals, 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, 2001a). The NRC assigned this project to the COT Committee on Acute Exposure Guideline Levels. The committee has expertise in toxicology, epidemiology, occupational health, pharmacology, medicine, pharmacokinetics, industrial hygiene, and risk assessment.

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 Committee on Acute Exposure Guideline Levels for final evaluation.

The NRC committee's review of the AEGL reports prepared by NAC and its contractors involves oral and written presentations to the committee by the authors of the reports. The NRC committee provides advice and recommendations for revisions to ensure scientific validity and consistency with the NRC guideline reports (NRC 1993, 2001a). 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 AEGL reports, the NRC committee cannot verify all of the data used by NAC. The NRC committee

relies on NAC for the accuracy and completeness of the toxicity data cited in the AEGL reports. Thus far, the committee has prepared seven reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009). This report is the eighth volume in that series. AEGL documents for acrolein, carbon monoxide, cis-1,2-dichloroethene, trans-1,2-dichloroethene, ethylenimine, fluorine, hydrazine, peracetic acid, propyleneimine, and sulfur dioxide are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes 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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Roster of the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

Committee Members

Henry Anderson
Wisconsin Department of Health
Madison, WI

Marc Baril
Institut de Recherche
Government of Canada

Lynn Beasley
U.S. Environmental Protection Agency
Washington, DC

Alan Becker
College of Health and Human Services
Missouri State University
Springfield, MO

Robert Benson
U.S. Environmental Protection Agency
Region VIII
Denver, CO

Edward Bernas
AFL-CIO
Homewood, IL

Iris Camacho
U.S. Environmental Protection Agency
Washington, DC

George Cushmac
Office of Hazardous Materials Safety
U.S. Department of Transportation
Washington, DC

Richard Erickson
U.S. Navy
Groton, CT

Neeraja Erranguntla
Texas Commission on Environmental Quality
Austin, TX

David Freshwater
U. S. Department of Energy
Washington, DC

Ralph Gingell
Shell Health Services
Houston, TX

John P. Hinz
U.S. Air Force
Brooks Air Force Base, TX

James Holler
Agency for Toxic Substances and Disease Registry
Atlanta, GA

Clarion E. Johnson
Exxon Mobil Corporation
Fairfax, VA

Glenn Leach
U.S. Army Center for Health Promotion and Preventive Medicine Toxicity Evaluation
Aberdeen Proving Grounds, MD

Richard W. Niemeier
National Institute for Occupational Safety and Health
Cincinnati, OH

Mattias Oberg
Swedish Institute of Environmental Medicine (Karolinska Institutet)
Stockholm, Sweden

Susan Ripple
The Dow Chemical Company
Midland, Michigan

George Rusch
Chair, NAC/AEGL Committee
Department of Toxicology and Risk Assessment
Honeywell, Inc.
Morristown, NJ

Daniel Sudakin
Oregon State University
Corvallis, OR

Marcel T. M. van Raaij
National Institute of Public Health and Environment (RIVM)
Bilthoven, The Netherlands

George Woodall
U.S. Environmental Protection Agency
Research Triangle Park, NC

Alan Woolf
Children's Hospiral
Boston, MA

Oak Ridge National Laboratory Staff

Cheryl Bast
Oak Ridge National Laboratory
Oak Ridge, TN

Kowetha Davidson
Oak Ridge National Laboratory
Oak Ridge, TN

Sylvia Talmage
Oak Ridge National Laboratory
Oak Ridge, TN

Robert Young
Oak Ridge National Laboratory
Oak Ridge, TN

National Advisory Committee Staff

Paul S. Tobin
Designated Federal Officer, AEGL Program
U.S. Environmental Protection Agency
Washington, DC

Ernest Falke
U.S. Environmental Protection Agency
Washington, DC

Iris A. Camacho
U.S. Environmental Protection Agency
Washington, DC

Sharon Frazier
U.S. Environmental Protection Agency
Washington, DC

Appendixes

6

Hydrazine[1]

Acute Exposure Guideline Levels

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P.L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hours (h). Three levels—AEGL-1 and AEGL-2 levels, and AEGL-3—will be developed for each of five exposure periods (10 and 30 min, 1 h, 4 h, and 8 h) and will be distinguished by varying degrees of severity of toxic effects. It is believed that the recommended exposure levels are applicable to the general population including infants and children, and other individuals who may be sensitive and susceptible. The three AEGLs have been defined as follows:

AEGL-1 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 notable discomfort, irritation, or certain

[1]This document was prepared by the AEGL Development Team composed of Robert A. Young (Oak Ridge National Laboratory) and Chemical Manager Richard Thomas (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guideline reports (NRC 1993, 2001).

asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that 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 sensitive subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that certain individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Hydrazine (m.w. 32.05) is a liquid at room temperature with a vapor pressure of 14.4 mm Hg at 25°C. This simple diamine (H_2NNH_2) is a powerful reducing agent. The chemical acts as an oxygen scavenger and is highly reactive with many other chemicals. Hydrazine is used in various chemical manufacturing processes (production of flexible and rigid foams, pesticides) and by the military as a missile and rocket propellant, and in power sources. U.S. production is estimated at 20 million pounds and world-wide production at 80 million pounds. Hydrazine has an ammonia-like odor with an odor threshold of 3.0 to 4.0 ppm.

Human data on the toxicity of hydrazine following acute inhalation exposure are limited to anecdotal accounts that lack definitive exposure data. The utility of this information is compromised by non-quantitative exposures, concurrent exposure with other chemicals, and involvement of simultaneous multiple exposure routes.

Data from animal studies indicate that hydrazine may be metabolized to acetylhydrazine, diacetylhydrazine, ammonia, and urea, and may form hydrazones with pyruvate and 2-oxoglutarate. The biotransformation of hydrazine is mediated, at least in part, by hepatic monooxygenases. The role of metabolism and absorption/excretion kinetics is uncertain regarding immediate portal-of-

entry toxic effects from acute inhalation exposures. The highly reactive nature of hydrazine *per se* is a plausible determinant of acute port-of-entry toxic effects.

AEGLs were based upon data sets defining toxicity end points that were specific for the AEGL level. No data were available with which to empirically determine a concentration-exposure duration relationship for hydrazine. This 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). Because there were no data to empirically derive the chemical-specific exponent, the default values of n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points were used in the $C^n \times t = k$ equation in accordance with the SOP manual.

AEGL-1 values were based upon a study by House (1964) in which male monkeys exhibited skin flushing and eye irritation after an initial 24-h continuous exposure to 0.4 ppm hydrazine. Although the monkeys in this study were subjected to the 24-h continuous exposure for an additional 89 days, only effects occurring during the first 24 h were considered in the development of the AEGL-1 values. In the absence of chemical specific data, an n of 3 was applied to extrapolate the 24-h (0.4 ppm) exposure from the House (1964) study to the AEGL -1 time frames ($k = 0.4\ ppm^3 \times 24\ h = 1.54\ ppm^3\ h$). An uncertainty factor of 3 was applied for interspecies variability because the surface contact irritation by the highly reactive hydrazine is not likely to vary greatly among species, and because a nonhuman primate was the test species. An uncertainty factor of 3 was applied for intraspecies variability because the contact irritation from the highly reactive hydrazine is not expected to vary greatly among individuals, including susceptible individuals. Because hydrazine is extremely reactive and the sensory-irritation effects are considered to be concentration dependent rather than time dependent, 0.1 ppm (the 30-min, 1-h, 4-h, and 8-h values were all approximately 0.1 ppm) was considered appropriate for all AEGL-1 durations.

The level of distinct odor awareness (LOA) for hydrazine is 63 ppm (see Appendix E). The odor LOA represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, about 10 % of the population will experience a strong odor intensity. The LOA may assist chemical emergency planners and responders in assessing the public awareness of the exposure due to odor perception.

The AEGL-2 was derived based upon data from a study by Latendresse et al. (1995) in which rats exposed to hydrazine (750 ppm) for 1 h exhibited nasal lesions. The 1-h exposure to 750 ppm values was scaled to AEGL-specific durations using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points. An uncertainty factor of 3 for interspecies variability was applied to account for uncertainties regarding species variability in the toxic response to inhaled hydrazine. Because the toxic response to acute low-level exposures results from direct contact of the highly reactive hydrazine, the reduction from a default value of 10 is justified. Similarly, an uncertainty factor of 3 was applied for intraspecies variability because the portal-of-entry effect of the reactive hydrazine is likely attributed to direct interaction with res-

piratory tract tissues. This contact irritation is not likely to vary considerably among individuals. A modifying factor of 2 was applied to account for data inadequacies regarding identification of toxic responses consistent with AEGL-2 level effects (i.e., serious or irreversible, but nonlethal, effects of acute inhalation exposure to hydrazine). Although the more recent studies such as those by Latendresse et al. (1995) and HRC (1993) appear to have reliable determinations of hydrazine concentrations, the overall data set for hydrazine is compromised by uncertainties in the accuracy of exposure concentration measurements due to the reactivity of hydrazine with the surfaces of the exposure apparatus. Therefore, an additional modifying factor of 3 has been applied to account for the impact of these deficiencies. This resulted in a total adjustment of 60-fold for derivation of AEGL-2 values. The critical effect (nasal lesions) is consistent with the continuum of hydrazine toxicity (i.e., respiratory tract irritation, pulmonary tissue damage, and potential tumorigenicity) and, therefore, was considered appropriate for AEGL-2 development.

The AEGL-3 values were derived based upon a rat inhalation study (HRC 1993). The lethality threshold was estimated by a three-fold reduction of the 1-h LC_{50} (3192 ppm/3 = 1064 ppm). This was considered a tenable estimate considering that rats survived multiple 1 h exposures to 750 ppm of hydrazine (Latendresse et al. 1995). This approach was also justified by the steep exposure-response curve for hydrazine. Temporal scaling was again applied using the exponential expression $C^n \times t = k$ where n = 3 for extrapolation to shorter times and n = 1 when extrapolating to longer times. A total uncertainty factor of 10 was applied for derivation of the AEGL-3 values as described for AEGL-2. Although the more recent study by HRC (1993) had reliable determinations of hydrazine concentrations, the overall data set for hydrazine is compromised by uncertainties in the accuracy of exposure concentration measurements due to the reactivity of hydrazine with the surfaces of the exposure apparatus. Therefore, an additional modifying factor of 3 was applied to account for the impact of these deficiencies. This resulted in a total adjustment of 30-fold for derivation of AEGL-3 values.

Cancer inhalation slope factors for hydrazine were derived and compared to AEGL values based upon 10^{-4}, 10^{-5}, and 10^{-6} cancer risk levels. The assessment revealed that AEGL-2 values derived from noncarcinogenic toxicity end points were greater than the exposure concentrations calculated for the 10^{-4} excess cancer risk level. However, the available animal data suggest that the tumorigenic response to inhaled hydrazine is a function of prolonged tissue irritation resulting from repeated exposures and not the result of a single low exposure. For this reason and because the AEGL values are applicable to rare events or single, once-in-a-lifetime exposures to limited geographic areas and small populations, the AEGL values based on noncarcinogenic end points were considered to be more appropriate.

The AEGL values, their respective toxicity end points, and references are summarized below in Table 6-1.

TABLE 6-1 Summary of AEGL Values for Hydrazine

Classification	10-min	30-min	1-h	4-h	8-h	End Point (Reference)
AEGL-1 (Nondisabling)	0.1 ppm (0.1 mg/m^3)	0.1 ppm (0.1 mg/m^3)	0.1 ppm (0.1 mg/m^3)	0.1 ppm (0.1 mg/m^3)	0.1 ppm (0.1 mg/m^3)	Eye and facial irritation in monkeys (House 1964)[a]
AEGL-2 (Disabling)	23 ppm 30 mg/m^3	16 ppm (21 mg/m^3)	13 ppm (17 mg/m^3)	3.1 ppm (4.0 mg/m^3)	1.6 ppm (2.1 mg/m^3)	Nasal lesions in rats (Latendresse et al. 1995)
AEGL-3 (Lethal)	64 ppm (83 mg/m^3)	45 ppm (59 mg/m^3)	35 ppm (46 mg/m^3)	8.9 ppm (12 mg/m^3)	4.4 ppm (5.7 mg/m^3)	Lethality in rats (HRC 1993)

[a]Because the contact irritation response to the extremely reactive hydrazine is concentration dependent rather than time-dependent, the AEGL-1 is the same for all time periods.

1. INTRODUCTION

Hydrazine, a simple diamine, is a powerful reducing agent. It acts primarily as an oxygen scavenger and is highly reactive with many other chemicals (WHO 1987). Contact with strong oxidizers (e.g., hydrogen peroxide, nitrogen tetroxide, chlorine, fluorine) will result in immediate ignition or explosions, and contact with catalytic metals may result in flaming decomposition. Hydrazine is used as a chemical intermediate in various manufacturing procedures including the manufacture of pharmaceuticals, plastic blowing agents, dyes, and agricultural chemicals. It is used extensive in military applications as a missile and rocket propellant, and in chemical power sources. (USAF 1989). Hydrazine also occurs naturally as a nitrogen fixation product of *Azobacter agile* (Raphaelian 1963). U.S. production is estimated at 20 million pounds and world-wide production at 80 million pounds.

The National Research Council Committee on Toxicology (NRC 1985) summarized the toxicologic data for hydrazine for development of Emergency and Continuous Exposure Guidance Levels. Garcia and James (1996) also summarized data regarding the toxicology of hydrazine for the development of Spacecraft Maximum Allowable Concentrations (SMACS).

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 provide meaningful insight into understanding toxicity mechanisms or for other special considerations.

The primary physicochemical data for hydrazine are presented in Table 6-2. Hydrazine may also occur as the methylated derivatives, monomethylhydrazine and dimethylhydrazine (symmetrical and unsymmetrical isomers). The reactivity of hydrazine is especially important regarding accurate assessment of

exposure concentrations under experimental conditions. Early reports (Comstock et al. 1954) noted such concerns when reporting concentrations of hydrazine in exposure chambers. Because of the extreme reactivity of the compound (up to 99% of the hydrazine would be lost to absorption onto the chamber walls or body surface of the test animals), nominal concentration estimates were found to be a gross overestimation of actual exposure concentrations.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Definitive information was not available regarding the acute lethality of humans following inhalation exposure to hydrazine. However, Sotaniemi et al. (1971) reported a fatality in a worker exposed to hydrazine once per week for six months. A post-exposure simulation provided an estimated hydrazine concentration of 0.05 ppm (0.071 mg/m^3). Possible renal involvement (tubular necrosis, inflammation, hemorrhage, and enlarged kidneys were noted and considered to be a contributing factor to the fatality), neurological effects (tremors), and pulmonary involvement were also noted.

TABLE 6-2 Chemical and Physical Data for Hydrazine

Parameter	Data	Reference
Chemical Name	Hydrazine	
Synonyms	Diamide; diamine; hydrazine base; hydrazine anhydrous; levoxine	O'Neil et al. 2001 USAF 1989
CAS Registry No.	302-01-2	O'Neil et al. 2001
Chemical formula	H2NNH2	O'Neil et al. 2001
Molecular weight	32.05	O'Neil et al. 2001
Physical state	Liquid	O'Neil et al. 2001
Odor	ammoniacal and pungent	WHO 1987
Melting/boiling/flash point	2.0°C /113.5°C /37.8°C	Weiss 1980
Specific gravity[a]	1.011 at 15°C/4°C	O'Neil et al. 2001
Solubility in water	Miscible	O'Neil et al. 2001
Vapor pressure	14.4 mm Hg at 25°C	Schiessl 1985
Relative vapor density	1.1	WHO 1987
Conversion factors in air	1 mg/m^3 = 0.76 ppm 1 ppm = 1.3 mg/m^3	USAF 1989

[a]Density of liquid at 15°C relative to the density of water at 4°C.

2.2. Nonlethal Toxicity

Hydrazine has an irritating, ammonia-like odor. An odor threshold of 3.0 to 4.0 ppm has been reported (Jacobson et al. 1955). Because of its irritating nature, a level of distinct odor awareness (LOA) was determined for hydrazine. The level of distinct odor awareness (LOA) for hydrazine is 63 ppm (see Appendix E). The odor LOA represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, about 10 % of the population will experience a strong odor intensity. The LOA may assist chemical emergency planners and responders in assessing the public awareness of the exposure due to odor perception.

2.2.1. Case Reports

A single exposure of a 35-year old man to 35% liquid hydrazine (exposure duration was approximately 5 min) was reported by Brooks et al. (1985). The incident involved dermal and oral exposure to liquid hydrazine of unknown dose level and resulted in a pins-and-needles sensation, rash, and disorientation within 2 h. Within 5 h the signs and symptoms included, muscle pain, diarrhea, nausea, abdominal cramping, and respiratory problems (chest tightness, coughing, wheezing). The exposure resulted in a prolonged asthma-like illness (reactive airways dysfunction syndrome) that persisted for 5-6 months.

Cognitive disorders were reported for a worker exposed to hydrazine (concentration unknown). Following removal from the exposure, some improvement in the condition of the individual was observed (Richter et al. 1992).

In an investigation of the role of acetylation phenotype on hydrazine metabolism and excretion by workers involved in the production of hydrazine hydrate, Koizumi et al. (1998) noted that the study population was routinely exposed to hydrazine concentrations of 0.07- 0.12 ppm (8-h TWA). There was no indication that this exposure resulted in signs of toxicity.

2.2.2. Epidemiologic Studies

Epidemiologic studies regarding nonlethal effects in humans involving exposure to hydrazine were limited to a study of workers in hydrazine manufacturing by Roe (1978), a follow-up study by Wald et al. (1984), a study by Contassot et al. (1987), and study by Morgenstern and Ritz (2001). Generally, the available epidemiological studies on worker populations from different facilities are inconclusive due to small cohort sizes in some studies, compromised record keeping, various confounding factors, and inadequate exposure characterizations.

In both the Roe (1978) study and the follow-up study by Wald et al. (1984), observed worker mortality (facility in the United Kingdom) did not differ significantly from the expected mortality, and no deaths were reported that

could be attributed to nasopharyngeal cancers. Because specific exposure concentrations were not available for this study, the exposure groups were categorized as little or no exposure, <1.0 ppm, and 1.0 to 10 ppm.

In the study by Contassot et al. (1987), a cohort of 130 male workers exposed to hydrazine for at least six months were divided into three exposure groups: low level (0.1 ppm), medium level (0.1 to 1.0 ppm) and high level (>1.0 ppm). Although initial conclusions indicated no excess risk of cancer, subsequent analysis suggested that the standard incidence ratio achieved significance for cancers in the high exposure group. A qualifying statement, however, noted that there were problems with record keeping and that the significance was greatly reduced when skin cancers were excluded.

Results of an occupational study of 6107 males (Rocketdyne Corp.) exposed (prior to 1980) to hydrazine and methylated hydrazines (1-methylhydrazine and 1,1-dimethylhydrazine) for at least two years during work associated with rocket propellants was reported by Morgenstern and Ritz (2001). Possible concurrent exposures to pulmonary toxicants such as asbestos, chlorine, fluorine, beryllium, hydrogen peroxide, rocket engine exhaust, and various solvents were noted. Hydrazine exposure was categorized as medium, high or no exposure based upon type of work. Relative to the group with no hydrazine exposure, the low-exposure group was not associated with excess lung cancer mortality but a relative risk of 1.68 (95% confidence interval of 1.12-2.52) was determined for the high exposure group. The investigators concluded that occupational exposure to hydrazine and other chemicals associated with the rocket engine testing increased lung cancer risk and possible risk to other cancers. Cancer risks for lymphopoietic and lung cancer were increased (rel. risk of 2.01 and 2.45, respectively) for earlier time periods (i.e., 1960s vs 1980s). Definitive exposure data were not provided in the study report.

2.3. Developmental and Reproductive Toxicity

Reports providing information regarding the reproductive and developmental effects of hydrazine exposure in humans were not available.

2.4. Genotoxicity

Human genotoxicity data relevant to AEGL derivation were not available.

2.5. Carcinogenicity

Wald et al. (1984) reported no significant increase in mortality (47 deaths reported) due to cancer in 427 workers exposed to an undetermined concentration of hydrazine. The follow-up period used in this study was relatively short and may have compromised the ability to detect a weak carcinogenic response.

Epidemiologic studies have also been conducted (see Section 2.2.2.).

2.6. Summary

Data regarding the effects of acute exposure of humans to hydrazine are lacking. Although anecdotal information (Brooks et al. 1985) is available, the reported situation involved exposure via multiple routes (dermal, oral, and probably inhalation) and no exposure concentration data were reported. Reports by Sotanieme et al. (1971) and Richter et al. (1992) regarding inhalation exposure also lacked definitive exposure data. Therefore, there are no human data available that are acceptable for derivation of AEGL values.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Discussions in this section are limited to those studies providing information on acute exposures or to longer-term studies that indicated lethality during the first few days of exposure. For example, MacEwen et al. (1981) conducted a 12-month inhalation exposure study using male and female F344 rats, Syrian golden hamsters, and C57BL/6 mice. Although slight (but statistically insignificant) increases in mortality were noted early during the exposure regimen, these observations could not be attributed to acute exposure but noted only at monthly intervals. Therefore, such data are not considered primary for derivation of AEGL values.

3.1.1. Nonhuman Primates

House (1964) exposed groups of 10 male Rhesus monkeys to hydrazine at an average concentration of 0.78 ppm (1 mg/m^3) (range: 0.25-1.38 ppm [0.33-1.8 mg/m^3]) continuously for 90 days. Hydrazine was introduced into the exposure chambers via saturation of a carrier gas (nitrogen) with hydrazine. The exposure of the monkeys was uninterrupted for the duration of the experiment. The hydrazine concentration was measured colorimetrically from samples extracted from the chamber at various times (10-18 samples/day for the first 10 days; 3 times/day thereafter). A 20% mortality was reported following completion of the 90-day exposure. The two deaths occurred during days 21-30 and 81-90.

3.1.2. Dogs

Acute inhalation exposure data for dogs are limited. In an inhalation study by Comstock et al. (1954), a mongrel dog was exposed to hydrazine at 18 mg/m^3 (14 ppm), 6 h/day, 5 days/week. The dog exhibited anorexia and fatigue by the

second day of exposure and vomiting ensued after day 2 with the dog becoming progressively weaker until week 13 when it died. Weatherby and Yard (1955) exposed two mongrel dogs to hydrazine (3-6 mg/m^3) for 6 h/day, 5 days/week. After 5 days of exposure both dogs exhibited muscular incoordination and weakness. On the seventh day, one dog died and the other was terminated. Pathological examination indicated primarily renal (proximal cortical congestion, capillary damage) and hepatic (central zone fatty changes, hyalinization of hepatocytes, distended bile canaliculi) involvement, with minor pulmonary effects.

An i.v.LD_{50} of 25 mg/kg was reported for dogs (Witkin 1956). The value is, however, based upon only two dose groups (20 and 30 mg/kg) with only two dogs per group. During a 10-day observation period, both dogs of the low dose group survived while both of the high dose group died within 2 h.

3.1.3. Rats

Several studies have examined the effect of acute exposure to hydrazine and methylated hydrazine derivatives. The testing protocols and quality of the studies varied considerably, and species variability was evident.

In a study reported by Comstock et al. (1954), groups of six male Wistar rats (150- 250 g) each were exposed to hydrazine vapors at a concentration of ≈20,000 mg/m^3 (≈15,280 ppm) for 0.5, 1, 2, or 4 h. Saturated hydrazine vapor was introduced into the chamber (20L, 25ºC) at a rate of 0.002 m^3/min. The rats were placed into the chamber after equilibrium was attained. Immediately after introduction into the chamber the rats began scratching and grooming themselves. After 1-2 min, their eyes were partially to completely closed. During the first 2 h of exposure, the rats exhibited alternating periods of restlessness and inactivity. The aforementioned signs are considered normal responses to exposure to a saturated vapor atmosphere. However, shortly thereafter, the rats exhibited pronounced salivation and a red-colored material (porphyrin secreted by the Harderian glands) was observed accumulating around the nares. Such porphyrin secretion is known to be a sensitive indicator of local irritation. The results of this study are shown in Table 6-3. Mortality rates of 33-67% were noted for the 4-h exposure period (latency period not specified). Hyperactivity and/or convulsions were observed in rats that died. No immediate deaths occurred during the 0.5-h exposure period but three of 18 rats had died within the 14-day postexposure period. Necropsy findings included pulmonary edema with localized damage to the bronchial mucosa. Incidence data for these findings were not provided. The results of this study are compromised by the difficulty in assessing chamber concentrations and the resulting extreme variability in the actual concentrations.

Comstock et al. (1954) also conducted an additional test in which the hydrazine concentration was more accurately determined by using a quantitative

TABLE 6-3 Acute Inhalation Toxicity of Hydrazine Vapor in Male Rats

Concentration (mg/m^3)[a]	Exposure Period (h)	C × t ($mg\text{-}h/m^3$)	Immediate Lethality	14-Day Lethality
20,000	4	80,000	4/6	5/6
20,000	4	80,000	3/6	4/6
20,000	2	40,000	2/6	3/6
20,000	2	40,000	0/6	4/6
21,000	1	21,000	0/6	0/6
20,000	1	20,000	0/6	2/6
20,000	1	20,000	0/6	0/6
21,000	0.5	10,500	0/6	0/6
20,000	0.5	10,500	0/6	2/6
20,000	0.5	10,500	0/6	1/6

[a]Nominal concentration, analytical determination would be considerably lower.
Source: Comstock et al. 1954. Reprinted with permission; copyright 1954, American Medical Association.

analytical method based upon hydrazine's reactivity with sulfuric acid. The test protocol was the same as for the preceding test. With the exception of one rat each in the 4-h and 1-h groups, exposure to hydrazine vapors did not result in immediate lethality. However, deaths were observed for all exposure durations during the 14-day postexposure period and occurred throughout the 14-day period. The results of this phase of the study are shown in Table 6-4.

Upon analyzing the immediate lethality of hydrazine when exposure is expressed as a concentration × time product (C × t), there does not appear to be any meaningful correlation. For example, deaths were observed at C × t values of 436 and 831 $mg\text{-}h/m^3$ while exposure as high as 1,600 $mg\text{-}h/m^3$ did not result in immediate death. When considering the lethality rate over a 14-day postexposure period, the highest C × t product (1,600 $mg\text{-}h/m^3$) resulted in a substantially higher lethality rate (83%) than lower c × t values (Table 6-5). However, an accurate and meaningful assessment of lethality relative to exposure expressed as a c × t product is compromised by the fact that determination of actual hydrazine concentration in the exposure chambers was highly variable and possibly of questionable accuracy, and that lethality was assessed as both immediate and up to 14 days postexposure. Additionally, these findings are compromised by the low number of animals in each of the exposure groups.

These same investigators also conducted multiple short-term exposure experiments in which rats were exposed to hydrazine at a average daily concentration of 295 mg/m^3 (actual concentration during the Day 1 exposure period was 288 mg/m^3) for 6 h/day, 5 days/week for 1 week. None of the 20 rats died following the initial 6-h exposure on day 1 although 16 of 20 rats died following completion of the 5-day exposure regimen. Body weight loss of 10-20 g and

signs of pulmonary toxicity (pulmonary edema with localized damage to the bronchial mucosa) were noted for surviving rats. Additional multiple, intermittent exposure experiments using hydrazine concentrations ranging from 26-140 mg/m^3 were also conducted and showed that initial exposures did not result in lethality but that signs of toxicity and death did occur following multiple exposures. There were no definitive relationships observed between exposure frequency and lethality.

TABLE 6-4 Acute Inhalation Toxicity in Rats Exposed to Hydrazine Vapor

Concentration (mg/m^3)[a]	Exposure Duration (h)	C × t ($mg\text{-}h/m^3$)	Immediate Lethality	14-Day Lethality
352	4	1,408	0/6	2/6
344	4	1,376	0/6	3/6
400	4	1,600	0/6	5/6
109	4	436	1/6	3/6
227	4	908	0/6	1/6
756	2	1,512	0/6	1/6
405	2	810	0/6	1/6
129	2	258	0/6	2/6
128	2	256	0/6	1/6
285	2	570	0/6	2/6
831	1	831	1/6	3/6
151	1	151	0/6	1/6
106	1	106	0/6	1/6
185	1	185	0/6	0/6

[a]Analytical determination based upon quantitative relationship of hydrazine/sulfuric acid reaction.
ND: Not determined; exposure time too short for chemical analysis.
Source: Comstock et al. 1954. Reprinted with permission; copyright 1954, American Medical Association.

TABLE 6-5 Lethality in Rats Following 1-Hour Nose-Only Exposure to 64% Hydrazine Aerosol[a]

Exposure Group (mg/L)	Males	Females	Total
Control	0/5	0/5	0/10
0.65	0/5	0/5	0/10
2.04	0/5	0/5	0/10
3.24	1/5	3/5	4/10
4.98	2/5	4/5	6/10

[a]With the exception of one female in the 3.24 mg/L exposure group that died 3 days post exposure, all deathsoccurred overnight following the exposure; there was a 14-day post-exposure observation period.

Jacobson et al. (1955) assessed the toxicity of hydrazine and the methylated derivatives of hydrazine using several species including male white rats (groups of 10; strain not specified) exposed to hydrazine and observed for up to 14 days. A 4-h LC_{50} of 750 mg/m^3 (570 ppm) was estimated. Based upon a ventilation rate of 0.223 m^3/day for rats (0.35 kg) (EPA 1986), this is equivalent to 112 mg/kg/day. Hydrazine appeared to be less toxic than the methylated hydrazine derivatives. These lethality data are summarized in Section 4.3. (see Table 6-9).

Witkin (1956) reported on the acute lethality of hydrazine in several animal species, including rats, following various routes of administration other than inhalation. LD_{50} values were determined by regression analysis using log-dose probit units from four dose groups of 10 male Wistar rats (100-200 g) administered hydrazine i.v., i.p., or orally. Deaths occurred in the groups given 40 and 70 mg/kg; specific doses for the lower dose groups were not provided. The LD_{50} determinations were based upon deaths occurring in a 10-day observation period. In rats, the i.v., i.p. and oral LD_{50} values were estimated at 55 ± 2.7, 59 ± 3.9, and 60 ± 3.8 mg/kg, respectively. Deaths occurred at days 1, 3, and 4 in the 40 mg/kg group (1 death on each day) and on days 1 (5 deaths), 3, 4, and 6 (1 death each day). These data are summarized in Section 7.2. (see Table 6-12).

House (1964) conducted 90-day continuous exposure of male Sprague-Dawley rats to an average concentration of 0.78 ppm (0.25-1.38 ppm) hydrazine. The treatment resulted in 98% mortality with deaths occurring after 41 days of treatment. Although it was noted that the exposed rats were "weak and sick early in the test," neither specific times nor characterization of the effects were provided.

An acute inhalation study to assess lethality of hydrazine in rats was conducted by Huntingdon Research Centre (HRC 1993). In this study, male and female Sprague-Dawley rats (5/sex/group) were exposed (nose only) for 1 h to an aerosol of hydrazine (64% aqueous solution, mass median aerodynamic diameter ± geometric standard deviation of 5.0 ± 2.56, 1.1 ± 3.56, 1.8 ± 3.04, and 2.4 ± 2.40 for the 0.65, 2.04, 4.98, and 3.24 mg/L exposure atmospheres, respectively). The rats were observed throughout the exposure period (clinical signs recorded at the end of chamber equilibration period and at 0.25, 0.5, 0.75, and 1 h during exposure) and daily (or more frequently as necessary) for an additional 14 days. During the exposure, the rats exhibited exaggerated respiratory movements. During the post-exposure observation period, clinical signs included death (two highest exposures only), exaggerated respiratory movements, noisy respiration, lethargy, secretions from the eyes, brown staining around the snout and jaws, and poorly groomed appearance. The lethality data are summarized in Table 6-5.

Using a log probit method, LC_{50} values for the 64% hydrazine atmosphere were estimated as: 9.0, 5.3, and 6.5 mg/L, respectively, for males, females, and sexes combined (equivalent to 9,000, 5,300, and 6,500 mg/m^3). Based upon hydrazine alone, these respective estimates were 5.8, 3.4, and 4.2 mg/L (equivalent to 5,800, 3,400, and 4,200 mg/m^3). Recovery from signs of exposure was ob-

served on day 2 for the 0.65 mg/L groups, and on days 3-4 for the 2.04 mg/L groups. For some rats in the higher exposure groups, exaggerated respiratory movements were observed throughout the post-exposure observation period.

3.1.4. Mice

Comstock et al. (1954) exposed groups of 10 female mice (strain not specified) to hydrazine vapor in various exposure protocols. Exposures (6 h/day for 5 days) to concentrations ranging from 160-611/mg/m^3 (average daily exposure of 295 mg/m^3) did not result in lethality until day 3. There did not appear to be a definitive concentration-effect relationship; three mice died on Day 3, 5 mice died on Day 4, but no deaths occurred on Day 5. Pathological examination revealed pulmonary edema and localized, unspecified damage to the bronchial mucosa.

Acute toxicity assays using groups of 10 female white mice (strain not specified) and other species were conducted by Jacobson et al. (1955). Based upon 4-h exposures, an LC_{50} of 330 mg/m^3 (252 ppm) was estimated. Based upon a ventilation rate of 0.039 m^3/day for a 30 g mouse (EPA 1986), this is equivalent to 17.9 mg/kg/day.

The acute lethality of hydrazine in mice following i.v., i.p., and oral administration was reported by Witkin (1956). LD_{50} values were determined by regression analysis using log-dose probit units from four dose groups of 10 male Webster-Swiss mice (20-30 g) although the actual doses of each group were not provided in the report. In mice, the i.v., i.p. and oral LD_{50} values were estimated at 57 ± 7.5, 62 ± 4.0, and 59 ± 7.2 mg/kg, respectively. These data are summarized along with data for other species in Section 7.2. The LD_{50} determinations were based upon deaths occurring in 10-day observation period. House (1964) conducted 90-day continuous exposure of male ICR Swiss albino mice to hydrazine at concentrations of 0.78 ppm (0.25-1.38 ppm). The treatment resulted in 99% mortality with deaths occurring after 41 days of treatment. Although it was noted that the exposed rats were "weak and sick early in the test", neither specific times nor characterization of the effects were provided.

3.1.5. Hamsters

MacEwen and Vernot (1981) exposed groups of 10 male Syrian golden hamsters (whole-body exposure) to hydrazine at concentrations of 2770, 2450, 2140, 1920, 1600, or 1280 ppm for 1 h. The hamsters were observed during the exposure and for 14 days following exposure. Deaths occurring during the exposure and during the 14-day postexposure period were used for estimating the LC_{50}. The lethality data for this experiment are shown in Table 6-6. Probit analysis was used to estimate an LC_{50} of 2,585 ppm.

TABLE 6-6 Lethality in Hamsters Following 1-Hour Inhalation (Whole Body) Exposure to Hydrazine[a]

Exposure (ppm)	Mortality	Comments
2270	9/10	3 Deaths within 1 h; 4 deaths within 15 h, 1 death at 3 days, and 1 death at 4 days
2450	3/10	1 Death at 12 h, 1 death at 1 day, and 1 death at 3 days
2140	3/10	1 Death at 5 min, 1 death at 1 day, and 1 death at 2 days
1920	3/10	1 Death at 1 day, a death at 3 days, and 1 death at 11 days
1600	2/10	1 Death at 1 h, 1 death at 11 days
1280	2/10	1 Death at 8 days and 1 death at 12 days

[a]14-Day postexposure observation period.

3.2. Nonlethal Toxicity

3.2.1. Nonhuman Primates

No data were located that specifically identified irreversible, nonlethal effects in nonhuman primates following acute exposure to hydrazine. House (1964) exposed groups of 10 male rhesus monkeys to hydrazine continuously at an average concentration of 0.78 ppm (1 mg/m^3) (range: 0.25-1.38 ppm [0.33-1.8 mg/m^3]) for 90 days. Hydrazine was introduced into the exposure chambers via saturation of a carrier gas (nitrogen) with hydrazine. The exposure of the monkeys was uninterrupted for the duration of the experiment. The hydrazine concentration was measured colorimetrically from samples extracted from the chamber at various times (10-18 samples/day for the first 10 days; 3 times/day thereafter). Although effects of exposure were observed within 24-48 h, the effects (skin flushing and signs of ocular irritation) would be considered reversible. It is important to note that during days 1 through 10, the exposure period of concern for the aforementioned effects, the exposure concentration averaged 0.4 ppm (0.52 mg/m^3). The incidences of these effects were not reported but their occurrence provides limited data associating the induction of a non-disabling and assumably reversible effect with exposure to a specific concentration of hydrazine. Pathological examinations at termination of the 90-day treatment period indicated involvement of the kidneys, heart and liver but these were not the result of acute exposure. Because the monkeys were sacrificed upon exposure termination, the reversibility of the pathological findings could not be determined.

3.2.2. Dogs

Data regarding serious and/or persistent effects in dogs following acute exposure to hydrazine were limited to studies by Comstock et al. (1954) and Weatherby and Yard (1955).

In the first study, two mongrel dogs were exposed to hydrazine at a concentration of 6 mg/m^3 (4 to 6 ppm), 6 h/day, 5 days/week for up to 28 weeks. During the first week, both dogs were slightly affected (lassitude) and during the middle of the second week refused food and lost weight. After 11 weeks of exposure muscular tremors were observed and additional effects (fatigue, anorexia, vomiting) occurred sporadically through week 27. At the end of week 28 both dogs appeared normal.

In the report by Weatherby and Yard (1955), two male mongrel dogs were exposed to hydrazine at concentrations of 3 to 6 mg/m^3 (2 to 5 ppm), 6 h per day, 5 days per week. After 5 days of exposure, the dogs were extremely weak and exhibited muscular incoordination. On the seventh day one dog was moribund and the other dog was terminated. In another experiment one male and one female dog were exposed similarly but to hydrazine concentrations of 4 to 8 mg/m^3 (3 to 6 ppm). Within 24 h, the male exhibited muscular incoordination and weakness but improved and remained asymptomatic until terminated. Necropsy of the first pair of dogs indicated extensive hepatic lesions while the second pair of dogs exhibited only minimal hepatic involvement.

3.2.3. Rats

House (1964) also exposed male Sprague-Dawley rats to hydrazine at an average concentration of 0.78 ppm for 90 days. The exposure resulted in 98% mortality and, although the authors noted that the rats appeared to be weak and sick early in the treatment, no assessment of reversibility of this condition was possible. Clinical chemistry parameters were measured prior to treatment, and at days 30 and 60. Treatment-related alterations were minimal (minor decrease in hematocrit and changes in polymorphonuclear leukocytes and urine specific gravity) but because of the 30-day and 60-day evaluations, could not be attributed to acute exposure. Assessment of reversibility was not possible because of the high mortality rate during the exposure period.

Becker et al. (1981) noted a 6.6% reduction in body weight and histopathologic changes (palor, fatty liver) in the livers of rats given hydrazine intragastrically at dose of 3 mg/kg/day for four days. Methylation of hepatic DNA was also detected.

MacEwen and Vernot (1981) exposed 10 male and 10 female F344 rats and 20 male hamsters to hydrazine at concentrations of 750 ppm for 1 h twice per week for five weeks. Although notable decrease in body weight were observed for the exposed animals, no deaths occurred indicating that a 1-h exposure at 750 ppm is not lethal in this species and strain.

In the study by Comstock et al. (1954), rats exposed to hydrazine at nominal concentrations of 81-630 ppm (106-831 mg/m^3) exhibited signs of irritation (restlessness, scratching, lacrimation, eye closure) within 1-2 min. Within 2 h, the rats exhibited alternating periods of hyperactivity and inactivity, and porphyrin secretion from the Harderian gland. Although delayed lethality (17-33% at

14 days) was associated with exposures as short as 0.5 h, it is possible that the irritation effects at 1-2 min (probably a response to vapor condensation) would be reversible upon removal from the test atmosphere.

Kulagina (1962) reported alteration of conditioned reflex responses in rats exposed for 2 h to 19 ppm hydrazine (24.7 mg/m^3). Adverse effects on motor coordination were observed in rats exposed to 0.74-4 ppm hydrazine (0.9-5.2 mg/m^3), 4 h/day, 6 days/week for 7 months. There were no deaths among these rats and the altered responses returned to normal 3-4 weeks after cessation of exposure. Although the exposure duration is subchronic, the report verifies that notable alterations in neurological responses in rats are reversible even after prolonged exposure. Although these data suggest that a C × t product of 3,494 mg-h/m^3 is not lethal for intermittent exposures.

More recently, Latendresse et al. (1995) conducted experiments in which groups of five male and five female F-344 rats and 10 male Syrian golden hamsters were exposed to 750 ppm hydrazine for 1 h. Control animals were exposed to air without hydrazine. Gross and histopathological examinations were conducted on the animals following euthanasia at 24 h after exposure. The 1-h exposure to hydrazine resulted in lesions of the nasal transitional epithelium. These lesions were characterized as minimal necrosis, mild to moderate exfoliation, minimal to moderate acute inflammation, and mild apoptosis. Another phase of this study exposed rats and hamsters for 10 weeks at 1 h per week to hydrazine at concentrations of 75 or 750 ppm. Male and female rats exposed to 750 ppm and female rats exposed to 75 ppm exhibited significant reductions in body weight ($p < 0.05$). Hamsters in the 750-ppm group also exhibited significant reductions ($p < 0.05$) in body weight gain compared to controls. Exposure-induced lesions including desquamation, necrosis, apoptosis, and squamous metaplasia were observed in the nasal transitional epithelium during the exposure period. Although apoptosis and squamous metaplasia were observed after the exposure, the alterations appeared to revert back to normal-appearing transitional epithelium with incidences of lesions at 24 months being low: epithelial hyperplasia (4/99 males, 1/95 females); polyploid adenomas (4/99 males, 6/95 females) and; squamous cell carcinoma (1/99 males) were also observed in rats held up to 28 months postexposure. Hamsters exposed to 750 ppm hydrazine (1 h/week for 10 weeks) exhibited similar incidences of hyperplasia (2/94) and neoplasia (5/94). However, none of the lesions observed in the exposed animals were seen in the control animals.

3.2.4. Mice

House (1964) also conducted inhalation exposure studies in male ICR Swiss mice. The protocol was identical as for rats (see Section 3.2.3.). A high mortality early in the exposure period (98% within 4 weeks) precluded the evaluation of reversibility of effects. There were no findings in mice relevant to non-disabling, reversible effects following acute exposure to hydrazine.

Kulagina (1962) noted alteration of conditioned reflex responses in mice exposed for 2 h to 19 ppm hydrazine (24.7 mg/m^3).

3.2.5. Hamsters

MacEwen and Vernot (1981) exposed 20 male Syrian golden hamsters to hydrazine at concentrations of 750 ppm for 1 h twice per week for five weeks. Although no deaths occurred, notable decreases (no statistical analysis performed) in body weight were observed for the exposed animals.

Latendresse et al. (1995) conducted experiments in which groups of 10 male Syrian golden hamsters were exposed to 750 ppm hydrazine for 1 h. Control animals were exposed to air without hydrazine. Gross and histopathological examinations were conducted on the animals following euthanasia at 24 h after exposure. The 1-h exposure to hydrazine resulted in lesions of the nasal transitional epithelium. These lesions were characterized as minimal necrosis, mild to moderate exfoliation, minimal to moderate acute inflammation, and mild apoptosis.

3.3. Developmental and Reproductive Toxicity

3.3.1. Rats

Developmental toxicity of parenterally administered hydrazine has been reported. Lee and Aleyassine (1970) reported fetal toxicity (reduced size, pallor, edema and petachiae) and lethality in rats following subcutaneous administration of hydrazine (8 mg/kg) during days 11-21 of gestation. The administered dose also resulted in marked maternal toxicity characterized by body weight loss.

In a study by Keller et al. (1982), pregnant Fischer 344 rats were administered hydrazine in physiologic saline i.p. at doses of 2.5 (n = 17), 5.0 (n = 19), or 10.0 (n = 6) mg/kg, on days 6 through 15 of gestation. Controls (n = 27) were given equivalent volumes of saline, i.p. A dose-response in no. of resorptions/litter was observed. This response was statistically significant ($p \leq 0.05$) at doses of 5.0 or 10 mg/kg. Maternal toxicity (body weight loss) was also observed in these groups during the treatment period. Pregnant rats were also exposed to hydrazine percutaneously (30-min, covered exposure of 2.5 cm square area) at doses of 5.0 or 50.0 g/kg on day 9 of gestation. The higher dose also resulted in a high incidence of embryolethality. Results of the i.p. injection experiment are shown in Table 6-7.

In a second experiment reported by Keller et al. (1982), pregnant F344 rats were given hydrazine (10 mg/kg, i.p.) on gestation days 7-9, 10-12, or 13-15. This protocol was used because the former dosing protocol resulted in excessive embryolethality that precluded meaningful assessment of possible developmental effects during later developmental periods. Based upon resorptions/litter,

fetal weight, and incidence of anomalies, exposure during gestation days 7-9 appeared to be the most critical. However, similar to the preceding experiment, dams exhibited body weight loss during the treatment period. The results of this experiment are shown in Table 6-8.

TABLE 6-7 Developmental Effects of Hydrazine in Rats Following i.p. Administration on Gestation Days 6-15

Parameter	Dose (mg/kg)			
	0	2.5	5.0	10
Number of litters	27	17	19	6
Implants/litter[a]	8.2 ± 0.6	8.1 ± 0.7	6.5 ± 0.7	7.0 ± 1.9
Resorptions/litter[a]	1.5 ± 0.4	1.8 ± 0.4	3.3 ± 0.7[b]	6.0 ± 2.3[b]
No. litters with >50% resorption	4	1	10	5
Fetal wt[a]	3.1 ± 0.04	3.1 ± 0.04	2.9 ± 0.1[b]	3.1 ± 0.3
No. fetuses examined	27(181)	17(107)	15(60)	1(6)
Litters (fetuses) affected	8(11)	4(5)	7(8)	1(3)
Anomalies[c]	6	3	4	3
Major malformations	7[d,e]	3[d]	4[f]	3

[a]Values are means ± S.E.
[b]Significantly different from control, $p \leq 0.05$.
[c]Supernumerary ribs, fused ribs, delayed ossification, moderate hydronephrosis, moderate dilation of brain ventricles, other similar but less frequently occurring abnormalities.
[d]Major malformation was anophthalmia.
[e]Three fetuses with anophthalmia in one litter.
[f]Major malformations were anophthalmia (2), right side aorta (1), and monorchid (1).
Source: Keller et al. 1982.

TABLE 6-8 Developmental Effects in Rats Following i.p. Administration of Hydrazine (10 mg/kg) at Various Times During Gestation

Parameter	Gestational Exposure Period			
	Control (6-15)	7-9	10-12	13-15
Number of litters	27	11	1	10
Implants/litter[a]	8.2 ± 0.6	7.5 ± 1.1	8.9 ± 1.0	7.7 ± 1.4
Resorptions/litter[a]	1.5 ± 0.4	6.1 ± 1.10[b]	0.8 ± 0.4	1.0 ± 0.3
Litters with >50% resorption	4	8	0	0
Fetal wt[a]	3.1 ± 0.04	2.7 ± 0.1[b]	3.1 ± 0.1	2.9 ± 0.5[b]
No. fetuses examined	27(181)	8(16)	10(81)	10(57)
Litters (fetuses) affected	8(11)	6[b](8)	4(4)	4(4)
Anomalies	6	8[c]	2	4
Major malformations	7	0	2[d]	4

[a]Values are means ± S.E.
[b]Significantly different from control, $p \leq 0.05$.
[c]Major malformations were anophthalmia and adrenal agenesis.
[d]Anomalies detected were supernumerary ribs (2), moderate hydronephrosis (2), and moderate hydrocephalus (4).
Source: Keller et al. 1982.

An inhalation exposure (nose-only) study, Keller (1988) exposed pregnant rats (strain not specified) on gestation day 9 to 500 or 50 ppm of hydrazine for 1 h. Although no teratogenic effects were observed, exposure to 500 ppm hydrazine resulted in 48% embryolethality that was concurrent with maternal toxicity. Embryolethality at 50 ppm hydrazine was similar to that observed for unexposed controls; 3% and 4%, respectively. However, data were lacking regarding exposure atmosphere analysis, characterization of the maternal toxicity, and protocol details.

3.4. Genotoxicity

There were no inhalation genotoxicity data available for hydrazine. Hydrazine has been shown to be mutagenic in various microbial tests and evidence of genotoxic potential in mammals has been shown following oral and parenteral administration (reviewed by NRC 1985; Garcia and James 1996). This review concluded that hydrazine has the potential for inducing somatic mutations. Intraperitoneal injection of hydrazine (10 to 120 mg/kg) in mice during the early stages of spermatogenesis did not induce unscheduled DNA synthesis (Sotomayor et al. 1982), and Epstein and Shafner (1968) reported negative results in mouse dominant-lethal test. However, positive results in sister chromatid exchange in various murine tissues have been reported (Couch et al. 1986; Neft and Conner 1989). *In vitro* studies (summarized in ATSDR 1997) have indicated the genotoxic potential of hydrazine with and without metabolic activation and include methyl DNA adducts in human but not hamster V79 cells, gene mutations in human teratoma cells, and unscheduled DNA synthesis. Hydrazine was positive in the Ames test using TA1535, TA100, TA1537, and TA98 strains of *Salmonella typhimurium* (Parodi et al. 1981) and mutagenicity was demonstrated in strain WP2 of *Escherichia coli* (Noda et al. 1986).

Leakakos and Shank (1994) reported that DNA methylation (presumably a requirement for oral and parenteral hydrazine-induced liver cancer in rodents) was detectable only when the dose of hydrazine was necrogenic (25 or 50 mg/kg). This conclusion was based upon findings of methylguanine adducts (7-methylguanine and O^6-methylguanine) in hepatic DNA of neonatal rats given subcutaneous injections of hydrazine. Inhibition of restriction at specific sites following necrogenic doses was provided as evidence of a hydrazine-specific genotoxic response.

3.5. Carcinogenicity

3.5.1. Dogs

There were no treatment related effects observed in male or female beagle dogs (four per group) exposed to hydrazine at concentrations of 0.25-5.0 ppm

(0.35-6.55 mg/m^3) 6 h per day, 5 days per week for one year (MacEwen et al. 1981).

Vernot et al. (1985) conducted 1-year inhalation exposure of dogs to hydrazine at concentrations of 0.25 or 1.0 ppm for 6 h/day, 5 days/week. The dogs were maintained an additional 38 months postexposure. No tumors attributed to hydrazine were observed in any of the dogs.

3.5.2. Rats

MacEwen et al. (1981) exposed groups of 100 rats of both sexes to 0.05-5.0 ppm (0.07-6.55 mg/m^3) hydrazine for one year (6 h/day, 5 days/week). Evidence of inflammatory changes in the respiratory tract were observed at the lowest exposure but were more prevalent and more severe at the highest exposure. The histopathologic changes included squamous cell metaplasia of the nasal cavity, larynx, and trachea. Hyperplastic changes were observed in the nasal and pulmonary epithelia, and inflammatory changes were observed in the larynx and trachea. At the highest exposure tested, male rats exhibited a significant increase in squamous metaplastic changes in the nasal region (47/99; $p \leq 0.001$), nasal epithelial hyperplasia (21/99; $p \leq 0.001$), squamous metaplasia of the larynx (18/29; $p \leq 0.001$) and trachea (10/97; $p \leq 0.001$), inflammatory changes in the larynx (72/92; $p \leq 0.001$) and trachea (52/97; $p \leq 0.001$), and pulmonary epithelia hyperplasia (6/99; $p \leq 0.001$). What appears to be a published report of this study is described below.

Vernot et al. (1985) reported on a 1-year inhalation exposure of rats to hydrazine at concentrations of 0.05, 0.25, 1.0, or 5.0 ppm for 6 h/day, 5 days/week. The rats were maintained an additional 18 months postexposure. A dose-dependent increased incidence was noted for benign nasal adenomatous polyps (58/98 treated vs 1/146 control in males, and 28/95 treated vs 0/145 control in females; $p \leq 0.01$) and villous polyps (12/98 vs 0/146 in males only; $p \leq 0.01$), and thyroid carcinomas (13/98 vs 1/146 males only; $p \leq 0.05$). The nasal tumors were often associated with chronic irritation. The increased incidence of thyroid carcinoma was significant (13/98 vs 7/146; $p \leq 0.5$) in the 5.0 ppm males at the end of the 18-month observation period. Squamous cell carcinomas and bronchial carcinomas were also increased in males but significantly so.

Latendresse et al. (1995) conducted experiments in which groups of five male and five female F-344 rats were exposed to 75 or 750 ppm hydrazine for 1 h/week for 10 weeks. Control animals were exposed to air without hydrazine. Male and female rats exposed to 750 ppm and female rats exposed to 75 ppm exhibited significant reductions in body weight ($p < 0.05$). Hamsters in the 750-ppm group also exhibited significant reductions ($p < 0.05$) in body weight gain compared to controls. Exposure-induced lesions including desquamation, necrosis, apoptosis, and squamous metaplasia were observed in the nasal transitional

epithelium during the exposure period. Although apoptosis and squamous metaplasia were observed after the exposure, the alterations appeared to revert back to normal-appearing transitional epithelium with incidences of lesions at 24 months being low: epithelial hyperplasia [4/99 males, 1/95 females]; polyploid adenomas [4/99 males, 6/95 females] and; squamous cell carcinoma [1/99 males]) were also observed in rats held up to 28 months postexposure. However, none of the lesions observed in the exposed animals were seen in the control animals.

3.5.3. Mice

Groups of 400 female C57BL/6 mice were exposed to hydrazine (0.05, 0.25, or 1.0. ppm) 6 h/day, 5 days/week for up to one year (MacEwen et al. 1981). A group of 800 female mice exposed to clean air served as controls. The mice appeared to be resistant to the oncogenic effects of hydrazine. The only significant response was 3% incidence (12/379; $p \leq 0.05$) in pulmonary adenomas in the highest exposure tested. A published report of this study appeared as Vernot et al. (1985).

The 1-year inhalation study by Vernot et al. (1985) also examined mice (400 females per group) exposed to hydrazine at concentrations of 0.05, 0.25, or 1.0 ppm for 6 h/day, 5 days/week. The mice were maintained an additional 15 months postexposure. As described above, pulmonary adenomas were slightly increased in mice of the 1.0 ppm group.

3.5.4. Hamsters

Latendresse et al. (1995) conducted experiments in which groups of 10 male Syrian golden hamsters were exposed to 75 or 750 ppm hydrazine for 1 h/week for 10 weeks. Control animals were exposed to air without hydrazine. Gross and histopathological examinations were conducted on the animals following euthanasia at 24 h after exposure. Hamsters exposed to 750 ppm hydrazine (1 h/week for 10 weeks) exhibited hyperplasia (2/94) and neoplasia (5/94). None of the lesions observed in the exposed animals were seen in the control animals.

Vernot et al. (1985) and MacEwen et al. (1981) also utilized hamsters in their 1-year inhalation exposure studies of hydrazine. Groups of 200 males hamsters were exposed to hydrazine at concentrations of 0.25, 1.0, or 5.0 ppm for 6 h/day, 5 days/week. The hamsters were maintained an additional year. Evidence of degenerative changes, including amyloidosis, was observed in hamsters exposed to 0.25 ppm hydrazine and higher. The incidence of nasal adenomatous polyps was significantly increased (16/160 vs 1/181; $p \leq 0.05$) in the 5.0-ppm group relative to unexposed controls.

3.6. Summary

Acute lethality data for inhalation exposure to hydrazine were available for dogs, rats, mice and hamsters, although the data for dogs are compromised by the small numbers of animals and the use of mongrels rather than a fixed breed. Some data from earlier studies are also compromised by inadequacies in accuracy of exposure concentration measurements, highly variable concentrations during the testing period, and variabilities in observation periods for assessing lethality. Acute lethality data following parenteral routes (i.e., iv, i.p.) and oral administration are available for dogs, rats, and mice. These data were discussed with reference to route-dependent variability in lethality. The route of administration does not appear to significantly affect the qualitative nature of hydrazine toxicity (Krop 1954; Witkin 1956; NRC 1985), although dose-response alterations are observed and nasal lesions appear to be more prominent in inhalation exposures. Some studies have also shown that hydrazine may induce embryolethality at maternally toxic doses.

There is evidence that long-term exposure of rats to hydrazine may cause an increased incidence in nasal tumors or histopathologic changes indicative of a possible tumorigenic response (Vernot et al. 1985; Latendresse et al. 1995). Based upon the animal data, however, it appears that repeated exposures resulting in long-term tissue irritation is instrumental in the observed tumorigenic responses.

Definitive exposure-response data regarding non-disabling, reversible health effects in animals following acute inhalation exposure to hydrazine were limited. Muscular incoordination and weakness was observed in dogs (Weatherby and Yard 1955), alteration of conditioned response behaviors was noted for rats (Kulagina 1962), and nasal lesions observed in rats following a single exposure (Latendresse et al. 1995).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Studies with animals have shown that hydrazine may be metabolized to acetylhydrazine, diacetylhydrazine, ammonia, and urea, and may form hydrazones with pyruvate and 2-oxoglutarate (Wright and Timbrell 1978; Timbrell et al. 1982; Preece et al. 1991; Timbrell 1992). These studies also indicated that urinary excretion to be a major route of elimination following various administration routes. The biotransformation of hydrazine is mediated, at least in part, by hepatic monooxygenases and acetyltransferases (Timbrell 1992; Koizumi et al. 1998).

Differential rates of hydrazine metabolism by humans and the role of acetylation phenotype was investigated by Koizumi et al. (1998). Acetylation phenotype was determined for 297 workers involved in the production of hydrazine

hydrate. Based on analysis of 12 individuals from this study population, the mean biological half-life of hydrazine among individual workers of various acetylation phenotype varied about 2-fold ($p < 0.05$); 3.94 ± 1.70 h, 2.25 ± 0.37 h, and 1.86 ± 0.67 h, respectively, for slow, intermediate and rapid acetylators. Exposure to hydrazine was reportedly 0.07-0.12 ppm (8-h TWA).

Timbrell (1992) reported that hepatic uptake of hydrazine by rats following intraperitoneal administration appeared to be a saturable process. In experiments with rats exposed via inhalation to hydrazine at concentrations of 10-500 ppm for 1 h, Llewellyn et al.(1986) found that 1.7-4% and 4.5-11.4% of the absorbed dose was excreted as urinary acetyl hydrazine and diacetylhydrazine, respectively.

The role of metabolism and absorption/excretion kinetics is uncertain regarding immediate port-of-entry toxic effects from acute inhalation exposures. The highly reactive nature of hydrazine may be instrumental in the manifestation of acute port-of-entry toxic effects. However, the systemic effects (e.g., convulsions, cardiovascular collapse) and delayed lethality attributed to hepatic and renal effects, may be affected by absorption, distribution and excretion kinetics, as well as metabolism processes. This is consistent with early reports of lipid accumulation in the liver and kidneys of experimental animals following single and repeated doses of hydrazine (Comstock et al. 1954).

4.2. Mechanism of Toxicity

Although the acute lethality of hydrazine has been demonstrated in several species following multiple routes of administration, time to lethality following inhalation exposure appears to be extremely variable. As exemplified in the studies by Comstock et al. (1954) and Witkin (1956), inhalation exposure to hydrazine for exposure periods (0.5 to 4 h) may result in lethality as long as 14 days following cessation of exposure. Such latency complicates the estimation of acute exposure values and their possible resultant effects. Additionally, some consideration must also be given to the steep slope of the concentration effect curve for lethal effects of hydrazine. Jacobson et al. (1955) noted the slope of the exposure concentration/lethality curve to be 7.32 ± 1.8 and 3.79 ± 1.6 (±SE) for rats and mice, respectively. The steep slope generated by the rat lethality data implies a relatively smaller ratio between the dose causing low mortality and that causing a high mortality. This is a relevant point of concern regarding establishing an effect level based upon hydrazine lethality. The available data suggest that there may be little margin between lethal effects and nonlethal effects following inhalation exposure to hydrazine.

4.3. Structure-Activity Relationships

The toxicity of methylated derivatives of hydrazine (monomethylhydrazine and the symmetrical and unsymmetrical isomers of dimethylhydrazine [1,1-

dimethylhydrazine and 1,2-dimethylhydrazine, respectively]) have also been studied. Jacobson et al. (1955) reported excessive salivation, vomiting, respiratory distress and convulsions in dogs exposed to monomethylhydrazine and unsymmetrical dimethylhydrazine. Fourteen day mortality in three groups of dogs (three dogs/group) exposed for 4 h to monomethylhydrazine at concentrations of 29, 21, and 15 ppm were 2/3, 2/3, and 0/3, respectively. Fourteen day mortality in three groups of dogs (three dogs/group) exposed for 4 h to unsymmetrical dimethylhydrazine at concentrations of 111, 52, and 24 ppm were 3/3, 1/3, and 0/3, respectively. In studies reported by Rinehart et al. (1960), 29/30 mice exposed continuously to symmetrical dimethylhydrazine (140 ppm) died within two weeks and 8/30 mice exposed to 75 ppm died within five weeks. Rinehart et al. (1960) also reported that 1/3 dogs exposed intermittently to symmetrical hydrazine (25 ppm) died within three days. For rodents, estimated LC_{50} values for monomethylhydrazine, unsymmetrical dimethylhydrazine and symmetrical dimethylhydrazine are shown in Table 6-9.

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

Witkin (1956) reported i.v., i.p., and oral LD_{50} 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 symmetrical dimethylhydrazine appeared to be somewhat more toxic in mice than was hydrazine. Results of this study showed that the unsymmetrical isomer of dimethylhydrazine was less acutely toxic than hydrazine or the other hydrazine derivatives.

TABLE 6-9 LC_{50} Values for Rodents Exposed to Monomethylhydrazine and Dimethylhydrazine Isomers

Species	LC_{50} (ppm)	LC_{50} (mg/m^3)
Monomethylhydrazine		
Rat	74	139
Mouse	56	105
Hamster	143	270
Unsymmetrical dimethylhydrazine		
Rat	252	618
Mouse	172	423
Hamster	392	962
Symmetrical dimethylhydrazine		
Rat	280-400	364-520

Source: Jacobson et al. 1955. Reprinted with permission; copyright 1955, American Medical Association.

House (1964) reported unsymmetrical dimethylhydrazine to be less toxic to monkeys, rats, and mice. Mortality rates over a 90-day inhalation exposure to 0.56 ppm (0.73 mg/m^3) were 20, 98, and 99% for monkeys, rats, and mice, respectively.

The database on hydrazine derivatives provides no additional information that would be applicable to deriving AEGL values for hydrazine.

4.4. Other Relevant Information

4.4.1. Species Variability

The limited available data suggest that the lethal concentration of hydrazine varies somewhat among the species tested. Some of this variability, however, may be attributed to the difficulties in accurately measuring and maintaining the experimental hydrazine concentrations, especially in earlier studies. As shown in Tables 6-12 and 6-13 in Section 7.2, both the LC_{50} and the LD_{50} values are very similar for rats and mice. The estimated LD_{50} for the dog suggests greater sensitivity but this value is based upon only two doses and two test animals per dose. Overall, there still appears to be uncertainty regarding species variability in the toxic response to hydrazine and, more importantly from the standpoint of AEGL development, uncertainty regarding the sensitivity of humans relative to laboratory species. Furthermore, definitive data were not available regarding species variability in irreversible, nonlethal effects of acute exposure to hydrazine.

4.4.2. Physical and Chemical Properties

The extreme reactivity of hydrazine also deserves special attention with regard to accurate assessment of experimental exposure concentrations. As shown in the studies of Jacobson et al. (1955) and Comstock et al. (1954), accurate and consistent measurement of hydrazine concentrations even under experimental conditions is difficult and subject to many variabilities (size of chamber, number and size of animals, chamber construction material, etc.). The highly reactive nature of hydrazine *per se* is a plausible determinant of acute port-of-entry toxic effects.

4.4.3. Concurrent Exposure Issues

Although data analyzing the adverse effects of concurrent exposure to hydrazine and other chemicals are not available, this may be an important issue, especially for those chemicals with irritant properties. Furthermore, hydrazine is a highly reactive reducing agent that may react with many other chemicals (especially oxidizers), thereby altering their effects on physiologic systems.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Human data were not available for deriving an AEGL-1. The odor threshold for hydrazine is 3 to 4 ppm.

5.2. Animal Data Relevant to AEGL-1

Data regarding the nonlethal, reversible effects of hydrazine on animals following acute exposures were limited. Data from some of the earlier studies were compromised by difficulties in determining the actual hydrazine concentrations in the exposure chambers. Acute exposures (<24 h) of animals to hydrazine resulted in irritation at various exposures. A cumulative exposure as low as 106 mg/m^3 for 1-2 min was reported to cause irritation in rats while exposure to 975 mg/m^3 for 1 h produced nasal lesions in rats. Eye and facial irritation in monkeys was noted following an exposure of 0.52 mg/m^3 for ≈24 h, and neurological effects (alteration of conditioned responses) were observed in mice following exposure to 24.7 mg/m^3 for 2 h. Repeated 8 h/day occupational exposure of rocket plant workers was without signs of acute toxicity (Koizumi et al. 1998).

5.3. Derivation of AEGL-1

The data from the study by House (1964) in which male monkeys were continuously exposed to hydrazine at 0.52 mg/m^3 (equivalent to 0.4 ppm average concentration for the first 10 days of the 90-day exposure period) resulting in skin flushing and swollen eyes after 24 h of exposure was used as the basis for the AEGL-1. Based upon the available data, this exposure represents the lowest exposure resulting in a definitive effect that could be considered consistent with the definition of an AEGL-1. Exponential scaling with the equation, $C^n \times t = k$ (ten Berge et al. 1986), was used to derive exposure duration-specific values. Data were unavailable for an empirical derivation of n in the equation, $C^n \times t = k$. It has been shown that 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. In the absence of chemical specific data, an n of 3 was applied to extrapolate the 24-h 0.4 ppm exposure from the House (1964) study to the 8-h AEGL -1 time frame ($k = 0.4\ ppm^3 \times 24\ h = 1.54\ ppm^3$-h). Because hydrazine is extremely reactive and the sensory-irritation effects are considered to be concentration dependent rather than time dependent, 0.1 ppm (the 30-min, 1-h, 4-h, and 8-h values were all approximately 0.1 ppm) was considered appropriate for all AEGL-1 durations. (Table 6-10 and Appendix A).

TABLE 6-10 AEGL-1 Values for Hydrazine

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1	0.1 ppm (0.1 mg/m^3)	0.1 ppm (0.1 mg/m^3)	0.1 ppm (0.1 mg/m^3)	0.1 ppm (0.1 mg/m^3)	0.1 ppm (0.1 mg/m^3)

A total uncertainty factor of 10 was applied to derive the AEGL-1 values (each uncertainty factor of 3 is actually the geometric mean of 1 and 10 [i.e., 3.16], hence; 3.16 × 3.16 = 10). An uncertainty factor of 3 was applied for interspecies variability because the surface contact irritation by the highly reactive hydrazine is not likely to vary greatly among species, and because a nonhuman primate was the test species. An uncertainty factor of 3 was applied for intraspecies variability because the contact irritation from the highly reactive hydrazine is not expected to vary greatly among individuals, including susceptible individuals.

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 hydrazine exposure.

6.2. Summary of Animal Data Relevant to AEGL-2

Data were limited regarding irreversible, nonlethal effects of acute exposure to hydrazine. AEGL-2 values were first derived based upon several studies. Using the data from Weatherby and Yard (1955) showing muscular incoordination and weakness in one of two dogs exposed for 6 h, results in the most conservative AEGL-2 estimates. These data, however, are greatly compromised by the use of only two animals (only one of which responded) and the use of mongrel dogs. The developmental toxicity data of Keller (1988) provides a reasonable data set for AEGL-2 derivation but results in AEGL-2 values that are somewhat higher than those derived using the other data sets. The data of Kulagina (1962) is of questionable use for AEGL derivation because of the subjective nature of assessing alterations in behavioral responses.

Results of a study in rats by Becker et al. (1981) identified long-term deleterious effects but not immediately disabling effects. The toxicity end points reported included body weight reduction, fatty liver and methylation of hepatic DNA following intragastric administration of hydrazine at a dose of 3 mg/kg/day for up to 4 days. These effects are considered severe enough to result in serious and irreversible impairment of health over time, especially if one considers the methylation of hepatic DNA to represent a possible precursor to a carcinogenic response. However, the use of route-to-route extrapolation may be

tenuous due to the uncertainties in toxicokinetics between inhalation and oral routes.

The study by Latendresse et al. (1995) appeared to provide the best data for AEGL-2 derivation. Results of this study showed the induction of nasal lesions in rats following a single 1-h exposure to 750 ppm hydrazine. The nasal lesions were characterized by histopathologic analysis and were shown to be reversible upon removal from exposure. This toxicologic response is indicative of an initial response that is part of a continuum of tissue damage resulting from hydrazine exposure. It is the highest tested exposure that did not lead to lethality and, due to its reversibility and a severity that is less than that consistent with AEGL-2 tier definition, is considered as the critical effect for AEGL-2 development. The experiments also utilized the inhalation exposure route, and measurement of hydrazine concentrations did not appear to be a confounding factor regarding the validity of the experimental results.

6.3. Derivation of AEGL-2

The data from the Latendresse et al. (1995) study showing nasal lesions (minimal necrosis, mild to moderate exfoliation, minimal to moderate acute inflammation, mild apoptosis) in rats following a 1-h exposure to 750 ppm was considered to be appropriate for setting AEGL-2 values. The study protocol and analytical techniques were superior to earlier studies and histopathologic data were available. The toxicity end point involved a specific region of the respiratory tract (nasopharyngeal region) and, although toxicologically and physiologically serious, was reversible upon removal from exposure.

Due to the extreme reactivity of hydrazine, exposure concentration measurements in earlier studies on multiple species were imprecise. An uncertainty factor of 3 for interspecies variability was applied to account for uncertainties regarding species variability in the toxic response to inhaled hydrazine. Because much of the toxic response to acute low-level exposures is likely a function of the extreme reactivity of hydrazine, the reduction from a default value of 10 is justified. An uncertainty factor of 3 was applied for intraspecies variability because the port-of-entry effect of the extremely reactive hydrazine is likely attributed to direct interaction with respiratory tract tissues. This contact irritation is not likely to vary considerably among individuals. Additionally, variability in acetylation phenotypes among humans and the subsequent effect on at least one aspect of hydrazine metabolism has been shown to vary approximately 2-fold. A modifying factor of 2 was applied to account for data inadequacies regarding the identification of toxic responses consistent with AEGL-2 level effects (i.e., serious or irreversible, but nonlethal, effects of acute inhalation exposure to hydrazine). Although the more recent studies such as those by Latendresse et al.(1995) and HRC (1993) appear to have more reliable determinations of hydrazine concentrations, the overall data set for hydrazine is compromised by uncertainties regarding the variability in response among species. At least some

of this variability may be the results of inaccurate exposure concentration measurements due to the reactivity of hydrazine with the surfaces of the exposure apparatus. Therefore, an additional modifying factor of 3 has been applied to account for the impact of these data deficiencies. This resulted in a total adjustment of 60-fold for derivation of AEGL-2 values (Table 6-11).

Because data were unavailable for an empirical derivation of n in the equation, $C^n \times t = k$, 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 A).

As previously noted, the data on nonlethal, irreversible effects resulting from acute exposure to hydrazine are limited. The key study (Latendresse et al. 1995) used to derive the AEGL-2 values appears to provide the highest confidence among the data available for AEGL-2 type effects or an estimation of a threshold for such effects.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

Although there is a report on one human fatality resulting from hydrazine exposure, the case involved repeated exposure to approximately 0.05 ppm(estimated from a post-exposure simulation) over a 6-month period (Sotaniemi et al. 1971). The confounding effects of a repeated exposure scenario (e.g., compromised tissue repair in the presence of repeated insults, excretion and detoxication kinetic considerations, etc.), and uncertainties regarding the estimate derived from a simulated exposure prevent the use of this report in deriving a defensible AEGL Level 3 value.

7.2. Animal Data Relevant to AEGL-3

Developmental toxicity of hydrazine by i.p. and percutaneous routes has been demonstrated in rats (Lee and Aleyassine 1970; Keller et al. 1982, Keller 1988). Because the significant findings (increased resorptions/litter, decreased fetal weight, embryolethality, increased incidences of anomalies) were concurrent with maternal toxicity (decreased body weight during gestational treatment period), it is difficult to attribute the developmental effects directly to hydrazine exposure *per se* and to consider hydrazine a selective developmental toxicant. Because of the route of administration and the inherent uncertainties of route-to-route extrapolation, the data from Lee and Aleyassine (1970) and Keller et al. (1982) were not used for deriving the AEGL-3 levels. Several studies utilizing inhalation exposures were considered for derivation of an AEGL-3 values.

The acute lethality of inhaled hydrazine has been reported by several investigators (Comstock et al. 1954; Jacobson et al. 1955; Keller 1988; HRC 1993). Keller (1988) reported embryolethality following 1-h exposure to 500

ppm hydrazine but experimental protocol details and analytical data are lacking. Although Keller (1988) reported maternal toxicity and embryolethality resulting from a 1-h exposure to 500 ppm hydrazine, Latendresse et al. (1995) reported only nasal lesions (necrosis, exfoliation, and acute inflammation) in rats and hamsters exposed to 750 ppm for 1 h but did not note any overt clinical signs of toxicity in exposed animals (body weight was decreased in those animals receiving multiple exposures but did not appear to be significant in those subjected to 1-h exposure). LC_{50} values of considerable variability have also been reported by several investigators (Comstock et al. 1954; Jacobson et al. 1955; MacEwen and Vernot 1981; HRC 1993). For comparison, summaries of LD_{50} and LC_{50} values are shown in Table 6-12 and 6-13, respectively.

7.3. Derivation of AEGL-3

Although several inhalation studies are available that provide data showing lethality or life-threatening effects acute exposure to hydrazine, the quality of the studies varies considerably. Earlier studies tended to be compromised to varying degrees by analytical deficiencies in determining the hydrazine concentration of the experimental exposures. Several studies were identified for derivation of AEGL-3 values (Appendix A). These included the acute exposure studies by Jacobson et al. (1955), Keller (1988), HRC (1993).

A notable range of values were obtained depending upon the study used. Although AEGL-3 values derived from the embryolethality data reported by Keller (1988) provide the most conservative AEGL-3 values, this study was compromised by the absence of details for experimental protocol and results (see Section 3.4.1). The AEGL-3 values derived from the Jacobson et al. (1955) data were similar although slightly lower.

The AEGL-3 values were derived based upon the data from the HRC study that provided a 1-h LC_{50} of 4.2 mg/L (3,192 ppm) in rats (both sexes). Although a 1-h LC_{01} of 334 ppm was estimated from the HRC data using the method of Litchfield and Wilcoxon (1949), it was considered to be inappropriate for derivation of AEGL-3 values because it was not consistent with the recent data from Latendresse et al. (1995) that showed 1-h exposure of rats to 750 ppm did not result in any lethalities. It is believed that a 3-fold reduction of the 1-h LC_{50} (3,192 ppm/3 = 1,064 ppm) provides an estimate of the lethality threshold that is consistent with the available data. For example, the Latendresse et al. (1995) study demonstrated that rats exposed to 750 ppm for 1 h per week for 10 consecutive weeks did not experience mortality.

TABLE 6-11 AEGL-2 Values for Hydrazine

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	23 ppm (30 mg/m^3)	16 ppm (21 mg/m^3)	13 ppm (17 mg/m^3)	3.1 ppm (4.0 mg/m^3)	1.6 ppm (2.1 mg/m^3)

TABLE 6-12 Summary of LD_{50} Values for Hydrazine in Studies by Witkin (1956) and Jacobson et al. (1955)

Species	LD_{50} (mg/kg)	Route of Administration	Time of Death	Reference
Rat	55	I.V.	10 d[a]	Witkin 1956
	59	I.P.	10 d	Witkin 1956
	60	Oral	10 d[a]	Witkin 1956
	112	Inhalation	4 h[b]	Jacobson et al. 1955
Mouse	57	I.V.	10 d[a]	Witkin 1956
	62	I.P.	10 d[a]	Witkin 1956
	59	Oral	10 d[a]	Witkin 1956
	18	Inhalation	4 h[b]	Jacobson et al. 1955
Dog	25	I.V.	10 d[a]	Witkin 1956

[a]Observation period.
[b]Duration of exposure; conversion to internal dose (mg/kg) based upon default values for body weight and ventilation rate for rats (EPA 1986).

TABLE 6-13 Summary of LC_{50} Values for Hydrazine in Studies by Jacobson et al. (1955), Comstock et al. (1954), HRC (1993), and MacEwen and Vernot (1981)

Species	LC_{50} (mg/m^3 [ppm])	Exposure Duration (h)	C × t ($mg\text{-}h/m^3$)	Reference
Rat	750 [570]	4	3,000	Jacobson et al. 1955
Rat	344 [260][a]	4	1,376	Comstock et al. 1954
Rat	831 [630][b]	4	3,324	Comstock et al. 1954
Rat	4,200 [3,192][c]	1	4,200	HRC 1993
Hamster	3,360 [2,585][d]	1	3,360	MacEwen and Vernot 1981
Mouse	330 [252]	4	1,320	Jacobson et al. 1955

[a]50% lethality at 8 days postexposure.
[b]50% lethality at 13 days postexposure.
[c]Value is for males and female combined (males 1-h LC_{50}: 5,800 mg/m^3; females 1-h LC_{50} 3,400 mg/m^3.
[d]14-day postexposure observation.

Additionally, 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. To obtain AEGL values, temporal scaling was performed using n = 3 when extrapolating to shorter time points (10 min and 30 min) and n = 1 when extrapolating to longer time points (4 and 8 h) using the $C^n \times t = k$ equation (Appendix A).

Uncertainty factors were applied as described for AEGL-2. An uncertainty factor of 3 for interspecies variability was applied to account for uncertainties regarding species variability in the lethal response to inhaled hydrazine. Because

much of the toxic response to acute low-level exposures is likely a function of the extreme reactivity of hydrazine and resulting direct-contact damage to tissues, the reduction from a default value of 10 is justified. An uncertainty factor of 3 was applied for intraspecies variability because the port-of-entry effect of the extremely reactive hydrazine is likely attributed to direct interaction with respiratory tract tissues. This contact irritation is not likely to vary considerably among individuals. A modifying factor of 3 for interspecies variability was applied to account for the high degree of variability in the data. As previously described in Section 6.3, the more recent studies by Latendresse et al. (1995) and HRC (1993) utilized more sophisticated exposure chambers assuring more reliable hydrazine exposures. However, the overall data set for hydrazine is still somewhat deficient in reliably determining species variability in the toxic response to inhaled hydrazine. The AEGL-3 values are shown in Table 6-14.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

A summary of the AEGLs for hydrazine and their relationship to one another are shown in Table 6-15. For AEGL development, an effort was made to identify exposures and toxicity end points specific for the three AEGL levels thereby avoiding the uncertainty involved in extrapolating severity of effects from one effect level (e.g. extrapolation of reversible, nondisabling effects from effects that are clearly lethal). For hydrazine three different data sets and toxic end points were used for derivation of the three AEGL tiers.

The values for the three AEGL tiers appear to be relationally valid, both among the exposure periods for a given AEGL tier as well as across the exposure durations of three AEGL tiers. Furthermore, exposure to AEGL-1 or AEGL-2 values for any of the specified durations, would not result in doses known to induce developmental toxicity in laboratory animals (5 mg/kg, Keller et al. 1982, see Section 3.4.1). It must be noted that the AEGL-1 values are very close to current detection limits (0.05-0.6 ppm) for hydrazine (OSHA 2003).

TABLE 6-14 AEGL-3 Values for Hydrazine

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-3	64 ppm (83 mg/m^3)	45 ppm (59 mg/m^3)	35 ppm (46 mg/m^3)	8.9 ppm (12 mg/m^3)	4.4 ppm (5.7 mg/m^3)

TABLE 6-15 Relational Comparison of AEGL Values for Hydrazine

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	0.1 ppm	0.1 ppm	0.1 ppm	0.1 ppm	0.1 ppm
AEGL-2 (Disabling)	23 ppm	16 ppm	13 ppm	3.1 ppm	1.6 ppm
AEGL-3 (Lethality)	64 ppm	45 ppm	35 ppm	8.9 ppm	4.4 ppm

The AEGL-1 was developed based upon skin flushing and swollen eyes in rhesus monkeys after 24 h continuous exposure to 0.5 mg hydrazine/m^3 (0.4 ppm) (House 1964). The exposure continued for 90 days and resulted in a 20% mortality although the first death did not occur until days 21-30. Pathological findings in the hydrazine-exposed monkeys were most notable in the heart, kidneys, and liver. It is assumed that the effects of concern regarding the AEGL-1 would have been reversible and not life-threatening. The data based upon effects in a nonhuman primate were considered to be more relevant than data from rodent species (Comstock et al. 1954; Kulagina 1962; Latendresse et al. 1995) described in Section 3.2.3. The AEGL-1 was further adjusted (to 0.1 ppm for all time periods) due to the extreme reactivity and potential for irritation below the odor threshold. Furthermore, an analysis of occupational exposure to hydrazine by Koizumi et al. (1998) indicated that repeated 8 h/day exposure to hydrazine at 0.1 ppm did not result in signs of toxicity.

The AEGL-2 was based upon data showing the induction of nasal lesions following a single 1-h exposure of rats to 750 ppm hydrazine (Latendresse et al. 1995). The lesions were reversible upon removal from the exposure. Although this end point is not consistent with the severity of effect routinely identified for AEGL-2 development, it represents the only definitive nonlethal end point associated with definitive exposure. The end point, albeit a conservative estimate for AEGL-2 type effects, does represent an important effect consistent with the continuum of hydrazine toxicity (i.e., respiratory tract irritation, tissue damage, and potential tumorigenicity). Therefore, it is considered an appropriate basis for AEGL-2 development.

The AEGL-3 is based upon lethality data in rats exposed by nose-only inhalation to hydrazine at concentrations of 0.65, 2.04, 3.24, and 4.98 mg/L (HRC 1993). The HRC report identified a 1-h LC_{50} of 3,192 ppm. This reported 1-h LC_{50} was reduced three-fold as an estimate of the lethality threshold and used in the development of the AEGL-3 values.

The divergence from order-of-magnitude uncertainty factor application in AEGL derivations was adopted for several reasons. For the AEGL-1 type effects that are of rapid onset (e.g., skin flushing eye irritation) and that may more be appropriately considered surface contact effects, interspecies variability may be small and, therefore, an uncertainty factor of 3 appeared to be justified. For such effects in acute exposure scenarios, the relevance of order-of-magnitude dose/exposure adjustments is questionable because the exposure duration may be insufficient for expression of interspecies and intraspecies variability in toxicodynamics and toxicokinetics. By definition, the AEGLs address "susceptible but not hyper-susceptible individuals". Therefore, a 3-fold adjustment was considered appropriate to account for some level of individual variability without being unrealistically conservative in the AEGL derivation. The order-of-magnitude adjustments are more likely to be relevant and appropriate in long-term exposures.

Because long-term inhalation exposure to hydrazine has been shown to be tumorigenic in several species, a cancer assessment was also performed (Ap-

pendix B). Following the methods of NRC (1986), AEGL-2 values were derived based on two available data sets. Both data sets identified nasal tumors in rats following 1-year inhalation exposure to hydrazine. Although data from the animal studies affirm the carcinogenic potential of hydrazine following inhalation exposure, the observed tumorigenic responses appear to be a function of prolonged tissue irritation resulting from long-term repeated exposures and are unlikely to occur following a single low exposure. This was especially evident in the study by Latendresse et al. (1995) that showed repeated exposures were necessary for reversible histopathologic changes in rat nasal epithelium. Additionally, the work reported by Leakakos and Shank (1994) showed that showed DNA methylation (presumably a requirement for oral and parenteral hydrazine-induced liver cancer in rodents) was detectable only when the dose of hydrazine was necrogenic. Therefore, it would appear that hydrazine AEGL values that address rare, or single once-in-a-lifetime exposures should not be based upon cancer risk.

A graphic representation of the AEGL values and their relationship to one another and to available data are shown in the category plot in Appendix D.

8.2. Comparison with Other Standards and Criteria

Exposure standards and guidelines for hydrazine have been established by several organizations. All currently available values are shown in Table 6-16. Because most of these standards are derived to be protective against any adverse health effects and in certain cases intended for repeated or prolonged exposure durations, they are comparable only to the AEGL-1 values. Hydrazine is a suspected human carcinogen (A2) based upon the formation of nasal tumors in rats exposed to hydrazine for one year (MacEwen et al. 1981), and the NRC SPEGLs were derived with respect to this carcinogenic potential. Although the AEGLs were not derived based upon carcinogenic potential, the AEGL-1 values vary by less than an order of magnitude relative to the NRC SPEGLs and the ACGIH TLV.

8.3. Data Adequacy and Research Needs

Definitive exposure-response data for hydrazine toxicity in humans are not available. However, qualitative information on the human experience affirms that hydrazine vapor is highly irritating. Animal data from earlier studies were often compromised by uncertain quantitation of exposure atmospheres, use of exposure durations that were not consistent with those of interest for AEGL development, poor exposure-response relationships for acute exposures, and imprecise characterization of toxicologic end points relative to acute exposures.

More recent studies in laboratory animals, however, utilized accurate and reliable methods for characterizing exposure concentrations and provided more focus on specific toxicologic end points (e.g., contact irritation, nasal lesions,

and lethality) resulting from acute exposures. Data from these studies enabled the development of AEGL values consistent with the methodologies described in the Standing Operating Procedures of the National Advisory Committee for AEGLs (NRC 2001).

Because the AEGL values 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 end points were considered to be more appropriate than those based upon a potential carcinogenic response. Furthermore, the available animal data suggest that the tumorigenic response to inhaled hydrazine is a function of prolonged tissue irritation resulting from repeated exposures and not the result of a single low exposure.

TABLE 6-16 Extant Standards and Guidelines for Hydrazine

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	0.1 ppm	0.1 ppm	0.1 ppm	0.1 ppm	0.1 ppm
AEGL-2 (Disabling)	23 ppm	16 ppm	13 ppm	3.1 ppm	1.6 ppm
AEGL-3 (Lethal)	64 ppm	45 ppm	35 ppm	8.9 ppm	4.4 ppm
ERPG-1(AIHA)[a]			0.5 ppm		
ERPG-2 (AIHA)			5 ppm		
ERPG-3 (AIHA)			30 ppm		
SPEGL (NRC)[b]			0.12 ppm	0.03 ppm	0.015 ppm
SMAC (NRC)[c]			4 ppm		
STPL(NRC)[d]	15 ppm	10 ppm	5 ppm		
IDLH (NIOSH)[e]		50 ppm	0.03 ppm		
REL-TWA (NIOSH)[f]			(2-h ceiling)		
PEL-TWA (NIOSH)[g]					1 ppm
TLV-TWA(ACGIH)[h]					0.01 ppm
MAK (Germany)[i]					-
MAC (The Netherlands)[j]					0.1ppm

[a]ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association) (AIHA 2002).

The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.

The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protection action.

The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects.

[b]SPEGL (Short-term Public Emergency Guidance Level, National Research Council). (NRC 1985)

[c]SMAC (Spacecraft Maximum Allowable Concentration, National Research Council) (Garcia and James 1996)

[d]STPL (Short-Term Public Exposure Limit, National Research Council). (Shaffer and Wands 1973)

[e]IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health) (NIOSH 1996) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms, or any irreversible health effects.

[f]REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits-Time Weighted Average, National Institute of Occupational Safety and Health) (NIOSH 2005) is defined analogous to the-TLV-TWA, with cancer notation.

[g]PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits Time Weighted Average, Occupational Health and Safety Administration) (OSHA 2003, 29 CFR 1910.1000 [2006]) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week.

[h]TLV-TWA (Threshold Limit Value-Time Weighted Average, American Conference of Governmental Industrial Hygienists) (ACGIH 2002) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[i]MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration]) (Deutsche Forschungsgemeinschaft [German Research Association] (DFG 2002) is defined analogous to the ACGIH-TLV-TWA.

[j]MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration] Dutch Expert Committee for Occupational Standards, The Netherlands) (MSZW 2000) is defined analogous to the ACGIH-TLV-TWA.

In lieu of definitive exposure-response data for humans, quantitative data in multiple animal species would serve to reduce the uncertainty in interspecies variability and also allow for more precise predictions regarding the toxicologic responses of humans following acute exposure to hydrazine. The use of an adequate numbers of animals in these studies would also assist in reducing the uncertainty regarding individual variability in the toxic response to hydrazine. Studies addressing toxic end points consistent with those of AEGL-1 and AEGL-2 type effects would allow for more precisely defining the thresholds for these levels.

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APPENDIX A

Derivation of AEGL Values

Derivation of AEGL-1

Key Study:	House (1964). Monkeys exposed continuously by inhalation to 0.4 ppm (0.52 mg/m^3) exhibited flushing of the face and eye irritation.
Uncertainty factors:	3 for interspecies variability (the highly reactive hydrazine appears to be equally irritating to all species); 3 represents the geometric mean of 10 (3.16) 3 for intraspecies variability (the contact irritation due to the extreme reactivity of hydrazine is not likely to vary among individuals); 3 represents the geometric mean of 10
Total uncertainty factor adjustment:	$3.16 \times 3.16 = 10$
Time scaling:	$C^3 \times t = k$ (ten Berge et al. 1986)
Calculations:	0.4 ppm/10 = 0.04 ppm $C^3 \times t = k$ $(0.04 \text{ ppm})^3 \times 1440 \text{ min} = 0.09216 \text{ ppm}^3\text{-min}$
10-min AEGL-1	$(0.04 \text{ ppm})^3 \times 1440 \text{ min} = 0.09216 \text{ ppm}^3\text{-min}$ $C^3 \times 10 \text{ min} = 0.09216 \text{ ppm}^3\text{-min}$ C = 0.21 ppm
30-min AEGL-1	$(0.04 \text{ ppm})^3 \times 1440 \text{ min} = 0.09216 \text{ ppm}^3\text{-min}$ $C^3 \times 30 \text{ min} = 0.09216 \text{ ppm}^3\text{-min}$ C = 0.15 ppm
1-h AEGL-1	$(0.04 \text{ ppm})^3 \times 1440 \text{ min} = 0.09216 \text{ ppm}^3\text{-min}$ $C^3 \times 60 \text{ min} = 0.09216 \text{ ppm}^3\text{-min}$ C = 0.12 ppm
4-h AEGL-1	$(0.04 \text{ ppm})^3 \times 1440 \text{ min} = 0.09216 \text{ ppm}^3\text{-min}$ $C^3 \times 240 \text{ min} = 0.09216 \text{ ppm}^3\text{-min}$ C = 0.07 ppm
8-h AEGL-1	$(0.04 \text{ ppm})^3 \times 1440 \text{ min} = 0.09216 \text{ ppm}^3\text{-min}$ $C^3 \times 480 \text{ min} = 0.09216 \text{ ppm}^3\text{-min}$ C = 0.06 ppm

Note: The above represents the basis for the initial AEGL-1 derivations. Because of the extreme reactivity of hydrazine and its great capacity as a direct-contact irritant, 0.1 ppm was adopted as the AEGL-1 for all time periods (the calculated values for 30 min, 1 h, 4 h, and 8 h are all approximately 0.1 ppm).

Derivation of AEGL-2

Key Study:	Latendresse et al. (1995). Rats exposed for 1 h to 750 ppm hydrazine exhibited nasal lesions. The lesions were reversible following cessation of exposure. Compared to unexposed controls, there was no significant increase in lethality in males exposed to a single 1-h exposure to 750 ppm or following 10 weekly 1-h exposures. Although a significant increased mortality ($p > 0.05$) was observed in female rats at 30 months, there was no increased lethality at 14.5 months following the single 1-h exposure. Furthermore, there were no deaths in rats following 10 consecutive weekly 1-h exposures. There was no significant difference in mortality of similarly exposed male and female hamsters at any time point. Therefore, the 750 ppm exposure represents an exposure that will result in notable irritation and histopathological changes.
Uncertainty factors:	3 for interspecies variability; available data disallow a definitive assessment of species variability although the direct-contact reactivity of hydrazine would limit dosimetric variability. 3 for intraspecies variability; available data (clinical signs and histopathologic correlates) indicate that hydrazine toxicity is a port-of-entry toxicant and acts by direct-contact mechanisms due to the extreme reactivity of hydrazine. The irritation and resulting tissue damage are not likely to vary among individuals. Additionally, variability in acetylation phenotypes among humans reportedly varies by approximately 2-fold thereby implying minimal variability in this aspect of hydrazine metabolism.
Modifying factor:	2 for data inadequacies; definitive exposure-response data specific to AEGL-2 level effects are unavailable for inhalation exposure. An additional modifying factor of 3 has been applied to account for the uncertainties in the measurement of exposure concentrations in earlier studies. While not an issue for recent studies such as Latendresse et al. (1995) and HRC (1993), this deficiency compromises the incorporation of older data into assessing species variability.
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 described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. 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.

Calculations:	750 ppm/60 = 12.5 ppm $C^3 \times t = k$ $(12.5 \text{ ppm})^3 \times 60 \text{ min} = 117188 \text{ ppm}^3\text{-min}$ $C^1 \times t = k$ $(12.5 \text{ ppm})^1 \times 60 \text{ min} = 750 \text{ ppm-min}$
10-min AEGL-2	$C^3 \times 10 \text{ min} = 117188 \text{ ppm}^3\text{-min}$ C = 23 ppm
30-min AEGL-2	$C^3 \times 30 \text{ min} = 117188 \text{ ppm}^3\text{-min}$ C = 16 ppm
1-h AEGL-2	C = 12.5 ppm (rounded to 13 ppm)
4-h AEGL-2	$C^1 \times 240 \text{ min} = 750 \text{ ppm}^1\text{-min}$ C = 3.1 ppm
8-h AEGL-2	$C^1 \times 480 \text{ min} = 750 \text{ ppm}^1\text{-min}$ C = 1.6 ppm

Derivation of AEGL-3

Key Study:	HRC 1993. Lethality in rats following 1-h nose-only inhalation exposure. A 3-fold reduction in the reported LC_{50} of 4.2 mg/L (3,192 ppm) is used as an estimate of the lethality threshold (3,192 ppm/3 = 1,064 ppm). The rat data from the recent Latendresse et al. (1995) study indicated that this exposure would not be lethal to rats exposed for 1 h. The steep exposure-response curve for hydrazine also suggests derivation of an $LC_{0\,1}$(3,192 ppm) derived by a Litchfield and Wilcoxon analysis may represent an exposure below the lethality threshold. Data from recent studies such as the HRC (1993) report and Latendresse et al. (1995) are also more reliable than older studies due to improved analytical techniques (older studies likely underestimated hydrazine concentrations due to its extreme reactivity).
Uncertainty factors:	3 for interspecies variability; the extreme reactivity of hydrazine resulted in compromised and variable exposure concentration data; the order-of-magnitude adjustment is considered adequate for to account for dosimetry differences among species. 3 for intraspecies variability; available data (clinical signs and histopathologic correlates) indicate that hydrazine toxicity is a port-of-entry toxicant and acts by direct-contact mechanisms that are not likely to vary by an order of magnitude across species.
Modifying factor:	3 for inadequacies regarding measurement of exposure concentrations in earlier studies which compromise a definitive assessment of species variability.

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 described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. 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.
Calculations:	1064 ppm/30 = 35.5 ppm $C^3 \times t = k$ $(35.5 \text{ ppm})^3 \times 60 \text{ min} = 2684333 \text{ ppm}^3\text{-min}$ $C^1 \times t = k$ $(35.5 \text{ ppm})^1 \times 60 \text{ min} = 2130 \text{ ppm-min}$
10-min AEGL-3	$C^3 \times 10 \text{ min} = 2684333 \text{ ppm}^3\text{-min}$ C = 64 ppm
30-min AEGL-3	$C^3 \times 30 \text{ min} = 2684333 \text{ ppm}^3\text{-min}$ C = 45 ppm
1-h AEGL-3	C = 35 ppm
4-h AEGL-3	$C^1 \times 240 \text{ min} = 2130 \text{ ppm-min}$ C = 8.9 ppm
8-h AEGL-3	$C^1 \times 480 \text{ min} = 2130 \text{ ppm-min}$ C = 4.4 ppm

APPENDIX B

Carcinogenicity Assessment for Hydrazine AEGLs

Key Study: Vernot et al. 1985

Administered Dose (ppm)	Human Equivalent Dose[a] (mg/kg/day)	Tumor Incidence[b]
0	0	0/146
0.05	0.0009	2/96
0.25	0.004	1/94
1.0	0.017	9/97
5.0	0.084	58/98

[a]Transformed animal dose (TAD) converted to human equivalent dose (HED): TAD × 20 m^3/day × 1/70 kg.HED entered into GLOBAL86; unit risk converted back to mg/m^3.
[b]Nasal adenomatous polyps, male rats (female rats and hamsters exhibited lower but statistically significant incidences [$p \leq 0.01$] as well).

The cancer assessment for acute inhalation exposure to hydrazine was conducted following the NRC methodology for EEGLs, SPEGLs and CEGLs (NRC 1986). The value derived from the animal data and GLOBAL86 was divided by 2.4 to adjust for dose and study duration ($[24 \text{ mos}/18 \text{ mos}]^3 = 2.4$). This adjustment accounts for the proportional effect of age on the tumorigenic response and provides the following VSD:

$$\text{Virtually safe dose (VSD) } d = 3.2 \times 10^{-7} \text{ mg/m}^3$$

Calculate 24-h exposure:

$$\text{24-h exposure} = d \times 25{,}600$$
$$= (3.2 \times 10^{-7} \text{ mg/m}^3) \times 25{,}600$$
$$= 0.008 \text{ mg/m}^3$$

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

$$\frac{\text{24 - h exposure}}{6} = \frac{0.008 \text{ mg/m}^3}{6} = 0.0013 \text{ mg/m}^3$$

$$0.0013 \text{ mg/m}^3 = \frac{1 \times 10^4}{1 \times 10^6 \text{ (risk at d)}} = 0.13 \text{ mg/m}^3$$

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). For a 1×10^{-4} risk:

24-h exposure = 0.13 mg/m^3 (0.1 ppm)
8-h = 0.39 mg/m^3 (0.3 ppm)
4-h = 0.78 mg/m^3 (0.6 ppm)

1-h = 3.12 mg/m^3 (2.4 ppm)
0.5-h = 6.24 mg/m^3 (4.7 ppm)

Because the derivation of the cancer slope factor requires conversion of animal doses to human equivalent doses, no reduction of exposure levels is applied to account for interspecies variability. For 10^{-5} and 10^{-6} risk levels, the 10^{-4} values are reduced by 10-fold or 100-fold, respectively.

Because long-term inhalation exposure to hydrazine has been shown to be tumorigenic in several species, a cancer assessment was also performed (Appendix B). Following the methods of NRC (1986), AEGL-2 values were derived based on two available data sets. Both data sets identified nasal tumors in rats following 1-year inhalation exposure to hydrazine. Although data from the animal studies affirm the carcinogenic potential of hydrazine following inhalation exposure, the observed tumorigenic responses appear to be a function of prolonged tissue irritation resulting from long-term repeated exposures and are unlikely to occur following a single low exposure. This was especially evident in the study by Latendresse et al.(1995) that showed repeated exposures were necessary for reversible histopathologic changes in rat nasal epithelium. This contention is also supported by the work of Leakakos and Shank (1994) that showed DNA methylation (presumably a requirement for oral and parenteral hydrazine-induced liver cancer in rodents) was detectable only when the dose of hydrazine was necrogenic. Therefore, it would appear that hydrazine AEGL values that address rare, or single once-in-a-lifetime exposures should not be based upon cancer risk.

Key Study: MacEwen et al. (1981) significant increased tumor incidence in mice (pulmonary adenomas), rats (nasal adenomas, adenocarcinomas), and hamsters (nasal cavity polyps) exposed to highest concentration. Exposure protocol: male and female rats exposed to hydrazine at 0, 0.05, 0.25, 1.0, or 5.0 ppm, 6 h/day, 5 days/week for one year; 12- to 38-month postexposure observation.

The cancer assessment for acute inhalation exposure to hydrazine was conducted following the NRC methodology for EEGLs, SPEGLs and CEGLs (NRC 1986).

Virtually safe dose (VSD) exposure level (d) of 2×10^{-4} ug /m^3 (2×10^{-7} mg/m^3) for a 1×10^{-6} risk level for hydrazine was selected (EPA 2002). This risk level was based upon an inhalation unit risk of 4.9×10^{-3} per ug /m^3 derived from the MacEwen et al. (1981) data using the linearized multistage procedure.

$$d = 2 \times 10^{-4} \text{ ug /m}^3$$

Assuming the carcinogenic effect to be a linear function of cumulative dose, a single-day exposure is equivalent to d × 25,600 days (average lifetime).

$$\text{24-h exposure} = d \times 25{,}600$$
$$= (2 \times 10^{-7} \text{ mg/m}^3) \times 25{,}600$$
$$= 0.005 \text{ mg/m}^3$$

Adjustment to allow for uncertainties in assessing potential cancer risks under short term exposures under the multistage model [Crump and Howe 1984]).

$$\frac{\text{24 - h exposure}}{6} = \frac{0.005\ \text{mg/m}^3}{6} = 0.0008\ \text{mg/m}^3$$

For a 1×10^{-4} risk, the extent of risk based on the 24-h exposure concentration becomes:

$$0.008\ \text{mg/m}^3 = \frac{1 \times 10^4}{1 \times 10^{-6}\ \text{(risk at d)}} = 0.08\ \text{mg/m}^3$$

If the exposure is limited to a fraction (f) of a 24-h period, the fractional exposure becomes 1/f × 24 h (NRC 1985). For a 1×10^{-4} risk:

24-h exposure = 0.08 mg/m^3 (0.06 ppm)
8-h = 0.24 mg/m^3 (0.2 ppm)
4-h = 0.48 mg/m^3 (0.4 ppm)
1-h = 1.9 mg/m^3 (1.5 ppm)
0.5 h = 3.8 mg/m^3 (2.9 ppm)

Because the derivation of the cancer slope factor requires conversion of animal doses to human equivalent doses, no reduction of exposure levels is applied to account for interspecies variability. For 10^{-5} and 10^{-6} risk levels, the 10^{-4} values are reduced by 10-fold or 100-fold, respectively.

APPENDIX C

Derivation Summary for Hydrazine AEGLs

DERIVATION SUMMARY

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
0.1 ppm	0.1 ppm	0.1 ppm	0.1 ppm	0.1 ppm

Key Reference: House, W.B. 1964. Tolerance Criteria for Continuous Inhalation Exposure to Toxic Materials. III. Effects on Animals of 90-day Exposure to Hydrazine, Unsymmetrical Dimethylhydrazine (UMDH), Decaborane, and Nitrogen Dioxide. ASD-TR-61-519 (III). Wright-Patterson Air Force Base, OH.

Test Species/Strain/Number: 10 male rhesus monkeys.

Exposure Route/Concentrations/Durations:
Inhalation: average of 0.78 ppm (range: 0.25-1.38 ppm) continuous (24 h/day, 7 days/week) exposure for 90 days; 0.4 ppm for first 10 days (determinant for AEGL-1)

Effects: Eye and facial irritation within 24 h.

End Point/Concentration/Rationale:
0.4 ppm for the first 24 h resulted in mild irritation which is a defined AEGL-1 end point.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3: Contact irritation is not likely to vary greatly among species because hydrazine is a highly reactive and direct acting irritant. Also, a nonhuman primate was the test species.
Intraspecies: 3: Hydrazine will be extremely reactive with all biological tissues resulting in irritation and reversible tissue damage upon contact. This process, especially for port-of-entry effects, is not expected to differ greatly among individuals.

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Not applied; insufficient data.

Time Scaling: $C^n \times t = k$ where $n = 3$ to scale from 24-h exposure to 4-h and 8-h exposure periods. Due to the extreme reactivity of hydrazine, however, the contact irritant effects were considered to be concentration dependent and, therefore, the 0.1 ppm concentration derived for the 4-h and 8-h periods was applied for all time periods.

Data Adequacy:
Quantitative data pertaining to AEGL-1 type effects are limited. The data provided by House (1964) for nonhuman primates, however, are consistent with the human experience regarding the irritant effects of low level hydrazine exposure.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
23 ppm	16 ppm	13 ppm	3.1 ppm	1.6 ppm

Reference: Latendresse, J.R., G.B. Marit, E.H. Vernot, C.C. Haun, and C.D. Flemming. 1995. Oncogenic potential of hydrazine in the nose of rats and hamsters after 1 or 10 1-h exposures. Fundam. Appl. Toxicol. 27(1): 33-48.

Test Species/Strain/Sex/Number:
5 male and 5 female Fischer-344 rats and 10 Syrian golden hamsters, 10/exposure group.

Exposure Route/Concentrations/Durations: Inhalation: 750 ppm for 1 h.

Effects:
Exposure Effect:
750 ppm for 1 h Nasal lesions (minimal necrosis, mild to moderate exfoliation, minimal to moderate acute inflammation, mild apoptosis; determinant for AEGL-2).

End Point/Concentration/Rationale:
750 ppm for 1 h resulted in nasal lesions (minimal necrosis, mild to moderate exfoliation, minimal to moderate acute inflammation, mild apoptosis) that were considered to be an estimate of a threshold for an AEGL-2 effect.
Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies:
3: An uncertainty factor of 3 for interspecies variability was applied to account for possible species-dependent uncertainties in the toxic response to inhaled hydrazine.
Intraspecies:
3: Hydrazine is extremely reactive with all biological tissues resulting in irritation and tissue damage upon contact. This process, especially for port-of-entry effects, is not expected to differ greatly among individuals. Additionally, variability in acetylation phenotypes among humans and the subsequent effect on at least one aspect of hydrazine metabolism has been shown to vary approximately 2-fold.

Modifying Factor: 2 for inadequacies in the database pertaining to AEGL-2 effects
3 for the uncertainties in the measurement of exposure concentrations in earlier studies. While not an issue for recent studies such as Latendresse et al. (1995) and HRC (1993), this deficiency compromises the use of older data for assessing species variability.

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling:
$C^n \times t = k$ where n = 1 or 3 (k = 117188 ppm^3-min when n = 3 and k = 750 ppm-min when n = 1); 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 exposure durations points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation.

Data Adequacy:
Although the toxicity end points selected for AEGL-2 derivation are not consistent with an effect severity consistent with the AEGL-2 definition, they are consistent with the continuum of effects known to occur as a result of hydrazine exposures that could result in more serious responses. Because of the know toxicity of hydrazine and its carcinogenic potential, the somewhat conservative approach was justified. Species variability is poorly defined due primarily to data deficiencies.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
64 ppm	45 ppm	35 ppm	8.9 ppm	4.4 ppm

Key Reference: Huntingdon Research Centre 1993. Hydrazine 64% Aqueous Solution: Acute Inhalation Toxicity in Rats 1-h Exposure. Huntingdon Research Centre, Cambridge, England. CMA 8/930523. Chemical Manufacturers' Association, Washington, DC.

Test Species/Strain/Sex/Number: Male and female Sprague-Dawley rats, 5/sex/group.

Exposure Route/Concentrations/Durations:
Inhalation: 0, 0.65, 2.04, 3.24, 4.9 mg/L for 1 h (nose-only exposure to 64% aerosol)

Effects

Concentration	Mortality
2.04 mg/L (1556 ppm)	0/10
3.24 mg/L (2472 ppm)	4/10
4.98 mg/L (6596 ppm	6/1

Reported LC_{50}: 4959 ppm (64% aerosol); 3192 ppm (hydrazine alone)

End Point/Concentration/Rationale:
When compared to the data from Latendresse et al. (1995), where rats survived multiple 1-h exposures to 750 ppm, the calculated 1-h LC_{01} of 334 ppm appeared to be unrealistically low and not scientifically defensible as an estimated lethality threshold. Therefore, a three-fold reduction in the 1-h LC_{50} (3192 ppm/3 = 1064 ppm) was determined to be an estimate of the lethality threshold for a 1-h exposure duration that is consistent with the currently available data.
Uncertainty Factors/Rationale:
Total uncertainty factor: 30
Interspecies:
3-An uncertainty factor of 3 for interspecies variability was applied to account for possible species-dependent uncertainties in the toxic response to inhaled hydrazine.
Intraspecies:
3-Hydrazine will be extremely reactive with all biological tissues resulting in irritation and severe tissue damage at high concentrations upon contact. This process, especially for port-of-entry effects, is not expected to differ greatly among individuals.

Modifying Factor: 3 for inadequacies regarding measurement of exposure concentrations in earlier studies which compromise a definitive assessment of species variability

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling: $C^n \times t = k$ where n = 1 or 3 (k=2684333 ppm^3-min when n = 3 and k = 2130 ppm-min when n = 1); 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:
Lethality data are available for several animal species. Lethality values quantitatively derived from a recent study were considered appropriate as the basis for AEGL-3 derivation. Species variability is poorly defined.

APPENDIX D

Category Plot for Hydrazine AEGLs

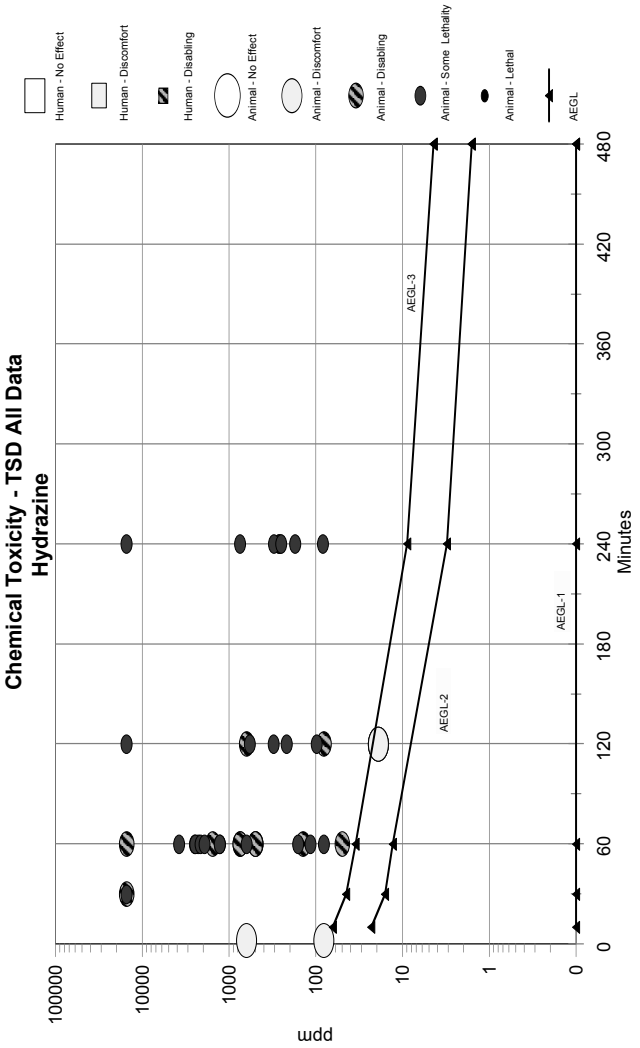

FIGURE D 1 Category plot for hydrazine.

APPENDIX E

Level of Distinct Odor Awareness (LOA) for Hydrazine

DERIVATION OF THE LOA: HYDRAZINE

The level of distinct odor awareness (LOA) represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, about 10 % of the population will experience a strong odor intensity. The LOA should help chemical emergency planners and responders in assessing the public awareness of the exposure due to odor perception. The LOA derivation follows the guidance given by van Doorn et al. (2002).

The odor detection threshold (OT_{50}) for hydrazine was calculated to be 4 ppm (van Doorn et al. 2002).

The concentration (C) leading to an odor intensity (I) of distinct odor detection (I = 3) is derived using the Fechner function:

$$I = k_w \times \log (C/OT_{50}) + 0.5$$

For the Fechner coefficient, the default of $k_w = 2.33$ will be used due to the lack of chemical-specific data:

$$3 = 2.33 \times \log (C/4) + 0.5 \text{ which can be rearranged to}$$
$$\log (C/4) = (3\text{-}0.5)/2.33 = 1.07 \text{ and results in}$$
$$C = (10^{1.07}) \times 4 = 47 \text{ ppm}$$

The resulting concentration is multiplied by an empirical field correction factor. It takes into account that in every day life factors, such as sex, age, sleep, smoking, upper airway infections and allergy as well as distraction, increase the odor detection threshold by a factor of 4. In addition, it takes into account that odor perception is very fast (about 5 seconds) which leads to the perception of concentration peaks. Based on the current knowledge, a factor of 1/3 is applied to adjust for peak exposure. Adjustment for distraction and peak exposure lead to a correction factor of 4 / 3 = 1.33.

The LOA for hydrazine is 63 ppm.

$$LOA = C \times 1.33 = 47 \text{ ppm} \times 1.33 = 63 \text{ ppm}$$