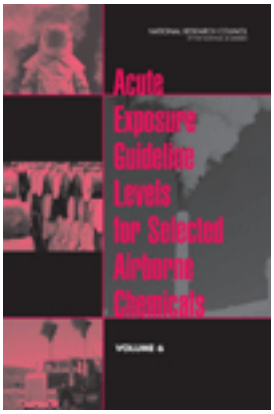

Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 6

Committee on Acute Exposure Guideline Levels, Committee on Toxicology, National Research Council

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 6

Committee on Acute Exposure Guideline Levels

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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.

Using the 1993 NRC guidelines report, the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances—consisting of members from EPA, the Department of Defense (DOD), the Department of Energy (DOE), the Department of Transportation, other federal and state governments, the chemical industry, academia, and other organizations from the private sector—has developed acute exposure guideline levels (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 the Committee on Acute Exposure Guideline Levels, which prepared this report. This report is the sixth volume in the

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

series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*. It reviews the AEGLs for allylamine, ammonia, aniline, arsine, crotonaldehyde, *trans* and *cis* + *trans*, 1, 1-dimethylhydrazine, 1, 2-dimethylhydrazine, iron pentacarbonyl, methyl hydrazine, nickel carbonyl, phosphine, and 8 metal phosphides for scientific accuracy, completeness, and consistency with the NRC guideline reports.

This report was reviewed in draft 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 this report: Deepak K. Bhalla, Wayne State University; David W. Gaylor, Gaylor and Associates, LLC; and Samuel Kacew, University of Ottawa.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by Robert Goyer, University of Western Ontario (Emeritus). Appointed by the National Research Council, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

After the review of the draft was completed, the committee evaluated AEGLs that were developed for 8 metal phosphides. Because the acute toxicity of metal phosphides results from the phosphine generated from hydrolysis of the metal phosphides, their AEGL values are likewise based upon phosphine AEGLs. Therefore Chapter 10 of this report was expanded to present AEGL values for phosphine and the metal phosphides. We wish to thank Ian Greaves, University of Minnesota, and Wallace Hayes, Harvard School of Public Health, for their review of this revised chapter. The review was overseen by Samuel Kacew.

The committee gratefully acknowledges the valuable assistance provided by the following persons: Ernest Falke, Marquea D. King, Iris A. Camacho, and Paul Tobin (all from EPA); George Rusch (Honeywell, Inc.); Cheryl Bast, Sylvia Talmage, Robert Young, and Sylvia Milanez (all from Oak Ridge National Laboratory). We are grateful to James J. Reisa, director of the Board on Environmental Studies and Toxicology (BEST), for his helpful comments. Other staff members who contributed to this effort are Raymond Wassel (senior program officer), Aida Neel (program associate), Ruth Crossgrove (senior editor), Radiah Rose (senior editorial assistant), and Mirsada Karalic-Loncarevic (manager, Technical Information Center). The committee particularly acknowledges

Kulbir Bakshi, project director for the committee, for bringing the report to completion. 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

William E. Halperin, *Chair*
Committee on Toxicology

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

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Introduction

This report is the sixth 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 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 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 (NRC 1968, 1972, 1984a,b,c,d, 1985a,b, 1986a,b, 1987, 1988, 1994, 1996a,b, 2000). COT has also published guidelines for developing emergency exposure guidance levels for military personnel and for astronauts (NRC 1986b, 1992). Because of 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 November1995 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 parts per million [ppm] or milligrams per cubic meter [mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic 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 unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

As described in *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 in vivo 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 exert multiple effects, all endpoints (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, the 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 five reports in the series Acute Exposure Guideline Levels for Selected Airborne Chemicals (NRC 2001b, 2002, 2003, 2004, 2007). This report is the sixth volume in that series. AEGL documents for allylamine, ammonia, aniline, arsine, crotonaldehyde, cis/trans-, crotonaldehyde, trans-iso, 1, 1-dimethylhydrazine, iron pentacarbonyl, methyl hydrazine, nickel carbonyl, phosphine, and 8 metal phosphides are each published as an appendix to 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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Appendixes

1

Allylamine[1]

Acute Exposure Guideline Levels

PREFACE

Under the authority of the Federal Advisory Committee Act (P.L. 92-463) of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances has been established to identify, review, and interpret relevant toxicologic and other scientific data and develop acute exposure guideline levels (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, 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 parts per million [ppm] or milligrams per cubic meter [mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could

[1]This document was prepared by the AEGL Development Team composed of Sylvia Milanez (Oak Ridge National Laboratory) and Loren Koller, Chemical Manager (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).

experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

Airborne concentrations below 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 susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Allylamine is a colorless or yellowish volatile liquid with a very sharp ammonia-like odor that is irritating to mucous membranes. It is highly flammable and moderately reactive with oxidizing materials. Industrially, it is used in the vulcanization of rubber and in the synthesis of pharmaceuticals. In addition to being a severe respiratory, eye, and skin irritant, allylamine is a cardiovascular toxin when administered at high doses orally, by injection, or by inhalation. Allylamine cardiotoxicity is proposed to be related to its metabolism to acrolein and hydrogen peroxide.

AEGL-1 values were based on a study in which 35 young adult human volunteers were exposed for 5 min to 2.5, 5, or 10 ppm allylamine (10-14 per concentration; sex and age not specified; Hine et al. 1960). A group was also exposed briefly to 14 ppm, which was reported as intolerable and exposure was almost immediately terminated. The subjects graded their sensory responses for eye irritation, nose irritation, pulmonary discomfort, central nervous system (CNS) effects (headache, nausea), and olfactory cognition on a five-point scale (0 = absent; 1 = slight; 2 = moderate; 3 = severe; 4 = extreme or intolerable). All subjects detected the odor of allylamine, and there were dose-related increases in the incidence of slight or moderate eye irritation (21%, 15%, 50%), nose irritation (50%, 54%, 100%), and pulmonary discomfort (29%, 46%, 50%) at 2.5, 5,

and 10 ppm, respectively. CNS effects were not dose related. The same AEGL-1 value was used for 10 min to 8 h because mild sensory irritation or discomfort does not generally vary greatly with time. The AEGL-1 point of departure was 1.25 ppm, which was obtained by applying a modifying factor (MF) of 2-2.5 ppm, which was the lowest effect level. The MF was used because exposure was for only 5 min, and it is unclear whether "moderate" irritation or discomfort is comparable to "notable" irritation or discomfort, which exceeds the scope of AEGL-1. An intraspecies uncertainty factor of 3 was applied because allylamine acts as a contact irritant, and the severity of its effects is not expected to vary greatly among humans. Also, use of a greater uncertainty factor would yield a concentration below 0.2 ppm, which was a no-effect level for workers exposed for up to 4 h (Shell Oil Co. 1992). The derived AEGL-1 value of 0.42 ppm for 10 min to 8 h is also consistent with two mouse respiratory irritation studies (Gagnaire et al. 1989, 1993), from which it is predicted that exposure for a few hours to 0.9 ppm would cause sensory irritation in humans but that 0.09 ppm would not (Alarie 1981).

AEGL-2 values were based on two studies. The 10-, 30-, and 60-min AEGLs were developed from the Hine et al. (1960) human 5-min exposure study that was used to derive AEGL-1 values but using 10 ppm as the point of departure. Ten ppm caused slight or moderate eye and nose irritation and pulmonary discomfort and was the no-observed-adverse-effect level (NOAEL) for "intolerable" irritation that occurred at 14 ppm. The same value was adopted for 10-60 min because the degree of irritation or discomfort resulting from exposure to 10 ppm was not expected to increase over a 1-h period beyond the scope of AEGL-2. An intraspecies uncertainty factor of 3 was used because allylamine acts as a contact irritant and the severity of its effects is not expected to vary greatly among humans. The resulting AEGL-2 value of 3.3 ppm was not adopted for 4 or 8 h, however, because a rat study (Guzman et al. 1961) indicated that exposure to 3.3 ppm for 4 or 8 h may cause cardiotoxicity. In the latter study, exposure to 40 ppm for 16 h was a NOAEL for cardiovascular lesions, which were seen from exposure to 60 ppm for 14 h (myofibril fragment damage, perivascular edema, and cellular infiltration). Time-concentration scaling was performed using the ten Berge et al. (1986) equation $C^n \times t = k$, where $n = 1.7$ was calculated from a linear regression of the Guzman et al. (1961) rat cardiotoxicity data. An interspecies uncertainty factor of 5 was applied because the mechanism of toxicity is similar among several mammalian species (and humans) but differences in susceptibility are unknown, and an uncertainty factor of 3 yields values approaching the no-observed-effect level (NOEL) for lethality from pulmonary lesions for a 4- or 8-h exposure. An intraspecies uncertainty factor of 10 was used because the variability of the cardiotoxic response to allylamine among humans is undefined, and potentially sensitive populations exist (diabetics, persons with congestive heart failure). This yields 4- and 8-h AEGLs of 1.8 and 1.2 ppm, respectively, indicating that for these longer exposure durations, cardiotoxicity is a more sensitive end point than eye and respiratory irritation.

AEGL-3 values were derived from a study on rat inhalation with a lethal concentration in 50% of the sample (LC_{50}) in which exposures were for 1, 4, or 8 h (Hine et al. 1960). All treated rats showed signs of eye and respiratory tract irritation, and some had lacrimation and red nasal discharge. Rats that died had stomachs distended with air, fluid-filled lungs, alveolar hemorrhage, and pulmonary edema. The NOEL for lethality, as represented by LC_{01} (1% lethality) values calculated using probit analysis, was the AEGL-3 end point. The 1-h, 4-h, and 8-h AEGLs were obtained using the respective LC_{01} values. The 10- and 30-min AEGLs were derived from the 1-h LC_{01} using the relationship $C^n \times t = k$, where n = 0.85 was calculated from the Hine et al.LC_{50} data. An uncertainty factor of 30 was applied: 10 to account for interspecies variability (lack of acute toxicity studies from other species with AEGL-3 level end points) and 3 for human variability (the steep dose-response (~2-fold increase in concentration caused mortality to increase from 0 to 100%) indicates that the NOEL for lethality due to direct destruction of lung tissue is not likely to vary greatly among humans). The derived AEGL-3 values, as well as the AEGL-1 and AEGL-2 values, are shown in Table 1-1.

1. INTRODUCTION

Allylamine is a colorless or yellowish volatile liquid that is highly flammable and moderately reactive with oxidizing materials (HSDB 2003). It is completely soluble in water with a pK_a of 9.7 and has a very sharp ammonia-like odor that is irritating to mucous membranes (Budavari et al. 1996; HSDB 2003; Boor and Hysmith 1987).[2] Industrially, it is used in the vulcanization of rubber and in the synthesis of commercial products, including mercurial diuretics, sedatives, and antiseptics (Benya and Harbison 1994). Allylamine is manufactured by the amination of alkyl halides (e.g., allyl chloride and ammonia) and is also a natural constituent of foodstuffs (Budavari et al. 1996; HSDB 2003).

In addition to being a severe respiratory, eye, and skin irritant, allylamine is cardiotoxic when administered at high doses orally, by inhalation, or by injection. It has been used to induce cardiac and vascular lesions in laboratory animals to model human cardiovascular disease. Allylamine cardiotoxicity is proposed to be related to its metabolism to acrolein and hydrogen peroxide in cardiac and vascular tissues (Boor and Hysmith 1987; Ramos et al. 1988). Allylamine lethal inhalation toxicity has been examined in rats and mice and its nonlethal inhalation toxicity in single- and multiple-exposure studies using monkeys, rats, mice, and rabbits. Studies with human volunteers and exposures in the workplace have yielded limited information about the irritant and toxic effects of short-term inhalation exposure. The allylamine odor threshold is

[2] pK_a is the negative log of the acid dissociation constant.

TABLE 1-1 Summary of AEGL Values for Allylamine

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1[a] (nondisabling)	0.42 ppm (0.98 mg/m^3)	0.42 ppm (0.98 mg/m^3)	0.42 ppm (0.98 mg/m^3)	0.42 ppm (0.98 mg/m^3)	0.42 ppm (0.98 mg/m^3)	Mild human irritation or discomfort (Hine et al. 1960)
AEGL-2 (disabling)	3.3 ppm (7.7 mg/m^3)	3.3 ppm (7.7 mg/m^3)	3.3 ppm (7.7 mg/m^3)	1.8 ppm (4.2 mg/m^3)	1.2 ppm (2.8 mg/m^3)	Human eye and respiratory irritation and NOAEL for severe irritation (≤1 h; Hine et al. 1960); NOAEL for cardiovascular lesions in rats (≥4 h; Guzman et al. 1961)
AEGL-3 (lethal)	150 ppm (350 mg/m^3)	40 ppm (93 mg/m^3)	18 ppm (42 mg/m^3)	3.5 ppm (8.2 mg/m^3)	2.3 ppm (5.4 mg/m^3)	Lethality NOEL in rats (Hine et al. 1960)

[a]Odor threshold is ≤2.5 ppm.

<2.5ppm based on the human study of Hine et al. (1960) and is reported as 6.2 ppm by Summer (1971). Allylamine chemical and physical properties are listed in Table 1-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No quantitative data were located regarding lethal allylamine exposure in humans. It was reported that allylamine inhalation may cause irregular respiration, cyanosis, excitement, convulsions, and death, although neither further details nor the source of this information was provided (HSDB 2003).

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold/Odor Awareness

A published odor threshold was not found for allylamine. An unpublished source (van Doorn et al. 2002) reported 3.7 ppm as the odor detection threshold (OT_{50}; that is, the concentration at which 50% of the odor panel observed an odor without necessarily recognizing it). A value of 3.7 conflicts with a sensory

TABLE 1-2 Chemical and Physical Data

Property	Descriptor or Value	Reference
Synonyms	Monoallylamine; 2-propenamine; 3-aminopropylene	Budavari et al. 1996
Chemical formula	$CH_2 = CHCH_2 NH_2$	Budavari et al. 1996
Molecular weight	57.10	Budavari et al. 1996
CAS registry number	107-11-9	Benya and Harbison 1994
Physical state	Liquid	Budavari et al. 1996
Color	Colorless or yellowish	HSDB 2003
Solubility in water	Completely miscible	Budavari et al. 1996
Acid ionization constant, pK_a	9.7	HSDB 2003
Vapor pressure	242 mm Hg at 25°C	HSDB 2003
Vapor density (air = 1)	1.97	Benya and Harbison 1994
Liquid density (water = 1)	0.76 at 20/4°C	Verschueren 1996
Melting point	–88°C	HSDB 2003
Boiling point	55-58°C	Budavari et al. 1996
Flammability/explosive limits	2.2-22%	HSDB 2003
Conversion factors	1 mg/m^3 = 0.428 ppm 1 ppm = 2.33 mg/m^3	Verschueren 1996

threshold experimental study, in which all 36 volunteers exposed to allylamine for 5 min reported "olfactory cognition" at the lowest concentration tested of 2.5 ppm (Hine et al. 1960; see Section 2.2.2). Additionally, if the methodology of van Doorn et al. (2002) is used to calculate an LOA (level of distinct odor awareness; see Appendix B), a value of 58 ppm is calculated, which exceeds a concentration (i.e., 14 ppm) found to be intolerable by humans (Hine et al. 1960). The method used to determine the 3.7-ppm odor threshold was not reported, which may explain its discrepancy with the Hine et al. study (e.g., a higher concentration may be needed for detection by sniffing for a few seconds than by inhalation for 5 min).

2.2.2. Experimental Studies

The sensory threshold for detecting inhaled allylamine was examined in 35 young adult human volunteers exposed for 5 min to 2.5, 5, 10, or 14 ppm (10-14 per concentration; sex and age not specified; Hine et al. 1960). It was not specified whether the same persons were exposed to more than one concentration. To compensate for the loss of allylamine upon the entrance of subjects into the 16,680-L chamber, the initial concentration of allylamine in the chamber

was about 10% greater than the target air allylamine concentration for the low concentrations and about 1% greater at the high allylamine concentrations (not specified which concentrations were considered low or high). The air allylamine concentration was continuously monitored by a recording infrared spectrophotometer. The subjects graded their sensory responses for eye irritation, nose irritation, pulmonary discomfort, CNS effects, and olfactory cognition on a five-point scale, ranging from "absent" to "extreme" (intolerable); results are shown in Table 1-3.

All test subjects detected the odor of allylamine at the lowest concentration tested (2.5 ppm). At 2.5, 5, and 10 ppm, respectively, there were dose-related increases in the incidence of slight or moderate eye irritation (21%, 15%, and 50%), nose irritation (50%, 54%, 100%), and pulmonary discomfort (29%, 46%, 50%). The incidence of slight or mild CNS effects, such as slight headache or nausea, was not dose related (21%, 0%, and 10% at 2.5, 5.0, and 10 ppm). At 14 ppm "irritation of [the] eyes, nose, and throat and pulmonary discomfort were considered intolerable, and exposure was terminated almost at once." The number of subjects exposed to 14 ppm and their individual sensory evaluations were not given.

Summer (1971) reported 6.2 ppm as the odor threshold for allylamine and 80 ppm as the concentration at which it becomes irritating to humans. It was not described in detail how these values were obtained (i.e. exposure duration, range of concentrations tested), although it appears that they may have been obtained by a panel of "sniffers," and thus exposure was for a few seconds. These values are much higher than the concentration (2.5 ppm) found to be detected by all exposed human subjects (13/13) within 5 min, with some subjects even experiencing mild respiratory irritation (Hine et al. 1960). The reason for the discrepancy between the two studies is unknown; it may be due to the different exposure durations.

TABLE 1-3 Sensory Responses of Human Subjects to a 5-Min Allylamine Inhalation Exposure[a]

	Exposure Concentration and Grade of Response														
	10 ppm (n = 10)					2.5 ppm (n = 13 or 14)					5 ppm (n = 13)				
Effect	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Olfactory cognition		3	9	1			4	9				2	5	3	
Eye irritation	11	1	2			11	2				5	4	1		
Nose irritation	7	5	2			6	6	1				5	5		
Pulmonary discomfort	10	2	2			7	6				5	4	1		
CNS effects	11	2	1			13					9	1			

[a]Test subjects graded their responses as follows: 0 = absent; 1 = slight; 2 = moderate; 3 = severe; 4 = extreme (intolerable).
Source: Data from Hine et al. 1960. Reprinted with permission; copyright 1960, American Medical Association.

2.2.3. Case Reports

Workers at a chemical manufacturing company exposed to mono-, di-, and tri-allylamine (simultaneously) occasionally reported symptoms, including tightness, congestion, and pain in the chest (especially on breathing or coughing), sore throat, runny nose, nausea, vomiting, red eyeballs, tightness in the jaw and behind the ears, and hurting teeth but had normal cardiac creatine phosphokinase levels and electrocardiograms (EKGs) (Shell Oil Co. 1992). The symptoms were ameliorated by drinking Coca-Cola. Neither the exposure time (typically several minutes) nor air allylamine concentration was measured. Plant supervisors and the company's industrial hygienist stated that symptoms were reported only when spills and leaks occurred, and 18 of 22 questionnaires filled out by workers (September-October 1981) checked "yes" for a question asking, "Was there was a spill or other unusual exposure at the time symptoms began?" The four people who checked "no" had numerous exposures and did not identify discrete incidents. To test a new stationary air sampler, ambient samples (no spills, etc.) were collected in five areas of the chemical plant (in September 1981) where workers could be present for up to 4 h on a typical day. In April 1982, personal monitoring was conducted by the company industrial hygienist. Workers were not evaluated. The air concentration was <0.1 to 0.2 ppm for monoallylamine, <0.01 to 0.3 ppm for diallylamine, and <0.01 to 0.6 ppm for triallylamine, all potential sources of product line leaks and of a maintenance procedure requiring opening of a product line. All air samples were below the limit of quantitation (LOQ) (0.5 or 5 ppm) for all three amines. People working in these areas wore protective clothing and/or respirators and were not examined. It is unlikely that symptoms would have been experienced by workers in either monitoring situation since there were no unintentional spills or leaks.

Guzman et al. (1961) carefully examined operators working with allylamine and did not find any cardiovascular effects, despite occasional complaints of irritation of the mucous membranes, nausea, and disagreeable odor. No experimental details or quantitative results were provided.

2.2.4. Accidents

During the course of an acute inhalation study in mice, leaks developed in the apparatus and the workers fixing the leaks were exposed to an unknown concentration of allylamine vapors (Hart 1939). [The mice were exposed to 24,437-31,035 ppm allylamine in a 5-L bell jar connected to a flowmeter, and airflow was 750 mL/min.] The vapors initially caused severe irritation of the mucous membranes of the nose, mouth, and eyes, which developed into an intense burning with lacrimation, coryza, and sneezing. The symptoms disappeared quickly (not specified) after exposure ceased.

2.3. Neurotoxicity

No human neurotoxicity studies were located with allylamine exposure by any route.

2.4. Developmental/Reproductive Toxicity

No studies on the developmental or reproductive effects of allylamine in humans were located.

2.5. Genotoxicity

No studies on the genotoxicity of allylamine in humans were located.

2.6. Carcinogenicity

No studies on the carcinogenicity of allylamine in humans were located (nor of its proposed metabolite, acrolein). Neither the U.S. Environmental Protection Agency (EPA) nor the International Agency for Research on Cancer (IARC) has classified allylamine as to its carcinogenic potential.

2.7. Summary

No human data were located involving acute lethal exposure to allylamine. Sensory irritation was experienced by volunteers exposed to 2.5-10 ppm for 5 min, whereas exposure to about 14 ppm was immediately intolerable (Hine et al. 1960). There were several case reports and accidents involving occupational exposure to allylamine, in which workers experienced chest pain and respiratory irritation, although neither exposure durations nor concentrations were available. No studies were located describing developmental, reproductive, genotoxic, or carcinogenic effects in humans.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Lethality as a toxic end point was described in several rat and mouse acute inhalation exposure studies. Kulagina (1975) reported an LC_{50} of 320 mg/m^3 (137 ppm) for mammals, although no further experimental details were provided.

3.1.1. Rats

Hine et al. (1960) determined allylamine LC_{50} values using groups of five male Long-Evans (Princeton strain) rats exposed for 1, 4, or 8 h. Exposure to evaporated liquid allylamine was in a 19.5-L cylindrical glass chamber. Air concentrations of allylamine were calculated using the standard gas concentration formula of Jacobs (1949); the actual concentration of allylamine in the chamber was not measured. The rats were observed for signs of toxicity during the exposure and for the ensuing 10 days. The resulting mortality and LC_{50} values as given by Hine et al. for the rats are shown in Table 1-4. At all concentrations tested, allylamine was irritating to the mucous membranes of the eyes and respiratory tract (as indicated by face-washing motions) and the rats appeared "depressed." At higher concentrations (not specified), there was lacrimation and nasal discharge, which became tinged with blood at the end of the exposure (exposure durations were not specified). Rats that died from allylamine exposure had stomachs distended with air, fluid-filled lungs with hemorrhage in the alveolar spaces, and pulmonary edema; those surviving the 10-day observation period had no notable gross or microscopic pathology.

Guzman et al. (1961) attempted to define the allylamine inhalation exposure required to produce heart lesions in male Long-Evans rats from a single exposure of allylamine. The allylamine concentrations tested were 20-100 ppm, and the exposure duration was 4-48 h (1-20 rats per exposure scenario; see Table 1-5). The rats (120-180 g) were killed periodically for histologic examination of the heart (i.e., 8 h to 14 days after the start of exposure). Heart lesions were found at most exposure concentrations, but in some cases lesions were not induced regardless of the exposure scenario. Rats exposed for ≤24 h generally had mild lesions. Two rats died spontaneously, one after 4 h of exposure to 100 ppm and one after 8 h of exposure to 40 ppm; only the latter had heart lesions (a fibrinoid degenerative thrombus, a vessel change, and diffuse cellular infiltrate). It is possible that lethality would have resulted in some of these cases were the animals not killed so quickly after cessation of exposure. The results are summarized in Table 1-5.

Guzman et al. (1961) also conducted a series of multiple-exposure allylamine inhalation studies to examine the cardiotoxic effects of prolonged exposure. Male Long-Evans rats (15/concentration) were given 50 7-h exposures to 0, 5, 10, 20, or 40 ppm (5 days/week; Hine et al. 1960; Guzman et al. 1961). Exposure to vaporized liquid allylamine was in 200-L stainless steel chambers. Air allylamine concentrations were sampled periodically, and allylamine was measured using a method designed to measure ammonia (Goldman and Jacobs 1953). No effects were seen in rats exposed to 5 ppm, with the exception of one rat that was considered an outlier (it had heart lesions, extensive abdominal tumors, hepatic abscess, and lung atelectasis). Rats exposed to 10 ppm and higher had lowered weight gain, which was correlated at 20 ppm with depletion of body fat. Rats exposed to 40 ppm became emaciated and had dull fur and,

TABLE 1-4 Lethality of Rats Exposed to Allylamine Vapor

Nominal Exposure Concentration (ppm)	Hours of Exposure	Mortality	Time of Death (from Start of Exposure)	Observations	LC_{50} (ppm)	LC_{01} (ppm)[a]
1,000	1	1/5	4 h	Eye and respiratory irritation, bloody nasal discharge, "depressed" appearance. Rats that died had stomachs distended with air and fluid-filled hemorrhagic lungs and pulmonary edema.	286	104
1,500		1/5	4 h			
2,250		3/5	2-4 h			
3,380		5/5	2-4 h			
133	4	0/5	—			
200		0/5	—			
300		3/5	2-4 h			
450		5/5	2-4 h			
89	8	0/5	—		177	69.2
133		0/5	—			
200		4/5	8-24 h			
300		5/5	8-24 h			

[a]Calculated by probit analysis from LC_{50} data.
Source: Data from Hine et al. 1960. Reprinted with permission; copyright 1960, American Medical Association.

enlarged hearts and 5/15 died (not reported how long after beginning of treatment). One-third of the 40-ppm rats had pneumonia with cyanosis, a thorax full of clear liquid, rust-colored lungs, and a small spleen. Liver weights were increased at all allylamine concentrations and kidney weight at 20 ppm; however, there was no relationship to concentration in either case. Lesions in the heart and blood vessels were induced in 1/9 animals examined that were exposed to 20 ppm and 8/8 at 40 ppm. The most common heart lesions were interstitial fibrosis with areas of necrosis, muscle bundle polymorphonuclear cell infiltration, and inflammation of the smaller blood vessels. This study is summarized with all other multiple-exposure inhalation animal studies (described in the following sections) in Table 1-6.

In an experiment to evaluate the effect of inhaled allylamine on EKGs, young adult Fischer 344 rats (5/sex) were exposed to 100 or 150 ppm for 6 h/day for 10 days over a 3-week-period (Lynch et al. 1983). Allylamine vapor was generated by metering liquid allylamine into the tangential air-feed manifold air stream at the top of the inhalation chamber; the concentration was monitored with an infrared analyzer. The EKGs were obtained prior to and on the day after the last allylamine exposure. Rats were killed and necropsied immediately following their EKGs; premature decedents were refrigerated and necropsied within 12 h of death if possible. During exposure, rats were seen sneezing and tearing, and they kept their eyes closed and their noses buried in their fur. Three of five males and three of five females in the 150-ppm group did not survive the 10-day exposure; all 100-ppm rats survived the 10-day treatment. Body weights

TABLE 1-5 Cardiotoxic Effects in Rats After a Single Allylamine Inhalation Exposure

Exposure Time (h)	Concentration (ppm)	Total No. of Rats Exposed	No. of Rats Killed at Given Time[a]	Lesion	Histologic Heart Changes
0	0	5	All at 14 days	0	Occasional suggestive areas of round-cell infiltration
4	100	8	2 at 4 days	0	Slight perivascular edema; possible cellular infiltrate
			1 death at 5 days	0 ?	One definite myocardial lesion
			2 at 5 days	+	
			3 at 7 days		
8	40	1	Died at 8 h	+	Fibrinoid degenerative thrombus, one decisive vessel change, diffuse cellular infiltrate
14	60	4	1 at 18 h	+	Scattered myofibril fragments with loss of striation
			1 at 2 days	+	Scattered myofibril fragments with loss of striation
				+	
			2 at 8 days		Perivascular edema, cellular infiltration
16	40	20	11 at 8-17 h	0	Occasional suggestive areas of round-cell infiltration, edema of some small vessel walls
			4 at 7 days	0	
			5 at 14 days	0	
20	50	3	1 at <20 h	+	Scattered myofibril fragments with loss of striation
			2 at 8 days	+	
					Widespread endothelial lesion
24	100/60[b] (6 h/18 h)	3	2 at <24 h	+	Scattered myofibril fragments with loss of striation, suggested perivascular lymphocytic cuffing
			1 at 2 days	+	
					Same, more pronounced
32	40	5	All at 3 days	+[c]	Well-established heart lesions in 2/5 rats
48	20	18	2 at 2 days	+	Several small areas of typical "infarcted cardiopathy"
			6 at 4 days	+	
			6 at 7 days	+	Several small areas of typical "infarcted cardiopathy"
			4 at 13 days	0	
					Several small areas of typical "infarcted cardiopathy"

[a]Calculated from the beginning of the exposure period. All animals were killed except as noted.
[b]Exposure was to 100 ppm for 6 h followed by 60 ppm for 18 h.
[c]This field was left blank in the study report but should be as shown here.
Source: Data from Guzman et al. 1961. Reprinted with permission; copyright 1961, American Medical Association.

TABLE 1-6 Allylamine Multiple-Exposure Rat Lethality Studies

Animal	Exposure Description	Concentration (ppm)	Effect	Reference
Long-Evans rats	7 h/day for 50 days (5 days/week)	5	No effect (one outlier)	Hine et al. 1960; Guzman et al. 1961
		10	Lower weight gain	
		20	Fat depletion; heart lesions (1/8)	
		40	Emaciation, heart lesions, pneumonia, 5/15 died (not specified when)	
F-344 rats	6 h/day for 10 days (5 days/week)	100	Eye and nasal irritation, cardiotoxicity, lower body weight (bw)	Lynch et al. 1983
		150	Eye and nasal irritation, cardiotoxicity, lower bw, 6/10 died	
F-344 rats	6 h/day, 5 days/week for ≤24 weeks	4	Lower bw starting at 2 weeks	Lynch et al. 1989
	Killed after 30, 60, 120 days	40	Lower bw; higher heart/bw ratio after 120 days	
	Killed after 30, 60, 120 days	80	Lower bw; higher heart/bw ratio and cardiotoxicity after ≥30 days, 22/50 died	
	Killed after 30, 60, 90 days			

were depressed for the 100- and 150-ppm animals, but they returned to control levels for the 100-ppm rats by the end of exposure. At both 100 and 150 ppm, heart weights and heart/body-weight ratios were increased and liver weights were decreased (statistical significance not specified), although the liver/body-weight ratios were unaffected. All 10 150-ppm rats had gross necrotic ventricular lesions. The EKGs of the survivors (while anesthetized) had an axis shift, complete inversion of the QRS complex, and attenuation of QRS amplitudes. The 100-ppm rats had less severe cardiac lesions and EKG changes.

In a follow-up study, Lynch et al. (1989) assessed cardiac toxicity in male and female F-344 rats (50 rats/group) exposed to 0, 4, or 40 ppm of allylamine for up to 24 weeks (Study I) and 0 or 80 ppm for up to 20 weeks (Study II). Exposure was for 6 h/day, 5 days/week. Rats were weighed every 2 weeks and were killed following 30, 60, or 120 days of exposure in Study I and 30, 60, or 90 days of exposure in Study II, at which time histopathology was performed. Clinical chemistry was evaluated at 30, 90, and 120 days and hematology and electrophysiology when the rats were put to death at 90 and 120 days. No treatment-related effects were seen in hematology or clinical chemistry parameters.

All treated animals had lowered body-weight gains throughout the study (values not given). The heart/body-weight ratio was increased in the 40-ppm rats after 120 days and in the 80-ppm rats at all time points but was accompanied by histopathologic changes (cardiac necrosis and fibrosis) in only the 80-ppm groups (all time points). Some of the 80-ppm rats (22/50) had moderate cardiac necrosis and died before being put to death, although the time of death was not given. Heart electrophysiology (PQ and QT intervals increased) was affected in only the 80-ppm males put to death at 90-days. This study is summarized in Table 1-6. (The description of this study was incomplete; only body weights were reported for 24 weeks for Group I and 20 weeks for Group II; other parameters were reported for only the 30-, 60-, 90-, and/or 120-day periods when rats were killed.)

3.1.2. Mice

During a 10-min inhalation exposure to 1.27 mM/L allylamine (31,035 ppm), 28 of 30 white mice died; the two survivors died within 48 h (Hart 1939). Mice exposed to 1.10 or 1.00 mM/L (26,881 and 24,437 ppm) had mortality rates of 8/30 and 14/30, respectively, after the 10-min treatment; all survivors died by 48 h after exposure. Clinical signs, in order of appearance, were nasooral irritation, ear flushing, irregular respiration, cyanosis, delirium, convulsions, coma, and death. Exposures were in a 5-L bell jar connected to a flowmeter; a flow rate of 750 cc/min was maintained through the jar. No other details of the allylamine concentration analysis were given.

3.2. Nonlethal Toxicity

Inhalation studies in which no lethality occurred were conducted using rats, mice, rabbits, and monkeys. The results are summarized in Table 1-7.

3.2.1. Nonhuman Primates

Three male rhesus monkeys and one female (2.4-3.7 kg) were administered 73 exposures of 40 ppm allylamine for 4 h/day, 5 days/week, and were subsequently examined for cardiac effects (Guzman et al. 1961). Exposure was in a 200-L steel chamber into which allylamine was delivered by a constant-drive syringe and vaporized; the air allylamine concentrations were measured periodically. The airflow in the chamber was not described; however, in another study conducted by the same group in which a 200-L chamber was used, the dynamic airflow ranged from 10 to 15 L/min (Hine et al. 1960). It was not reported whether there were any control animals. EKGs were performed on the monkeys at the beginning and at the end of the experimental period. None of

TABLE 1-7 Multiple-Exposure Nonlethal Animal Studies

Animal	Concentration (ppm)	Exposure Description	Effect	Reference
Long-Evans rats	40	7 h/day for 10 days (5 day/week)	Acute arteriole inflammation, focal muscle bundle necrosis, EKG changes.	Guzman et al. 1961
		7 h/day for 20 days	As for 10 days but more severe; "healing" seen in some areas.	
		7 h/day for 40 days	Fragmentation of muscle bundles, edematous arterioles (non-acute).	
Long-Evans rats Rhesus monkeys Albino rabbits	40	4 h/day for 73 days (5 day/week)	No detectable (gross or microscopic) heart lesions	Guzman et al. 1961
Swiss mice	27	6 h/day for 4-14 days	No histologic changes in nose, trachea, lungs	Zissu 1995

the animals died prematurely, and there were no gross or microscopic heart lesions, alterations in heart/body-weight ratios, or changes in EKGs after the 73 exposures.

3.2.2. Rats

Guzman et al. (1961) conducted an extensive series of both single-exposure and multiple-exposure studies to define the conditions that cause cardiotoxicity in male Long-Evans rats. In the single-exposure study, rats received 20-100 ppm of allylamine for 4-48 h. In the multiple-exposure study the rats received 50 (5 days/week) 7-h exposures to 5-40 ppm allylamine. Since mortality occurred at the highest doses tested in each study, they are described in Section 3.1.1 and summarized in Table 1-5. Guzman et al. also conducted two multiple-exposure experiments in which mortality did not occur; these are described below.

To determine the rate of induction of heart lesions, Guzman et al. subjected groups of 9-11 male Long-Evans rats to 10, 20, or 40 7-h exposures to 40 ppm allylamine (one rat had 17 exposures). Rats were killed immediately after the final exposure for gross and microscopic examination. EKGs were performed on the rats at the beginning and at the end of the experimental period. After 10 exposures, pathologic changes seen in the heart varied from inflammation of the smaller arteriole walls to focal necrosis of large areas of muscle bun-

dles. Similar but more severe changes occurred after 20 exposures, and "stages of healing" were seen in some areas. Heart lesions seen after 40 exposures appeared different: They were not "acute" and consisted of fragmentation of muscle bundles with replacement by loose edematous fibrous tissue, as well as edema in the arteriole outer coat. Abnormal EKGs (mainly elevation of the ST segment) were seen in some of the rats with heart lesions.

In another experiment, Guzman et al. examined species, differences in susceptibility to the cardiotoxic effect of allylamine. Rats (10 males) were exposed to 40 ppm of allylamine for 4 h/day for 73 days (5 days/week). Rabbits and monkeys were similarly treated, as described in the following sections. The prolonged treatment resulted in no detectable gross or microscopic heart lesions or deaths in the rats; other effects (such as irritation) were not addressed.

In an inhalation exposure study for which there were incomplete experimental data (e.g., number of animals exposed, exposure duration labeled as "variable," individual animal results; Research Pathology Associates 1984), F-344 rats exposed to 100 or 150 ppm of allylamine for 5 or 10 days (hours/day not specified) had moderate myocardial necrosis. In another part of the study, nearly all rats of both sexes exposed to 80 ppm for 30, 60, 90, or a "variable" number of days had slight or moderate myocardial necrosis and fibrosis. Thymic atrophy and hepatocellular necrosis were found in two to four animals/sex in the "variable" -days exposure group, although no controls were available for comparison of incidences.

3.2.3. Mice

The RD_{50} (i.e., concentration of allylamine causing a 50% decrease in the breathing rate; Gagnaire et al. 1989) of male OF_1 Swiss mice was determined to be 9 ppm in two oronasal exposure studies. In one study, exposure was for a total of 15 min to 3-12 ppm (Gagnaire et al. 1989), and in the other total exposure was for 60 min to 6.3, 16.4, 23.6, or 43.3 ppm (Gagnaire et al. 1993). Mice were exposed by enclosing the head in a 200-L stainless steel exposure chamber into which allylamine vapor was delivered by bubbling air through the liquid amine. The effect on breathing rate was maximal 10-15 min after exposure in both studies; recovery after the 15-min exposure occurred within 1 min; recovery after the 60-min exposure was slower.

Pulmonary toxicity was analogously assessed in anesthetized, tracheally cannulated (TC) mice exposed to 38, 59, 79, or 205 ppm of allylamine for 120 min and an $RD_{50}TC$ of 157 ppm was determined ($RD_{50}TC$ is the concentration of allylamine causing a 50% decrease in the breathing rate of tracheally cannulated mice; Gagnaire et al. 1993). The maximal decrease in the breathing rate was seen after 15-60 min of exposure; recovery after the 120-min exposure was incomplete at 79 and 205 ppm during the ensuing 30-min observation period. The higher value of the $RD_{50}TC$ compared to the RD_{50} indicated that the respira-

tory toxicity of allylamine was primarily related to its upper-airway irritant effects.

Zissu (1995) exposed male OF_1 Swiss mice by inhalation of 27 ppm allylamine (target concentration based on 3 times the RD_{50}) for 6 h/day for 4, 9, or 14 days. No mortality occurred and no histologic lesions were seen in any part of the nasal passages (respiratory or olfactory epithelium) or in the trachea or lungs. Zissu concluded that respiratory histopathologic changes were not a function of sensory irritation for allylamine.

3.2.4. Rabbits

No gross or microscopic heart lesions were detected in five male albino rabbits exposed 73 times to 40 ppm allylamine for 4 h/day (5 days/week; there were three controls; Guzman et al. 1961). The animals' heart/body-weight ratios were normal, there were no mortalities, and no clinical observations (e.g., irritation) were reported. Exposure was in a 200-L steel chamber into which allylamine was delivered by a constant-drive syringe and vaporized; the chamber concentrations were measured periodically.

The method of Draize was used to evaluate the degree of eye irritation in the rabbits' eyes to which 0.05 mL of undiluted compound (38 mg) was applied, followed by a 20-second (s) wash with distilled water (Hine et al. 1960). Readings were made after 1, 24, 48, and 72 h; allylamine proved to be too irritating to the rabbits' eyes to permit differential measurements.

3.3. Neurotoxicity

No studies were located that assessed the neurotoxicity of allylamine exposure on animals.

3.4. Developmental/Reproductive Toxicity

No studies were located that assessed in vivo effects of allylamine exposure on animals. The embryotoxic potential of allylamine was estimated using the in vitro Chick Embryotoxicity Screening Test (CHEST) and fertilized eggs from White Leghorn fowl (Jelinek et al. 1985). The beginning of the embryotoxicity range on day 1.5 (defined as a shortening of the embryo trunk length after a 24-h exposure) was between 3 and 30 µg/embryo (i.e., highest ineffective concentration to lowest effective concentration). Application of 3-30 µg allylamine to 2- to 4-day-old embryos until day 8 did not result in body malformations; the mortality rate was 48%.

3.5. Genotoxicity

Allylamine was not mutagenic in the *Salmonella*/microsome preincubation assay when tested at concentrations of 0, 1, 3, 10, 33, 100, 333, 1,000, or 3,333 µg/plate using strains TA98, TA100, TA1535, and TA1537. Testing was in the presence or absence of Aroclor-induced rat or hamster liver S9 (Zeiger et al. 1987). Negative results were also obtained by Lijinsky and Andrews (1980) with the *Salmonella*/microsome preincubation assay using strains TA98, TA100, TA1535, TA1537, and TA1538 (1-1,000 µg/plate) and by McMahon et al. (1979) using 10 *Salmonella* and *E. coli* tester strains and agar plates with gradients of 0.1-1,000 µg/mL allylamine, with or without Aroclor-induced rat or hamster liver S9.

3.6. Carcinogenicity

No studies on the carcinogenicity of allylamine in animals were located. Neither EPA nor IARC has classified allylamine as to carcinogenicity. The allylamine metabolite acrolein EPA weight-of-evidence characterization, under the 1999 Draft Revised Guidelines for Carcinogen Risk Assessment, is that the potential carcinogenicity of acrolein cannot be determined because the existing "data are inadequate for an assessment of human carcinogenic potential for either the oral or inhalation route of exposure" (EPA 2004).

3.7. Summary

Allylamine inhalation caused cardiotoxicity in rats in several single- and multiple-exposure studies, which, unfortunately, did not record any accompanying sensory irritation. Cardiovascular lesions were not found following inhalation exposure in species other than rats but were induced in a variety of animal species by the oral, parenteral, inhalation, and intravenous routes (Boor et al. 1979; Boor and Hysmith 1987). The single-exposure data from Guzman et al. (1961) suggest that exposure concentration is a relatively greater factor than time in inducing cardiotoxicity. For example, 0/20 rats developed lesions from exposure to 40 ppm for 16 h, but 4/4 had cardiac lesions from exposure to 60 ppm for 14 h. Consistent with this result, the concentration-time relationship as defined by the ten Berge et al. (1986) equation $C^n \times t = k$ yields 1.7 as the exponent n using this study's data.

No in vivo developmental, reproductive, or carcinogenicity studies were located. Allylamine was not mutagenic in any conducted *Salmonella*/microsome preincubation assays.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No information was located regarding allylamine metabolism after inhalation exposure, but some animal toxicokinetic data were found for oral and intravenous administration.

In a toxicokinetics study conducted by Boor (1985), allylamine was absorbed by male Sprague-Dawley rats within minutes of gavage administration of 150 mg/kg radiolabeled allylamine. Radioactivity was found in numerous organs, the greatest amount being in the aorta and coronary arteries, where levels were about 5- to 10-fold greater than in most other organs, including the myocardium. A fraction (30-40%) of the animals, however, had counts in the aorta that were 10- to 20-fold lower than those of the majority of the animals at all time points. The liver and kidney had the next highest amounts of radioactivity. Radioactivity was quickly eliminated: Liver counts dropped to low levels by 45 min and the half-life was $\leq$1 h in other organs, including the adrenals, aorta, coronaries, heart, kidneys, and lung. Half-lives were not determined for some organs due to low and irregular levels of label in the postabsorptive phase (brain, blood, liver, pancreas, skeletal muscle, spleen, and fat). About 60% of the given radioactivity was excreted in the urine by 24 h, after which time there was little additional excretion, possibly due to retention in blood and other organs. No radioactivity was found in the feces at any time (up to 96 h after gavage).

Orally administered allylamine was shown to be metabolized to acrolein and hydrogen peroxide, which may both be responsible for the observed toxic effects (Boor et al. 1987). The metabolite acrolein has been detected in both rat and human aorta, myocardium, and liver homogenates incubated with allylamine (Boor and Nelson 1982). The acrolein is believed to be subsequently conjugated with glutathione to form 3-hydroxypropylmercapturic acid, which was the sole metabolite in the urine of Sprague-Dawley rats collected 24 and 48 h after gavage with 150 mg/kg radiolabeled allylamine (2 μCi/kg ^{14}C-labeled; Boor et al. 1987). Male Sprague-Dawley rats given 5-150 mg/kg of allylamine by gavage excreted 44-48% of the given dose as 3-hydroxypropylmercapturic acid over 0-24 h, and only 3% during 24-48 h, whereas 75% of a given dose of acrolein (13 mg/kg) was metabolized to 3-hydroxypropylmercapturic acid after 24 h (Sanduja et al. 1989). Consistent with glutathione involvement in allylamine metabolism, a depletion of reduced glutathione in the aorta, blood, and lungs was shown to occur and be maximal 1-6 h after gavage treatment with allylamine (Awasthi and Boor 1994).

It is proposed that the metabolism of allylamine to acrolein and hydrogen peroxide occurs via benzylamine oxidase, which is a form of amine oxidase with high activity in vascular tissue, especially the aorta (Boor et al. 1987). Consistent with this, the benzylamine oxidase inhibitor, semicarbazide, protected myocytes from toxic effects of allylamine in vitro, whereas the monoamine oxidase inhibitors clorgyline and pargyline were ineffective (Ramos et al. 1988).

4.2. Mechanism of Toxicity

Allylamine has been shown to cause severe myocardial damage and vascular smooth muscle lesions in a variety of animal species upon acute exposure (Boor and Hysmith 1987). It has been used to cause lesions (proliferation of smooth muscle cells and fibrosis) that mimic human atherosclerosis by the oral, parenteral, inhalation, and intravenous routes (Boor et al. 1979; Boor and Hysmith 1987). Allylamine cardiovascular toxicity was shown in many mammalian species to be dependent on metabolism of allylamine by semicarbazide-sensitive amine oxidase (SSAO) to acrolein, hydrogen peroxide, and ammonia (Lyles 1996). SSAO is found in many tissues in mammals. Its activity in human and rat tissue homogenates was shown to be the highest in the aorta, followed by the lungs and digestive system, but very little activity was found in cardiac endothelial cells or myocytes (Lewinsohn et al. 1978; Lyles 1996). (SSAO activity was measured as nanomoles of benzylamine hydrochloride metabolized/ milligrams of protein/30 min.)

Mechanisms proposed for allylamine-induced cardiovascular toxicity implicate the metabolite acrolein as the major toxicant. One mechanism proposes that the cardiac and vascular damage is caused by lipid peroxidation by acrolein, modulation of the cellular glutathione status, and damage of the mitochondrial membranes by acrolein (or another unknown metabolite) and hydrogen peroxide (Awasthi and Boor 1994; Ramos et al. 1994). Consistent with mitochondrial membrane injury, 20 min after intravenous injection of allylamine, aortic mitochondrial malate dehydrogenase activity decreased, whereas cytosolic malate dehydrogenase activity increased (Hysmith and Boor 1985). Examination of Sprague-Dawley rats 1, 3, and 5 h after gavage with 150 mg of allylamine/kg showed a marked depletion in free-sulfhydryl (SH) content in the aorta, epicardium, and endocardium; a marked increase in the formation of thiobarbiturate-reactive substance by aortic mitochondria; and increased capacity to generate hydroxyl radicals (deoxyribose degradation method) in the aorta (Awasthi and Boor 1994).

More recently, Conklin et al. (2001) proposed a two-step model for allylamine-induced cardiotoxicity: (1) metabolism of allylamine by SSAO to acrolein, hydrogen peroxide, and ammonia and (2) injury of the coronary artery vascular smooth muscle cells by acrolein and possibly the other metabolites, which causes its hypercontraction and vasospasm and results in ischemia and subendocardial necrosis. This model was supported by a study in which isolated rings of rat coronary artery and thoracic aorta incubated with 100-1,000 μM allylamine or acrolein exhibited increased basal tension and vasospasm (increased contraction and slow-wave vasomotion) and irreversibly inhibited vessel contractility (Conklin et al. 2001). There was no effect, however, on endothelium-dependent acetylcholine-induced relaxation of either vessel. Pretreatment with the SSAO inhibitor semicarbazide reduced or eliminated most effects in both tissues. Effects for the two compounds were similar, with some qualitative and quantitative differences. Conklin et al. also showed that SSAO activity was

comparable in human homogenized coronary arteries and aorta, and both were inhibited by semicarbazide.

4.3. Structure-Activity Relationships

The structurally related secondary amines di(β-methyl-allyl)amine, diallylamine, and β-methylallylamine caused a greater incidence of mortality than allylamine (on a molar basis) during a 10-min exposure of white mice (Hart 1939). The mice exhibited the same symptoms as those produced by allylamine during the 10 min (e.g., nasooral irritation followed by vasodilation of the extremities, arrhythmic respiration, cyanosis, convulsions, coma, and death). Inhalation of allyl chloride and allyl alcohol generally appeared to have effects similar to that of allylamine.

A comparison of the LC_{50} values derived by Hine et al. (1960) indicated that allylamine was about twice as toxic as triallylamine and about 10 times as toxic as diallylamine. Saturation of the double bond decreased toxicity, as *n*-propylamine was considerably less toxic in both acute and chronic vapor exposure than allylamine.

The concentration of allylamine that lowered the breathing rate of male OF_1 Swiss mice by 50% after 15 min of exposure (the RD_{50}),—9 ppm—was comparable to the RD_{50} values of other allylic respiratory tract irritants: diallylamine (4 ppm), allyl glycidyl ether (5.7 ppm), allyl acetate (2.9 ppm), allyl alcohol (3.9 ppm), allyl ether (5 ppm), and acrolein (2.9 ppm), although it was much lower than that of other nonallylic amines (RD_{50} values of 51-202 ppm; Gagnaire et al. 1989).

4.4. Other Relevant Information

4.4.1. Species Variability

Allylamine has been used experimentally to induce and study cardiovascular lesions in rats, dogs, calves, monkeys, and rabbits when administered intravenously, intradermally, orally, and/or by intraarterial injection (Boor et al. 1979; Boor and Hysmith 1987). The lesions were shown to be dependent on the metabolism of allylamine by SSAO, of which tissue levels were greatest in the aorta and coronary arteries (Lewinsohn et al. 1978; Conklin et al. 2001; Boor and Hysmith 1987; Lyles 1996). SSAO specificity for allylamine as a substrate has not been determined, and Lyles (1996) has shown that substrate specificity of plasma and tissue SSAO varied considerably among species for a number of aromatic and aliphatic amines. Inhalation exposure was also capable of inducing cardiovascular lesions, although this was shown only in rats. The data thus suggest that a similar mechanism is responsible for cardiovascular injury in many

mammalian species (also humans), but the susceptibility of different species by the inhalation route is unknown.

Data were scant regarding species variability from acute lethal exposures. Although the oral lethal dose in 50% (LD_{50}) of the rats and mice was within a factor of 2 (Boor and Hysmith 1987), LC_{50} was determined only for rats.

4.4.2. Susceptible Populations

Two populations exist that may be susceptible to allylamine toxicity due to their increased levels of plasma SSAO activity. This enzyme metabolizes allylamine to acrolein, hydrogen peroxide, and ammonia, which was shown to be a key step in allylamine-induced cardiovascular damage in several animal studies. Elevated levels of SSAO were found in patients with insulin-dependent diabetes mellitus (Boomsma et al. 1995) and congestive heart failure (Boomsma et al. 1997). SSAO levels increased with the severity of the disease, and patients with both maladies had higher SSAO levels than those with either malady alone. Since endothelial dysfunction is present in both diseases, Boomsma et al. speculated that SSAO may be involved in the pathogenesis of vascular endothelial damage.

4.4.3. Concentration-Exposure Duration Relationship

The AEGL-1 was based on mild irritation experienced by human volunteers from exposure to 2.5 ppm of allylamine for 5 min (Hine et al. 1960). No concentration-time scaling was performed because mild irritant effects do not generally vary greatly with time and the same AEGL-1 value was used for 10 min to 8 h.

The 10, 30, and 60-min AEGL-2 values were based on human exposure to 10 ppm for 5 min, which caused slight or moderate eye and nose irritation, pulmonary discomfort, and severe olfactory cognition and which was the NOAEL for "extreme or intolerable" irritation (Hine et al. 1960). The same AEGL-2 value was adopted for 10-60 min because the degree of irritation from exposure for 5 min was not expected to increase over a 1-h period beyond the scope of AEGL-2. The 4- and 8-h AEGL-2 values were derived from the Guzman et al. (1961) rat cardiotoxicity study, which was also used to determine the exponent n = 1.7 in ten Berge et al. (1986) concentration-time relationship equation $C^n \times t = k$. In the Guzman et al. study, male Long-Evans rats were exposed to 20-100 ppm of allylamine for 4-48 h (shown in Table 1-5), and the responses designated as "+" for histologic heart changes were used in the regression analysis to obtain n. An outlier that died after an 8-h exposure to 40 ppm was excluded (a very similar value is obtained for n if this outlier is included, although R^2 decreases from 0.89 to 0.86). The regression output and graph obtained from the Guzman et al. data are shown in Appendix B.

The Guzman et al. rat study would have yielded 4.1 ppm for the 1-h AEGL-2. The same value would be appropriate for 10 and 30 min because scaling from 16 h to <1 h involves unacceptably high inherent uncertainty (analogous to scaling from ≥4 h to 10 min) and the 1-h value would be adopted to be protective of human health. However, the human irritation study (Hine et al. 1960) yielded AEGL-2 values of 3.3 ppm for 10-60 min, providing a more sensitive end point for this time period than the rat cardiotoxicity study.

For allylamine AEGL-3 derivation, the exponent n was determined by regression analysis to be 0.85 (rounded from 0.8458), based on the rat LC_{50} study of Hine et al. (1960; shown in Table 1-4). In this study, male Long-Evans rats were exposed for 1, 4, or 8 h, each time to four different concentrations of allylamine (air allylamine concentrations were calculated and not measured). Rats that died from exposure had stomachs distended with air, fluid-filled lungs, alveolar hemorrhage, and pulmonary edema. The regression output graph obtained from the Hine et al. data is shown in Appendix B.

4.4.4. Concurrent Exposure Issues

Inhalation exposure (whole-body) can also result in inadvertent exposure of the skin, which can potentially add significantly to allylamine toxicity. Several studies indicate that allylamine is absorbed through the skin and can cause acute lethality. Application of 0.05 or 0.10 mL allylamine (39 and 76 mg, respectively, based on a density of 0.76 g/mL) on a 1-cm^2 piece of toweling to the shaved abdominal skin of albino rats caused skin necrosis and death after 5-18 h (animal weight not given; Hart 1939). Application of 0.025 mL (19 mg) of allylamine caused slight skin irritation. In a skin corrosivity study conducted by Springborn Life Sciences (1989), one of three New Zealand female albino rabbits died from 3 min of skin exposure to 0.5 mL (about 176 mg/kg) allylamine applied on a gauze patch. The animal died between 1 and 24 h after exposure and had dark red lungs on necropsy. The two surviving rabbits had labored breathing and decreased activity as well as edema and hair loss directly below the area of the test article application. All three rabbits had skin corrosion (necrosis) immediately after the 3-min exposure, and eschar formation was evident from 24 h through the 7-day observation period.

Hine et al. (1960) determined a dermal LD_{50} of 35 mg/kg from an occluded exposure of New Zealand male rabbits for several hours to 13, 25, 50, or 100 mg of allylamine/kg (using undiluted allylamine, 0.76 g/mL). No deaths resulted from the application of 13 or 25 mg/kg of allylamine (observation period unclear, perhaps several weeks); 3/3 rabbits died 3-24 h after treatment with 50 mg allylamine/kg, and 3/3 died 3-4 h after application of 100 mg. There was considerable local erythema and eschar formation at the application site. Rabbits that died usually had fluid in the pleural cavity and dilation of the gastroenteric veins. All had severely congested lungs. Liver lesions were seen in one rabbit that died 8 h after exposure and in one rabbit killed 10 days after exposure.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

Two human studies were considered potentially useful for AEGL-1 derivation. Hine et al. (1960) conducted a quantitative experiment in which 35 volunteers were exposed to 2.5, 5, or 10 ppm of allylamine for 5 min and to 14 ppm for <1 min. All subjects detected the odor, and there were dose-related increases in the incidence of slight or moderate eye irritation (21%, 15%, 50%), nose irritation (50%, 54%, 100%), and pulmonary discomfort (29%, 46%, 50%) at 2.5, 5, and 10 ppm, respectively. Those exposed briefly to 14 ppm reported it to be intolerable. CNS effects (i.e., slight headache and nausea) were reported but were not dose related. In the other human study, stationary air samplings at various areas of a chemical manufacturing plant showed ambient concentrations of allylamine ranging from <0.1 to 0.2 ppm, as well as di- and tri-allylamine at roughly similar air concentrations (each <0.1 to 0.6 ppm; Shell Oil Co. 1992). Worker exposure to these concentrations was for up to 4 h/day over an undefined period of days/years, but workers were not examined when these air concentrations were measured. Workers experienced chest tightness/congestion/pain, sore throat, runny nose, nausea, vomiting, red eyeballs, tightness in the jaw and behind the ears, and hurting teeth only when spills or leaks occurred, at which time allylamine concentrations were not measured.

5.2. Summary of Animal Data Relevant to AEGL-1

There were no short-term animal studies appropriate for an AEGL-1 determination. In many studies the focus was on a cardiotoxicity end point, and observations regarding irritation or other reversible effects were not reported (e.g., Guzman et al. 1961; see Section 6.2).

5.3. Derivation of AEGL-1

AEGL-1 values were based on the Hine et al. (1960) a study in which 35 young adult human volunteers were exposed for 5 min to 2.5, 5, or 10 ppm of allylamine, which caused dose-related increases in the incidence of slight or moderate eye irritation, nose irritation, and pulmonary discomfort but not CNS effects. The same AEGL-1 value was used for 10 min to 8 h because mild sensory irritation or discomfort does not generally vary greatly with time. The AEGL-1 point of departure was 1.25 ppm, which was obtained by applying a modifying factor of 2 to 2.5 ppm, which was the lowest effect level. The MF was used because exposure was for only 5 min and it is unclear whether “moderate” irritation or discomfort is comparable to “notable” irritation or discomfort, which exceeds the scope of AEGL-1. An intraspecies uncertainty factor of

3 was applied because allylamine acts as a contact irritant, and the severity of its effects is not expected to vary greatly among humans. Also, use of a greater uncertainty factor would yield a concentration below 0.2 ppm, which was a no-effect level for workers exposed for up to 4 h (Shell Oil Co. 1992). The derived AEGL-1 value of 0.42 ppm for 10 min to 8 h is also consistent with two mouse respiratory irritation studies (Gagnaire et al. 1989, 1993), from which it is predicted that exposure for a few hours to 0.9 ppm would cause sensory irritation in humans but that 0.09 ppm would not (Alarie 1981). According to Alarie, exposure to 0.1 of the RD_{50} (i.e., 0.9 ppm) for several hours to days should result in some sensory irritation in humans, whereas $0.01 \times RD_{50}$ (0.09 ppm) should cause no sensory irritation. The results are summarized in Table 1-8.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

The only human study useful for AEGL-2 derivation is that of Hine et al. (1960), which was used to derive AEGL-1 values. Human volunteers exposed for 5 min to 2.5-10 ppm allylamine had slight to moderate eye and nose irritation and pulmonary discomfort, whereas at the next higher concentration tested, ~14 ppm, exposure was "intolerable" (extreme pulmonary discomfort and irritation of the eyes, nose, and throat) and was almost immediately terminated.

6.2. Summary of Animal Data Relevant to AEGL-2

The only relevant single-exposure study evaluated male Long-Evans rats exposed to 20-100 ppm for 4-48 h and examined histologically 8 h to 14 days after the start of exposure (Guzman et al. 1961). Heart lesions included scattered myofibril fragments with loss of striation, perivascular edema, and cellular infiltration.

AEGL-2 values can also be derived from two multiple-exposure rat studies conducted by Guzman et al. (1961), using a single exposure as a conservative estimate of exposure duration. Male Long-Evans rats given 50 7-h exposures to 0, 5, 10, 20, or 40 ppm of allylamine (5 days/week) had no effects at 5 ppm; lowered weight gains at 10 ppm; heart and blood vessel lesions and depletion of body fat at 20 ppm; and cardiotoxicity, lung congestion, emaciation, and

TABLE 1-8 AEGL-1 Values for Allylamine

10 min	30 min	1 h	4 h	8 h
0.42 ppm ($0.98\ mg/m^3$)	0.42 ppm ($0.98\ mg/m^3$)	0.42 ppm ($0.98\ mg/m^3$)	0.42 ppm ($0.98\ mg/m^3$)	0.42 ppm ($0.98\ mg/m^3$)

5/15 mortality at 40 ppm (Hine et al. 1960; Guzman et al. 1961). AEGL-2 values could be derived using a single exposure to 10 ppm (20 ppm would be a NOEL for lethality). In a second experiment, rats were examined after 10, 20, or 40 7-h exposures to 40 ppm, revealing extensive heart and blood vessel histologic changes and altered EKGs after 10 exposures (Guzman et al. 1961); a single 7-h exposure to 40 ppm could be used to derive AEGL-2 values.

6.3. Derivation of AEGL-2

AEGL-2 values were based on two studies: the 10-, 30-, and 60-min values were based on sensory irritation in human volunteers (Hine et al. 1960), and the 4- and 8-h values were based on cardiotoxicity in rats (Guzman et al. 1961) because cardiotoxicity was a more sensitive end point than sensory irritation when exposure was for 4 or 8 h.

The 10-, 30-, and 60-min AEGLs were developed from the Hine et al. human 5-min exposure study that was used to derive AEGL-1 values, but using 10 ppm as the point of departure. Ten ppm caused slight or moderate eye and nose irritation and pulmonary discomfort and was the NOAEL for "intolerable" irritation that occurred at 14 ppm. The same value was adopted for 10-60 min because the degree of irritation or discomfort resulting from exposure to 10 ppm was not expected to increase over a 1-h period beyond the scope of AEGL-2. An intraspecies uncertainty factor of 3 was used because allylamine is acting as a contact irritant, and the severity of its effects is not expected to vary greatly among humans. The resulting AEGL-2 values of 3.3 ppm were not adopted for 4 or 8 h, however, because a rat study (Guzman et al. 1961) indicated that exposure to 3.3 ppm for 4 or 8 h may cause cardiotoxicity. In the latter study, exposure to 40 ppm for 16 h was a NOAEL for cardiovascular lesions, which were seen from exposure to 60 ppm for 14 h (myofibril fragment damage, perivascular edema, and cellular infiltration). Time-concentration scaling was performed using the ten Berge et al. (1986) equation $C^n \times t = k$, where $n = 1.7$ was calculated from a linear regression of the Guzman et al. (1961) rat cardiotoxicity data. An interspecies uncertainty factor of 5 was applied because the mechanism of toxicity is similar among several mammalian species (and humans), but differences in susceptibility are unknown, and an uncertainty factor of 3 yields values approaching the NOEL for lethality from pulmonary lesions for a 4- or an 8-h exposure. An intraspecies uncertainty factor of 10 was used because the variability of the cardiotoxic response to allylamine among humans is undefined, and potentially sensitive populations exist (diabetics, persons with congestive heart failure). This yields 4- and 8-h AEGLs of 1.8 and 1.2 ppm, respectively, indicating that for these longer exposure durations, cardiotoxicity is a more sensitive end point than eye and respiratory irritation. The AEGL-2 values for allylamine are summarized in Table 1-9; the calculations are detailed in Appendix A.

TABLE 1-9 AEGL-2 Values for Allylamine

10 min	30 min	1 h	4 h	8 h
3.3 ppm (7.7 mg/m^3)	3.3 ppm (7.7 mg/m^3)	3.3 ppm (7.7 mg/m^3)	1.8 ppm (4.2 mg/m^3)	1.2 ppm (2.8 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

Although it was noted that acute allylamine exposure may lead to death (HSDB 2003), no quantitative human data were located for AEGL-3 derivation.

7.2. Summary of Animal Data Relevant to AEGL-3

There were two single-exposure rat studies and one multiple-exposure rat study that were considered for AEGL-3 derivation. In one single-exposure study, Long-Evans rats were exposed for 1, 4, or 8 h to determine the LC_{50} values for allylamine (Hine et al. 1960). Rats dying from exposure had stomachs distended with air, fluid-filled lungs, alveolar hemorrhage, and pulmonary edema. In a single-exposure study conducted by Guzman et al. (1961), male Long-Evans rats were administered 20-100 ppm for 4-48 h, and were examined histologically 8 h to 14 days after the start of dosing. One rat (of eight tested) died after exposure to 100 ppm for 4 h and had cardiovascular lesions.

In a multiple-exposure study conducted by Lynch et al. (1983), Fischer 344 rats (5/sex) exposed to 100 or 150 ppm of allylamine for 6 h/day for 10 days all survived exposure to 100 ppm, but 3/5 males and 3/5 females died at 150 ppm. Both dose groups had increased heart weights and heart lesions, and the 150-ppm rats had altered EKGs; a single 6-h exposure to 100 ppm could be considered a NOEL for lethality.

7.3. Derivation of AEGL-3

The Hine et al. (1960) rat LC_{50} study was used to derive AEGL-3 values. Rats that died had stomachs distended with air, fluid-filled lungs, alveolar hemorrhage, and pulmonary edema. The 1-h, 4-h, and 8-h AEGLs were obtained directly from the 1-h, 4-h, and 8-h LC_{01} values (533.2, 104.1, and 69.2 ppm, respectively) calculated by probit analysis from the mortality data. The 10-min and 30-min AEGLs were derived from the 1-h LC_{01} using the relationship $C^n \times t = k$, where $n = 0.85$ was calculated from this study LC_{50} data. An uncertainty factor of 30 was applied: 10 to account for interspecies variability (lack of acute toxicity studies from other species with AEGL-3 level end points) and 3 for hu-

man variability [the steep dose-response (~2-fold increase in concentration caused mortality to increase from 0 to 100%) indicates that the NOEL for lethality due to direct destruction of lung tissue is not likely to vary greatly among humans]. The Hine et al. study had a high level of confidence because all of the three LC_{01} values were obtained from the mortality data of 20 animals (four concentrations for each exposure time, five rats at each concentration), and extrapolation was only required for the 10- and 30-min time points. The derived AEGL-3 values are shown in Table 1-10; calculations are detailed in Appendix A.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

A summary of the AEGL values for allylamine and their relationship to one another is shown in Table 1-11. Extrapolation across time was performed by exponential scaling (ten Berge et al. 1986) using the relationship $C^n \times t = k$, where n = 1.7 for 4- and 8-h AEGL-2 derivations and n = 0.85 was used for AEGL-3 derivation. Concentration-time scaling was not performed for developing AEGL-1 values or the 10 to 60 min AEGL-2 values.

AEGL-1 values were based on a study in which 35 young adult human volunteers were exposed for 5 min to 2.5, 5, or 10 ppm of allylamine (Hine et al. 1960). A group was also exposed briefly to 14 ppm, which was reported as intolerable, and exposure was almost immediately terminated. All subjects detected the odor of allylamine, and there were dose-related increases in the incidence of slight or moderate eye irritation (21%, 15%, 50%), nose irritation

TABLE 1-10 AEGL-3 Values for Allylamine

10 min	30 min	1 h	4 h	8 h
150 ppm ($350\ mg/m^3$)	40 ppm ($93\ mg/m^3$)	18 ppm ($42\ mg/m^3$)	3.5 ppm ($8.2\ mg/m^3$)	2.3 ppm ($5.4\ mg/m^3$)

TABLE 1-11 Summary of AEGL Values for Allylamine

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	0.42 ppm ($0.98\ mg/m^3$)	0.42 ppm ($0.98\ mg/m^3$)	0.42 ppm ($0.98\ mg/m^3$)	0.42 ppm ($0.98\ mg/m^3$)	0.42 ppm ($0.98\ mg/m^3$)
AEGL-2 (disabling)	3.3 ppm ($7.7\ mg/m^3$)	3.3 ppm ($7.7\ mg/m^3$)	3.3 ppm ($7.7\ mg/m^3$)	1.8 ppm ($4.2\ mg/m^3$)	1.2 ppm ($2.8\ mg/m^3$)
AEGL-3 (lethal)	150 ppm ($350\ mg/m^3$)	40 ppm ($93\ mg/m^3$)	18 ppm ($42\ mg/m^3$)	3.5 ppm ($8.2\ mg/m^3$)	2.3 ppm ($5.4\ mg/m^3$)

(50%, 54%, 100%), and pulmonary discomfort (29%, 46%, 50%) at 2.5, 5, and 10 ppm, respectively. The incidence of CNS effects was not dose related. The same AEGL-1 value was used for 10 min to 8 h because mild sensory irritation or discomfort does not generally vary greatly with time. The AEGL-1 point of departure was 1.25 ppm, which was obtained by applying a modifying factor of 2-2.5 ppm, which was the lowest effect level. The MF was used because exposure was for only 5 min and it is unclear whether "moderate" irritation or discomfort is comparable to "notable" irritation or discomfort, which exceeds the scope of AEGL-1. An intraspecies uncertainty factor of 3 was applied because allylamine acts as a contact irritant, and the severity of its effects is not expected to vary greatly among humans. Also, use of a greater uncertainty factor would yield a concentration below 0.2 ppm, which was a no-effect level for workers exposed for up to 4 h (Shell Oil Co. 1992). The derived AEGL-1 value of 0.42 ppm for 10 min to 8 h is also consistent with two mouse respiratory irritation studies (Gagnaire et al. 1989, 1993), from which it is predicted that exposure for a few hours to 0.9 ppm would cause sensory irritation in humans but that 0.09 ppm would not (Alarie 1981).

AEGL-2 values were based on two studies. The 10-, 30-, and 60-min AEGLs were developed from the Hine et al. (1960) human 5-min exposure study that was used to derive AEGL-1 values, but using 10 ppm as the point of departure. Ten ppm caused slight or moderate eye and nose irritation and pulmonary discomfort and was the NOAEL for "intolerable" irritation that occurred at 14 ppm. The same value was adopted for 10-60 min because the degree of irritation or discomfort resulting from exposure to 10 ppm was not expected to increase over a 1-h period beyond the scope of AEGL-2. An intraspecies uncertainty factor of 3 was used because allylamine acts as a contact irritant, and the severity of its effects is not expected to vary greatly among humans. The resulting AEGL-2 values of 3.3 ppm were not adopted for 4 or 8 h, however, because a rat study (Guzman et al. 1961) indicated that exposure to 3.3 ppm for 4 or 8 h may cause cardiotoxicity. In the latter study, exposure to 40 ppm for 16 h was a NOAEL for cardiovascular lesions, which were seen from exposure to 60 ppm for 14 h (myofibril fragment damage, perivascular edema, and cellular infiltration). Time-concentration scaling was performed using the ten Berge et al. (1986) equation $C^n \times t = k$, where $n = 1.7$ was calculated from a linear regression of the Guzman et al. rat cardiotoxicity data. An interspecies uncertainty factor of 5 was applied because the mechanism of toxicity is similar among several mammalian species (and humans), but differences in susceptibility are unknown, and an uncertainty factor of 3 yields values approaching the NOEL for lethality from pulmonary lesions for a 4- or an 8-h exposure. An intraspecies uncertainty factor of 10 was used because the variability of the cardiotoxic response to allylamine among humans is undefined, and potentially sensitive populations exist (diabetics, persons with congestive heart failure). This yields 4- and 8-h AEGLs of 1.8 and 1.2 ppm, respectively, indicating that for these longer exposure durations, cardiotoxicity is a more sensitive end point than eye and respiratory irritation.

AEGL-3 values were derived from a rat inhalation LC_{50} study in which exposures were for 1, 4, or 8 h (Hine et al. 1960). All treated rats showed signs of eye and respiratory tract irritation, and some had lacrimation and red nasal discharge. Rats that died had stomachs distended with air, fluid-filled lungs, alveolar hemorrhage, and pulmonary edema. The NOEL for lethality, as represented by LC_{01} values calculated using probit analysis, was the AEGL-3 toxicity end point. The 1-h, 4-h, and 8-h AEGLs were obtained using the respective LC_{01} values. The 10-min and 30-min AEGLs were derived from the 1-h LC_{01} using the relationship $C^n \times t = k$, where $n = 0.85$ was calculated from this study's LC_{50} data. An uncertainty factor of 30 was applied: 10 to account for interspecies variability (lack of acute toxicity studies from other species with AEGL-3 level end points) and 3 for human variability [the steep dose-response (~2-fold increase in concentration caused mortality to increase from 0 to 100%) indicates that the NOEL for lethality due to direct destruction of lung tissue is not likely to vary greatly among humans].

8.2. Comparison with Other Standards and Guidelines

The existing standards and guidelines for allylamine are shown in Table 1-12. There are currently no established U.S. standards for exposure to allylamine. In a preliminary criteria document that has not been accepted, the National Institute for Occupational Safety and Health recommended an occupational exposure limit of 0.6 ppm as the ceiling limit for any 15-min period in a 10-h work shift (NIOSH 1979; cited in Boor and Hysmith 1987); this document is out of print and was not available for use in the present AEGL report). In the former Soviet Union the maximum allowed daily (8-h) concentration in work room air was 0.5 mg/m^3 (0.2 ppm; ILO-CIS 1991).

TABLE 1-12 Extant Standards and Guidelines for Allylamine (Values in ppm)

Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	0.42	0.42	0.42	0.42	0.42
AEGL-2	3.3	3.3	3.3	1.8	1.2
AEGL-3	150	40	18	3.5	2.3
LLV (Sweden)[a]					2
STV (Sweden)[b]	6 (15 min)				

[a]LLV (level limit value), Swedish Occupational Exposure Limit Values, by Ordinance of the Swedish National Board of Occupational Safety and Health, adopted July 28, 2000; defined analogous to the ACGIH TLV-TWA.
[b]STV (short-term value), Swedish Occupational Exposure Limit Values, by Ordinance of the Swedish National Board of Occupational Safety and Health, adopted July 28, 2000; defined as a recommended value consisting of a time-weighted average for exposure during a reference period of 15 min.

Guzman et al. (1961) recommended that under normal operating circumstances air allylamine concentrations should not be greater than 5 ppm, presumably based on examination of operators working with allylamine and on results obtained in an earlier study where humans were exposed to 2.5-14 ppm of allylamine for 5 min (Hine et al. 1960).

Gagnaire et al. (1989, 1993) derived an RD_{50} value of 9 ppm for allylamine (concentration in air causing a 50% reduction in the breathing rate of mice from a 15-min inhalation exposure) and based on $0.1 \times RD_{50}$, proposed <1 ppm as the highest permitted industrial exposure. At this concentration, humans are expected to experience slight discomfort; $0.01 \times RD_{50}$ would be expected to produce no sensory irritation; $0.03 \times RD_{50}$ (the geometric mean of 0.1 and 0.01), that is, 0.27 ppm, is suggested to be a convenient Threshold Limit Value (Gagnaire et al. 1989).

8.3. Data Adequacy and Research Needs

The data available for AEGL-1 derivation were adequate. Two human exposure studies were available with consistent results, and the developed AEGL values were supported by a mouse RD_{50} study. An odor threshold was not definitively established to confirm that the 0.42-ppm concentration that was derived for AEGL-1 would be detectable by humans.

The database for AEGL-2 and AEGL-3 was moderate. An AEGL-2 data gap was the lack of acute exposure studies in which cardiotoxicity occurred with animals other than rats. Although there were data indicating that the mechanism of allylamine toxicity was similar among mammals and between rats and humans, there was no information regarding the relative species susceptibilities. There were no AEGL-3 level end point acute toxicity studies with species other than rats, and further studies are needed. The key study for AEGL-3 derivation was based on calculated air allylamine concentrations, and it was not stated whether these were confirmed experimentally. This study, however, was well conducted.

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APPENDIX A

Derivation of AEGL-1 Values

Key study:	Hine et al. (1960). Thirty five young adult human volunteers were exposed for 5 min to 2.5, 5, or 10 ppm of allylamine (10-14/concentration; sex and age not specified). A group was also exposed briefly to 14 ppm, which was reported as intolerable, and exposure was almost immediately terminated. All subjects detected the odor of allylamine, and there were dose-related increases in the incidence of slight or moderate eye irritation (21%, 15%, 50%), nose irritation (50%, 54%, 100%), and pulmonary discomfort (29%, 46%, 50%) at 2.5, 5, and 10 ppm, respectively. The AEGL-1 point of departure was 1.25 ppm, which was obtained by applying a modifying factor of 2 to the lowest effect level of 2.5 ppm.
Toxicity end point:	Mild sensory irritation or discomfort in humans exposed to 1.25 ppm for 10 min to 8 h.
Scaling:	None: The same AEGL-1 value was used for 10 min to 8 h because mild sensory irritation or discomfort does not vary greatly with time.
Uncertainty Factors:	Total uncertainty factor: 3.
Interspecies:	Not applicable.
Intraspecies:	3; allylamine acts as a contact irritant, and the severity of its effects is not expected to vary greatly among humans. Also, use of a greater uncertainty factor would yield a concentration below 0.2 ppm, which was a no-effect level for workers exposed for up to 4 h (Shell Oil Co. 1992).
Modifying factor:	2, because exposure was for only 5 min and it is unclear whether “moderate” irritation or discomfort is comparable to “notable” irritation or discomfort, which exceeds the scope of AEGL-1.

Calculations:

10-min AEGL-1:	2.5 ppm/6 = 0.42 ppm (0.98 mg/m$^{3)}$
30-min AEGL-1:	2.5 ppm/6 = 0.42 ppm (0.98 mg/m^3)
1-h AEGL-1:	2.5 ppm/6 = 0.42 ppm (0.98 mg/m^3)
4-h AEGL-1:	2.5 ppm/6 = 0.42 ppm (0.98 mg/m$^{3)}$
8-h AEGL-1:	2.5 ppm/6 = 0.42 ppm (0.98 mg/m^3)

Derivation of AEGL-2 Values

10, 30, and 60 min

Key study:	Hine et al. (1960); same study used to derive AEGL-1 values. Young adult human volunteers (35; sex and ages unknown) were exposed to 2.5, 5, 10, or 14 ppm. The AEGL-2 point of departure was 10 ppm, which caused slight or moderate eye and nose irritation and pulmonary discomfort and was the NOAEL for "intolerable" irritation seen at 14 ppm.
Toxicity end point:	Human sensory irritation or discomfort; NOAEL for "intolerable" irritation.
Scaling:	None; the degree of irritation or discomfort resulting from exposure to 10 ppm was not expected to increase over a 1-h period beyond the scope of AEGL-2.
Uncertainty factors:	Total uncertainty factor: 3.
Interspecies:	Not applicable.
Intraspecies:	3; used because allylamine acts as a contact irritant, and the severity of its effects is not expected to vary greatly among humans.

Calculations for 10, 30, and 60 min:

10 ppm/3 = 3.3 ppm (7.7 mg/m^3)

4 and 8 h

Key study:	Guzman et al. (1961). Male Long-Evans rats exposed to 40 ppm for 16 h had heart morphology comparable to controls (NOAEL), but rats exposed to 60 ppm for 14 h had cardiovascular lesions consisting of scattered myofibril fragments with loss of striation, perivascular edema, and cellular infiltration (LOAEL).
Toxicity end point:	NOAEL for cardiovascular lesions.
Scaling:	$C^{1.7} \times t = k$ (ten Berge et al. 1986); n = 1.7 was calculated from a linear regression of the Guzman et al. (1961) rat cardiotoxicity data.
Uncertainty factors:	Total uncertainty factor: 50.
Interspecies:	5; the mechanism of toxicity is similar among several mammalian species (and humans), but differences in susceptibility are unknown; 3 yields values approaching NOEL for lethality from pulmonary lesions.
Intraspecies:	10; the variability of cardiotoxic response among humans is unknown, and potentially sensitive populations exist (diabetics, persons with congestive heart failure).

Calculations for 4 and 8 h:

$$\frac{\text{Concentration}}{\text{UF}} \quad \frac{40 \text{ ppm}^{1.7} \times \text{time (16 h)} = k = 10.95 \text{ ppm}^{1.7}\text{-h}}{(50)}$$

4-h AEGL-2:	$C^{1.7} \times 4 \text{ h} = 10.95 \text{ ppm}^{1.7}\text{-h}$ 4-h AEGL-2 = 1.8 ppm (4.2 mg/m^3)
8-h AEGL-2:	$C^{1.7} \times 8 \text{ h} = 10.95 \text{ ppm}^{1.7}\text{-h}$ 8-h AEGL-2 = C = 1.2 ppm (2.8 mg/m^3)

Derivation of AEGL-3 Values

Key study:	Hine et al. 1960. Rat inhalation LC_{50} study. All treated rats showed signs of eye and respiratory tract irritation, and some had lacrimation and red nasal discharge. Rats dying from exposure had stomachs distended with air,

fluid-filled lungs, alveolar hemorrhage, and pulmonary edema.

Toxicity end point: Lethality NOELs, estimated from LC_{01} values obtained by probit analysis:
1-h LC_{01} = 533 ppm
4-h LC_{01} = 104 ppm
8-h LC_{01} = 69.2 ppm

Scaling: $C^{0.85} \times t = k$ (data from Hine et al. 1960; ten Berge et al. 1986).

Note: Only the 10- and 30-min AEGL-3 values required scaling (used the 1-h LC_{01}).

Uncertainty factors: Total uncertainty factor: 30.

Interspecies: 10; to account for the lack of acute toxicity studies with AEGL-3 end points from other species.

Intraspecies: 3; steep dose-response (~2-fold increase in concentration caused mortality to increase from 0 to 100%) indicates the NOEL for lethality due to direct destruction of lung tissue is not likely to vary greatly among humans.

Calculations for 10 and 30 min:

$$\frac{\text{Concentration}}{\text{UF}} \quad \frac{533\ \text{ppm}^{0.85}}{(30)} \times \text{time (1 h)} = k = 11.54\ \text{ppm}^{0.85}\text{-h}$$

10-min AEGL-3: $C^{0.85} \times 0.167\ \text{h} = 11.54\ \text{ppm}^{0.85}\text{-h}$
10-min AEGL-3 = 150 ppm (350 mg/m^3)

30-min AEGL-3: $C^{0.85} \times 0.5\ \text{h} = 11.54\ \text{ppm}^{0.85}\text{-h}$
30-min AEGL-3 = 40 ppm (93 mg/m^3)

Calculations for 1, 4, and 8 h:

1-h AEGL-3: C = 533 ppm (= LC_{01})
1-h AEGL-3 = 533 ppm/30 = 18 ppm (42 mg/m^3)

4-h AEGL-3: C = 104 ppm (= LC_{01})
4-h AEGL-3 = 104 ppm/30 = 3.5 ppm (8.2 mg/m^3)

8-h AEGL-3: C = 69.2 ppm (= LC_{01})
8-h AEGL-3 = 69.2 ppm/30 = 2.3 ppm (5.4 mg/m^3)

APPENDIX B

Derivation of the Level of Distinct Odor Awareness

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 responders in assessing public awareness of the exposure due to odor perception. The LOA derivation follows the guidance given by van Doorn et al. (2002).

An odor detection threshold (OT_{50}; i.e., the concentration at which 50% of the odor panel observed an odor without necessarily recognizing it) of 3.7 ppm was reported for allylamine by van Doorn et al (2002). This value conflicts with a sensory threshold experimental study in which all 36 volunteers exposed to allylamine for 5 min reported "olfactory cognition" at the lowest concentration tested of 2.5 ppm. Proceeding with the use of 3.7 ppm yields the following:

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:

$$3 = 2.33 \times \log (C/3.7) + 0.5, \text{ which can be rearranged to log}$$
$$(C/3.7) = (3 - 0.5) / 2.33 = 1.07 \text{ and results in}$$
$$C = (10^{1.07}) \times 3.7 = 43.5 \text{ ppm.}$$

The resulting concentration is multiplied by an empirical field correction factor. It takes into account that in everyday life such factors as sex, age, sleep, smoking, upper-airway infections and allergies, and 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 s), which leads to the perception of concentration peaks. Based on current knowledge, a factor of 1/3 is applied to adjust for peak exposure. Adjustment for distraction and peak exposure leads to a correction factor of 4/3 = 1.33.

$$LOA = 43.5 \times 1.33 = 58 \text{ ppm.}$$

The calculated LOA for allylamine is 58 ppm, which exceeds a concentration (i.e., 14 ppm) found to be intolerable by humans (Hine et al. 1960). Therefore, the calculated LOA conflicts with human empirical data, as did the OT_{50}, and neither the LOA nor the OT_{50} is considered valid.

APPENDIX C

Time-Scaling Calculations

Allylamine: AEGL-2 n-Value Derivation

Derivation of n for $C^n \times t = k$, Based on Rat Cardiotoxicity Data (Guzman et al. 1961)

Input Data:				Regression Output:	
Concentration	Log Concentration	Time (h)	Log Time		
100	2.0000	4	2.3802	Intercept	3.4443
60	1.7782	14	2.9243	Slope	–0.5845
50	1.6990	20	3.0792	R Squared	0.8922
40	1.6021	32	3.2833	Correlation	–0.9446
20	1.3010	48	3.4594	Degrees of freedom	3
				Observations	5

n = 1.71.
k = 781244.19.

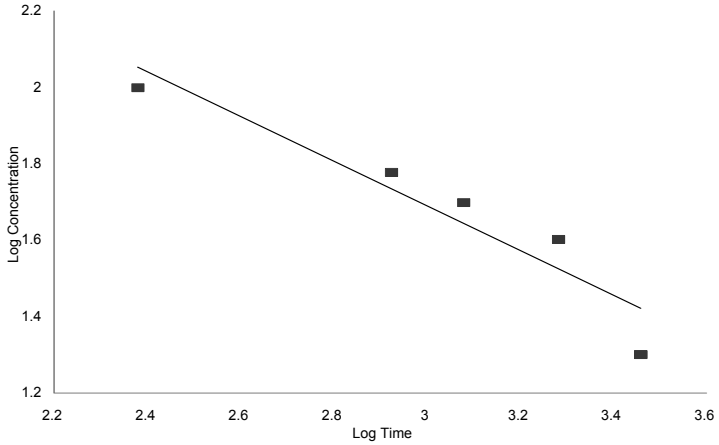

FIGURE 1-1 Best-fit concentration (ppm allylamine) × time (exposure duration in hours) curve. Linear progression of rat lethality data.

Allylamine: AEGL-3 n-Value Derivation

Derivation of n for $C^n \times t = k$, Based on Rat LC_{50} Study Data of Hine et al. (1960)

Input Data:				Regression Output:	
Concentration	Log Concentration	Time (h)	Log Time	Intercept	3.2567
1,933	3.2862	1	0.0000	Slope	–1.1823
286	2.4564	4	0.6021	R^2	0.9798
177	2.2480	8	0.9031	Correlation	–0.9898
				Degrees of freedom	1
				Observations	3

n = 0.8457765
k = 568.14929.

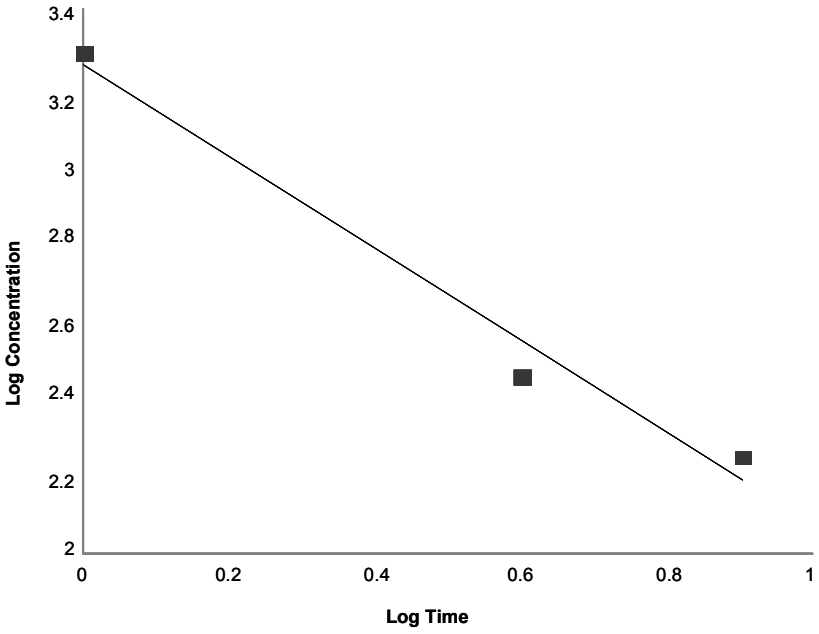

FIGURE 1-2 Best-fit concentration (ppm allylamine) × time (exposure duration in hours) curve. Linear progression of rat lethality data.

APPENDIX D

Category Plot for Allylamine

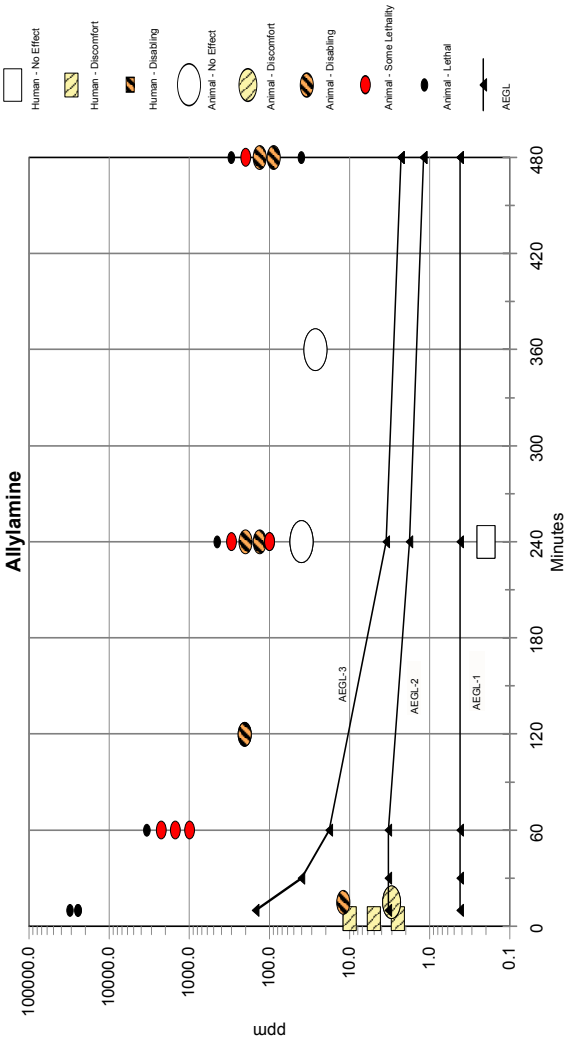

FIGURE 1-3 Category plot of human and animal toxicity data compared with AEGL values.

APPENDIX E

Acute Exposure Guideline Levels for Allylamine

Derivation Summary for Allylamine AEGLs (107-11-9)

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
0.42 ppm	0.42 ppm	0.42 ppm	0.42 ppm	0.42 ppm

Key Reference: Hine, C.H., J.K. Kodama, R.J. Guzman, and G.S. Loquvam. 1960. The toxicity of allylamines. Arch. Environ. Health 1:343-352.

Test Species/Strain/Number: Young adult human volunteers (age and sex not specified), 10-14/concentration

Exposure Route/Concentrations/Durations: Inhalation; 2.5, 5, or 10 ppm for 5 min; 14 ppm <1 min.

Effects: All subjects detected the odor of allylamine. At 2.5, 5, and 10 ppm, respectively, there were dose-related increases in the incidence of slight or moderate eye irritation (21%, 15%, 50%), nose irritation (50%, 54%, 100%), and pulmonary discomfort (29%, 46%, 50%). The incidence of CNS effects was not dose related. The AEGL-1 point of departure was 1.25 ppm, which was obtained by applying a modifying factor of 2 to the lowest effect level of 2.5 ppm, to ensure that effects do not exceed AEGL-1 severity.

End point/Concentration/Rationale: Mild sensory irritation or discomfort in humans exposed to 1.25 ppm for 10 min to 8 h.

Uncertainty Factors/Rationale:
Uncertainty Factors: Total uncertainty factor: 3.
Interspecies: Not applicable.
Intraspecies: 3; allylamine acts as a contact irritant, and the severity of its effects is not expected to vary greatly among humans. Also, use of a greater uncertainty factor would yield a concentration below 0.2 ppm, which was a no-effect level for workers exposed for up to 4 h (Shell Oil Co. 1992).

Modifying Factor: 2; applied because exposure was for only 5 min and it is unclear whether "moderate" irritation or discomfort is comparable to "notable" irritation or discomfort, which exceeds the scope of AEGL-1.

Animal to Human Dosimetric Adjustment: None.

Time Scaling: None; same AEGL value is adopted for 10 min to 8 h because mild sensory irritation or discomfort is not expected to vary greatly over time.

Data Adequacy: Dataset was adequate. A human experimental study was used to develop AEGL-1 values, which are supported by an occupational monitoring study indicating 0.2 ppm was a no-effect level in workers (Shell Oil Co. 1992) and by two mouse RD_{50} studies (Gagnaire et al. 1989, 1993) from which it is predicted that 0.9 ppm should result in some sensory irritation in humans, whereas 0.09 ppm should cause no sensory irritation (Alarie 1981).

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
3.3 ppm	3.3 ppm	3.3 ppm	1.8 ppm	1.2 ppm
Key Reference: Hine, C.H., J.K. Kodama, R.J. Guzman, and G.S. Loquvam. 1960. The toxicity of allylamines. Arch. Environ. Health 1:343-352.			Key Reference: Guzman, R.J., G.S. Loquvam, J.K. Kodama, and C.H. Hine. 1961. Myocarditis produced by allylamines. Arch. Environ. Health 2:62-73.	
Test Species/Strain/Sex/Number: Young adult humans (age and sex unspecified), 10-14/concentration			Test Species/Strain/Sex/Number: Male Long-Evans rats; 1-20/group, as shown in Table 1-5 of Section 3.1.1.	
Exposure Route/Concentrations/Durations: Inhalation; 2.5, 5, or 10 ppm for 5 min; 14 ppm <1 min.			Exposure Route/Concentrations/Durations: Inhalation; exposure to 20-100 ppm for 4-48 h, as shown in Table 1-5 of Section 3.1.1. Rats within dose groups were killed for analysis 8 h to 14 days after the start of exposure.	
Effects: At 2.5, 5, and 10 ppm, respectively, there were dose-related increases in the incidence of slight or moderate eye irritation (21%, 15%, 50%), nose irritation (50%, 54%, 100%), and pulmonary discomfort (29%, 46%, 50%); the point of departure was 10 ppm, which was NOAEL for "intolerable" seen at 14 ppm.			Effects: Depending on exposure scenario, ranged from no noted cardiovascular effects to severe myocardial and/or cardiovascular lesions; there were several deaths, as shown in Table 1-5 of Section 3.1.1. The LOAEL for cardiovascular lesions was exposure to 60 ppm for 14 h, and the NOAEL was exposure to 40 ppm for 16 h.	
End point/Concentration/Rationale: Sensory irritation or discomfort in humans and the NOAEL for "intolerable" irritation.			End point/Concentration/Rationale: Exposure to 40 ppm for 16 h was the NOAEL for cardiovascular lesions.	
Uncertainty Factors/Rationale: Total uncertainty factor: 3. Interspecies: Not applicable. Intraspecies: 3: Used because allylamine is acting as a contact irritant, and the severity of its effects is not expected to vary greatly among humans.			Uncertainty Factors/Rationale: Total uncertainty factor: 50. Interspecies: 5; mechanism of toxicity is similar among several mammalian species (and humans), but differences in susceptibility are unknown; 3 yielded values approaching the NOEL for lethality from pulmonary lesions. Intraspecies: 10; variability of cardiotoxic response among humans is unknown, and potentially sensitive populations exist (diabetics, persons with congestive heart failure).	
Modifying Factor: None.			Modifying Factor: None.	
Animal to Human Dosimetric Adjustment: None.			Animal to Human Dosimetric Adjustment: None.	

(Continued)

AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
3.3 ppm	3.3 ppm	3.3 ppm	1.8 ppm	1.2 ppm

Time Scaling: None, because the degree of irritation is expected to remain within the scope of AEGL-2 for 60 min.

Time Scaling: $C^n \times t = k$, where n = 1.7 [n is based on regression analysis of Guzman et al. (1961) cardiotoxicity data].

Data Adequacy: Dataset was limited but adequate. All derived AEGL-2 values were well below 14 ppm, which was "intolerable" to human volunteers (Hine et al. 1960).

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
150 ppm	40 ppm	18 ppm	3.5 ppm	2.3 ppm

Reference: Hine, C.H., J.K. Kodama, R.J. Guzman, and G.S. Loquvam. 1960. The toxicity of allylamines. Arch. Environ. Health 1:343-352.

Test Species/Strain/Sex/Number: Long-Evans rats, five/dose group.

Exposure Route/Concentrations/Durations: Inhalation for 1, 4, or 8 h; see below:

Effects: All treated rats showed signs of eye and respiratory tract irritation, and some had lacrimation and red nasal discharge. Rats that died had stomachs distended with air, fluid-filled lungs, alveolar hemorrhage, and pulmonary edema. Mortality rates and calculated LC_{50} and LC_{01} values are as follows:

1-h exposure		4-h exposure		8-h exposure	
Concentration	Mortality	Concentration	Mortality	Concentration	Mortality
1,000 ppm	1/5	133 ppm	0/5	89 ppm	0/5
1,500 ppm	1/5	200 ppm	0/5	133 ppm	0/5
2,250 ppm	3/5	300 ppm	3/5	200 ppm	4/5
3,380 ppm	5/5	450 ppm	5/5	300 ppm	5/5
LC_{50} = 1933 ppm		LC_{50} = 286 ppm		LC_{50} =177 ppm	
LC_{01} = 533 ppm		LC_{01} = 104 ppm		LC_{01} = 69.2 ppm	

End point/Concentration/Rationale: LC_{01} values, representing the lethality NOEL, were calculated by probit analysis using 1-, 4-, and 8-h exposure data from the key study.

Uncertainty Factors/Rationale:
Total uncertainty factor: 30.
Uncertainty factors: Total uncertainty factor: 30.
Interspecies: 10; to account for the lack of acute toxicity studies with AEGL-3 end points from other species.
Intraspecies: 3; steep dose-response (~2-fold increase in concentration caused mortality to increase from 0 to 100%) indicates the NOEL for lethality due to direct destruction of lung tissue is not likely to vary greatly among humans.

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Not applied.

Time Scaling: $C^n \times t = k$, where n = 0.85, based on regression analysis of key study. Time scaling was used only for derivation of the 10- and 30-min values, using the 1-h LC_{01}.

Data Adequacy: The dataset was limited but adequate. The key rat study was well conducted, and the data were internally consistent.

2

Ammonia[1]

Acute Exposure Guideline Levels

PREFACE

Under the authority of the Federal Advisory Committee Act (P.L. 92-463) of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances has been established to identify, review, and interpret relevant toxicological and other scientific data and develop acute exposure guideline levels (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, 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 parts per million [ppm] or milligrams per cubic meter [mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could

[1]This document was prepared by the AEGL Development Team composed of Kowetha Davidson (Oak Ridge National Laboratory) and Susan Ripple (Chemical Manager and National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances member). 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).

experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

Airborne concentrations below 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 susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Ammonia is a colorless, corrosive, alkaline gas that has a very pungent odor. The odor detection level ranges from 5 to 53 ppm. Ammonia is used as a compressed gas and in aqueous solutions. It is also used in household cleaning products, in fertilizers, and as a refrigerant. Exposure to ammonia occurs as a result of accidents during highway and railway transportation, accidental releases at manufacturing facilities, and farming accidents.

Ammonia is very soluble in water. Because of its exothermic properties, ammonia forms ammonium hydroxide and produces heat when it contacts moist surfaces, such as mucous membranes. The corrosive and exothermic properties of ammonia can result in immediate damage (severe irritation and burns) to the eyes, skin, and mucous membranes of the oral cavity and respiratory tract. In addition, ammonia is effectively scrubbed in the nasopharyngeal region of the respiratory tract because of its high solubility in water.

The database for ammonia consisted primarily of case reports, human studies, and experimental studies on lethality and irritation in animals. The case reports were of limited use for quantitative evaluation, but the human and animal studies contained quantitative data useful for deriving AEGL values.

No reliable quantitative exposure data were available for humans dying as a result of accidental exposure to ammonia. One case report noted the death of

an individual exposed to a high unknown concentration of ammonia. Other case reports also contained no exposure estimates but showed that high concentrations of ammonia caused severe damage to the respiratory tract, particularly in the tracheobronchial and pulmonary regions. Death was most likely to occur when damage caused pulmonary edema. Nonlethal, irreversible, or long-term effects occurred when damage progressed to the tracheobronchial region, manifested by reduced performance on pulmonary function tests, bronchitis, bronchiolitis, emphysema, and bronchiectasis. Nondisabling reversible effects were manifested by irritation to the eyes, throat, and nasopharyngeal region of the respiratory tract. The odor of ammonia can be detected by humans at concentrations >5 ppm; the odor is highly penetrating at 50 ppm (10 min). Human volunteers exposed to ammonia showed slight irritation at 30 ppm (10 min); moderate irritation to the eyes, nose, throat, and chest at 50 ppm (10 min to 2 h); moderate to highly intense irritation at 80 ppm (30 min to 2 h); highly intense irritation at 110 ppm (30 min to 2 h); unbearable irritation at 140 ppm (30 min to 2 h), and excessive lacrimation and irritation at 500 ppm. Reflex glottis closure, a protective response to inhaling irritant vapors, occurred at 570 ppm for 21- to 30-year-old subjects, 1,000 ppm for 60-year-old subjects, and 1,790 ppm for 86- to 90-year-old subjects.

Acute lethality studies in animals showed that the lethal concentration in 50% (LC_{50}) of the rats ranged from 40,300 ppm for a 10-min exposure to 7,338 and 16,600 ppm for 60-min exposures. For the mouse, LC_{50} values were 21,430 ppm for a 30-min exposure (almost all animals died in less than 13 min), 10,096 ppm for a 10-min exposure, and 4,230 and 4,837 ppm for 60-min exposures. Comparative data for the same exposure duration show that mice were more sensitive than rats to the acute exposure to ammonia (10-min LC_{50} values for mice and rats are 10,096 and 40,300 ppm, respectively). The lowest lethal concentration was 1,000 ppm for a cat exposed via an endotracheal tube, which probably exacerbated the effects in the tracheobronchial region (bronchopneumonia, bronchitis, bronchiolitis, and emphysema) by bypassing the scrubbing action of the nasopharyngeal region. Rats exposed by inhalation to lethal concentrations of ammonia showed signs of dyspnea, irritation to the eyes and nose, and hemorrhage in the lungs. Mice exposed to lethal concentrations of ammonia showed signs of irritation to the eyes and nose, along with tremors, ataxia, convulsions, seizures, and pathological lesions in the alveoli. Effects at nonlethal concentrations in mice and rats consisted of mild effects on the respiratory epithelium of the nasal cavity (mice and rats), reduction in the respiratory rate (mice), and evidence of eye irritation (rat). The RD_{50} (concentration causing a 50% reduction in respiratory rate) for the mouse was 300 ppm for a 30-min exposure.

The AEGL-1 value was based on a study in which 2/6 human subjects experienced faint irritation after exposure to ammonia at 30 ppm for 10 min (MacEwen et al. 1970). An interspecies uncertainty factor is not applied because human data are used to derive the AEGL-1. An intraspecies uncertainty factor of 1 was applied because ammonia is a contact irritant and is efficiently scrubbed

in the upper respiratory tract, particularly at the low AEGL-1 concentration. Irritation would be confined to the upper respiratory tract, and members of the population are not expected to respond differently. Atopic subjects, including asthmatics, responded similarly to nonatopics to brief nasal exposure to ammonia, and exercising subjects experienced only nonsignificant clinical changes in pulmonary function after exposure to ammonia. Asthmatic and exercising individuals are not expected to respond differently from nonasthmatic or resting individuals. Time scaling is not applied because upper respiratory tract irritation at low ammonia concentrations is not expected to become more severe with duration of exposure; adaptation may occur during prolonged exposure to ammonia. Therefore, the AEGL-1 value is 30 ppm for all exposure durations.

The AEGL-2 values were based on "offensive irritation" to the eyes and respiratory tract experienced by nonexpert human subjects (unfamiliar with the effects of ammonia or with laboratory studies) exposed to 110 ppm of ammonia for 2 h (Verberk 1977). The response of the nonexpert subjects ranged from "no sensation" to "offensive" eye irritation, cough, or discomfort and from "just perceptible" or "distinctly perceptible" to "offensive" throat irritation. However, AEGL-2 derivation was based on the response of the most sensitive nonexpert subjects. No residual effects were reported after termination of exposure, and pulmonary function was not affected by exposure. At the next higher concentration, some subjects reported the effects as unbearable and left the chamber after 30 min to 1 h; none remained for the full 2 h. An intraspecies uncertainty factor of 1 was selected because ammonia is a contact irritant, it is efficiently scrubbed in the upper respiratory tract, and any perceived irritation is not expected to be greater than that of the most sensitive nonexpert subject. The range of responses for this group is considered comparable to the range of responses that would be encountered in the general population, including asthmatics. Investigations have shown a link between nasal symptoms or allergic rhinitis and asthma, with rhinitis preceding the development of asthma, and studies have shown that atopic subjects, including asthmatics, and nonatopic subjects do not respond differently to a brief nasal exposure to ammonia. Exposure to exercising subjects showed only nonsignificant clinical changes in pulmonary function during exposure to ammonia at concentrations up to 336 ppm. In addition, a child experienced less severe effects than an adult exposed to very high concentrations of ammonia. The equation $C^n \times t = k$, where $n = 2$, was used to extrapolate to 5-, 10-, and 30-min exposure durations. This equation was based on mouse and rat lethality data. The AEGL-2 values are 220, 220, 160, 110, and 110 ppm for exposure durations of 10 and 30 min and 1, 4, and 8 h, respectively. The value of 110 ppm was adopted for the 4- and 8-h values, because the maximum severity rating for irritation in the Verberk (1977) study changed very little between 30 min and 2 h and is not expected to change for exposures up to 8 h. The 30-min value was also adopted as the 10-min AEGL-2 value because time scaling would yield a 10-min AEGL-2 of 380 ppm, which might impair escape.

The AEGL-3 values were based on LC_{01} values of 3,317 and 3,374 ppm derived by probit analysis of mouse lethality data reported by Kapeghian et al.

(1982) and MacEwen and Vernot (1972), respectively. An interspecies uncertainty factor of 1 was applied to the mouse data because the mouse was the most sensitive species among mammals and the mouse is considered unusually sensitive to respiratory irritants. An uncertainty factor of 3 was applied to account for intraspecies variability because concentrations of ammonia that are life threatening cause severe tracheobronchial and pulmonary damage and these effects are not expected to be more severe in asthmatics than in nonasthmatics, in children than adults, or in exercising than nonexercising individuals (see rationale for AEGL-2), but tracheobronchial and pulmonary effects may occur at a lower concentration in the elderly. Investigations showed that reflex glottis closure (protective mechanism) is 3-fold less sensitive in the elderly than in young subjects; this mechanism may be applicable only when concentrations of ammonia exceed 570 ppm. In addition, a larger interspecies or intraspecies uncertainty factor would lower the 30-min AEGL-3 to approximately 500 ppm, which was tolerated by humans without lethal or long-term consequences. ten Berge's equation ($C^n \times t = k$) was used to extrapolate to the relevant exposure durations. The value of n was calculated from the regression coefficients (b_1/b_2) for the mouse lethality data reported by ten Berge et al. (1986). The 5-min AEGL value was requested by the ammonia industry. The AEGL values and toxicity end points are summarized in Table 2-1.

1. INTRODUCTION

Ammonia is a colorless, corrosive, alkaline gas that has a very pungent odor, detectable by humans at concentrations >5 ppm. It can be liquefied under pressure. Ammonia is very soluble in water; it forms ammonium hydroxide when it contacts moist surfaces, producing heat because of its exothermic prop-

TABLE 2-1 Summary of AEGL Values for Ammonia

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	30 ppm (21 mg/m^3)	30 ppm (21 mg/m^3)	30 ppm (21 mg/m^3)	30 ppm (21 mg/m3)	30 ppm (21 mg/m3)	Mild irritation (MacEwen et al. 1970)
AEGL-2 (disabling)	220 ppm (154 mg/m^3)	220 ppm (154 mg/m^3)	160 ppm (112 mg/m^3)	110 ppm (77 mg/m3	110 ppm (77 mg/m3)	Irritation: eyes and throat; urge to cough (Verberk 1977)
AEGL-3 (lethal)	2,700 ppm (1,888 mg/m^3)	1,600 ppm (1,119 mg/m^3)	1,100 ppm (769 mg/m^3)	550 ppm (385 mg/m3)	390 ppm (273 mg/m3)	Lethality (Kapeghian et al. 1982; MacEwen and Vernot 1972)

erty. Ammonia and air will explode when ignited under some conditions (not otherwise described). Although it is generally regarded as nonflammable, ammonia is classified as a flammable gas by the National Fire Protection Association (Budavari et al. 1989; Lewis 1993; Pierce 1994). Table 2-2 summarizes the physical and chemical properties of ammonia.

TABLE 2-2 Physical and Chemical Data

Property	Descriptor or Value	Reference
Chemical name	Ammonia	
Synonyms	Anhydrous ammonia, ammonia gas, AM-Fol, nitro-sil, R 717, spirit of hartshorn, UN1005 (DOT)	
CAS registry no.	7664-41-7	
Chemical formula	NH_3	Weast et al 1984
Molecular weight	17.03	Weast et al 1984
Physical state	colorless gas (or liquid)	Lewis 1993
Vapor pressure	8.5 atm at 20°C	Lewis 1993
Density (liquid)	0.6818 at 33.35°C, 1 atm 0.6585 at 15°C, 2.332 atm 0.6386 at 0°C, 4.238 atm 0.6175 at 15°C, 7.188 atm 0.5875 at 35°C, 13.321 atm	O'Neil et al. 2001
Specific volume	22.7 ft^3/lb at 70°C	Lewis 1993
Critical temperature	132.9°C	Pierce 1994
Pressure at critical temperature	111.5 atm	Pierce 1994
Solubility	89.9 g/100 mL cold water	Weast et al. 1984
Boiling/freezing point	–33.5°C/–77°C	Lewis 1993
Autoignition temperature	650°C (1,204°F)	Lewis 1993
Explosive limit	16-25% by volume in air	Pierce 1994
Ionization constants	K_b 1.774×10^{-5}, K_a 5.637×10^{-10} at 25°C	Pierce 1994
Alkalinity	1% solution, pH = 11.7	Pierce 1994
Conversion	1 ppm = 0.7 mg/m^3 at 25°C, 1 atm 1 mg/m^3 = 1.43 ppm	Pierce 1994

Ammonia is produced commercially by a modified Haber reduction process using atmospheric nitrogen and a hydrogen source. Ammonia is used as a compressed gas, as an aqueous solution (28%) called aquammonia, and as a household cleaning product (10%). It is widely used as a fertilizer, where the anhydrous gas or aqueous solution is injected directly into the soil. Ammonia is also used as a refrigerant in commercial installations, and it is used in the manufacture of other chemicals (Pierce 1994).

Ammonia is transported on highways (in tanker trucks), by railways, in pipelines, and on barges. Exposure to the general public can occur from accidents during transportation on highways and railways, during transfer between transportation vessels and storage vessels, by accidental releases at manufacturing facilities, and from farming accidents during soil application.

The data evaluated for AEGL derivation were obtained from case studies of accident victims exposed to high concentrations of ammonia, experimental studies in humans exposed to lower but irritating concentrations of ammonia, and experimental studies on lethality and irritation in animals. Additional data are available on long-term exposure to ammonia in the agricultural industry (feeding lots and poultry houses) but are not considered relevant for deriving acute exposure values for ammonia.

2. HUMAN TOXICITY DATA

2.1. Human Lethality

Quantitative exposure estimates of acute lethality of ammonia in humans are not well documented. In one case study the exposure concentration was estimated, but the duration was not. Another study reconstructs the exposure due to an accidental spill resulting in deaths. The remaining studies document the types of effects encountered when humans are acutely exposed to lethal concentrations of ammonia.

A worker was exposed to a very high concentration of ammonia vapor, estimated as 10,000 ppm. Duration of exposure was not reported, but it could have been a few minutes; nevertheless, the worker continued to perform his duties for an additional 3 h after the exposure. He experienced coughing, dyspnea, and vomiting soon after exposure. Three hours after initial exposure, his face was "red and swollen," his mouth and throat were "red and raw," his tongue was swollen, his speech was difficult, and he had conjunctivitis. He died of cardiac arrest 6 h after exposure. An autopsy revealed marked respiratory irritation, denudation of the tracheal epithelium, and pulmonary edema (Mulder and Van der Zalm 1967).

Caplin (1941) reported on 47 persons accidentally exposed to ammonia in an enclosed area (air raid shelter). The patients were divided into three groups depending on the degree to which they were affected: mildly, moderately, or severely. No deaths occurred among the nine mildly affected patients. Three of

27 moderately affected patients showed signs and symptoms similar to pulmonary edema and died within 36 h. Nine moderately affected patients developed bronchopneumonia within 2-3 days, and three died 2 days after the onset. The mortality rate for the moderately affected patients was 22% (6/27). The 11 severely affected patients developed pulmonary edema; seven died within 48 h. The mortality rate for the severely affected patients was 63% (7/11). Walton (1973) reported on the death of one of seven workers exposed to ammonia in an industrial accident. The autopsy report noted marked laryngeal edema, acute congestion, pulmonary edema, and denudation of the bronchial epithelium. These studies show that individuals who develop pulmonary edema (evidence of damage to alveolar region) after inhaling ammonia are more likely to die than those who do not.

Individuals who are acutely exposed to high concentrations of ammonia and survive the immediate effects may die weeks to months later, probably due to secondary effects of exposure. A 25-year-old man died 60 days after exposure to a high concentration of ammonia in a farming accident (Sobonya 1977). The autopsy report noted damage to the bronchial epithelium, bronchiectasis, mucus and mural thickening of the smallest bronchi and bronchioles, fibrous obliteration of small airways, and a purulent cavitary pneumonia characterized by large numbers of *Nocardia asteroides* (nocardial pneumonia). Three co-workers exposed in the accident died immediately. Hoeffler et al. (1982) reported on the case of a 30-year-old woman who died 3 years after exposure to ammonia during an accident involving a tanker truck carrying anhydrous ammonia (Houston accident). Her injuries resulted in severe immediate respiratory effects, including pulmonary edema. She required mechanically assisted respiration throughout her remaining life. Bronchiectasis was detected 2 years after exposure and confirmed on autopsy. The autopsy examination also showed bronchopneumonia and cor pulmonale (heart disease secondary to pulmonary disease). According to the authors, the bronchiectasis may have been due to bacterial bronchitis or to the chemical injury.

In the Houston accident, the crash of a tanker truck released 17.2 tonnes of pressurized anhydrous ammonia. The chemical cloud extended 1,500 m downwind and was 550 m wide. Five people were killed, 178 were injured, some with permanent disabling injuries (not otherwise described). The fatalities and disabling injuries occurred within about 70 m of the accident (NTSB 1979). The Potchefstroom, South Africa accident involved a pressurized ammonia storage tank that failed and instantaneously released 38 tonnes of anhydrous ammonia into the atmosphere. Eighteen people died and an unknown number were injured (Lonsdale 1975). A visible cloud extended about 300 m wide and about 450 m downwind; all deaths occurred within 200 m of the release point (Pedersen and Selig 1989). Pedersen and Selig used the WHAZAN gas dispersion model, which incorporated meteorological data and physicochemical data for ammonia to predict the concentration isopleths for ammonia released during both the Houston and Potchefstroom accidents. For the Houston accident, a 10,000-ppm isopleth extended 600 m long and 350 m wide, the 5,000-ppm isopleth was

835 m long and 430 m wide, the 2,500-ppm isopleth was 875 m long and 420 m wide, and the 1,200-ppm isopleth was to 1,130 m long and 400 m wide. The investigators reported that their model overestimated the distance to zero deaths (200m) by 2.9 times for the Houston accident and by 2.5 times for the Potchefstroom accident. Pederson and Selig estimated the risk due to a few minutes, exposure to ammonia as very high for the general population at 10,000 ppm, as high for risk of fatalities among the general population and as very high for the vulnerable population (elderly people, children, and people with respiratory or heart disorders) at 5,000 ppm, and as some risk to the general population and high risk to the vulnerable population at 2,500 ppm.

Pedersen and Selig estimated the LC_{50} for a 30-min exposure to the general population to be 11,500 ppm. They did not report their actual LC_{50} estimate for the vulnerable population, but it would be lower than that estimated for the general population.

Mudan and Mitchell (1996) used the HGSYSTEM gas dispersion model to estimate atmospheric ammonia concentrations generated at the time of the ammonia accident in Potchefstroom. They provided upper-bound (wind speed = 1 m/s) and lower-bound (wind speed = 2 m/s) estimates of ammonia concentration based on distance from the release point and the time after release. Instantaneous concentrations were estimated to be in excess of 500,000 ppm (upper bound) within 50 m of the release point. The model predicted rapidly decreasing concentrations, such that, by 1 min after the release, concentrations would fall below 100,000 ppm. Mudan and Mitchell estimated that personnel were exposed to ammonia concentrations exceeding 50,000 ppm for the first 2 min, decreasing to 10,000 ppm during the next 3-4 min. The charts provided by Mudan and Mitchell of the South Africa accident showed that 10 workers were in Zone 1 (50 m of the release point) at the time of release; seven died (100% mortality for workers exposed outside). All survivors in Zone 1 remained sheltered inside buildings and therefore would not have experienced the outside atmospheric ammonia concentrations predicted by the model. Five deaths occurred in Zone 2 (50-100 m). Workers in Zone 2 who were upwind and outside at the time of the release survived, as did those who escaped in an upwind direction. Workers in Zone 2 who were downwind and outside at the time of release or attempted to escape downwind did not survive (except for one worker who escaped downwind; 83% mortality of workers exposed). All Zone 2 victims who died were outside; whereas individuals who were inside buildings survived. Five deaths occurred in Zone 3 (100 to ~200 m). Four victims were found downwind and >150 m from the release point, and another victim was found <150 m from the release point and in a crosswind location. The charts did not show the location or number of any survivors downwind and inside or outside buildings in Zone 3 (i.e., no data were available from the charts to determine if there were individuals who remained outside buildings in Zone 3 and survived). Therefore, the mortality rate cannot be calculated for Zone 3. It appears that within 150 m of the release point, individuals downwind of the ammonia cloud and outside a building were not likely to survive, but individuals downwind and sheltered indoors

or those upwind whether or not they were sheltered indoors were likely to survive. Thus, the lack of data on survivors in the path of the plume precludes estimating ammonia concentrations associated with zero mortality. RAM TRAC (1996) used the results of the HGSYSTEM gas dispersion model to predict 5-min ammonia concentrations of 87,479 ppm for 60% mortality, 73,347 ppm for 26% mortality, and 33,737 ppm for zero mortality for the Potchefstroom accident. RAM TRAC estimated a 5-min LC_{50} of 83,322 ppm. See Section 7.1 for details of the evaluation of dose reconstruction models.

Henderson and Haggard (1943) reported that, exposure to ammonia at concentrations >2,500 ppm for durations $\geq$30 min is dangerous to humans. They noted that concentrations $\geq$5,000 ppm are rapidly fatal to humans.

2.2. Nonlethal Toxicity

2.2.1. Experimental Studies, Case Reports, and Anecdotal Data

The available literature detailing the disabling, long-term, or irreversible effects of inhaling ammonia gas or vapor is quite extensive. However, none of the studies contain quantitative exposure data. The acute effects of inhaling high nonlethal concentrations of ammonia include burns to the eyes and oral cavity and damage to the nasopharyngeal and tracheobronchial regions of the respiratory tract. Manifestations of damage include conjunctivitis, corneal burns, visual impairment, pain in the pharynx and chest, cough, dyspnea, hoarseness, aphonia, rales, wheezing, rhonchi, hyperemia and edema of the pharynx and larynx, tracheitis, bronchiolitis, and purulent bronchial secretions (Levy et al. 1964; Walton, 1973; Hatton et al. 1979; Montague and Macneil 1980; Flury et al. 1983; O'Kane 1983). Cyanosis, tachycardia, convulsions, and abnormal electroencephalograms also have been described for some patients (Kass et al. 1972; Walton 1973; Hatton et al. 1979; Montague and Macneil 1980). Pulmonary edema occurred in some patients who survived (Caplin 1941) but is most often seen in fatal cases. A few case studies are described below to document some of the disabling or irreversible injuries seen in individuals who inhaled high concentrations of ammonia. Some of the injuries would probably have resulted in death without rescue and medical treatment. The duration of exposure is reported when known.

Short-term recovery from serious injury due to inhaling ammonia is exhibited by three children and a 17-year-old female exposed to high but unknown concentrations of ammonia in the Houston accident (Hatton et al. 1979). These patients suffered second- or third-degree burns to the body, damage to the eyes, burns to the oral mucosa, upper-airway obstruction (probably due to damage to the laryngeal and tracheobronchial regions), and some pulmonary damage. All four patients recovered within 7-32 days. Nine of 14 patients exposed to an unknown concentration ammonia by inhalation for only a few seconds or few min-

utes showed moderate symptoms of chest abnormalities or airway obstruction and recovered within 6.3 days (average) (Montague and Macneil 1980).

Two young women accidentally exposed to anhydrous ammonia fumes (concentration unknown) for 30 or 90 min continued to show effects more than 2 years after exposure (Kass et al. 1972). One woman was found unconscious 90 min after the accident, and the other woman was exposed when she went outdoors for 30 min after the accident. The accident in which these two women were injured involved a railroad tanker car carrying 33,000 gal of anhydrous ammonia; 8 people died and 70 were injured. A heavy fog kept the ammonia vapors close to the ground for a long period of time after the accident. Damage to the eyes caused marked visual deterioration. Bronchiectasis was detected 2 years after exposure, and pulmonary function tests showed abnormalities indicative of small-airway obstruction. Various tests and examinations showed areas of atelectasis and emphysema in the lungs, thickened alveolar walls with histiocytic infiltration into the alveolar spaces, and mucous and desquamated cells in the bronchiolar lumen. Some of these effects may be secondary to the damage caused by ammonia. The woman exposed for 90 min was carrying her 1-year-old child, who was exposed at the same time. The child became "quite ill" but recovered completely except for a chemical scar on his abdomen (Kass et al. 1972).

In another accident, four patients (three farm workers and one refrigeration technician) who had been struck in the face and upper body with liquid ammonia had damage to their tracheobronchial regions, causing upper-airway obstruction and injury to the respiratory tract persisting for 2 years after the accident (Levy et al. 1964). A man splashed with liquid ammonia during a refrigeration accident showed evidence of peripheral (possibly bronchiolitis) and central airway obstruction 5 years after the accident (Flury et al. 1983). Tubular bronchiectasis was detected 8 years after exposure of a 28-year-old man to a high concentration of anhydrous ammonia in an industrial accident. Twelve years after exposure, the man continued to have a productive cough, frequent bronchial infections, dyspnea upon exertion, and severe airflow obstruction (62% reduction in forced expiratory volume at 1 s, FEV_1; Leduc et al. 1992). O'Kane (1983) described several patients who had been exposed to ammonia vapor by inhalation for 5 min. One developed necrotizing pneumonia and was "left with chronic infective lung disease", one had persistent hoarseness and a productive cough for several months, and a third was left with a diffusion defect that was 75% of normal. Finally, Shimkin et al. (1954) described a man who developed epidermoid carcinoma 6 months after ammonia was splashed on his upper lip and nose. The authors postulated that the carcinoma was due to a single-exposure chemical trauma that exteriorized a latent cutaneous carcinoma. There was no evidence that ammonia caused the carcinoma.

Nondisabling and reversible effects of inhaling ammonia have been documented in several experimental studies of human subjects exposed to ammonia at various concentrations and durations. These studies are summarized below.

Five or six laboratory workers inhaled the exhaust fumes generated in an exposure chamber for an inhalation study and noted that the disagreeable odor and respiratory distress would prevent a person from voluntarily remaining in an atmosphere containing 170 ppm of ammonia (average concentration, 140-200 ppm) for an appreciable length of time (Weatherby 1952).

Henderson and Haggard (1943) reported that, based on observations of human responses to ammonia, the lowest concentration (or threshold) to cause coughing is 1,720 ppm, the lowest concentration to cause eye irritation is 698 ppm, and the lowest concentration to cause throat irritation is 408 ppm. They reported the least detectable odor to be 53 ppm. Pierce (1994) reported the odor threshold as 5-53 ppm.

McLean et al. (1979) examined the effect of ammonia on nasal airway resistance (NAR) in atopic and nonatopic human subjects. Ammonia (100 ppm at a pressure of 9 newtons/cm^2) was introduced into each nostril for 5, 10, 15, 20, or 30 seconds (s). NAR was measured every minute for 5 min and then every 2 min for 10 min (total of 10 measurements over a 15-min period) using a pneumotachograph attached to a face mask. The same subjects were used for each successive ammonia exposure, which immediately followed the NAR measurements. The nonatopic subjects were screened based on strict criteria that included a questionnaire, physical examination, spirometry, nasal smear for eosinophils, and a battery of 19 prick and six intracutaneous tests. Nonatopic subjects could have no personal or immediate family history of atopic disease (allergic rhinitis, asthma, or atopic dermatitis), could have no more than 5% eosinophils in their nasal smears, and had to have a negative prick test reaction. Atopic subjects were screened based on a characteristic history of allergic rhinitis and at least one 3+ or 4+ prick test reaction. Some of the atopic subjects had a history of asthma. All subjects had been symptom-free for several weeks before the study, and none were taking medications that would influence skin or mucosal tests. Baseline NAR measurements were made for a 15-min period before introducing the ammonia. Additional tests included introducing 0.1 mL of aerosolized phosphate-buffered saline, 0.1 mL atropine, or 0.1 mL chlorpheniramine maleate into the nostrils, each followed by ammonia for 20 s.

The NAR after ammonia exposure to nonatopic and atopic subjects increased significantly with time of exposure from 5 to 20 s. Only a small further increase was noted for subjects exposed for 30 s compared with 20 s. The percent increase for atopic compared with nonatopic subjects was similar, and there was no difference between the allergic rhinitis subjects with or without a history of asthma. Atropine inhibited the response to ammonia in atopic and nonatopic subjects by up to 89%, whereas chlorpheniramine had no effect on the NAR induced by ammonia. The study's authors noted that the results of atropine and chlorpheniramine administration suggest that ammonia irritancy is mediated primarily by a parasympathetic reflex on the nasal vasculature and not via histamine release (McLean et al. 1979).

The Industrial Bio-Test Laboratories (1973) determined the irritation threshold in 10 human volunteers exposed to ammonia at four different concen-

trations (32, 50, 72, or 143 ppm) for 5 min. Irritation was defined as any annoyance to the nose, throat, eyes, mouth, or chest. The results are summarized in Table 2-3. The subjects showed dose-related responses for dryness of the nose and also eye, throat, nasal, and chest irritation. The severity of the effects was not noted.

MacEwen et al. (1970) studied six human volunteers exposed head only to ammonia at concentrations of 30 and 50 ppm for 10 min. The scale for intensity/description of irritation to the nose and eyes was as follows: 0, no irritation/not detectable; 1, faint/just perceptible, not painful; 2, moderate/moderate irritation; 3, strong/discomforting, painful, but may be endured; and 4, intolerable/exceedingly painful, cannot be endured. The scale for odor intensity/description was as follows: 0, no odor/no detectable odor; 1, very faint/ minimum but positively perceptible odor; 2, faint/weak odor, readily perceptible; 3, easily noticeable/moderate intensity; 4, strong/highly penetrating; and 5, very strong/ intense. At 30 ppm, two subjects reported irritation as faint (grade = 1) and three as not detectable (grade = 0); one gave no response. Also at 30 ppm, the odor was strong or highly penetrating for three subjects (grade = 4) and easily noticeable or moderate (grade = 3) for two subjects; no response was given by one subject. At 50 ppm, four subjects reported the irritation as moderate (grade = 2), faint or just perceptible (grade = 1) for one, and not detectable (grade = 0) for another. The odor was strong or highly penetrating (grade = 4) for all six subjects inhaling 50 ppm of ammonia. This study showed a concentration-related increase in the intensity of the response to ammonia at concentrations of 30 and 50 ppm.

Silverman et al. (1949) studied seven male subjects exposed to 500 ppm of anhydrous ammonia by means of a nose and mouth mask; six subjects were exposed for 30 min and one for 15 min. The inspired ammonia concentration was calculated, and the expired ammonia concentration was analyzed in grab samples taken every 3 min. The analytical technique consisted of a modified Nessler's reagent using a Klett photoelectric colorimeter. The sensitivity of the technique was 0.5 μg of ammonia. Respiratory rate and minute volume were

TABLE 2-3 Effect of Ammonia Inhalation on Human Volunteers Exposed for 5 Min

Effects	32 ppm	50 ppm	72 ppm	134 ppm
Dryness of the nose	+ (1)[a]	+ (2)	—	—
Nasal irritation	—	—	+ (2)	+ (7)
Eye irritation	—	—	+ (3)	+ (5)
Lacrimation	—	—	—	+ (5)
Throat irritation	—	—	+ (3)	+ (8)
Chest irritation	—	—	—	+ (1)

[a]Number of volunteers showing a response out of a total of 10 participating.
Source: Data from Industrial Bio-Test Laboratories 1973, as cited in NIOSH 1974.

measured for each subject. Throat irritation was reported by two subjects. Nasal irritation with stuffiness similar to that of a cold or nasal dryness was reported by six subjects. The stuffiness lasted for about 24 h. Only two subjects were able to continue nasal breathing for the full 30 min, the others changing to mouth breathing on account of nasal dryness and irritation. Hypoesthesia (decreased sensitivity) of the skin around the nose and mouth was experienced by all subjects, and excessive lacrimation was reported by two. Hyperventilation (increases in the respiratory rates and minute volumes) occurred in all subjects. Hyperventilation occurred immediately in three subjects, was delayed for 10-30 min in the remaining four, and fluctuated with a 25% decrease at 4- to 7-min intervals. The increase in the minute volume was 141-289%. No coughing was reported; the authors noted that 1,000 ppm caused immediate coughing. This study showed that irritation of the upper respiratory tract and throat occurred in subjects inhaling 500 ppm of anhydrous ammonia for 15-30 min. There was no difference in the effects noted in the subject inhaling ammonia for 15 min and those inhaling ammonia for 30 min.

Verberk (1977) examined the effects of ammonia on respiratory function and recorded the subjective responses of two groups of subjects. One group consisted of eight individuals familiar with the effects of ammonia and who had no previous exposure (expert group, 29-53 years old); the other group consisted of eight university students unfamiliar with the effects of ammonia or with experiments in laboratory situations (nonexpert group, 18-30 years old). The subjects were paid for their participation and were informed that the study involved subjective effects and posed no danger to their health at the concentrations used. The subjects had the opportunity to leave the chamber before the test was completed. Four members of each group were smokers. Each group was exposed to ammonia at concentrations of 50, 80, 110, and 140 ppm for up to 2 h. Subjective responses (e.g., smell, eye irritation, throat irritation, cough) were recorded every 15 min and parameters of respiratory function (vital capacity, forced expiratory volume ($FEV_{1\ s}$), forced inspiratory volume ($FIV_{1\ s}$) were measured before exposure and after the 2-h exposure. Subjective responses were rated on a scale of 0-5 (0 = no sensation; 1 = just perceptible; 2 = distinctly perceptible; 3 = nuisance; 4 = offensive; and 5 = unbearable). Chamber concentrations were monitored instantaneously using an infrared spectrometer. There was no effect on respiratory function in either group inhaling any concentration of ammonia.

Table 2-4 summarizes the average and range of responses for both groups. Generally, the expert group scored responses lower than those of the nonexpert group. Four nonexpert subjects exposed to 140 ppm left the exposure chamber between 30 min and 1 h, and none remained in the chamber for the full 2 h. The greatest difference in responses between the expert and nonexpert groups was in general discomfort. The expert group perceived no general discomfort even after exposure to the highest concentration for 2 h, whereas the four nonexpert subjects perceived their general discomfort to range from "distinctly perceptible" to "unbearable" after 1 h. This study showed dose- and duration-response relation-

TABLE 2-4 Average (Range) Scores of Subjective Responses of Expert and Nonexpert Subjects Exposed to Ammonia[a]

	50 ppm		80 ppm		110 ppm		140 ppm[c]	
Response	Expert	Nonexpert	Expert	Nonexpert	Expert	Nonexpert	Expert	Nonexpert[c]
Smell								
½ h	2.0 (1-3)[b]	2.5 (2-3)	2.0 (1-3)	3.0 (2-4.5)	2.0 (2-3)	3.0 (2-4)	2.0 (1-3)	4.0 (2-4.5)
1 h	2.0 (1-3)	2.5 (1-4)	2.0 (1-3)	3.0 (2-4)	2.0 (2-3)	3.0 (2-4)	2.0 (1-3)	4.0 (3.5-4.5)
2 h	2.0 (0.5-3)	3.0 (2-4)	1.5 (0.5-3)	3.0 (2-4)	2.0 (1.5-3)	3.0 (2-4)	2.0 (1-3)	WD[c]
Eye irritation								
½ h	1.5 (0-3)	0.8 (0-3)	1.5 (1-2)	1.5 (0-4)	2.5 (1-3)	2.5 (0-4)	3.0 (1.5-3.5)	3.0 (1-4.8)
1 h	1.5 (0-3)	0.8 (0-3)	2.0 (0-3)	1.5 (0-3)	2.5 (2-3.5)	2.5 (0-4)	2.0 (2-3)	3.5 (1-5)
2 h	1.0 (0-2)	1.2 (0-3)	1.5(0-2)	2.0 (0-4)	2.0 (0.3-3)	2.5 (0-4)	2.5 (1-3)	WD
Throat irritation								
½ h	0.4 (0-2)	0.4 (0-1)	0.8 (0-2)	1.0 (0-3	1.5 (0-3.5)	2.0 (0-4)	1.0 (0-2)	3.7 (3.5-5)
1 h	0.4 (0-3)	0.5 (0-3)	1.0 (0-3)	1.4 (1-3)	1.4 (0-3)	2.5 (1-4)	1.5 (0-2)	4.5 (2-4)
2 h	0.7 (0-3)	1.5 (0.3)	0.8 (0-2)	2.0 (0-4)	1.0 (0-2)	3.0 (2-4)	1.0 (0-3.7)	WD
Urge to cough								
½ h	0.2 (0-1.2)	0.2 (0-1)	0.3 (0-1)	0.5 (0-2)	0.8 (0-2)	1.5 (0-2)	0.5 (0-2)	2.0 (0-5)
1 h	0.3 (0-2)	0.2 (0-2)	0.5 (0-2)	1.0 (0-2)	0.5 (0-3.5)	1.7 (0-3)	0.6 (0-2.5)	1.7 (0-3)
2 h	0.3 (0-2)	0.4 (0-2)	0.4 (0-2)	0.3 (0-4)	0.3 (0-2.5)	1.7 (0-4)	0.4 (0-2.3)	WD
General discomfort								
½ h	0	0.1 (0-1)	0	1.0 (0-3)	0.2 (0-2)	1.0 (0-3)	0	2.2 (0-4)
1 h	0	0.2 (0-1)	0	1.2 (0-3)	0.2 (0-1)	1.2 (0-3)	0	3.3 (0-4.7)
2 h	0	1.0 (0-2)	0	1.3 (0-3)	0.3 (0-1)	1.5 (0-4)	0	WD
Irritation to chest	Similar to urge to cough, but scores tended to be a little lower.							

[a]Expert subjects: individuals who were familiar with the effects of ammonia and who had no previous exposure; nonexperts students were unfamiliar with the effects of ammonia or with experiments in laboratory situations.
[b]Based on a scale of 1-5: 0 = no sensation; 1 = just perceptible; 2 = distinctly perceptible; 3 = nuisance; 4 = offensive; and 5 = unbearable.
[c]Only four of the nonexpert subjects tolerated the ammonia for 1 h; none of the nonexpert subjects tolerated the ammonia for 2 h.
Source: Adapted from Verberk 1977.

ships for the effects of ammonia, particularly for the nonexpert subjects. This study also showed that general knowledge about the chemical may help alleviate the concern about exposure and the intensity of the symptoms experienced during exposure.

Cole et al. (1977) studied the effects of exercise on 18 servicemen who inhaled ammonia at concentrations of 71, 106, 144, or 235 mg/m^3 (102, 152, 206, or 336 ppm). The subjects were exposed for durations of between 95 and 120 min while cycling under a load of 20 watts increased up to 180 watts in 20-watt increments (based on assumptions of "zero time" and extrapolation from figures of Cole et al.). The same subjects served as their own controls. Measurements of respiratory parameters (respiratory rate, minute volume, tidal volume, and oxygen uptake) and cardiac frequency were taken under control conditions when the subjects inhaled air only and during the experimental conditions when the subjects inhaled ammonia. During exposure to ammonia, the subjects noted only a sensation in the nose and a slight dryness of the mouth. Minute volume was decreased by 8%, 10%, and 6% at 152, 206, and 336 ppm, respectively, compared with control measurements; statistical significance was achieved for all three concentrations. However, no clear dose-related trend was observed relative to the control measurements. The tidal volume was significantly decreased (9 and 8%, respectively) and respiratory frequency was increased (10 and 8% respectively) at 206 and 336 ppm compared with the control values, but there was no clear dose-response relationship. The small changes in tidal volume and respiratory frequency are unlikely to be clinically significant.

Sundblad et al. (2004) studied the acute effects of repeated low-level ammonia exposures of human subjects at rest and performing ergometric exercise. Twelve healthy atopic adults (seven females and five males, 21-28 years old, with a mean age of 25) with no reported present or past symptoms of allergy or airway disease were exposed in a 20-m^3 stainless steel chamber to ammonia at 0, 5, and, 25 ppm for 3 h on three separate occasions separated by at least 7 days in which subjects did not undergo experimental ammonia exposures. Exposure concentrations were monitored by infrared spectrophotometry. During each 3-h exposure period, 1.5 h was spent at seated rest and 1.5 h was spent exercising at 50 watts on a bicycle ergometer; activity was changed every 30 min. At specific times during exposure and 1.5 h postexposure, the subjects rated their level of discomfort related to odor, eyes, and airway symptoms and general symptoms (such as headache, dizziness, nausea, "feeling of intoxication") on a scale of 0-100. The general symptoms were characterized by Sundblad and co-workers as central nervous system (CNS) effects. Sundblad et al. (2004) performed no neurophysiological measurements or studies showing systemic uptake of ammonia.

Subjective symptom rankings by questionnaire exhibited a dose-response relationship. Based on examination of questionnaire results, Sundblad et al. (2004) noted a tendency of sensory adaptation to "solvent smell" among those exposed to 5 ppm but not those exposed to 25 ppm. Ratings of symptoms related to eye and respiratory irritation and general symptoms were significantly greater in the 25-ppm exposure group than those of controls, while about half of the

symptoms experienced by the 5-ppm exposure group exhibited higher rankings than in the control group. Average rating of irritation and the CNS symptoms did not exceed "rather" (rating of 48). All symptomatic effects were transient.

Sundblad et al. (2004) collected pretrial and posttrial measurements to characterize lung function, methacholine challenge, cell composition in nasal lavage fluids, total and differential peripheral leukocyte counts, complement factor C3b, exhaled nitric oxide, body temperature, and peak expiratory flow. Under the Sundblad et al. experimental protocol, ammonia at 5 or 25 ppm did not induce detectable changes in pulmonary function or total cell concentration in nasal lavage fluid or induce an exposure-related bronchial response to methacholine, an increase in exhaled nitric oxide, an increase in the total or differential leukocyte, or a change in complement factor C3b.

Ferguson et al. (1977) reported that workers in their company in 1972 did not voluntarily use gas masks until ammonia concentrations reached 400 or 500 ppm. They also reported that before 1951 workers were subjected to continuous concentrations ranging from 150 to 200 ppm. To establish the bounds for controlled exposure studies, they conducted two reconnaissance experiments. In the first experiment they reported that four male subjects were able to tolerate "continued exposure" of 130-150 ppm (duration not reported) after exposure to lower concentrations for <2 h. In the second experiment they noted that in the bicarbonate plant, after 30 min of acclimation at 100 ppm, a 30-s exposure at 300 ppm was just barely tolerable.

In the controlled exposure study, Ferguson et al. assessed the effect of ammonia on six (three groups of two) human volunteers (industrial workers) exposed to concentrations of 25, 50, or 100 ppm after exposure to the same concentrations during a 1-week practice period. The subjects were exposed at a sodium bicarbonate plant in areas where concentrations of 25 and 50 ppm were achieved; the subjects were exposed to 100 ppm in an exposure chamber. Ammonia concentrations were monitored each half hour using detector tubes certified by the National Institute for Occupational Safety and Health (NIOSH) that had an overall accuracy of ±10%. Exposure periods ranged from 2 to 6 h/day for 5 weeks. There was no adverse effect on respiratory function and no increase in the frequency of eye, nose, and throat irritation with increasing concentrations. The only complaints were lacrimation and nasal dryness during brief excursions above 150 ppm. There was no interference with performance of work duties and no effect on pulse rate or respiratory function during exercise (i.e., no effect on physical or mental ability to perform work duties) that was consistent with concentration or duration. Definite redness of the nasal mucosa occurred in one subject exposed to 100 ppm with excursion up to 200 ppm, but the effect cleared by the next morning (i.e., no lasting effects occurred). Four of the six subjects were exposed to different concentrations, making it difficult to establish trends related to exposure concentration or duration.

Erskine et al. (1993) measured the threshold concentration of ammonia required to elicit reflex glottis closure, which is a protective response stimulated by inhaling irritant or noxious vapors at concentrations too low to produce

cough. It is accompanied by a brief pause in inspiration. The investigators measured glottis closure in 102 healthy nonsmoking subjects, ranging from 17 to 96 years old, after single intermittent breaths of ammonia vapor using an inspiratory pneumotachograph. The results showed a strong positive correlation coefficient of .85 between age and the threshold concentration. The younger subjects were more sensitive, with the reflex response occurring at 571±41.5 ppm (± standard error) in subjects 21-30 years old compared with 1,791±52 ppm (± standard error) in subjects 86 to 95 years old. The threshold was about 1,000 ppm for 60-year-old subjects. The data showed that younger people are about three times more sensitive to the induction of this protective mechanism (glottis closure) by ammonia than the elderly.

2.2.2. Epidemiologic Studies

Holness et al. (1989) compared the respiratory effects in a group of 58 workers (51 production and six maintenance workers at Allied Chemical Canada, Ltd.) exposed to ammonia during the production of soda ash with 31 control workers from stores and offices. The exposed group had worked in soda ash production for an average of 12.2 years. The workers were assessed at the beginning of a workweek and at the end of the workweek. They were assessed based on a questionnaire, sense of smell, and pulmonary function. The time-weighted average ammonia concentration was 9.2±1.4 ppm (mean ± standard deviation) for the exposed workers compared with 0.3±0.1 ppm for a control group assessed over one workweek. The investigators reported essentially no differences in the parameters assessed comparing the first and last days of the workweek and no differences based on level or length of exposure to ammonia. There were no differences between the two groups.

Minor pulmonary function deficits have been observed in swine workers exposed to ammonia, in combination with dust and endotoxin (Reynolds et al. 1996). While ammonia levels as high as 200 ppm have been reported (Carlile 1984), mean exposure levels of 4-7 ppm are more typical for workers (Reynolds et al. 1996; Donham et al. 1995). Confounding due to exposure to multiple agents and lack of information on clinical symptoms limit the usefulness of these data.

2.3. Summary

Numerous case studies describing disabling, irreversible, or long-term effects on humans inhaling ammonia at high concentrations were available in the literature. However, measured concentrations were not available for any of these studies.

Dose reconstruction has been conducted using WHAZAN and HGSYSTEM models to predict atmospheric ammonia concentrations produced dur-

ing the Houston and Potchefstroom accidents. LC_{50} values were estimated from results of each model. An evaluation of these models is presented in Section 7.1.

Sensitive individuals include children, elderly people, and people with respiratory or heart disorders. For very brief (<1 min) high-level exposures, decreased sensitivity of reflex glottis closure in elderly people implies a loss of protective reflexes, which could increase the risk of damage to the lower respiratory tract from the effects from inhaled ammonia in the elderly.

Ammonia causes severe irritation and burning to the skin, eyes, oral cavity, and respiratory tract, particularly mucous surfaces immediately upon contact due to the rapid conversion of ammonia to the very caustic ammonium hydroxide. Therefore, acute exposure to very high concentrations of ammonia severely damages the pulmonary region (bronchiolar and alveolar) of the respiratory tract, with permanent injury or death likely, even with prompt medical attention. Pulmonary edema, in particular, signals a poor prognosis for recovery in the short term, and secondary effects such as bronchiectasis, bronchopneumonia, and emphysema have occurred in individuals who survived for several days or sometimes several years. The damage caused by ammonia is progressive down the respiratory tract, starting with irritation of the nasopharyngeal region, extending to the tracheobronchial region, and finally the bronchiolar and alveolar regions.

Humans who have inhaled ammonia at concentrations high enough to experience disabling effects without causing death usually experience severe damage to the eyes, oral cavity, and respiratory tract involving the tracheobronchial region. Severe damage to the eyes can cause permanent visual deterioration or blindness. Damage to the pharynx and/or tracheobronchial regions may cause airway obstruction that could lead to death if medical help is not available. Damage to the lungs (particularly the bronchioles) may be manifested by bronchopneumonia. Chronic effects of acute exposure to ammonia (manifested years after exposure) have included bronchiectasis, bronchiolitis, atelectasis, emphysema, chronic bronchitis, and reduced performance in pulmonary function tests. The long-term effects are considered to be secondary to the initial damage caused by ammonia.

Nondisabling and reversible effects of ammonia are summarized in Table 2-5.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Groups of 10 male CFE rats were exposed to 0, 6,210, 7,820, or 9,840 ppm (0, 4,343, 5,468, or 6,881 mg/m^3, respectively) of ammonia for 1 h; surviving

TABLE 2-5 Summary of Nondisabling and Reversible Effects of Inhaled Ammonia in Humans

Concentration	Duration of Exposure	Effect[a]	Reference
5 ppm	3 h, with rest and exercise for 1.5 h each	Subjective rating of eye discomfort and smell, headache, dizziness, and "feeling of intoxication" significantly greater than of controls; sensory adaptation to odor; no exposure-related change in pulmonary function, increase in nasal cells, no increase in exhaled NO, and no alteration in bronchial response to methacholine.	Sundblad et al. 2004
25 ppm	3 h, with rest and exercise for 1.5 h each	Subjective rating of eye, upper respiratory, and throat irritation, smell, headache, dizziness, and "feeling of intoxication" significantly greater than of controls; no sensory. Adaptation to odor; no exposure-related change in pulmonary function, increase in nasal cells, no increase in inhaled NO, and no alteration in bronchial response to methacholine.	Sundblad et al. 2004
30 ppm	10 min	Odor was moderately intense to highly penetrating; irritation was faint or not detectable.	MacEwen et al. 1970
32 ppm	5 min	Nasal dryness.	Industrial Bio-Test Laboratories 1973
50 ppm	5 min	Nasal dryness.	Industrial Bio-Test Laboratoris 1973
50 ppm	10 min	Highly penetrating odor; moderate irritation.	MacEwen et al. 1970
50 ppm	30 min	Moderately intense odor; moderate irritation to eyes and nose; mild irritation to throat and chest; slight urge to cough; slight general discomfort.	Verberk 1977
50 ppm	1 h	Highly intense odor; moderate irritation to eyes, nose, throat, and chest; mild urge to cough; slight general discomfort.	Verberk 1977
50 ppm	2 h	Offensive odor; moderate irritation to eyes, nose, throat, and chest; mild urge to cough; mild general discomfort	Verberk 1977
72 ppm	5 min	Nasal, eye, and throat irritation.	Industrial Bio-Test Laboratories 1973
80 ppm	30 min	Highly intense odor; highly intense eye and nose irritation; moderate throat and chest irritation; mild urge to cough; moderate general discomfort.	Verberk 1977
80 ppm	1 h	Highly intense odor; moderate eye, nose, throat, and chest irritation; mild urge to cough; moderate general discomfort.	Verberk 1977

(Continued)

TABLE 2-5 Continued

Concentration	Duration of Exposure	Effect[a]	Reference
80 ppm	2 h	Highly intense odor; highly intense eye, nose, throat, and chest irritation; highly intense urge to cough; and moderate general discomfort.	Verberk, 1977
100 ppm	5-30 s	Significant increase in nasal airway resistance, but atopic subjects, including asthmatics, responded similarly to the nonatopic subjects.	McLean et al. 1979
100 ppm	2-6 h/day, 5 weeks	No adverse effects on respiratory function and no increase in frequency of eye, nose, or throat irritation.	Ferguson et al. 1977
110 ppm	30 min	Highly intense odor; highly intense eye, nose, throat, and chest irritation, mild urge to cough, and moderate general discomfort.	Verberk 1977
110 ppm	1 h	Highly intense odor; highly intense eye, nose, throat, and chest irritation; moderate urge to cough; moderate general discomfort.	Verberk 1977
110 ppm	2 h	Highly intense odor; highly intense eye, nose, throat, chest irritation; urge to cough; general discomfort.	Verberk 1977
140 ppm	30 min	Highly intense odor; unbearable eye, nose, throat, and chest irritation; mild urge to cough; moderate general discomfort.	Verberk 1977
140 ppm	1 h	Highly intense odor; unbearable eye, nose, throat, and chest irritation; moderate urge to cough; moderate general discomfort.	Verberk 1977
140 ppm	2 h	Highly intense odor; unbearable eye and nose irritation; highly intense throat and chest irritation; highly intense urge to cough; unbearable general discomfort.	Verberk 1977
143 ppm	5 min	Nose, eye, throat, and chest irritation; lacrimation.	Industrial Bio-Test Laboratories 1973
500 ppm	15-30 min	Nose and throat irritation; nasal dryness and stuffiness; excessive lacrimation; hyperventilation; unbearable.	Silverman et al. 1949
570 ppm	Single breath	Threshold for reflex glottis closure, 21 to 30-year-old subjects.	Erskine et al. 1993
1,000 ppm	Single breath	Threshold for reflex glottis closure, 60-year-old subjects.	Erskine et al. 1993
1,000 ppm	NR	Immediate urge to cough.	Silverman et al. 1949
1,790 ppm	Single breath	Threshold for reflex glottis closure, 86 to 90-year-old subjects.	Erskine et al. 1993

[a]The categories from Verberk (1977) have been recategorized as follows: just perceptible = slight; distinctly perceptible = mild; nuisance = moderate; offensive = highly intense; unbearable = unbearable.
NR = not reported.

animals were observed for 14 days (MacEwen and Vernot 1972). Signs of eye and nasal irritation were seen immediately, followed by labored breathing and gasping. Surviving animals exposed to the low concentration weighed less than controls on day 14, and gross examination showed mottling of the liver and fatty changes at the two highest concentrations. All rats exposed to 6,210 ppm survived, and eight exposed to 7,820 ppm and nine exposed to 9,840 ppm died. The LC_{50} was 7,338 ppm (95% confidence interval = 6,822-7,893 ppm).

Appelman et al. (1982) calculated LC_{50} values for 7- to 8-week-old male and female Wistar rats exposed to ammonia by inhalation. Five animals of each sex per group were exposed to ammonia at concentrations ranging from 9,870 to 37,820 mg/m^3 (14,114-54,083 ppm) for 10, 20, 40, or 60 min and observed for 14 days. Clinical signs of toxicity during exposure included restlessness, closing of the eyes, signs of eye irritation (particularly for 60-min exposures), eye discharge (after 30 min), wet noses, and nasal discharge. Mouth breathing and signs of dyspnea also were observed; the signs of dyspnea disappeared within 24 h after exposure terminated. Gross findings included hemorrhagic lungs in animals dying early and those killed at termination. The lowest concentrations causing death were 23,389 mg/m^3 (33,446 ppm) for a 10-min exposure to males, 18,290 mg/m^3 (26,155 ppm) for a 20-min exposure (30% mortality) to males, 12,620 mg/m^3 (18,047 ppm) for a 40-min exposure to males, and 9,870 mg/m^3 (14,114 ppm) for a 60-min exposure to males and females. The LC_{50} values and mortality rates for male, female, and male and female rats combined as reported by Appelman et al. (1982) are summarized in Table 2-6. The data showed that the LC_{50} values were significantly higher in male rats than in females for the 20-, 40-, and 60-min exposures.

Coon et al. (1970) exposed male and female Sprague-Dawley or Long-Evans rats repeatedly or continuously to ammonia for various durations. No clinical signs of toxicity or gross pathologic findings were reported for 15 rats exposed to 222 ppm (155 mg/m^3) 8 h/day for 6 weeks. No deaths or clinical signs of toxicity were reported for 15 rats similarly exposed to 1,101 ppm (770 mg/m^3); nonspecific inflammatory changes, which were slightly more severe than in controls, were observed in the lungs. Continuous exposure of 15 rats to 57 ppm (40 mg/m^3) for 114 days resulted in no clinical signs of toxicity or other clinically significant effects compared with the controls. Continuous exposure of 48 rats to ammonia for 90 days resulted in no clinical signs of toxicity or other effects at 182 ppm (127 mg/m^3). Mild nasal discharge observed in about 25% of 49 rats was the only clinical sign attributed to the 90-day continuous exposure to 375 ppm (262 mg/m^3). Mild signs of dyspnea, nasal irritation, and 98% mortality occurred among 51 rats exposed to 651 ppm (455 mg/m^3) continuously for 65 days (exposure terminated early); histopathologic examinations were not conducted on these animals. Thirteen of 15 rats (87%) died during a 90-day continuous exposure to 672 ppm (470 mg/m^3). Histopathologic lesions included focal or diffuse interstitial pneumonitis in the lungs of all animals examined and renal tubular calcification, bronchial epithelial calcification, renal tubular epi-

TABLE 2-6 Acute Lethality Data for Male and Female Rats Exposed to Ammonia

Experimental Concentration (ppm)	Exposure Time (min)	Mortality Rate			LC_{50} (ppm)
29,959	10	0/5	0/5	0/10	
33,433		1/5	0/5	1/10	
37,766		5/5	1/5	6/10	37,094 (male)
38,925		5/5	0/5	5/10	44,945 (female)
54,083		5/5	4/5	9/10	40,300 (male and female)
26,155	20	3/5	0/5	3/10	
27,213		1/5	0/5	1/10	
28,814		5/5	2/5	7/10	25,511 (male)
29,201		3/5	3/5	6/10	32,661 (female)
33,176		5/0	4/5	9/10	28,595 (male and female)
18,047	40	2/5	0/5	2/10	
19,176		4/5	1/5	5/10	
22,694		4/5	1/5	5/10	17,532 (male)
23,295		5/5	3/5	8/10	23,724 (female)
24,081		5/5	2/5	7/10	20,300 (male and female)
14,114	60	2/5	1/5	3/10	
14,629		4/5	0/5	4/10	
16,159		5/5	0/5	5/10	14,086 (male)
17,875		5/5	1/5	6/10	19,691 (female)
18,933		5/5	2/5	7/10	16,600 (male and female)

Source: Appelman et al. 1982. Reprinted with permission; copyright 1982, *American Industrial Hygiene Association Journal*.

thelial cell proliferation, myocardial fibrosis, and fatty changes in the liver of several animals. These effects also occurred in control animals, but the severity was greater in the exposed animals.

3.1.2. Mice

Silver and McGrath (1948) calculated the LC_{50} value for mice exposed to ammonia (6.1-9.0 mg/L or 8,723-12,870 ppm) by inhalation for 10 min and observed for 10 days. The concentrations of ammonia in the exposure chamber were measured analytically. Each group consisted of 20 mice (sex and strain not specified). During exposure the mice closed their eyes, exhibited great excitement initially but soon became quiet, gasped, pawed, scratched their noses, and convulsed before dying. At the lowest concentration of 8,723 ppm, 25% of the animals died, and 80% died at the highest concentration of 12,870 ppm. Overall 90/180 mice died during the second 5-min of exposure and another eight died during the observation period. The other animals surviving exposure recovered rapidly. The LC_{50} for the 10-min exposure was 7.06 mg/L (10,096 ppm).

Groups of 10 male CF1 mice were exposed to ammonia at analytically measured concentrations of 0, 3,600, 4,550, or 5,720 ppm (0, 2,520, 3,185, 4,004 mg/m^3) for 1 h (MacEwen and Vernot 1972). Immediately upon exposure, the animals showed signs of nasal and eye irritation, followed by labored breathing and gasping. Animals surviving the low and intermediate concentrations lost weight during the 14-day observation period. Gross examination of surviving mice showed mild congestion of the liver at the intermediate and high concentrations. Three mice exposed to 4,500 ppm died, and nine exposed to 5,720 ppm died, but none exposed to 3,600 ppm died. The LC_{50} was 4,837 ppm (95% confidence interval = 4,409-5,305 ppm).

In a study by Hilado et al. (1977), four Swiss mice per group were exposed to 7,143-28,571 ppm of ammonia for 30 min. Exposure concentrations were calculated rather than measured analytically. One mouse died at 19,048 ppm, two at 21,429 ppm, three at 23,810 ppm, and four each at 26,190 and 28,571 ppm. All deaths occurred during exposure except the death at the lowest concentration, which occurred 1 day after exposure. No deaths occurred after exposure to concentrations of 14,286 ppm or lower. The LC_{50} value was reported as 21,000 ppm for the 30-min exposure. In 1978, Hilado et al. reported the LC_{50} as 21,430 ppm for the 30-min exposure; the previous value was probably rounded to two significant figures.

Kapeghian et al. (1982) determined the LC_{50} value for male albino ICR mice (12/group) exposed to 1,190-4,860 ppm of ammonia for 1 h. Concentrations of ammonia in the exposure chambers were measured analytically. The animals were observed for 14 days following exposure. A control group exposed to air only was included for comparison. Clinical signs, which were noted immediately and lasted 5-10 min, included excitation/escape behavior, rapid vigorous tail revolution, blinking and scratching (eye and nose irritation), and dyspnea. As signs of irritation decreased, the animals became less active and other signs of toxicity were noted, including tremors, ataxia, clonic convulsions, frothing, coma, final tonic extensor seizure, and death. At the higher concentrations, almost all deaths (90%) occurred during the first 15-20 min of exposure and as late as 45 min at the lower concentrations. Additional deaths occurred during the first 3 days following exposure. All deaths occurred at concentrations $\geq$3,950 ppm (25 to 100% mortality). The mortality response was 22/24 at 4,860 ppm; 8/12 at 4,490 ppm; 5/12 at 4,220 ppm; 3/12 at 3,950 ppm; and 0/12 at 3,440, 2,130, 1,340, and 1,190 ppm. The LC_{50} was 4,230 ppm for the 1-h inhalation exposure to ammonia. Other effects observed during the 14-day observation period included lethargy, dyspnea, weight loss, and a "humped back" appearance. The pathologic lesions occurring in mice that died during exposure included acute vascular congestion, intra-alveolar hemorrhage, disruption of alveolar septal continuity, and acute congestion of hepatic sinusoids and blood vessels. In animals surviving the 14-day observation period, pathologic lesions included mild to moderate pneumonitis (dose-related severity), focal atelectasia in the lungs (4,860 ppm), and degenerative hepatic lesions (dose-related sever-

ity, 3,440 to 4,860 ppm). The author did not discuss specific effects in animals exposed to concentrations less than 3,440 ppm.

Groups of 12 male albino ICR mice were exposed to ammonia at concentrations of 0, 1,350, or 4,380 ppm for 4 h and the effects of ammonia on hexobarbital-induced latency to hypnosis (time to loss of righting reflex) and sleeping time were assessed 1 h after exposure terminated (Kapeghian et al. 1985). All mice exposed to 1,350 ppm survived; three mice exposed to 4,380 ppm died during exposure and one died during hexobarbital hypnosis. Latency to hypnosis was significantly reduced in animals exposed to both concentrations compared with controls exposed to air only. Hexobarbital sleeping time was significantly increased in animals exposed to 4,380 ppm of ammonia. The hexabarbital effects were not attributed directly to exposure to ammonia.

3.2. Nonlethal Toxicity

3.2.1. Rats

Dalhamn (1956) studied the effect of inhaling ammonia on tracheal ciliary activity in male Wistar rats. Two or three rats per group were exposed to 0, 3, 6.5, 10, 20, 45, or 90 ppm of ammonia for 10 min. No effects were observed in rats exposed to air. In rats exposed to ammonia, ciliary activity ceased in 7-8 min with 3 ppm, 150 s with 6.5 ppm, 20 s with 20 ppm, 10 s with 45 ppm, and 5 s with 90 ppm. Thus, the time required for ciliary activity to cease showed a concentration-response relationship. Within 20-30 s after exposure was terminated, ciliary activity resumed.

The behavioral activity (wheel running) was assessed in three male Long-Evans rats exposed sequentially to the following concentrations of ammonia: 100, 300, 300, or 100 ppm for 6 h for each session with 2 days separating each session (Tepper et al. 1985). The activity of the rats on the running wheel was recorded during exposure and the time between exposures. The rats had previously been exposed to ozone in a similar experiment that was terminated 2 weeks before starting the experiment with ammonia. Controls were not described, but the performance of treated animals was compared to control performances, probably conducted before exposure to ozone. Exposure to 100 ppm of ammonia resulted in an immediate 61% reduction in activity compared with control activity; activity on the wheel ceased almost completely throughout exposure at 300 ppm. After termination of exposure to either 100 or 300 ppm, the activity of the rats steadily increased to 154% and 185%, respectively, compared with that of controls during the first 4 h postexposure.

Groups of eight male rats (Crl:COBS CD[SD]) were exposed to ammonia at concentrations of 15, 32, 310, or 1,157 ppm for 24 h (Schaerdel et al. 1983). No behavioral changes or evidence of irritation to the eyes or mucous membranes were observed. Blood gases (pO_2 and pCO_2) and pH were measured at 0, 8, 12, and 24 h; no changes were noted for pCO_2 and pH. Small changes within

the normal range for rats occurred for pO_2. Groups of seven rats were also exposed continuously to ammonia at concentrations of 0, 4, 24, 44, 165, or 714 ppm for 3 or 7 days. Minimal lesions were seen in the respiratory epithelium of the nasal cavity in animals exposed for 7 days (the authors did not indicate which concentrations of ammonia caused the lesions).

Pinson et al. (1986) showed that respiratory mycoplasmosis is exacerbated by exposure to ammonia. Groups of F344/N rats infected with *Mycoplasma pulmonis* or uninfected were exposed continuously to 100 ppm of ammonia for 3, 5, 7, and 9 days after inoculation to assess the histopathologic effect on the respiratory tract. Ammonia caused hyperplasia and degenerative lesions in the respiratory epithelium of the anterior nasal cavity. Submucosal inflammatory lesions were minimal in uninfected animals exposed to ammonia; these lesions were prominent in infected animals and more severe in infected animals exposed to ammonia. There were inconsistencies in the write-up of this report.

Groups of five female Wistar rats were exposed to gaseous ammonia at concentrations of 0, 25, or 300 ppm for 6 h/day for 5, 10, or 15 days (Manninen et al. 1988). Clinical signs of toxicity were not described. Gross lesions included large hemorrhages on the surfaces of the lungs in several exposed rats (exposure group not reported) and a few control rats, suggesting that the effect may not be treatment related. There were no signs of tracheobronchial or alveolar damage or histopathological effects in the respiratory tract. The liver and kidneys were normal in appearance.

3.2.2 Mice

Barrow et al. (1978) calculated RD_{50} values for ammonia, based on its sensory irritant effects on the upper respiratory tract of the mouse. The RD_{50} is the concentration expected to elicit a 50% reduction in respiratory rate. Barrow et al. predicted that the RD_{50} concentration would elicit intense sensory irritation and is expected to be rapidly incapacitating to humans. Groups of four outbred male Swiss Webster mice were exposed to ammonia by inhalation for 30 min. The authors did not report the concentration of ammonia inhaled by the mice, but judging by the graphic representations, the concentrations were 100, 200, 400, and 800 ppm. The maximum depression in respiratory rate was achieved within the initial 2 min of exposure, after which the response diminished. The RD_{50} was 303 ppm (95% confidence limits = 188-490 ppm) for a 30-min inhalation exposure to ammonia. There was no microscopic examination of the respiratory tract.

In a follow-up study, Buckley et al. (1984) assessed the histopathologic effects of repeated exposures to ammonia at the RD_{50} concentration of 303 ppm. Groups of 16-24 male Swiss-Webster mice were exposed to 303 ppm of ammonia for 6 h/day for 5 days; an unexposed group served as the control. The respiratory tract was examined in one-half the animals killed immediately after terminating exposure and in the other half killed 3 days later. The authors did not

describe any clinical signs of toxicity. Histopathological findings, which were confined to the respiratory epithelium of the nasal cavity, included minimal exfoliation, erosion, ulceration and necrosis; moderate inflammatory changes; and slight squamous metaplasia. No lesions were seen in the tracheobronchial or pulmonary regions.

In a similar study, Zissu (1995) exposed groups of 10 male Swiss OF_1 mice to ammonia at analytically measured concentrations of 0.3 × RD_{50} (78.0 ppm), RD_{50} (257 ppm), or 3 × RD_{50} (711 ppm) for 6 h/day for 4, 9, or 14 days. The three target concentrations were 90.9, 303, and 909 ppm. Control mice were exposed to filtered air. The entire respiratory tract was examined microscopically. No clinical signs of toxicity were noted for mice exposed to ammonia. Pathologic lesions including rhinitis with metaplasia and necrosis were seen only in the respiratory epithelium of the nasal cavity of mice inhaling 711 ppm (3 × RD_{50}); the severity of the lesions increased with duration of exposure, ranging from moderate on day 4, to severe on day 9, and very severe on day 14. No lesions were seen in the controls or in mice inhaling the lower concentrations of ammonia. In contrast to the study conducted by Buckley et al. (1984), this study showed no lesions in the nasal cavity of mice exposed to 257 ppm, which is near the RD_{50} of 303 ppm.

Behavioral activity (wheel running) was assessed in 6 male Swiss mice exposed sequentially to ammonia at 100, 300, 300, or 100 ppm for 6 h each session with 2 days separating each session (Tepper et al. 1985). The activity of the mice on the running wheel was recorded during each 6-h exposure and for 2 days after each exposure. These mice had been previously exposed to ozone in a similar experiment terminated 2 weeks before starting the experiment using ammonia. Controls were not described, but the performance of treated animals was compared to control performances, probably conducted before exposure to ozone. At 100 ppm, activity showed an initial increase during the first hour, followed by a marked decrease during the third and fourth hours, and an increase exceeding control activity during the fifth and sixth hours. At 300 ppm, activity was suppressed throughout exposure; it returned to control levels after exposure was terminated. The results suggest that the mice adapted to inhaling 100 ppm of ammonia but not to 300 ppm. The authors attributed the decreased activity to the sensory irritant property of ammonia.

3.2.3. Cats

Four groups of five stray mixed-breed cats were fitted with cuffed endotracheal tubes and subjected to a battery of pulmonary function tests (baseline results) followed by exposure to 1,000 ppm of ammonia gas for 10 min to evaluate the effect of ammonia on pulmonary function and lung pathology. Two unexposed cats were housed with the experimental cats for pathologic comparison (Dodd and Gross 1980). On days 1, 7, 21, and 35 following exposure, a group of cats was given pulmonary function tests, killed, and examined for gross

and microscopic lesions in the lungs. Signs of toxicity included poor general condition, severe dyspnea, anorexia, dehydration, bronchial breath sounds, sonorous and sibilant rhonchi, and coarse rales. Pulmonary function tests showed evidence of airway damage throughout the experiment and central lung damage on day 21. Gross examination of the lungs showed congestion, hemorrhage, edema, and evidence of interstitial emphysema and collapse. Bronchopneumonia, which caused the death of one animal, was commonly seen after day 7. Microscopic examination showed necrosis and sloughing of the bronchial epithelium accompanied by acute inflammation on day 1; no notable findings occurred in the bronchiolar or alveolar regions. Healing of the mucosal epithelium of the bronchi was noted on day 7, and varying degrees of bronchitis, bronchiolitis, bronchopneumonia, and bulbous emphysema were seen on days 21 and 35. The authors attributed the effects on days 21 and 35 to opportunistic bacteria or viruses. They suggested that the effects of ammonia are biphasic, consisting of an acute phase, which could cause death, and a secondary phase, which could cause debilitating chronic respiratory dysfunction.

3.2.4. Other Species

Boyd et al. (1944) exposed groups of healthy rabbits to ammonia at 10,010 ppm (range 5,005 to 12,441 ppm) [7,000 mg/m^3, range 3,500-8,700 mg/m^3] for 1 h before or after intratracheal cannulation, which was inserted to collect respiratory tracheal fluid. The mean survival time was 33 h for rabbits exposed before cannulation and 18 h for rabbits exposed after cannulation. Signs of toxicity included marked excitation during the early stages of exposure followed by a "curare-like paralysis." The major effects of exposure occurred in the respiratory tract at both concentrations, the tracheobronchial and pulmonary regions of animals exposed to ammonia after cannulation and the pulmonary region of animals exposed before cannulation. Microscopically, the trachea and bronchi appeared normal in rabbits exposed before cannulation but were severely damaged in animals exposed after cannulation. Bronchiolar (damage to epithelial lining) and alveolar effects (congestion, edema, atelectasis, hemorrhage, and emphysema) were similar in both groups.

Groups of three rabbits, 15 guinea pigs, two dogs, and three monkeys were exposed to ammonia 8 h/day for 6 weeks at concentrations of 222 or 1,101 ppm (155 or 770 mg/m^3; Coon et al. 1970). No clinical signs of toxicity or other clinically significant effects occurred in animals exposed to 222 ppm except for focal pneumonitis in one monkey. The only effects observed at 1,101 ppm were mild to moderate lacrimation and dyspnea in the dogs and rabbits during the first week of exposure only and nonspecific inflammatory changes in the lungs of guinea pigs. The same number of animals of each species was exposed continuously to 57 or 672 ppm (40 or 470 mg/m^3) for 90 days; no clinical signs of toxicity or other clinically significant effects were observed at 57 ppm. At 672 ppm, marked eye irritation (heavy lacrimation) and nasal discharge were seen in dogs

and erythema, discharge, and corneal opacity were seen in the rabbits. Hemorrhagic lesions occurred in the lungs of one dog and moderate lung congestion in two rabbits. Focal or diffuse interstitial pneumonitis was seen in all animals; renal tubular calcification, bronchial epithelial calcification, renal tubular epithelial cell proliferation, myocardial fibrosis, and fatty changes in the liver were observed in several animals of each species. Similar lesions were seen in control animals but were more severe in the treated animals. Four guinea pigs died during the experiment (Coon et al. 1970).

3.3. Summary

The LC_{50} values for mice and rats are presented in Table 2-7. The LC_{50} for rats ranged from 7,338 and 16,600 ppm for 60-min exposures to 40,300 ppm for a 10-min exposure. The LC_{50} for mice ranged from 4,230 ppm for a 60-min exposure to 10,096 ppm for a 10-min exposure. The lowest experimental concentrations associated with lethality are summarized in Table 2-8.

Rats exposed to lethal concentrations of ammonia showed signs of dyspnea and irritation to the eyes and nose and hemorrhage in the lungs (Appelman et al. 1982). Mice exposed to lethal concentrations of ammonia showed signs of irritation to the eyes and nose, labored breathing, and gasping, along with tremors, ataxia, convulsions, and seizures; pathologic lesions occurred in the alveoli (Silver and McGrath 1948; MacEwen and Vernot 1972; Kapeghian et al. 1982).

Nondisabling reversible effects in laboratory animals were mild after single exposures and transient after repeated exposures (subchronic duration), suggesting that adaptation occurred. Rats showed a decrease in tracheal ciliary activity during exposure to 3-90 ppm for 10 min (Dalhamn 1956), a decrease in motor activity (wheel running) during exposure to 100 ppm for 6 h, and a complete cessation of motor activity during exposure to 300 ppm for 6 h (Tepper et al. 1985). Mice exposed to the same concentrations of ammonia showed responses similar to those of the rats. Another study in rats exposed to concentrations of ammonia ranging from 15 to 1,157 ppm for 24 h did not show any behavioral changes or irritation to the eyes or mucous membranes; only minimal effects on the respiratory epithelium of the upper respiratory tract were seen after continuous exposure to concentrations up to 714 ppm for several days (Schaerdel et al. 1983). A 50% reduction in the respiration rate (RD_{50}) was noted in mice exposed to about 300 ppm for 30 min (Barrow et al. 1978). Repeated exposures of the mice to the RD_{50} for 6 h/day for 3 or 7 days did not cause pathologic lesions in the respiratory epithelium (Buckley et al. 1984), but exposure to approximately three times the RD_{50} (711 ppm) resulted in slight to moderate exfoliation, erosion, ulceration, and necrosis of the respiratory epithelium of the nasal cavity; no lower respiratory tract lesions were produced (Zissu 1995). The RD_{50} is considered to be incapacitating to humans (Barrow et al. 1978). There was no evidence of pulmonary lesions in mice or rats exposed to a single nonlethal concentration of ammonia.

TABLE 2-7 Comparison of Acute Lethality (LC_{50}) Data in Different Species

Species	LC_{50}		Exposure Time (min)	Reference
	mg/m^3	ppm		
Rat	28,130	40,300	10	Appelman et al. 1982
Mouse	7,060	10,096	10	Silver and McGrath 1948
Rat	19,960	28,595	20	Appelman et al. 1982
Mouse	14,986	21,430	30	Hilado et al. 1978
Rat	14,170	20,300	40	Appelman et al. 1982
Rat	5,131	7,338	60	MacEwen and Vernot 1972
Rat	11,592	16,600	60	Appelman et al. 1982
Mouse	3,383	4,837	60	MacEwen and Vernot 1972
Mouse	2,858	4,230	60	Kapeghian et al. 1982

TABLE 2-8 Lowest Experimental Concentrations Causing Death

Species	Concentration (ppm)	Exposure Time (min)	% Mortality	Reference
Mouse	8,723	10	25	Silver and McGrath 1948
Mouse	19,048	30	25	Hilado et al. 1977
Mouse	3,950	60	25	Kapeghian et al. 1982
Mouse	4,550	60	30	MacEwen and Vernot 1972
Mouse	4,380	240[a]	25	Kapeghian et al. 1985
Rat	33,433	10	10	Appelman et al. 1982
Rat	26,155	20	30	Appelman et al. 1982
Rat	18,047	40	20	Appelman et al. 1982
Rat	14,114	60	30	Appelman et al. 1982
Cat	1,000	10	5	Dodd and Gross 1980

[a]No observation period after exposure.

Signs of eye and respiratory irritation were observed in several species exposed continuously or repeatedly to ammonia for 6 weeks to 114 days (Coon et al. 1970). Except for nonspecific inflammation of the lungs at 1,101 ppm, repeated daily exposures to rats of 57 ppm for 114 days or 222 or 1,101 ppm for 6 weeks (8 h/day) produced no effects. Almost all rats died after continuous exposure to 651 or 672 ppm for 65 days. Repeated exposures to 1,101 ppm for 6 weeks (8 h/day) produced transient dyspnea and lacrimation in dogs and rabbits, whereas continuous exposure to 672 ppm for 90 days resulted in signs of irritation to the eyes and nose and pathologic lesions in the lungs of dogs and rabbits and pneumonitis in several species (dog, rabbit, guinea pig, and monkey). Studies on repeated exposures showed that mice are more sensitive than other species; for example, mice exposed to 771 ppm for only a few days showed pathologic effects, whereas other species required higher concentrations or longer exposure durations to produce pathologic or clinical effects (Coon et al. 1970).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism, Disposition, and Kinetics

Ammonia is a product of amino acid and protein metabolism; therefore, it is found naturally in the body. The normal concentration of ammonia in the blood of humans is about 1 μg/mL. The liver rapidly detoxifies ammonia to urea in order to maintain the isotonic system (Visek 1972; Pierce 1994).

The concentration of ammonia in blood remains stable (not altered significantly) after inhalation exposure of humans to very high concentrations of ammonia gas, indicating a lack of appreciable absorption from the respiratory tract or rapid detoxification. Leduc et al. (1992) reported normal concentrations of ammonia in the blood of a 28-year-old man exposed to an unknown concentration of ammonia gas that was sufficient to cause severe tracheobronchial injury. Swotinsky and Chase (1990) presented no supporting data but stated that individuals with impaired liver function could have elevated levels of ammonia in blood after inhalation exposure.

Silverman et al. (1949) reported no changes in blood or urine ammonia, urea, or nonprotein nitrogen in seven human subjects exposed to ammonia at concentrations of 350-500 ppm for 30 min. The concentration of ammonia in expired air remained stable at 350-400 ppm after 10-27 min of exposure, suggesting an equilibrium with the concentration in inhaled air. Within 3-8 min following exposure, the concentration of ammonia in expired air decreased to preexposure levels. The calculations of Silverman et al. indicated that, if all the retained ammonia was absorbed into the blood, there would have been no significant change in blood or urine urea, ammonia, or nonprotein nitrogen.

Animal studies have shown, however, that blood ammonia levels may be altered following inhalation exposure. Schaerdel et al. (1983) measured ammonia levels in the blood of rats 8, 12, and 24 h after inhalation exposures to 15, 32, 310, or 1,157 ppm of ammonia for 24 h. The values were corrected by preexposure concentrations (control). The blood ammonia concentrations 8 and 12 h after exposure to 15 and 32 ppm and 24 h after exposure to 15 ppm were slightly below those of the controls. The concentrations of ammonia in the blood of rats exposed to 310 and 1,157 ppm exceeded control levels and showed a peak at 8 h and time-related decreases at 12 and 24 h postexposure. Mayan and Merilan (1976) found no significant increase in the blood ammonia levels in male Holstein calves after exposure to 50 or 100 ppm of ammonia for 2.5 h compared with the preexposure levels. Blood urea nitrogen and pH were not significantly altered after exposure to ammonia. Adult female rabbits exposed to 50 or 100 ppm of ammonia for 2.5-3 h showed a significant increase in blood urea nitrogen at 100 ppm and no significant increase in blood pH (Mayan and Merilan 1972).

During exposure, ammonia is efficiently retained (scrubbed) in the nasopharyngeal region of the respiratory tract, thus protecting the lower regions from damage. However, the work by Silverman et al. (1949) indicated that scrubbing

of ammonia in the nasopharyngeal area is concentration and time dependent. Landahl and Herrmann (1950) showed that 91-93% of ammonia [concentrations = 40, 200, or 300 mg/m^3 (57, 286, or 429 ppm); flow rate = 18 L/min] inhaled by human subjects was retained in the respiratory tract during a single inspiration. At the same flow rate, 83% of inhaled ammonia was retained in the nose.

Mongrel dogs exposed to 150-500 mg/m^3 (215-715 ppm) of ammonia vapor retained 74-83% of the inhaled ammonia in the entire respiratory tract; 76-80% of inhaled ammonia can be retained in the upper respiratory tract (Egle 1973). The duration of exposure was not reported. Ventilatory rate and tidal volume had no effect on retention. Other experiments showed 78-80% retention in the lower respiratory tract and 88% retention in the upper respiratory tract when mechanical devices were used to bypass the upper and lower respiratory tracts.

4.2. Mechanism of Toxicity

Ammonia is an irritant gas that produces effects immediately on contact with moist mucous membranes of the eyes, mouth, and respiratory tract via the formation of ammonium hydroxide (a corrosive alkali) or the production of heat (Wong 1995). Because of its irritant properties, individuals coming into contact with ammonia vapor (or gas) will try to escape as quickly as possible (Swotinsky and Chase 1990). The odor threshold for ammonia is lower than its irritancy effect and serves as a warning of its presence.

4.3. Structure-Activity Relationship

Ammonia is an alkaline substance, and its corrosiveness is not different from that of other corrosive agents such as calcium, sodium, potassium hydroxide, and calcium oxide. Aerosols or vapors and fumes are very caustic on contact with moist mucous membranes, causing injury of the respiratory tract and eyes (Pierce 1994).

4.4. Other Relevant Information

4.4.1. Odor

The odor threshold for ammonia is between 5 and 53 ppm (Pierce 1994), suggesting that it has adequate warning properties. Ferguson et al. (1977) reported the odor threshold for ammonia in the presence of mixed odors as 10-20 ppm. The odor of ammonia at 30 ppm described as moderately intense by 2/6 subjects and highly penetrating by 3/6, indicating that the odor threshold was clearly exceeded at 30 ppm (MacEwen et al. 1970). A group of nonexpert and

expert subjects judged the odor of 50 ppm of ammonia to be just perceptible to nuisance during the first 30 min of exposure and just perceptible to offensive after 2 h.

Ferguson et al. (1977) conducted a study showing adaptation to concentrations up to 150 ppm of ammonia, with excursions up to 200 ppm, in individuals acclimated to 25-100 ppm for 1 week. More details of this study are described in Section 2.2.1.

4.4.2. Species Variability

ten Berge et al. (1986) found that mice are usually more sensitive (to irritants) than other mammals. The most direct comparison of mice and rats to inhalation exposure to ammonia can be found in Table 2-7 of this chapter. These data show that the mouse is 2.7 to 4 times more sensitive to inhalation exposure to ammonia than the rat.

4.4.3. Susceptible Populations

Erskine et al. (1993) showed that the glottis of elderly people (86-90 years old) is less responsive to inhalation exposure to ammonia than younger people (21-30 years old); the two age groups differed by a factor of 3. McLean et al. (1979) showed that nonatopic and atopic subjects, some of whom had a history of asthma, responded similarly in a nasal airway resistance (NAR) test to 100 ppm of ammonia introduced into each nostril under pressure for up to 30 s. The increased NAR was attributed to parasympathetic reflex and not to histamine release. Ammonia is water soluble and efficiently scrubbed in the nasopharyngeal regions; ammonia would not reach the tracheobronchial and pulmonary regions of the respiratory tract until the scrubbing action has been saturated. It is unlikely that concentrations detected only by odor or irritation to the nasal cavity or eyes would reach the tracheobronchial and pulmonary regions and have a differential effect on asthmatic individuals.

4.4.4. Concentration-Exposure Duration Relationship

Appelman et al. (1982) used multiple linear weighted regression to show the general correlation between concentration, time, and mortality expressed as probit. They derived the following equation:

$$\text{Probit} = a \ln c + b \ln t - q,$$

where a, b, and q are the regression parameters; c is the concentration (mg/m^3 or ppm); and t is the time of exposure. The values for regression parameters for the

combined sexes were as follows: a = 4.62, b = 2.30, and q = 47.8. The quotient for b/a is equal to n. Converting the above equation to

$$\text{Probit} = 2.30 \ln [C^{2.02} \times t] - 47.8$$

shows that the relationship of any concentration and time corresponding to a mortality rate can be expressed as $C^n \times t = k$, where n = 2.02. ten Berge et al. (1986) reported an n value of 2 and confidence intervals of 1.6 and 2.4 for ammonia. ten Berge et al. (1986) also noted that the value of the exponent n should be derived empirically.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Human data relevant for deriving the AEGL-1 value are summarized in Section 2.3, Table 2-5. Faint or no detectable irritation was reported for exposure to 30 ppm for 10 min (MacEwen et al. 1970), and moderate irritation was reported for exposure to 50 ppm for 10 min to 2 h (MacEwen et al. 1970; Verberk 1977). Moderate irritation also was reported for exposure to 80 ppm for up to 1 h. No adverse effect on respiratory function has been reported for exposure to ammonia at concentrations of 140 ppm for 2 h or up to 500 ppm for 30 min (Verberk 1977; Silverman et al. 1949).

5.2. Animal Data Relevant to AEGL-1

Animal studies were available, but none was judged to be adequate for deriving AEGL-1 values in view of the available human data.

5.3. Derivation of AEGL-1

Humans experience either faint or no irritation after exposure to ammonia at 30 ppm for 10 min (MacEwen et al. 1970); therefore, 30 ppm was used to derive AEGL-1 values. An interspecies uncertainty factor is not applied to these data because the AEGL value is based on human data. An intraspecies uncertainty factor of 1 was selected because ammonia is efficiently scrubbed in the upper respiratory tract, and if irritation occurs, it would be confined to the nasal cavity (and possibly the eyes). Nonatopic and atopic subjects, including asthmatics, responded similarly in a nasal airway resistance test when 100 ppm of ammonia was introduced into each nostril for up to 30 s (McLean et al. 1979); therefore, asthmatic individuals are not expected to respond differently than nonasthmatic individuals. Exercising subjects showed only a clinically nonsig-

nificant decrease in pulmonary function after exposure to higher concentrations of ammonia (Cole et al. 1977); therefore, exercise is not expected to cause an appreciable difference in effects experienced during exposure to AEGL-1 concentrations. The same value is proposed for 5, 30, 60, 240, and 480 min, because any effects that occur are not expected to become more severe with duration of exposure because adaptation occurs during prolonged exposure. AEGL-1 values are summarized in Table 2-9. The AEGL-1 value of 30 ppm for all time points is supported by observations that humans reported similar intensities of response after exposure to 50 ppm for 10 min to 2 h (MacEwen et al. 1970; Verberk 1977).

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

Data detailing disabling, irreversible, or long-term effects of ammonia were discussed in Section 2.2.1. The immediate response of individuals exposed to severe irritating concentrations of ammonia is to escape. Therefore, only those people who are incapacitated and unable to escape or those who are not rescued by others would remain in an atmosphere containing highly irritating concentrations of ammonia. They would be in danger with prolonged continuous exposure. The case studies on irreversible or long-term effects of ammonia did not report exposure concentrations and cannot be used to derive AEGL values. Several studies showing reversible irritation in humans had quantitative exposure data judged suitable for deriving AEGL-2 levels. These studies are summarized in Table 2-10. The subjects in the Verberk (1977) study were exposed to concentrations ranging from 50 to 140 ppm for durations ranging up to 2 h, and this study established exposure concentrations and durations of exposure considered to be offensive and unbearable but reversible. Other studies provide additional data to support to the Verberk study. Silverman et al. (1949) exposed subjects to 500 ppm of ammonia for 30 min by means of a half mask; there was no direct contact of the eyes with the ammonia. Ferguson et al. (1977) reported no adverse effects on respiratory function in human volunteers exposed for 2-6 h/day for 5 days to ammonia levels as high as 100 ppm.

There are difficulties in determining the ammonia concentrations associated with irreversible effects for the longer exposure times (4 or 8 h). Reversible

TABLE 2-9 AEGL-1 Values for Ammonia

5 min	10 min	30 min	1 h	4 h	8 h
30 ppm (21 mg/m^3)	30 ppm (21 mg/m^3)	30 ppm (21 mg/m^3)	30 ppm (21 mg/m^3)	30 ppm (21 mg/m^3)	30 ppm (21 mg/m^3)

TABLE 2-10 Nonlethal Effects of Ammonia on Humans and Experimental Animals

Species	Concentration (ppm)	Exposure Time (min)	Effect	Reference
Human	50	10	Moderate irritation (NOS).	MacEwen et al. 1970
Human	110	120	Irritation: eyes, nose, throat, chest.	Verberk 1977
Human	140	30	Irritation: eyes, nose, throat, chest; urge to cough.	Verberk 1977
Human	140	120	Nuisance irritation: eyes, throat; urge to cough.	Verberk 1977
Human	143	5	Irritation: eyes, mouth, nose, throat, chest.	Ind. Bio.-Test Lab. 1973
Human	571	One breath	Threshold for glottis closure in young males.	Erskine et al. 1993
Human	500	30	Only 2 of 7 subjects tolerated ammonia via nose breathing; irritation effects: nose and throat; lacrimation, hyperventilation, decreased respiratory function.	Silverman et al. 1949
Mouse	303	30	RD_{50} (50% depression in respiratory rate)	Barrow et al. 1978

[a]Based on $C^2 \times t = k$.
Abbreviations: NA, not applicable; NOS, not otherwise specified.

effects may become irreversible and irreversible effects may become lethal due to delays in medical treatment as well as to continued exposure. Furthermore, exposure concentrations were not measured for the cases in which severe but reversible damage occurred in the respiratory tract. Therefore, AEGL-2 levels for ammonia can be determined from studies reporting "unbearable" upper respiratory tract irritation, which could potentially impair the ability to escape, rather than the threshold for irreversible or long-term effects. The unbearable concentrations are much lower than those that would be associated with the threshold for irreversible damage to the respiratory tract.

6.2. Animal Data Relevant to AEGL-2

The RD_{50} (30-min exposure) of 303 ppm for the mouse (Barrow et al. 1978), which is predicted to cause intense sensory irritation and rapid incapacitation in humans, produced histopathological lesions in the nasal cavity but not

in the tracheobronchial or pulmonary regions in mice exposed repeatedly for 5 days (Buckley et al. 1984). Tepper et al. (1985) showed that mice exposed to 300 ppm ceased motor activity (wheel running) during the entire 6-h exposure period. These mice had prior ozone exposure that may have affected the outcome of the study.

6.3. Derivation of AEGL-2

The AEGL-2 values were based on "offensive" irritation to the eyes and respiratory tract experienced by nonexpert human subjects (unfamiliar with the effects of ammonia or with laboratory studies) exposed to 110 ppm of ammonia for 2 h (Verberk 1977). The responses of the nonexpert subjects ranged from "no sensation" to "offensive" for eye irritation, cough, or discomfort and from "just perceptible" or "distinctly perceptible" to "offensive" for throat irritation. No residual or irreversible effects were reported after termination of exposure, and pulmonary function was not affected by exposure. At the next higher concentration of 140 ppm, some subjects reported the effects to be unbearable and left the chamber between 30 min and 1 h; none remained for the full 2 h. Some irritation to the eyes, nose, throat, and chest along with a disagreeable odor are expected at the AEGL-2 level. An interspecies uncertainty factor is not applied to these data because the AEGL values are based on human data. An intraspecies uncertainty factor of 1 was selected because ammonia is a contact irritant, it is efficiently scrubbed in the upper respiratory tract, and any perceived irritation is not expected to be greater than that of the most sensitive nonexpert subject. The range of responses for this group is considered comparable to the range of responses that would be encountered in the general population, including asthmatics. Investigations have shown a link between nasal symptoms or allergic rhinitis and asthma, with rhinitis preceding the development of asthma (Corren 1997), and studies have shown that atopic subjects, including asthmatics, and nonatopic subjects respond similarly to a brief nasal exposure to ammonia (McLean et al. 1979). Exposure to exercising subjects showed only clinically nonsignificant changes in pulmonary function during exposure to ammonia at concentrations up to 336 ppm (Cole et al. 1977). In addition, a child experienced less severe effects than an adult exposed to very high concentrations of ammonia (Kass et al. 1972).

Time scaling across the pertinent timeframes was based on the ten Berge et al. (1986) equation ($C^n \times t = k$, where C = concentration, n = 2, and k is a constant). The value of n was derived from mouse and rat lethality data and was reported by Appelman et al. (1982) and ten Berge et al. (1986). The value of 110 ppm was adopted as the 4- and 8-h values, because the maximum severity rating for irritation in the Verberk (1977) study changed very little between 30 min and 2 h and is not expected to change for exposures up to 8 h. The 30-min value was also adopted as the 10-min AEGL-2 value because time scaling would yield a

10-min value (380 ppm) that might impair escape. The AEGL-2 values are summarized in Table 2-11.

The AEGL values are supported by other studies showing that exposures up to 100 ppm were tolerated by human subjects for 2-6 h without causing serious effects (Ferguson et al. 1977). The data of Cole et al. (1977) and Silverman et al. (1949) showed no serious irreversible effects at 336 or 500 ppm, respectively.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

Although numerous case studies describing lethal and potentially life-threatening exposures to ammonia resulting from various accidental releases were found in the literature, the lack of definitive information on actual exposure concentrations limits the usefulness of these studies for establishing AEGL-3 values. Substantial uncertainties are associated with the values derived from the gas dispersion models (WHAZAN and HGSYSTEM). In both cases, estimates for atmospheric ammonia concentrations were used as surrogates for exposure concentration. For the South Africa ammonia accident, the HGSYSTEM dispersion model did not address exposure estimates for the survivors sheltered inside buildings or the people located upwind from the release. This fact alone renders any analysis derived from the WHAZAN or RAM TRAC, which includes individuals sheltered inside buildings, inadequate for estimating human survival levels. The HGSYSTEM model of the South Africa accident may be unable to address releases from multiple sources, unable to model a delayed transport scenario or puff expansion in calm wind followed by wind transport, and is limited by the complex meteorological conditions (Mazzola 1996). In a more detailed analysis of the HGSYSTEM model and dose reconstruction models in general, Mazzola (1997) noted that (1) the absence of real-time meteorological data during and subsequent to the release would significantly limit the confidence in using HGSYSTEM modeling results; (2) the HGSYSTEM may be unable to accurately simulate the complex thermodynamics of anhydrous ammonia releases; (3) the HGSYSTEM is unable to address indoor concentrations; and (4) the Benign Bubble hypothesis cannot be proven in the absence of three-dimensional wind field data. Mazzola also noted other sources of uncertainties in the HGSYSTEM model of the Potchefstroom, South Africa, ammonia accident as reported by Mudan and Mitchell (1996); as the levels of uncertainty

TABLE 2-11 AEGL-2 Values for Ammonia

10 min	30 min	1 h	4 h	8 h
220 ppm (154 mg/m^3)	220 ppm (154 mg/m^3)	160 ppm (112 mg/m^3)	110 ppm (77 mg/m^3)	110 ppm (77 mg/m^3)

accumulate and become very large, confidence in the final results diminishes. Therefore, atmospheric ammonia concentrations generated by the HGSYSTEM model cannot serve as a surrogate for exposure and should not be used to derive AEGL values.

Because of the inability to estimate the response variable, the inability to estimate concentrations to individuals sheltered inside buildings, and the uncertainties associated with accident dose reconstruction as surrogates for exposure, animal data are preferred for deriving AEGL-3 values. Although there is an inherent weakness in extrapolating from experimental animal concentrations to human exposure, animal studies are strengthened by having measured exposure concentrations and known response data. Therefore, an approach using experimental animal data, where exposure estimates are more reliable, is recommended for deriving AEGL-3 values.

7.2. Animal Data Relevant to AEGL-3

Data from the rat studies reported by Appelman et al. (1982) and MacEwen and Vernot (1972) and the mouse studies reported by Silver and McGrath (1948), MacEwen and Vernot (1972), and Kapeghian et al. (1982) were considered relevant to deriving AEGL-3 values. The rat study by Appelman et al. and the mouse studies by Kapeghian et al. and MacEwen and Vernot were well conducted. However, the results of the Appelman et al. study were based on four different exposure durations, whereas only one exposure duration was used in the mouse studies by Kapeghian et al. and MacEwen and Vernot. ten Berge et al. (1986) noted that mice are more sensitive to respiratory irritants than other mammalian species. The two mouse studies, however, produced similar LC_{50} values (4,230 and 4,837 ppm), which increases the confidence in using the mouse data to derive the AEGL-3 values. In addition, probit analysis of the rat data reported by MacEwen and Vernot (1972) produced an LC_{50} value of 7,338 ppm for a 60-min exposure; this value is less than one-half the LC_{50} of 16,600 ppm derived by Appelman et al. The discrepancy in the two studies increases the uncertainty of using the rat data to derive AEGL-3 values. A study in the cat provided the lowest lethal concentration of 1,000 ppm (Dodd and Gross 1980). Lower respiratory tract lesions produced in cats exposed to ammonia are similar to those described for humans. However, the cats were exposed using a cuffed endotracheal tube, which bypassed the nasopharyngeal region where a significant amount of scrubbing occurs. This method of exposure could produce more severe tracheobronchial lesions than would occur from nose breathing. It should be noted that the cat study used only one ammonia concentration and one exposure duration; it was not designed to evaluate exposure-related effects. Because of inconsistencies in the results of the rat studies and the exposure method used for cat the study, the mouse studies are considered the most suitable for deriving AEGL-3 values.

7.3. Derivation of AEGL-3

LC_{01} values derived from the mouse and rat studies are presented in Table 2-12. AEGL-3 values are derived using the data for mice reported by Kapeghian et al. (1982) and MacEwen and Vernot (1972). The 60-min LC_{01} derived by the probit analysis of Kapeghian et al. is 3,317 ± 195 ppm (± standard error), and the 60-min LC_{01} derived by probit analysis of the MacEwen and Vernot data is 3,374 ± 376 ppm. The LC_{01} values from the two mouse studies are similar and both have small standard errors. These values compare closely with the 2,932 ppm 60-min LC_{01} derived from use of regression coefficients from the combined mouse datasets of Kapeghian et al. (1982) and Silver and McGrath (1948) as presented by ten Berge et al. (1986) (see Table 2-12). For comparison, LC_{01} values using the rat data reported by Appelman et al. (1982) and MacEwen and Vernot (1972) also are presented. The Benchmark Dose approach was applied to the Kapeghian et al. and MacEwen and Vernot mouse data; the resulting $BMDL_{05}$ values derived from the probit model are 3,278 and 3,219 ppm, respectively.

The mouse is unusually sensitive to exposure to respiratory irritants, including ammonia (ten Berge et al. 1986); therefore, an interspecies uncertainty factor of 1 was applied to the LC_{01} for the mouse. An uncertainty factor of 3 was applied to account for intraspecies variability because concentrations of ammonia that are life threatening cause severe tracheobronchial and pulmonary damage and these effects are not expected to be more severe in asthmatics than in nonasthmatics (McLean et al. 1979), more severe in children than adults (Kass et al. 1972), or more severe in exercising than in nonexercising individuals (Cole et al. 1977; see rationale for AEGL-2), but tracheobranchial and pulmonary effects may occur at a lower concentration in the elderly. Investigations showed that reflex glottis closure (protective mechanism) is 3-fold less sensitive in the elderly than in young subjects (Erskine et al. 1993); this mechanism may be

TABLE 2-12 LC_{01} Estimates for Ammonia Derived from Animal Data

Exposure Time (min)	Concentration (ppm)					
	Mouse[a]	Mouse[b]	Mouse[c]	Mouse[d]	Rat[a]	Rat[b]
5	9,800	11,688	11,487	6,031	34,356	17,899
30	4,104	4,772	4,690	2,462	14,134	7,307
60	2,932	3,374	3,317	1,741	10,024	5,167
240	1,494	1,687	1,658	871	5,042	2,584
480	1,067	1,193	1,172	616	3,575	1,827

[a]Concentrations derived using Appelman et al. (1982) regression coefficients $b_0 = 47.8$, $b_1 = 4.64$, and $b_2 = 2.30$ for the rat and ten Berge et al. (1986) regression coefficients $b_0 = 54.5$, $b_1 = 5.95$, and $b_2 = 2.89$ for the mouse.
[b]Derived from data reported by MacEwen and Vernot 1972; n = 2.
[c]Derived from data reported by Kapeghian et al. 1982; n = 2.
[d]Derived from data reported by Silver and McGrath 1948; n = 2.

applicable only when concentrations of ammonia exceed 570 ppm. A larger interspecies or intraspecies uncertainty factor would lower the 30-min AEGL-3 value to approximately 500 ppm, which was tolerated by humans without lethal or long-term consequences (Silverman et al. 1949). Therefore, applying a total uncertainty factor of 3 to the LC_{01} values of 3,317 or 3,374 ppm results in an AEGL-3 value of 1,100 ppm for the 1-h duration. ten Berge's equation was used to extrapolate to the relevant exposure durations. The value of n was calculated from the regression coefficients (b_1/b_2) for mouse data reported by ten Berge et al. (1986). The AEGL-3 values for 10, 30, 60, 240, and 480 min are presented in Table 2-13.

No verified lethal concentrations for ammonia in humans were found in the available literature. However, Silverman et al. (1949) reported that 1,000 ppm induced an immediate urge to cough. Legters (1980) noted that coughing may indicate that the adsorptive (scrubbing) capacity of the upper respiratory tract has been exceeded and that ammonia is penetrating the lower respiratory passages. Data presented in Section 2.1 show that death in humans exposed to ammonia is associated with damage to the lower respiratory tract, and data presented in Section 2.2.1 showed effects caused by ammonia on the lower respiratory tract that would be lethal without prompt medical attention. Therefore, concentrations of ammonia that exceed the scrubbing capacity of the upper respiratory tract and cause coughing, which indicates lower respiratory effects, have potentially serious effects. Although no experimental studies were available for exposures to ammonia for durations longer than 1 h, there is a need to derive AEGL-3 values for 4- and 8-h exposures. Kass et al. (1972) showed that the ammonia cloud formed after an accident does not always dissipate rapidly. In the accident with the railroad car, a heavy fog kept the ammonia cloud close to the ground for a prolonged period of time.

The AEGL-3 value for 8 h is supported by studies in rats, rabbits, guinea pigs, dogs, and monkeys showing that daily 8-h exposures to 1,101 ppm for 6 weeks caused no deaths (Coon et al. 1970). The only effects observed were nonspecific inflammation (rats and guinea pigs), lacrimation (dogs and rabbits), and dyspnea (dogs and rabbits).

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

The AEGL values are summarized in Table 2-14. Ammonia is irritating upon immediate contact with mucous surfaces of the eyes, mouth, and respiratory tract. The following factors were taken into account in proposing the AEGL values. Inhaling low concentrations of ammonia causes mild irritation to the eyes, nose, and throat, which is reversible upon termination of exposure. Individuals will attempt to escape immediately from atmospheres containing ammo-

TABLE 2-13 AEGL-3 Values for Ammonia

10 min	30 min	1 h	4 h	8 h
2,700 ppm (1,888 mgm^3)	1,600 ppm (1,119 mgm^3)	1,100 ppm (769 mgm^3)	550 ppm (385 mgm^3)	390 ppm (273 mgm^3)

TABLE 2-14 AEGL Values for Ammonia

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Primary References)
AEGL-1 (nondisabling)	220 ppm (154 mgm^3)	30 ppm (21 mgm^3)	30 ppm (21 mgm^3)	30 ppm (21 mgm^3)	30 ppm (21 mgm^3)	Mild irritation (MacEwen et al. 1970)
AEGL-2 (disabling)	220 ppm (154 mgm^3)	220 ppm (154 mgm^3)	160 ppm (112 mgm^3)	110 ppm (77 mgm^3)	110 ppm (77 mgm^3)	Irritation: eyes and respiratory tract, urge to cough (Verberk 1977)
AEGL-3 (lethal)	2,700 ppm (1,888 mgm^3)	1,600 ppm (1,119 mgm^3)	1,100 ppm (769 mgm^3)	550 ppm (385 mgm^3)	390 ppm (273 mgm^3)	Threshold for lethality (LC_{01}) (Kapeghian et al. 1982; MacEwen and Vernot 1972)

nia at concentrations considered highly irritating or intolerable. Reflex glottis closure and nasopharyngeal scrubbing may protect the lower respiratory tract from potential injury during brief exposures. When the scrubbing capacity of the nasopharyngeal region is exceeded, the potential for damage to the lower regions of the respiratory tract increases. Most deaths occur when damage causes pulmonary edema or airway obstruction. However, recovery from airway obstruction is usually assured with medical treatment, whereas pulmonary edema may lead to death even with medical treatment.

8.2. Comparison of AEGLs with Other Standards and Criteria

Table 2-15 summarizes standards and guidelines established by various agencies and organizations. The AEGL values are similar to the values recommended by other organizations and agencies. The 1-h ERPG-3 (750 ppm) is slightly less than the proposed AEGL-3 value of 1,100 ppm, the ERPG-2 value (150 ppm) is slightly less than the AEGL-2 value of 110 ppm, and ERPG-1 value (25 ppm) is the same as the AEGL-1 value. NIOSH's IDLH is slightly

TABLE 2-15 Extant Standards and Guidelines for Ammonia

Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	30 ppm	30 ppm	30 ppm	30 ppm	30 ppm
AEGL-2	220 ppm	220 ppm	160 ppm	110 ppm	110 ppm
AEGL-3	2,700 ppm	1,600 ppm	1,100 ppm	550 ppm	390 ppm
ERPG-1 (AIHA)[a]			25 ppm		
ERPG-2 (AIHA)			150 ppm		
ERPG-3 (AIHA)			750 ppm		
EEGL (NRC)[b]			100 ppm		100 ppm (24 h)
PEL-TWA (OSHA)[c]					50 ppm
IDLH (NIOSH)[d]		300 ppm			
REL-TWA (NIOSH)[e]					25 ppm
REL-STEL (NIOSH)[f]	35 ppm (15 min)				
TLV-TWA (ACGIH)[g]					25
TLV-STEL (ACGIH)[h]	35 ppm (15 min)				
MAK (Germany)[i]					20
MAK Peak Limit (Germany)[j]					
OELV (Sweden)[l] (Dutch)	50 ppm (15 min)				25 ppm
SMAC[m]			20 ppm		14 ppm (24 h)

[a]ERPG (emergency response planning guideline, American Industrial Hygiene Association) (AIHA 2000). 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-1 for ammonia is based on a concentration associated with a mild odor perception or mild irritation. 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 protective action. At the ERPG-2 level, ammonia will likely have a strong odor and cause some eye and upper respiratory irritation in susceptible populations, but serious effects are unlikely. 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. The ERPG-3 for ammonia is based on the median lethal concentrations of 7,340-16,600 ppm for the rat and 4,230-4,840 ppm for the mouse. This concentration may cause respiratory distress and severe eye and nasal irritation.

[b]EEGL (Emergency exposure guidance level, National Research Council) (NRC 1987). The EEGL is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace but avoids death, other se-

(Continued)

TABLE 2-15 Continued

vere acute effects, and long-term or chronic injury. The EEGL for ammonia is based on effects experienced by subjects exposed to it at 140 ppm for up to 2 h.

[c]PEL-TWA (permissible exposure limit–time-weighted average, Occupational Health and Safety Administration) (OSHA 1999) is defined analogous to the ACGIH TLV-TWA but is for exposures of no more than 10 h/day, 40 h/week.

[d]IDLH (immediately dangerous to life and health, National Institute of Occupational Safety and Health) (NIOSH 1997) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms or any irreversible health effects. The IDLH for ammonia is based on acute toxicity data in humans.

[e]REL-TWA (recommended exposure limit–time-weighted average, National Institute of Occupational Safety and Health) (NIOSH 1997) is defined analogous to the ACGIH TLV-TWA.

[f]REL-STEL (recommended exposure limit–short-term exposure limit) (NIOSH 1997) is defined analogous to the ACGIH TLV-STEL.

[g]TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value-time-weighted average) (ACGIH 2001) 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.

[h]TLV-STEL (Threshold Limit Value–short-term exposure limit) (ACGIH 2001) is defined as a 15-min TWA exposure, which should not be exceeded at any time during the workday even if the 8-h TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 min and should not occur more than four times per day. There should be at least 60 min between successive exposures in this range.

[i]MAK (maximale arbeitsplatzkonzentration [maximum workplace concentration]) (Deutsche Forschungsgemeinschaft [German Research Association] 2000) is defined analogous to the ACGIH TLV-TWA.

[j]MAK spitzenbegrenzung (peak limit [give category]) (Deutsche Forschungsgemeinschaft [German Research Association] 2000) constitutes the maximum average concentration to which workers can be exposed for a period up to 30 min with no more than two exposure periods per work shift; total exposure may not exceed 8-h MAK.

[k]MAC (maximaal aanvaarde concentratie [maximal accepted concentration]) (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is defined analogous to the ACGIH TLV-TWA.

[l]OELV (occupational exposure limit value) (Swedish National Board of Occupational Safety and Health 1996) is the maximum acceptable average concentration (time-weighted average) of an air contaminant in respiratory air. An occupational exposure limit value is either a level limit value (one working day) or a ceiling limit value (15 min or some other reference time period).

[m]SMACs (spacecraft maximum allowable concentrations) (NRC 2000) provide guidance on chemical exposures during normal operations of spacecraft as well as emergency situations. Short-term (1-24 h) SMACs refer to concentrations of airborne substances (such as a gas, vapor, or aerosol) that will not compromise the performance of specific tasks by astronauts during emergency conditions or cause serious or permanent toxic effects. Such exposures may cause reversible effects such as mild skin or eye irritation but are not expected to impair judgment or interfere with proper responses to emergencies. The 1- and 24-h SMACs are based on concentrations that would cause only slight mucosal irritation (Wong 1995).

higher than the value for the AEGL-2 30-min exposure. Mahlum and Sasser (1991) determined maximum exposure levels for operators in nuclear reactor control rooms. The recommended 2-min exposure limit was 300 ppm, which would allow a person to perform their task, don protective clothing, and suffer no long-lasting effects.

8.3. Data Adequacy and Research Needs

A large body of data was available for deriving AEGL values for ammonia. The studies on lethal or irreversible effects in humans did not have quantitative exposure estimates. However, human studies on upper respiratory tract irritation with quantitative exposure were available. In the human studies available, subjects were exposed to ammonia at concentrations that ranged from odor detection levels to concentrations causing "unbearable" irritation to the respiratory tract and eyes. Human studies using concentrations of ammonia higher than those reported in this document have the potential for causing more severe irritation and are not necessary for further documenting of exposure-response relationships in humans. The available human data were considered adequate for deriving AEGL-1 and -2 values. Lethality data were available for two animal species, and these data were considered adequate for deriving AEGL-3 values. The only data deficiency of note was the lack of lethal data for rodents for exposure periods longer than 1 h.

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APPENDIX A

Derivation of AEGL-1 Values

Key study:	MacEwen et al. 1970
Toxicity end point:	Faint or irritation (humans)
Time scaling:	None
Uncertainty factors:	Interspecies: NA Intraspecies: 1
Calculations:	
10-min: AEGL-1:	30 ppm/UF = 30 ppm/L = 30 ppm
30-min, 1-, 4-, and 8-h:	AEGL-1: Same as AEGL-1: 30 ppm

Derivation of AEGL-2 Values

Key study:	Verberk 1977
Toxicity end point:	Irritation: eyes and upper respiratory tract in humans
Time scaling:	$C^n \times t = k$; n = 2 (ten Berge et al. 1986)
Uncertainty factors:	1 for intraspecies variability; not applicable for interspecies sensitivity
Calculations:	
Point of departure:	110 ppm for 2 h
10-min AEGL:	Same as the 30-min value = 220 ppm
30-min AEGL-2:	$C^n \times t = k$; C = 110 ppm, t = 120 min, n = 2 $C = (k/t)^{1/2} = (1.45 \times 10^6$ ppm•min/30 min$)^{1/2}$ C = 220 ppm
1-h AEGL-2:	$C = (k/t)^{1/2} = (1.45 \times 10^6$ ppm•min/30 min$)^{1/2}$ C = 160 ppm

4-h AEGL-2: C = 110 ppm, same as the POD

8-h AEGL-2: C = 110 ppm, same as the POD

Derivation of AEGL-3 Values

Key study: Kapeghian et al. 1982;
MacEwen and Vernot 1972

Toxicity end point: Lethality: the LC_{50} for the two sets of mouse data were extrapolated to an LC_{01}

Time scaling: $C^n \times t = k$; n = 2 (ten Berge et al. 1986)

Uncertainty factors: Three for intraspecies variability; one for interspecies sensitivity

Calculations:

1-h AEGL-3: C = 3,317 ppm/3 (uncertainty factor) = 1,106 ppm
C = 3,374 ppm/3 (uncertainty factor) = 1,125 ppm

Kapeghian et al. 1982: $C^n \times t = k$; C = 1,106 ppm, t = 60 min, n = 2,
$k = 7.335 \times 10^7$ ppm•min
$C = (k/t)^{1/2} = (7.335 \times 10^7 \text{ ppm•min}/60 \text{ min})^{1/2}$
C = 1,106 ppm = 1,100 ppm

MacEwen and Vernot 1972: $C^n \times t = k$; C = 1,125 ppm, t = 60 min, n = 2,
$k = 7.59 \times 10^7$ ppm•min
$C = (k/t)^{1/2} = (7.59 \times 10^7 \text{ ppm•min}/60 \text{ min})^{1/2}$
C = 1,125 ppm = 1,100 ppm

10-min AEGL -3: $C = (k/t)^{1/2} = (7.335 \times 10^7 \text{ ppm•min}/10 \text{ min})^{1/2}$
C = 2,708 ppm = 2,700 ppm
$C = (k/t)^{1/2} = (7.59 \times 10^7 \text{ ppm•min}/10 \text{ min})^{1/2}$
C = 2,755 ppm = 2,700 ppm

30-min AEGL-3: $C = (k/t)^{1/2} = (7.335 \times 10^7 \text{ ppm•min}/30 \text{ min})^{1/2}$
C = 1,564 ppm = 1,600 ppm
$C = (k/t)^{1/2} = (7.59 \times 10^7 \text{ ppm•min}/30 \text{ min})^{1/2}$
C = 1,591 ppm = 1,600 ppm

4-h AEGL-3: $C = (k/t)^{1/2} = (7.335 \times 10^7 \text{ ppm•min}/240 \text{ min})^{1/2}$
$C = 553 \text{ ppm} = 550 \text{ ppm}$
$C = (k/t)^{1/2} = (7.59 \times 10^7 \text{ ppm•min}/240 \text{ min})^{1/2}$
$C = 562 \text{ ppm} = 560 \text{ ppm}$

8-h AEGL-3: $C = (k/t)^{1/2} = (7.335 \times 10^7 \text{ ppm•min}/480 \text{ min})^{1/2}$
$C = 391 \text{ ppm} = 390 \text{ ppm}$
$C = (k/t)^{1/2} = (7.59 \times 10^7 \text{ ppm•min}/480 \text{ min})^{1/2}$
$C = 398 \text{ ppm} = 400 \text{ ppm}$

APPENDIX B

Acute Exposure Guideline Levels for Ammonia

Derivation Summary for Ammonia AEGLS

AEGL-1 VALUES

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

Reference: MacEwen, J.D.; J. Theodore, and E. H. Vernot. 1970. Human exposure to EEL concentrations of monomethylhydrazine, AMRL-TR-70-102, Paper No. 23. In: Proc. 1st Ann. Conf. Environ. Toxicol., September 9-11, 1970, Wright-Patterson AFB, OH. Pp. 355-363.

Test species/Strain/Sex/Number: Humans.

Exposure route/Concentrations/Durations: Inhalation.

Effects: 30 ppm for 10 min: 2/6 subjects reported faint irritation; 3/6 reported no irritation; 1/6 provided no response.

End point/Concentration/Rationale: Faint irritation in human subjects exposed to 30 ppm of ammonia for 10 min. The responses by all subjects exposed to 30 ppm of ammonia were consistent with the definition of AEGL-1 or below the definition of AEGL-1.

Uncertainty factors/Rationale:
Total uncertainty factor: 1.
Interspecies: Not applicable.

Intraspecies: 1; Ammonia is a contact irritant and is efficiently scrubbed in the upper respiratory tract, particularly at the low AEGL-1 concentration; therefore, members of the population are not expected to respond differently to effects confined to the upper respiratory tract. Atopics, including asthmatics, and nonatopics responded similarly to a brief nasal exposure to ammonia. Exercising subjects showed only a clinically nonsignificant decrease in pulmonary function after exposure to ammonia.

(Continued)

AEGL-1 VALUES Continued

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

Modifying factor: 1.

Animal to human dosimetric adjustment: Not applicable.

Time scaling: The severity of upper respiratory tract irritation is not expected to increase with duration of exposure to low concentrations of ammonia; therefore, the same value is applied to all AEGL-1 exposure duration.

Data adequacy: Upper respiratory tract irritation at 30 ppm and above is well documented in the literature. Therefore, sufficient data were available to document the irritation threshold.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
220 ppm	220 ppm	160 ppm	110 ppm	110 ppm

Reference: Verberk, M.M. 1977. Effects of ammonia on volunteers. Int. Arch. Occup. Environ. Health 39:73-81.

Test species/Strain/Sex/Number: Humans, mixed sex; 8 expert and 8 nonexpert subjects.

Exposure route/Concentrations/Durations: Inhalation; 50, 80, 110, or 140 ppm for durations up to 2 h.

Effects: 50 ppm: just perceptible to offensive odor; no sensation to nuisance eye, nose, and throat irritation; no sensation to distinctly perceptible urge to cough, chest irritation, or general discomfort.
80 ppm: just perceptible to offensive odor; no sensation to offensive eye, nose, throat, and chest irritation and urge to cough; no sensation to nuisance general discomfort;
110 ppm: distinctly perceptible to offensive odor; no sensation to offensive eye, nose, throat, and chest irritation, urge to cough, or general discomfort;
140 ppm: just perceptible to offensive odor; just perceptible to unbearable eye irritation; no sensation to offensive nose, throat, and chest irritation, urge to cough, or general discomfort;
severity ratings: 0 = no sensation, 1 = just perceptible, 2 = distinctly perceptible, 3 = nuisance, 4 = offensive, and 5 = unbearable.

End point/Concentration/Rationale: 110 ppm for 2 h; respiratory tract and eye irritation and urge to cough ranged from “no sensation” to “offensive” during the 2-h exposure of the nonexpert subjects. The AEGL-2 derivation was based on the response (offensive irritation) of the most sensitive nonexpert subjects. The responses changed very little between 30 min and 2 h. The nonexperts considered the effects to be near the maximum response (offensive), whereas the expert responses were always of a lesser degree.

(Continued)

AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
220 ppm	220 ppm	160 ppm	110 ppm	110 ppm

Uncertainty factors/Rationale:
Total uncertainty factor: 1.
Interspecies: Not applicable.
Intraspecies: 1; Ammonia is a contact irritant and is efficiently scrubbed in the upper respiratory tract, and any perceived irritation experienced by the general public including sensitive individuals at low AEGL-2 concentrations is not expected to be greater than that of the most sensitive nonexpert subject. Atopics, including asthmatics, and nonatopics responded similarly to a brief nasal exposure to ammonia; a child experienced less severe effects than that of an adult exposed to high concentrations of ammonia; and exercising subjects showed only a nonclinically significant decrease in pulmonary function after exposure to ammonia.

Modifying factor: 1; POD was from a controlled exposure study on human subjects.

Animal to human dosimetric adjustment: Not applicable.

Time scaling: $C^n \times t = k$, where n = 2 based on an analysis of empirical mouse and rat lethality data in which the times of exposure ranged from 10 to 60 min (ten Berge et al. 1986). Values for 4 and 8 h are the same as the POD because the responses of the subjects did not change considerably between 30 min and 2 h and are not expected to change for exposures up to 8 h. The 10-min AEGL-2 is the same as the 30-min AEGL-2 because the time-scaled value of 380 ppm might impair escape.

Data adequacy: The AEGL-2 values were based on a study using human subjects exposed to ammonia for 2 h; the responses of the subjects ranged from "no sensation" to "offensive," which is expected to be comparable to the range of responses in the general public, including sensitive individuals. Case reports of long-term or irreversible effects in humans with exposure estimates were not available in the literature.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
2,700 ppm	1,600 ppm	1,100 ppm	550 ppm	390 ppm

References: MacEwen, J.D., and E.H. Vernot. 1972. Toxic Hazards Research Unit Annual Technical Report. SysteMed Report No. W-72003, AMRL-TR-72-62. Sponsor: Aerospace Medical Research Laboratory, Wright-Patterson AFB, OH. (I);
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Test species/Strain/Number: CF1 or ICR male mice, 10 or 12 per group.

(Continued)

AEGL-3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
2,700 ppm	1,600 ppm	1,100 ppm	550 ppm	390 ppm

Exposure route/Concentrations/Durations:
Inhalation: 0, 3,600, 4,550, or 5,700 ppm for 1 h (I).
Inhalation: 0; 1,190; 1,340; 2,130; 3,400; 3,950; 4,220; 4,860 ppm for 1 h (II).

Effects:
(I): Clinical signs: nasal and eye irritation, labored breathing, gasping, convulsions, and low body weight gain.
Mortality: 3,600 ppm (0/10), 4,500 ppm (3/10), and 5,720 ppm (9/10); LC_{01}: 3,374 ppm.
(II): Clinical signs: eye and nasal irritation, hypoactivity, labored breathing, ataxia, convulsions, weight loss.
(III): Mortality: ≤3,440 ppm (0/12), 3,950 ppm (3/12), 4,220 ppm (5/12), 4,490 ppm (8/12), and 4,860 ppm (12/12); LC_{01}: 3317 ppm.

End point/Concentration/Rationale: Lethality; LC_{01} = 3,374 ppm (I) and 3,317 ppm (II) for 1 h are the estimated thresholds for lethality derived by probit analysis of the data. Both numbers when divided by an uncertainty factor of 3 give the same result when the AEGL value is expressed to two significant figures.

Uncertainty factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1, The mouse was unusually sensitive to ammonia compared with other mammalian species. An UF of 3 would yield a 30 min AEGL-3 value below a level that humans can tolerate (500 ppm) for 30 min.
Intraspecies: 3, Life-threatening concentrations of ammonia cause severe tracheobronchial and pulmonary effects and these effects, are not expected to be more severe in asthmatics than in nonasthmatic individuals, more severe in children than in adults, or more severe in exercising than resting individuals, but tracheobronchial and pulmonary effects may occur at a lower concentration in the elderly than in young adults. Reflex glottis closure (protective mechanism) is 3-fold less sensitive in the elderly than in young subjects; this mechanism may only be applicable when concentrations of ammonia exceed 570 ppm.

Modifying factor: 1.

Animal to human dosimetric adjustment: 1.

Time scaling: $C^n \times t = k$ where n = 2 based on an empirical analysis of mouse and rat lethality data in which the durations of exposure ranged from 10 to 60 min (ten Berge et al. 1986).

Data adequacy: No quantitative exposure data were available for humans who died from exposure to ammonia. Lethality data were available for two animal species—mice and rats. The AEGL-3 values were based on two mouse studies that were in close agreement, although they were conducted 12 years apart by two different laboratories.

APPENDIX C

CATEGORY PLOT FOR AMMONIA

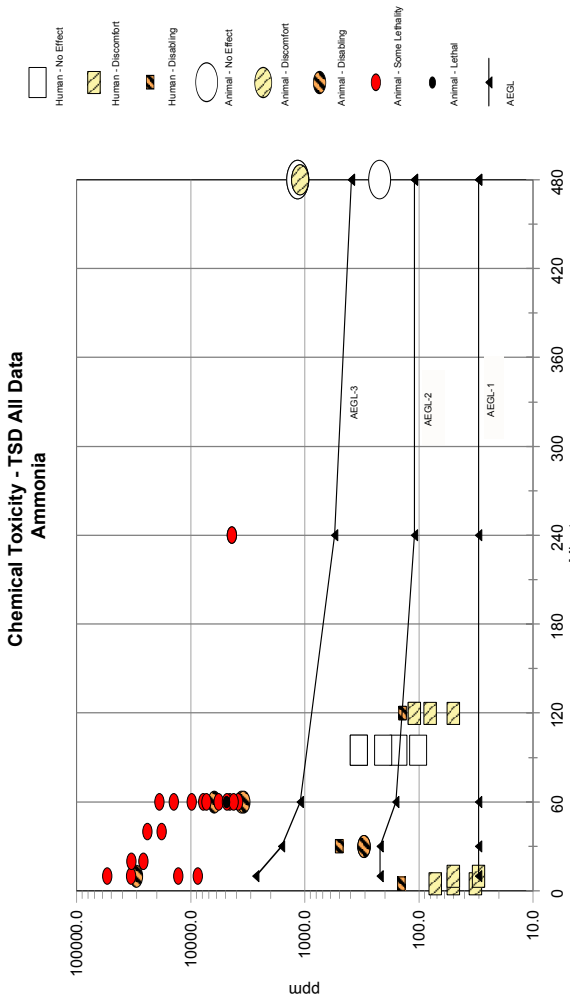

FIGURE 2-1 Chemical toxicity TSD all data—ammonia.

3

Aniline[1]

Acute Exposure Guideline Levels

UPDATE OF ANILINE AEGLS

In Volume 1 of the series Acute *Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2000), acute exposure guideline level (AEGL) values were developed for 30 minutes (min) and 1, 4, and 8 hours (h). Since that time, AEGL values have also been developed for 10-min exposures. This document updates Volume 1 to include 10-min values. The Summary below is from Volume 1 and contains additional discussion to address the development of 10-min values.

SUMMARY

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

[1]This document was prepared by AEGL Development Team members Robert Snyder and George Rodgers of the National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances (NAC) and Sylvia Talmage of the Oak Ridge National Laboratory. The NAC reviewed and revised the document, which was then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC Committee concludes that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NAC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

No reliable data on human exposures via the inhalation route were located. All AEGL values are based on a study in which rats were exposed to concentrations of 0, 10, 30, 50, 100, or 150 parts per million (ppm) for 8 or 12 h (Kim and Carlson 1986). The only reported effect was methemoglobin formation. The relationship between aniline concentration and methemoglobin formation appeared to be linear. Furthermore, the relationship between methemoglobin formation and time, between 3 and 8 h, was also linear when the aniline concentration was held constant at 100 ppm. Methemoglobin reached an asymptote at 8 h. Based on the linear relationships between aniline concentration and methemoglobin formation and between methemoglobin formation and time at a constant aniline concentration, a linear relationship between concentration and exposure duration ($C^1 \times t = k$) was chosen for time-scaling aniline concentrations to the appropriate AEGL exposure durations. Although the key study (Kim and Carlson 1986) used an 8-h exposure, methemoglobin measurements were taken at several time points during the study, and other studies with 4-h (E.I. du Pont de Nemours 1982; Pauluhn 2002) and 10-min exposures (Kakkar et al. 1992) support the derived AEGL values. Thus, the 8-h AEGL values from the Kim and Carlson study were extrapolated back to 10 min. Following a 10-min exposure, the concentration of methemoglobin in blood is unlikely to reach steady state, as typically seen 6-8 h after the initiation of exposure.

The AEGL-1 was based on an exposure of rats to a concentration of 100 ppm for 8 h, which resulted in elevation of methemoglobin from a control value of 1.1% (range, 0.4-2.1%) to 22%. A review of the published data indicates that methemoglobin levels of 15-20% in humans result in clinical cyanosis but no hypoxic symptoms. Although inhalation data for comparison purposes are not available, oral ingestion data suggest that humans may be considerably more sensitive to methemoglobin-forming chemicals than rats. Therefore, a default uncertainty factor of 10-fold was used for interspecies extrapolation (NRC 1993). Several sources also indicate that newborns may be more sensitive to methemoglobin-forming chemicals than adults. Because of the lack of specific quantitative data on sensitive human subpopulations and the fact that there are data suggesting greater susceptibility of infants, a default uncertainty factor of 10-fold was also used for intraspecies extrapolation. It is believed that an intraspecies uncertainty factor of 10 is protective of the general population, including susceptible individuals. A default uncertainty factor of 10 for each of the interspecies and intraspecies variabilities is also supported by the small database of information and the lack of reliable human inhalation studies. The data were scaled across time using $C^1 \times t = k$ because of data indicating a linear relationship between concentration and exposure duration as related to methemoglobin formation. The AEGL-1 values are supported by the data of Pauluhn (2002) in which dogs exposed to 46 ppm for 4 h had the same methemoglobin concentration (4.7%) as rats exposed to 50 ppm for 8 h (Kim and Carlson 1986; at 50 ppm, methemoglobin steady state in the blood is attained after several hours but prior to the full 8-h exposure).

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

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

Several studies with rats support the AEGL-3 values. A 10-min exposure to aniline at 15,302 ppm resulted in no clinical signs (Kakkar et al. 1992), and a 4-h exposure at 359 ppm (E. I. du Pont de Nemours 1982) resulted in severe toxic effects but no deaths. Dividing each of these values by a total uncertainty factor of 100 and scaling across time using $C^1 \times t = k$ results in values similar to those derived from the Kim and Carlson study. Studies with repeated exposures of rats resulted in additional effects on the blood and spleen, but concentrations up to 87 ppm, 6 h/day, 5 days/week, for 2 weeks were not disabling or life-threatening.

The derived AEGLs are listed in Table 3-1. Because aniline is absorbed through the skin in quantities sufficient to produce systemic toxicity, a skin notation was added to the summary table. The reported odor threshold for aniline ranges from 0.012 to 10 ppm. Therefore, the odor of aniline will be noticeable by most individuals at the AEGL-1 concentrations. The odor is somewhat pungent but not necessarily unpleasant.

TABLE 3-1 Summary of AEGL Values for Aniline[a]

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1[b] (nondisabling)	48 ppm (182 mg/m^3)	16 ppm (61 mg/m^3)	8.0 ppm (30 mg/m^3)	2.0 ppm (7.6 mg/m^3)	1.0 ppm (3.8 mg/m^3)	22% methemoglobin: cyanosis (Kim and Carlson 1986)
AEGL-2 (disabling)	72 ppm (274 mg/m^3)	24 ppm (91 mg/m^3)	12 ppm (46 mg/m^3)	3.0 ppm (11 mg/m^3)	1.5 ppm (5.7 mg/m^3)	41% methemoglobin: lethargy (Kim and Carlson 1986)

(Continued)

TABLE 3-1 Continued

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-3 (lethal)	120 ppm (456 mg/m^3)	40 ppm (152 mg/m^3)	20 ppm (76 mg/m^3)	5.0 ppm (19 mg/m^3)	2.5 ppm (9.5 mg/m^3)	>70% methemoglobin: lethality (extrapolated from data of Kim and Carlson 1986)

[a]Cutaneous absorption of the neat material may occur, adding to the systemic toxicity.
[b]The aromatic, amine-like odor of aniline will be noticeable by most individuals at these concentrations.

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4

Arsine[1]

Acute Exposure Guideline Levels

UPDATE OF ARSINE AEGLS TO INCLUDE 10-MINUTE VALUES

In Volume 1 of the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2000), acute exposure guideline level (AEGL) values were developed for 30 minutes (min), and 1, 4, and 8 hours (h). Since that time, AEGL values have also been developed for 10-min exposures. This document updates Volume 1 to include 10-min values. The Summary below is from Volume 1 and contains additional discussion to address the development of 10-min values.

SUMMARY

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

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

[1]This document was prepared by AEGL Development Team member Richard Thomas of the National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances (NAC) and Robert Young of the Oak Ridge National Laboratory. The NAC reviewed and revised the document, which was then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC Committee concludes that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NAC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

Exposure-response data from animal studies were used to derive AEGL values for arsine. AEGL values derived with animal data that had complete exposure data were more scientifically valid than AEGLs estimated from limited anecdotal human data. The greater conservatism afforded by the animal data is justified by the incomplete and often equivocal data for human exposures, the documented extreme toxicity of arsine, and the known latency involved in arsine-induced lethality. The AEGL values for the various exposure periods of concern (10 min, 30 min, 1 h, 4 h, and 8 h) were scaled from the experimental exposure duration using exponential scaling ($C^n \times t = k$, where C is exposure concentration, t is exposure duration, and k is a constant). Data were unavailable to empirically derive a scaling factor (n) for arsine. The concentration exposure-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived exponent, and to obtain conservative and protective AEGL values, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation.

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

The AEGL-2 values were based on exposure levels that did not result in significant alterations in hematologic parameters in mice exposed to arsine for 1 h (Peterson and Bhattacharyya 1985). Uncertainty factor application included a factor of 10-fold interspecies variability because of uncertainties regarding species-specific sensitivity to arsine-induced hemolysis. Uncertainty regarding intraspecies variability was limited to a factor of 3-fold, because the hemolytic response is likely to occur to a similar extent and with similar susceptibility in most individuals. This was based on the assumption that physiologic parameters (e.g., absorption, distribution, metabolism, structure of the erythrocyte and its response to arsine, renal responses) would not vary among individuals of the same species to such an extent that the response severity to arsine would be altered by an order of magnitude. Additionally, individual variability (i.e., variability in erythrocyte structure/function or response of the kidney to hemolysis) is not likely to have a significant impact on any of the proposed subcellular mechanisms of arsine toxicity. The steep exposure-response curves from animal data also affirm the limited variability in response. Furthermore, the AEGL-2

values were developed using an exposure resulting in no significant hemolysis in mice exposed to arsine at 5 ppm for 1 h, and, therefore, additional reduction of the values was unwarranted.

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

Time scaling was performed as previously described for the AEGL-2 tier. The three AEGL exposure levels reflect the narrow range between exposures resulting in minor effects and those producing lethality. A conservative approach in the development of AEGLs for arsine was justified by the confirmed steep dose-response curve, the induction of hemolysis by arsine at extremely low concentrations, and the potential of hemolysis to progress to life-threatening renal failure. It is also noted that all of the AEGL values are near or below the odor threshold for arsine. A summary of AEGL values is shown in Table 4-1.

TABLE 4-1 Summary of AEGL Values for Arsine

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1	NR[a]	NR[a]	NR	NR	NR	Not recommended due to steep dose-response relationship and mechanism of toxicity and because toxicity occurs at or below the odor threshold
AEGL-2	0.30 ppm (0.9 mg/m^3)	0.21 ppm (0.7 mg/m^3)	0.17 ppm (0.5 mg/m^3)	0.04 ppm (0.1 mg/m^3)	0.020 ppm (0.06 mg/m^3)	Absence of significant hematological alterations in mice consistent with the known continuum of arsine toxicity (Peterson and Bhattacharyya 1985)
AEGL-3	0.91 ppm (2.9 mg/m^3)	0.63 ppm (2.0 mg/m^3)	0.50 ppm (1.6 mg/m^3)	0.13 ppm (0.4 mg/m^3)	0.06 ppm (0.2 mg/m^3)	Estimated threshold for lethality in mice (Peterson and Bhattacharyya 1985)

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

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5

Crotonaldehyde, *trans* and *cis* + *trans*[1]

Acute Exposure Guideline Levels

PREFACE

Under the authority of the Federal Advisory Committee Act (P.L. 92-463) of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances has been established to identify, review, and interpret relevant toxicologic and other scientific data and develop acute exposure guideline levels (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, 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 parts per million [ppm] or milligrams per cubic meter [mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

[1]This document was prepared by the AEGL Development Team composed of Sylvia Milanez (Oak Ridge National Laboratory) and Doan Hansen (Chemical Reviewer) [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).

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 susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Crotonaldehyde is a colorless, flammable liquid and a potent eye, skin, and respiratory irritant. Inhaled crotonaldehyde can cause a burning sensation in the nasal and upper respiratory tract, lacrimation, coughing, bronchoconstriction, pulmonary edema, and deep lung damage. Crotonaldehyde is used primarily for the manufacture of sorbic acid and other organic chemicals. It is found in tobacco smoke and is a combustion product of diesel engines and wood but also occurs naturally in meat, fish, and many fruits and vegetables.

Crotonaldehyde exists as the *cis* and the *trans* isomer; commercial crotonaldehyde is a mixture of the two isomers consisting of >95% *trans* isomer. Because no in vivo exposure studies were located for the individual isomers (information was for the commercial mixture), the AEGL values in this document apply to both *trans*-crotonaldehyde (123-73-9) and the *cis-trans* mixture (4170-30-3).

AEGL-1 values were derived from a Health Hazard Evaluation conducted by National Institute for Occupational Safety and Health (NIOSH) in which workers exposed to approximately 0.56 ppm of crotonaldehyde for <8h reported occasional minor eye irritation (Fannick 1982). The same exposure concentration was adopted for 10 min to 8 h because the critical end point (minor eye irritation in humans) was mild and mild irritant effects do not vary greatly over time. A total uncertainty factor of 3 was applied to account for intraspecies variability, because the eye irritation is a direct surface-contact effect not subject to pharmacokinetic differences between individuals.

AEGL-2 values were based on a pulmonary function study in which rats were exposed for 5-240 min to 10-580 ppm of crotonaldehyde; individual exposure concentrations and durations were not given (Rinehart 1967). Rats had reduced pulmonary gas uptake ability and, above 8,000 ppm-min, proliferative lesions of the respiratory bronchioles. Exposures above 16,000 ppm-min induced pulmonary edema and death. AEGL-2 values were calculated by dividing 8,000 ppm-min by 10, 30, 60, 240, or 480 min because concentration and time appeared to be equally important factors in altering the pulmonary uptake of CO and ether (supported by $n = 1.2$ derived from an LC_{50} study [a lethal concentration in 50% of the rats] by Rinehart [1967]). A total uncertainty factor of 30 was used: 10 for interspecies uncertainty (because the actual exposure concentration and time were not known for the key study and there was a lack of supporting animal studies) and 3 for intraspecies uncertainty (although human variability to crotonaldehyde toxicity is not well-defined, a greater uncertainty factor was judged inappropriate because it yields 4- and 8-h AEGL-2 concentrations that caused only mild irritation in workers exposed for up to 8 h; Fannick 1982).

The AEGL-3 was based on an LC_{50} study in which rats were exposed to crotonaldehyde vapor for 5 min to 4 h (Rinehart 1967). Most deaths occurred by 4 days after exposure. The animals had clear or slightly blood-tinged nasal exudate; the rats that died within 1 day also had terminal convulsions. Necropsy showed that a few rats had pulmonary congestion. The 10-min, 30-min, 1-h, and 4-h AEGLs were obtained using the respective LC_{01} values calculated by probit analysis from the mortality data. The 8-h AEGLs were derived from the 4-h LC_{01} using the relationship $C^n \times t = k$, where $n = 1.2$ was derived by ten Berge et al. (1986) from this study LC_{50} data. A total uncertainty factor of 10 was applied: 3 for interspecies uncertainty because interspecies variability was small (LC_{50} values for rats, mice, and guinea pigs were within a factor of 2.5, and these studies yield similar or higher AEGL-3 values) and 3 for intraspecies uncertainty because great human variability is unlikely given the homogeneity of the animal data and a larger uncertainty factor yields 8-h AEGL-3 concentrations that caused only mild irritation in workers exposed for up to 8 h (Fannick 1982). A summary of AEGL values is shown in Table 5-1.

A cancer inhalation slope factor was derived for crotonaldehyde and used to estimate the 10^{-4} excess cancer risk from a single 30-min to 8-h exposure, as shown in Appendix D. Crotonaldehyde concentrations associated with a 10^{-4} excess cancer risk were 25-fold greater than the toxicity-based AEGL-2 values for 30 to 480 min. The noncarcinogenic end points were considered to be more appropriate for AEGL-2 derivation because (1) there is insufficient evidence that inhalation is a route that results in crotonaldehyde-induced liver lesions or neoplasia at concentrations comparable to the AEGL-2 values; (2) the data used to derive the cancer slope factor were very weak (the key study had only one dose group and one control group; the high dose was excluded due to lack of fit), and most of the neoplastic changes were benign; (3) AEGL values are applicable to rare events or single, once-in-a-lifetime exposures, and the data indicate that

TABLE 5-1 Summary of AEGL Values for Crotonaldehyde

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1[a] (nondisabling)	0.19 ppm (0.55 mg/m^3)	0.19 ppm (0.55 mg/m^3)	0.19 ppm (0.55 mg/m^3)	0.19 ppm (0.55 mg/m^3)	0.19 ppm (0.55 mg/m^3)	Mild eye irritation in humans (Fannick 1982)
AEGL-2 (disabling)	27 ppm (77 mg/m^3)	8.9 ppm (26 mg/m^3)	4.4 ppm (13 mg/m^3)	1.1 ppm (3.2 mg/m^3)	0.56 ppm (1.6 mg/m^3)	Impaired pulmonary function, NOAEL for bronchiole lesions (Rinehart 1967)
AEGL-3 (lethal)	44 ppm (130 mg/m^3)	27 ppm (77 mg/m^3)	14 ppm (40 mg/m^3)	2.6 ppm (7.4 mg/m^3)	1.5 ppm (4.3 mg/m^3)	Lethality NOEL (Rinehart 1967).

[a]Odor threshold has been reported as 0.035-1.05 ppm.

TNM neoplasms resulted from lifetime treatment; and (4) a direct comparison of estimated TNM cancer risk and AEGL values is not appropriate due to large differences in the methodologies used to obtain these numbers.

1. INTRODUCTION

Crotonaldehyde ($CH_3CH = CHCHO$) exists as a *cis* isomer (15798-64-8) and a *trans* isomer (123-73-9) or as a mixture of the two isomers (4170-30-3). Commercial crotonaldehyde (4170-30-3) consists of >95% *trans* isomer and <5% *cis* isomer (Budavari et al. 1996; IARC 1995). With the exception of one reported odor detection level, no physical or chemical data or human or animal studies were located for the *cis* or *trans* isomers individually; all available information was for the commercial (*cis*-*trans*) mixture. Therefore, the AEGL values prepared in this document will apply to both *trans*-crotonaldehyde (123-73-9) and the *cis*-*trans* mixture (4170-30-3). The Occupational Safety and Health Administration (OSHA), NIOSH, and the American Conference of Governmental Industrial Hygienists (ACGIH) have adopted the same occupational exposure limits (permissible exposure limit, recommended exposure limit, Threshold Limit Value) for both isomers.

Crotonaldehyde is a potent lacrimator and an extreme eye, respiratory, and skin irritant. Exposures to sufficiently high concentrations have produced choking, coughing, and a burning sensation on the face, in the nasal and oral passages, and in the upper respiratory tract as well as bronchoconstriction and pulmonary edema (HSDB 2005). Its odor threshold has been reported as 0.035-0.2

ppm (Verschueren 1996), 0.037-1.05 ppm (Ruth 1986), 0.038 ppm (Tepikina et al. 1997), and 0.12 ppm (*trans* isomer; Amoore and Hautala 1983).

Human exposure to crotonaldehyde occurs from both man-made and natural sources. Crotonaldehyde has been identified in exhaust from jet, gasoline; and diesel engines; from tobacco smoke; and from the combustion of polymers and wood (IARC 1995). Crotonaldehyde occurs naturally in meat, fish, many fruits (apples, grapes, strawberries, tomatoes) and vegetables (cabbage, cauliflower, Brussel sprouts, carrots), bread, cheese, milk, beer, wine, and liquors (IARC 1995). It is emitted from volcanoes, from the Chinese arbor vitae plant, and from pine and deciduous forests (IARC 1995; HSDB 2005). Crotonaldehyde has been detected in drinking water, wastewater, human milk, and expired air from nonsmokers.

Crotonaldehyde is a very flammable liquid (Budavari et al. 1996). It is manufactured commercially by adding aldol to a boiling dilute acid solution and removing the crotonaldehyde by distillation. Crotonaldehyde is used primarily for the production of sorbic acid; it is also used for the synthesis of butyl alcohol, butyraldehyde, quinaldine, thiophenes, pyridenes, dyes, pesticides, pharmaceuticals, rubber antioxidants, and chemical warfare agents and as a warning agent in locating breaks and leaks in pipes (IARC 1995, Budavari et al. 1996; Verschueren 1996). Crotonaldehyde degrades in the atmosphere by reacting with photochemically produced hydroxyl radicals (half-life of about 11 h) or ozone (half-life of about 15.5 days; HSDB 2005).

U.S. production of crotonaldehyde in 1975 was >2,000 pounds, and about 463 pounds was imported into the United States in 1984 (HSDB 2005). The chemical and physical properties of crotonaldehyde are listed in Table 5-2; discrete information was not available for the *trans* isomer of crotonaldehyde, and the information given is for the *cis*-*trans* mixture (except for synonyms and the CAS registry numbers).

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Crotonaldehyde vapor "may be fatal" if inhaled or absorbed through the skin; no further information was provided (Eastman Chemical Co. 1998).

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold and Odor Awareness

A wide range of concentrations have been reported for the human odor detection and irritation thresholds for crotonaldehyde, perhaps in some cases due

TABLE 5-2 Chemical and Physical Data

Property	Descriptor or Value	Reference
Synonyms	4170-30-3: 2-butenal, crotonal, crotonic aldehyde, 1-formyl-propene, β-methylacrolein 123-73-9: (E)-2-butenal, (E)-crotonaldehyde, *trans*-2-butenal, *trans*-crotonaldehyde	IARC 1995
Chemical formula	$CH_3CH = CH - CHO$	Budavari et al. 1996
Molecular weight	70.09	Budavari et al. 1996
CAS registry number	4170-30-3 (mixture of *cis* and *trans* isomers) 123-73-9 (*trans* isomer)	IARC 1995
Physical state	Liquid	Budavari et al. 1996
Color	White liquid; yellows on contact with air	NIOSH 2002
Solubility in water	18.1 g/100 g at 20°C	Budavari et al. 1996
Vapor pressure	19 mmHg at 20°C	Verschueren 1996
Vapor density (air = 1)	2.41	Budavari et al. 1996
Liquid density (water = 1)	0.853 at 20/20°C	Budavari et al. 1996
Melting point	–76.5°C	Budavari et al. 1996
Boiling point	104.0°C at 760 mm	Budavari et al. 1996
Flammability/explosion limits	2.1-15.5%	NIOSH 2002
Conversion factors	1 mg/m^3 = 0.349 ppm; 1 ppm = 2.87 mg/m^3	Verschueren 1996, IARC 1995

to analytical measurement errors (Steinhagen and Barrow 1984). Amoore and Hautala (1983) reported the odor threshold to be 0.12 ppm for *trans*-crotonaldehyde, whereas the irritation threshold was 14 ppm and 19 ppm for the nose and eyes, respectively. In several secondary sources, the odor detection threshold for crotonaldehyde was given as 0.035-1.05 ppm and the irritation threshold was 8.0 ppm (Ruth 1986; Verschueren 1996). In a study in which 25 volunteers were exposed to 0.02-2.3 mg/m^3 (0.007-0.8 ppm) of crotonaldehyde, the odor was detected by several persons at the lowest concentration tested, and roughly half the people were able to detect the odor at 0.11 mg/m^3 (0.038 ppm; Tepikina et al. 1997). The test subjects were exposed to each concentration repeatedly (about 2-4 times) to eliminate guessing and also to "pure air" to give a point of reference (i.e., incidence of false positives). An unpublished source (van Doorn et al. 2002) reported 0.069 ppm and 0.063-0.2 ppm as the *trans*-crotonaldehyde and *cis*-crotonaldehyde odor detection thresholds, respectively (OT_{50}; i.e., concentration at which 50% of the odor panel observed an odor without necessarily recognizing it).

2.2.2. Experimental Studies

Twelve healthy males ages 18-45 were exposed for 10 or 15 min to 12 mg/m^3 (about 4.1 ppm) in a 100-m^3 chamber at 20-25°C with a wind velocity of 1 mph (exposure duration was unclear from the study text; Sim and Pattle 1957). Crotonaldehyde vapor was produced by bubbling air through a known volume of liquid until all of the liquid evaporated; air samples were analyzed for concentration by using a bubbler containing hydroxylamine hydrochloride solution at pH 4.5 and noting the pH change. The men reported the crotonaldehyde vapor to be highly irritating to all mucosal surfaces, particularly the nose and upper respiratory tract (Sim and Pattle 1957). Lacrimation occurred after an average of 30 s, but eye irritation "did not increase after onset of lacrimation." A confounding factor in the experiment was that there were no restrictions on the men's activities, and they were allowed to smoke tobacco during exposure; smoking or activity levels were not provided.

The threshold for crotonaldehyde irritation in humans was reported as 0.0005 mg/liter (L) (0.17 ppm; Trofimov 1962). In this experiment, volunteers inhaled crotonaldehyde vapor through a mask for 1 min; it was not specified how the vapor was generated or how the concentrations were measured. Factors taken into account were odor detection and irritation of the eyes and mucous membranes of the nose and trachea; it was not specified on which of these end points the estimated irritation threshold was actually based. Trofimov suggested that the maximum permissible concentration of crotonaldehyde in air should be limited to 0.0005-0.0007 mg/L (0.17-0.24 ppm) to prevent irritation.

2.2.3. Occupational and Other Exposures

Laboratory personnel (two or three people) who "sniffed" 15 ppm of crotonaldehyde vapor for a few seconds (<30 s) during brief openings of animal chambers reported that the odor was very strong but not intolerable and that there was no eye discomfort. The personnel who "sniffed" 45-50 ppm of crotonaldehyde vapor only momentarily noted that the odor was "very strong, pungent, and disagreeable, but not particularly biting to nasal passages" (Rinehart 1967, 1998). Lacrimation was not induced in the subjects, although they experienced a burning sensation of the conjunctivae and a strong desire to blink repeatedly.

NIOSH conducted a Health Hazard Evaluation in a chemical plant (Sandoz Colors and Chemicals) in East Hanover, New Jersey, at the request of workers at the plant, some of whom complained of occasional minor eye irritation (Fannick 1982). NIOSH measured crotonaldehyde air concentrations using midget impingers; analysis was performed using gas chromatography with flame ionization detection. Eight air samplers were placed near the vats of chemicals and two were worn by the NIOSH industrial hygienist, who was near the vats most of the time. These measurements likely overestimated the actual exposure concentrations because workers were allowed to move about and were not near

the vats during an entire 8-h work shift. NIOSH determined that the average crotonaldehyde concentration of general air samples was 1.6 mg/m^3 (0.56 ppm; range, <0.35 to 1.1 ppm; 0.35 ppm was the limit of quantitation). The two personal samples were 0.66 and 0.73 ppm. These workers were also simultaneously exposed to acetic acid and small amounts of acetaldehyde (which occasionally caused a perceptible sweet odor), 3-hydroxybutyraldehyde, and dimethoxane. Crotonaldehyde was probably the most potent irritant among these chemicals, based on its greater quantity and its much lower RD_{50} (reference dose—the concentration that decreases the respiration rate of mice by 50% due to respiratory irritation [Schaper, 1993; Fannick 1982]).

Fieldner et al. (1954) reported that inhalation exposure to crotonaldehyde at 3.5-14 ppm was sufficiently irritating to wake a sleeping person and that 3.8 ppm was irritating within 10 s. Dalla Vale and Dudley (1939) compiled a list of "threshold values" that produce a noticeable odor in the air. The list included crotonaldehyde at 7.3 ppm, which the authors characterized as an eye and a nose irritant. (Experimental details for these two studies were not available.) A summary of the human studies is presented in Table 5-3.

2.3. Neurotoxicity

No human neurotoxicity studies were located for crotonaldehyde exposure by any route.

2.4. Developmental and Reproductive Toxicity

No human studies were located that described developmental or reproductive effects resulting from acute exposure to crotonaldehyde.

2.5. Genotoxicity

Crotonaldehyde (5-250 μM) induced sister chromatid exchanges, structural (but not numerical) chromosome aberrations, and micronuclei in cultured human lymphocytes and Namalva cells (a permanent lymphoblastoid cell line; Dittberner et al. 1995). The micronuclei were centromere-negative by fluorescence in situ hybridization using a human centromere-specific DNA probe, indicating crotonaldehyde was acting by a clastogenic mechanism.

Nath et al. (1998) compared the levels of crotonaldehyde adducts in gingival tissue DNA from human smokers and nonsmokers using a ^{32}P-postlabeling high-performance liquid chromatography method. Smokers had significantly higher levels of the DNA adducts than the nonsmokers (5.5- to 8.8-fold increase). Crotonaldehyde (without exogenous activation) also was shown to bind

TABLE 5-3 Human Crotonaldehyde Exposure Data

Exposure Concentration	Exposure Time	End Point and Confounding Factors	Reference
0.035-0.2 ppm 0.037-1.05 ppm 0.12 ppm	Undefined (a few seconds)	Odor thresholds from secondary sources; descriptions of most of the original studies were unavailable.	Verschueren 1996; Ruth 1986; Amoore and Hautala 1983
0.038 ppm	Undefined (few seconds)	Subjects were exposed multiple times. Roughly half detected odor at this air concentration.	Tepikina et al. 1997
0.17 ppm	1 min	Odor detection and/or irritation; exposure through mask; undefined analytical method.	Trofimov 1962
0.56 ppm (up to 1.1 ppm)	<8 h	Occasional eye irritation; concentration up to 1.1 ppm; co-exposure to other chemicals.	Fannick 1982
4.1 ppm	15 min (10 min)	Marked respiratory irritation; lacrimation in ~30 s; co-exposure to cigarette smoke.	Sim and Pattle 1957
3.5-14 ppm 3.8 ppm	Undefined 10 s	Irritation sufficient to wake a sleeping person "Irritating within 10 s; no further details.	Fieldner et al. 1954
7.3 ppm	Undefined (seconds?)	Very sharp odor and strong irritation to the eye and nose; no experimental details.	Dalla Vale and Dudley 1939
8 ppm 14 ppm (nose) 19 ppm (eyes)	Undefined (a few seconds)	Irritation threshold; methods used to determine or define "irritation" were not given.	Ruth 1986; Amoore and Hautala 1983; Amoore and Hautala 1983
15 ppm	<30 s	Lab workers "sniffed" crotonaldehyde. Odor strong but not intolerable; no eye discomfort.	Rinehart 1967
45-50 ppm	<30 s	Lab workers "sniffed" crotonaldehyde. Odor strong, pungent, and disagreeable; burning sensation of conjunctivae but no lacrimation.	Rinehart 1967

the DNA of human fibroblasts in vitro (Wilson et al. 1991). Hecht et al. (2001) showed that deoxyguanosine and DNA Schiff-base adducts that formed after crotonaldehyde exposure were unstable at the nucleoside level but stable in DNA.

2.6. Carcinogenicity

No human data were located that described carcinogenicity associated with crotonaldehyde exposure. In 1991 the U.S. Environmental Protection Agency (EPA) classified crotonaldehyde as in group C (a possible human carcinogen; EPA 2002) based on limited animal data (Chung et al. 1986; see Section 3.6). The International Agency for Research on Cancer (IARC) concluded that there was inadequate evidence for humans and in experimental animals to establish the carcinogenicity of crotonaldehyde and placed it in group 3 (not classifiable as to its carcinogenicity to humans; IARC 1995).

2.7. Summary

No information concerning acute lethal human exposure to crotonaldehyde was located. Values reported for the odor detection and irritation thresholds in humans were quite variable, ranging from 0.035 to 1.05 ppm and 0.17 to 14 ppm, respectively. The variation may be due to differences in exposure conditions or analytical measurements of concentration, which were often not reported. For example, laboratory workers who intentionally "sniffed" crotonaldehyde for a few seconds found 15 ppm strong but not intolerable, whereas in other studies 3.5-14 ppm (duration unknown) was sufficiently irritating to wake up a sleeping person, and volunteers exposed to 4.1 ppm for 15 min (and also possibly to tobacco smoke) experienced respiratory irritation and lacrimation after an average of 30 s. Workers exposed occupationally to concentrations up to 1.1 ppm crotonaldehyde (along with several other chemicals) reported occasional mild eye irritation. There are no data to indicate that crotonaldehyde is neurotoxic or a human carcinogen by any route of exposure. Crotonaldehyde was clastogenic in cultured human cells. Crotonaldehyde DNA adducts were detected in human buccal cells, in higher levels in smokers than nonsmokers. The chemistry of crotonaldehyde and its direct reactions with DNA and deoxyguanosine have been characterized.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Death resulting from acute inhalation exposure to crotonaldehyde has been reported in rats, mice, guinea pigs, and rabbits. The available studies are summarized in Table 5-4.

TABLE 5-4 Acute Lethality of Crotonaldehyde Inhalation Exposure in Animals

Species	Exposure Time	Concentration (ppm)	End Point; Reference
Rat	30 min	35-2450	LC_{50}= 1400 ppm. Gasping, eyes tightly shut, lacrimation, nose secretion during treatment; hyperemia in lungs, heart, kidneys, liver, spleen, and brain (Skog 1950).
Rat	1 min 10 min	"Saturated" (~40,000)	LC_0; no other effects described. $LC_{100;}$ no other effects described. (Smyth and Carpenter 1944; Smyth 1966; Union Carbide Corp. 1992)
Rat	6 h	35-98	$LC_{0;}$ rats had pink extremities, nasal irritation, and labored breathing
	6 h on days 1,2,4	94-108	$LC_{\geq 75}$; rats gasped, had pink extremities, one death after day 1, two after day 4 (other killed on day 5). Lungs were congested.
	6 h	133; 166; 359	$LC_{100;}$ all died within 2 days except for 1 rat inhaling 166 ppm; rats gasped, had nasal irritation, pink extremities, and weight loss.
	30-43 min; 2 h	2,094-16,229 907; 1,256	LC_{100}; death within 2 hours; gasping, pink extremities, tremors, convulsions, salivation, and prostration (Eastman Kodak Corp. 1992).
Rat	5 min 10 min 15 min 30 min 60 min 4 h	1,920-4,640 800-2,050 550-1,290 370-890 370-640 50-200	LC_{50} = 3132 LC_{50} = 1480 LC_{50} = 809 LC_{50} = 593 LC_{50} = 391 LC_{50} = 88	All rats gasped, had lowered respiratory rate, lost weight; excitatory stage was seen at ≥1000 ppm; most deaths by day 4, some had clear or blood-stained nasal discharge; few rats had pulmonary congestion (Rinehart 1967; see Table 5-5).
Rat	4 h	~70 (not stated)	LC_{50} = 70 ppm; no other effects described (Voronii et al. 1982).

(Continued)

TABLE 5-4 Continued

Species	Exposure Time	Concentration (ppm)	End Point; Reference
Mouse	2 h	~530 (not stated)	LC_{50} = 530; face rubbing, respiratory distress, excitation, convulsions, lung hemorrhage, edema in lungs and brain, glomerular capillary damage (Trofimov 1962).
Mouse	2 h	~200 (not stated)	LC_{50} = 200 ppm; no other effects described (Voronii et al. 1982).
Guinea pig	5 min 30 min 15 min 30 min	1,000 1,000 2,000 2,000	LC_0; no other effects described. LC_{50}; no other effects described. LC_{50}; no other effects described. LC_{100}; no other effects described (Smyth 1966).
Mouse Guinea pig	38 min 64 min 68 min 86 min	1,021 ppm vapor 2,663 mg/m^3 aerosol 1,021 ppm vapor 2,663 mg/m^3 aerosol	LC_{100} exposures. Animals blinked, closed their eyes, and rubbed their faces with their paws, then settled down and breathed deeply and slowly until they convulsed just prior to death. All animals had fluid in the pleural cavity and expanded, edematous, and hemorrhagic lungs with distended alveoli and ruptured alveolar septa due to bronchial constriction; livers appeared enlarged and there was fluid in the peritoneal cavity (Salem and Cullumbine 1960).
Rabbit	65 79min	1,02 1ppm vapor 2,663 mg/m^3 aerosol	

3.1.1. Rats

Skog (1950) obtained a 30-min LC_{50} of 4,000 mg/m^3 (1,400 ppm) for 48 white rats exposed to 100-7,000 mg/m^3 (35-2,450 ppm) of crotonaldehyde vapor (sex, individual concentrations tested, and rats per concentration were not given). Exposure concentrations were not measured analytically but were calculated from the amount of air used to vaporize a measured amount of liquid crotonaldehyde to achieve the target concentration. During treatment the rats gasped and jerked their heads backward at each breath, shut their eyes, lacrimated, and had heavy nose secretion. Exposure was followed by a 3-week observation period; all rats that died did so on or before the second day after treatment. The surviving animals breathed with a "snuffling" sound for 4-5 days after cessation of exposure. Histological examination of the lungs, heart, kidneys, liver, spleen, and brain from at least four rats revealed hyperemia and hemorrhage in the lungs, heart, liver, and kidneys; no edema was evident in the lungs.

Rinehart (1967) conducted an extensive series of experiments to assess the acute toxicity of crotonaldehyde in male Wistar rats. The rats were exposed for 5 min to 4 h and observed for 2 weeks; exposure concentrations and durations are given in Table 5-5. Crotonaldehyde vapors were generated by bubbling nitrogen gas through liquid crotonaldehyde (90% pure) and mixing this with air; the oxygen concentration was maintained at ≥17.8%. Exposure was in either a 20-L glass chamber or a 1,700-L wooden chamber (the latter was used for lower concentrations; which were not specified). Crotonaldehyde concentrations were measured two to five times over the exposure period using a colorimetric reaction with modified Schiff-Elvove reagent; the analytical concentrations were about 42% of the nominal concentration (range: 29-61%). Rinehart suggested that the discrepancy between the nominal and analytical concentrations was due to crotonaldehyde absorption on chamber walls, oxidation, and/or polymerization. The 30-min LC_{50} obtained by Rinehart (600 ppm) was about 2-fold lower than that obtained by Skog; 1950; 1,400 ppm). Rinehart suggested this difference may have been due to a loss of crotonaldehyde between the point of vapor generation and the animal breathing zone.

During exposure, rats inhaling ≥ 1,000 ppm developed an excitatory stage, and all treated animals had signs of respiratory distress (gasping and lowered respiratory rate) that persisted for several days in some cases. Treated rats lost up to 25% of their body weight within the first 3 days, roughly in proportion to their exposure concentration. Most deaths occurred within 4 days after exposure; these animals had clear or slightly blood-stained nasal discharge; rats that died within a day had terminal convulsions. Death from days 5-14 were attributed to secondary infections. Necropsy showed that a few animals had pulmonary congestion but that other organs were grossly normal. Rinehart visually estimated LC_{50} values from log-probit plots and obtained values similar to those that can be obtained by probit analysis using the method of Litchfield and Wilcoxon (the estimated and calculated LC_{50} values are shown in Table 5-5).

TABLE 5-5 Mortality of Rats Exposed to Crotonaldehyde Vapor for 5-240 Minutes

Exposure Time (min)	Analytical Concentration (ppm)	Cumulative Mortality at Selected Times After Exposure (days)					LC_{50} Calculated (estimated)[a]
		1	2	4	7	14	
5	1,920	0/5	0/5	0/5	0/5	0/5	3,132 ppm
	2,420	0/5	0/5	0/5	0/5	1/5	(3,150 ppm)
	2,680	0/5	1/5	1/5	1/5	1/5	
	3,180	3/5	3/5	3/5	3/5	3/5	
	4,160	4/5	4/5	4/5	4/5	4/5	
	4,640	4/5	5/5	5/5	5/5	5/5	
10	800	0/12	0/12	0/12	1/12	1/12	1,480 ppm
	1,110	0/12	0/12	0/12	1/12	4/12	(1,380 ppm)
	1,380	3/12	4/12	4/12	4/12	6/12	
	1,820	6/12	7/12	7/12	7/12	7/12	
	2050	8/12	8/12	9/12	9/12	9/12	
15	550	0/10	0/10	0/10	0/10	0/10	809 ppm
	680	0/10	2/10	2/10	2/10	2/10	(750 ppm)
	750	2/10	4/10	4/10	4/10	5/10	
	850	2/10	3/10	5/10	5/10	7/10	
	980	3/10	6/10	6/10	7/10	7/10	
	1,090	3/10	5/10	7/10	8/10	8/10	
	1,290	5/10	7/10	10/10	10/10	10/10	
30	370	0/10	0/10	0/10	0/10	0/10	593 ppm
	420	1/10	2/10	2/10	2/10	2/10	(600 ppm)
	530	2/10	4/10	4/10	4/10	4/10	
	675	4/10	6/10	6/10	6/10	6/10	
	800	5/10	7/10	7/10	7/10	8/10	
	890	6/10	9/10	9/10	9/10	9/10	
60	370	1/10	1/10	2/10	3/10	4/10	391 ppm
	400	3/10	4/10	5/10	5/10	6/10	(380 ppm)
	490	3/10	5/10	6/10	6/10	7/10	
	590	4/10	6/10	7/10	7/10	7/10	
	640	8/10	9/10	10/10	10/10	10/10	
240	50	0/10	0/10	1/10	1/10	1/10	88 ppm
	60	0/10	0/10	2/10	2/10	2/10	(85 ppm)
	70	0/10	1/10	3/10	3/10	4/10	
	100	4/10	5/10	5/10	5/10	6/10	
	120	5/10	5/10	8/10	8/10	8/10	
	200	6/10	6/10	9/10	9/10	9/10	

[a] LC_{50} for the 14-day mortality data were calculated by probit analysis in May 1998; values in parentheses are the LC_{50} estimates given by Rinehart (1967).

Source: Adapted from Rinehart 1967. Reprinted with permission; copyright 1967, *American Industrial Hygiene Association Journal*.

Several of the rat acute lethality studies summarized in Table 5-4 were sparsely described and omitted significant details of the experimental procedure and/or results. In related studies described by Smyth and Carpenter (1944), Smyth (1966), and Union Carbide Corp. (1992), six male albino rats exposed to a flowing stream of air saturated with crotonaldehyde vapor (about 40,000 ppm) for 1 min had 0 deaths, whereas exposure for 10 min killed the six rats in the ensuing 2-week observation period. Voronii et al. (1982) reported a 4-h LC_{50} of 200 mg/m^3 (70 ppm) for white rats during an observation period of 2 weeks. In preliminary acute toxicity studies, groups of three or four rats (sex and strain not specified) were exposed to nominal crotonaldehyde concentrations of 2,094-16,229 ppm for 30-43 min, 907 or 1,256 ppm for 2 h, 133-359 ppm for 6 h, or 94-108 ppm for 6 h/day on days 1, 2, and 4 (Eastman Kodak Corp. 1992). Many animals died, as shown in Table 5-4. Symptoms included gasping, labored breathing, pink extremities, tremors, convulsions, salivation, and prostration. Microscopic examination of unspecified animals revealed lung congestion.

3.1.2. Mice

Salem and Cullumbine (1960) exposed groups of 50 mice to a mean concentration of 2,925 mg/m^3 (1,021 ppm) of crotonaldehyde vapor or to 2,663 mg/m^3 of crotonaldehyde aerosol in a 1-m^3 plate-glass exposure chamber. The aerosol particle size was estimated to be 0.7 μm in diameter. Upon exposure, the mice initially blinked, closed their eyes, and rubbed their faces with their paws but then settled down and breathed deeply and slowly until they convulsed just prior to death. The mice died after an average exposure of 38 min for the vapor and 64 min for the aerosol. All animals had fluid in the pleural cavity and expanded, edematous, and hemorrhagic lungs with distended alveoli and ruptured alveolar septa due to bronchial constriction. The livers appeared enlarged, and there was fluid in the peritoneal cavity.

The mean lethal concentration or LC_{50} for white mice exposed to crotonaldehyde for 2 h was stated to be 530 ppm by Trofimov (1962) and 200 ppm by Voronii et al. (1982). Trofimov reported that the animals rubbed their faces with their paws and displayed respiratory distress and that microscopic examination showed lung hemorrhage, edema in the lungs and brain, and disintegration of renal glomerular capillaries.

3.1.3. Guinea Pigs

Three of six guinea pigs exposed to 2,000 ppm of crotonaldehyde vapor (nominal) for 15 min or 1,000 ppm for 30 min died. Exposure to 1,000 ppm (nominal) for 5 min resulted in 0 deaths, whereas six of the died from a 30-min exposure to 2,000 ppm (further details not provided; Smyth 1966).

All 20 guinea pigs died following exposure for an average of 68 min to crotonaldehyde vapor at 2,925 mg/m^3 (1,021 ppm) or for 86 min to crotonaldehyde aerosol at 2,663 mg/m^3 (0.7 μ in diameter) (Salem and Cullumbine 1960). Initially, exposed animals blinked, closed their eyes, and rubbed their faces with their paws but then settled down and breathed deeply and slowly until they convulsed just prior to death. All animals had fluid in the pleural cavity and expanded, edematous, and hemorrhagic lungs with distended alveoli and ruptured alveolar septa due to bronchial constriction. The livers appeared enlarged, and there was fluid in the peritoneal cavity.

3.1.4. Rabbits

Death ensued in five rabbits exposed for an average of 65 min to crotonaldehyde vapor at 2,925 mg/m^3 (1,021 ppm) or for 79 min to crotonaldehyde aerosol at 2,663 mg/m^3 (0.7 μ in diameter) (Salem and Cullumbine 1960). Initially, exposed animals blinked, closed their eyes, and rubbed their faces with their paws but then settled down and breathed deeply and slowly until they convulsed just prior to death. All animals had fluid in the pleural cavity and expanded, edematous, and hemorrhagic lungs with distended alveoli and ruptured alveolar septa due to bronchial constriction. The livers appeared enlarged, and there was fluid in the peritoneal cavity.

3.2. Nonlethal Toxicity

3.2.1. Rats

Alterations in pulmonary performance caused by exposure to 10-580 ppm of crotonaldehyde for 5 min to 4 h were investigated using Wistar rats (Rinehart 1967). Pulmonary performance was evaluated by measuring the rates of ether and CO absorption over a 24-h period following crotonaldehyde exposure; typical evaluations were at 1, 2, 6, 10, and 24 h postexposure (Rinehart 1998). A parallel drop in CO and ether uptake implies that the pulmonary ventilation rate was reduced (compared to preexposure levels); a greater drop in CO than ether absorption suggests that the diffusion rate of oxygen from air in the lungs into the blood was reduced (Rinehart and Hatch 1964). The individual concentrations and exposure times were not given; rather test responses were presented for five ranges of concentration times time (Ct) due to variations found among animals within any given exposure scenario. Twelve rats were tested in each exposure range, as shown in Table 5-6. Crotonaldehyde caused a parallel dose-dependent decrease in CO and ether uptake rates that were significant at the 5% or 10% level (for CO and ether, respectively) for Ct of ≥2,000 ppm-min. Death occurred in four animals before 24 h (time not specified) treated with 16,000-32,000 ppm-

TABLE 5-6 Pulmonary Responses of Rats That Inhaled 10-580 ppm of Crotonaldehyde for 5-240 min

Concentration × Time Range (ppm-min)	Geometric Mean Concentration × Time	Number of Animals	CO Uptake Rate (% of preexposure ± 1 SD)	Ether Uptake Rate (% of preexposure ± 1 SD)
Controls	0	12	99.5 ± 12.5	103.1 ± 12.8
1,000-2,000	1,330	12	92.9 ± 9.0	94.8 ± 9.4
2,000-4,000	2,730	12	89.9 ± 5.6**	92.8 ± 5.7*
4,000-8,000	5,390	12	86.7 ± 11.3**	91.0 ± 14.9*
8,000-16,000	10,940	12	73.3 ± 12.8**	81.2 ± 9.6**
16,000-32,000	21,430	10	58.3 ± 10.8**	67.0 ± 9.2**
16,000-32,000 (animals died)	28,900	4	<40	<40

Significantly different from controls: *$p \leq .10$, **$p < .05$.

Source: Rinehart 1967. Reprinted with permission; copyright 1967, *American Industrial Hygiene Association Journal*.

min (geometric mean = 28,900 ppm-min). Concentration and time were stated to be roughly equally important in determining toxicity. The maximal depression in the uptake of the gases occurred 6-10 h after treatment, with subsequent recovery taking 24-72 h. Animals exposed to >8,000 ppm-min and autopsied 3 days after exposure had proliferative lesions of the respiratory bronchioles. Edema was evident only at high Ct values (>16,000 ppm-min), where death occurred within 24 h. Based on these results, Rinehart (1967) concluded that "crotonaldehyde is predominantly a typical deep lung irritant," with the point of attack being the bronchiole and not the alveolus itself.

The concentration of crotonaldehyde calculated to reduce the respiration rate of male F344 rats by 50% upon exposure for 10 min (RD_{50}) was 23.2 ppm (Babiuk et al. 1985). Rats (four per concentration) were exposed to five to eight different concentrations (not specified). Crotonaldehyde vapor was generated in a modified impinger and was carried to the inlet of a head-only exposure chamber by a nitrogen stream; chamber concentrations were continuously monitored with an infrared gas spectrophotometer. Rats that were exposed 6 h/day for 9 days to 15 ppm of formaldehyde, followed by challenge on day 10 with crotonaldehyde, had a similar RD_{50} (20.5 ppm), indicating desensitization was not caused by prior formaldehyde inhalation (Babiuk et al. 1985).

Rats (sex and strain not specified) were exposed for 30 min to 12.7, 1.3, 0.28, 0.14, or 0.02 mg/m^3 of crotonaldehyde vapor (Tepikina et al. 1997). After 72 h, some animals were necropsied (exposure concentration not specified), and changes were seen in the morphology of the lung and liver tissues of rats exposed to 12.7 or 1.3 mg/m^3. The nature of the changes and the analytical technique used to measure crotonaldehyde in air were not described.

3.2.2. Mice

The RD_{50} (i.e., 50% reduction in respiration rate) values for crotonaldehyde vapor in male Swiss-Webster mice and B6C3F1 mice were 3.53 and 4.88 ppm, respectively (Steinhagen and Barrow 1984). Mice were exposed to crotonaldehyde for 10 min in a head-only exposure chamber, and their breathing rates were measured using plethysmographic techniques (Alarie 1966). The crotonaldehyde chamber concentrations were continuously monitored with an infrared gas spectrophotometer (Steinhagen and Barrow 1984).

3.2.3. Rabbits

The threshold concentration of crotonaldehyde in air that was irritating to the mucosa of rabbits was reported as 0.05 mg/L (17.5 ppm; Trofimov 1962).

Respiration and heart rate were significantly decreased in male rabbits that inhaled 5 ppm of crotonaldehyde for <10 min (Ikeda et al. 1980).

3.2.4. Cats

The threshold concentration of crotonaldehyde in air that was irritating to the mucosa of cats was 0.009 mg/L (3.15 ppm; Trofimov 1962).

3.3. Neurotoxicity

No neurotoxicity animal studies were located with crotonaldehyde exposure by any route.

3.4. Developmental and Reproductive Toxicity

No mammalian developmental or reproductive toxicity studies were located with crotonaldehyde exposure by any route.

3.5. Genotoxicity

Crotonaldehyde (≤0.5 μL/assay) was mutagenic in *Salmonella typhimurium* TA100 when tested using a modified liquid suspension protocol, with or without metabolic activation (Lijinsky and Andrews 1980; Neudecker et al. 1981, 1989; Lutz et al. 1982; Zeng et al. 1986; Eder et al. 1992, 1993). There was no evidence for mutagenicity using the standard Ames plate-incorporation assay (Simmon et al. 1977; Florin et al. 1980; Cooper et al. 1987). The *Salmo-*

nella tester strains TA1535, TA1537, TA1538, and TA98 did not show an increase in the number of revertants when using either the liquid suspension or plate incorporation methods (Florin et al. 1980; Lijinsky and Andrews 1980; Neudecker et al. 1981). The high cytotoxicity of crotonaldehyde and formation of pinpoint colonies confounded the assay (Eder et al. 1993).

Crotonaldehyde was not genotoxic in the SOS chromotest using *E. Coli* PQ37 and PQ243. In this test the *sfi A* gene-linked β-galactosidase activity is determined as a measure of the induction of the SOS repair system by xenobiotics. The lack of a response may have been a result of inadequate exposure concentration, which was intended to prevent crotonaldehyde bacteriotoxicity (Eder et al. 1992). When ethanol was used as the crotonaldehyde solvent instead of DMSO, a positive response was obtained with *E. Coli* PQ37 (Eder et al. 1993). A weak SOS response was seen in *Salmonella typhimurium* TA1535/pSK1002 without metabolic activation (Benamira and Marnett 1992).

Crotonaldehyde did not induce mitotic recombination in *Saccharomyces cerevisiae* D3 (Simmon et al. 1977).

Adult male *Drosophila melanogaster* injected with 3,500 ppm of crotonaldehyde (0.2-0.3 μL) 24-48 h before mating had a significant increase in sex-linked recessive lethals and in reciprocal (heritable) translocations (Woodruff et al. 1985). Males fed 4,000 ppm of crotonaldehyde for 3 days, however, failed to exhibit increased sex-linked recessive lethality. Chromosome breakage and reciprocal translocations were both detected.

Crotonaldehyde inhibited DNA synthesis in HeLa cells (Zeng et al. 1986) and induced chromosome aberrations and sister chromatid exchanges in CHO cells (Galloway et al. 1987). Unscheduled DNA synthesis was not induced by incubation of rat hepatocyte primary cell cultures with up to 7 mM crotonaldehyde (Williams et al. 1989).

Crotonaldehyde (without exogenous activation) was shown to bind to calf thymus DNA in vitro (Chung et al. 1984). In binding studies with nucleosides and 5-mononucleotides, crotonaldehyde formed three types of adducts with deoxyguanine and 2-deoxyguanosine 5-monophosphate (1,N^2 and 7,8 adducts, and 1,N^2 /7,8 bis-adducts), but there were no detectable products with the other nucleosides or 5-mononucleotides (Eder and Hoffman 1992). Crotonaldehyde DNA adducts were formed in CHO cells treated in culture (Foiles et al. 1990).

A ^{32}P-postlabeling method has detected the cyclic 1,N^2-propanedeoxyguanosine adduct (0.24 μmol/mol guanine) in the skin of mice treated topically with 1.4 mmol crotonaldehyde (Chung et al. 1989). Small amounts of this cyclic adduct have also been detected in the livers of untreated rats, mice, and humans (1.0-1.7, 0.2-1.0, and 0.3-2.0 adducts per 10^6 guanine residues, respectively; Nath and Chung 1994). DNA adducts were detected in the livers, lungs, kidneys, and large intestine (~3, 2, 1, and 0.5 adducts per 10^8 guanines) of 8-week old female F344 rats 20 h after receiving 300 mg/kg of crotonaldehyde in 1-mL corn oil by gavage (Eder et al. 1997). Most adducts were in the liver. No adducts were detected in untreated females in the same study.

Crotonaldehyde caused DNA-protein crosslinks in vitro, assayed using a filter-binding assay based on the precipitation of ^{3}H-labeled plasmid DNA (pUC13) bound to calf-thymus histones (Kuykendall and Bogdanffy 1992). A 2-h treatment of the shuttle vector plasmid pZ189 with crotonaldehyde caused DNA damage including point mutations, deletions, insertions, and inversions; the vector was transfected into the human lymphoblastoid cell line GM0621 (Czerny et al. 1998).

Oral (2 g/L for 50 days) or intraperitoneal administration of crotonaldehyde to strain Q mice caused production of polyploid cells at all stages of spermatogenesis, degenerated spermatogenic cells in the seminiferous tubules, and abnormal pairing of sex chromosomes at diakinesis or metaphase I (Moutschen-Dahmen et al. 1976; Auerbach et al. 1977).

3.6. Carcinogenicity

No inhalation exposure studies were located. One chronic oral bioassay was located in which male F344 rats were given 0, 0.6, or 6.0 mM of crotonaldehyde in drinking water for 113 weeks (Chung et al. 1986). This is equivalent to inhalation exposure to 0, 7.2, and 72 ppm, respectively, by route-to-route extrapolation, as described in Appendix D. The high-dose group had approximately 10% lower body weight gain starting at week 8, and 10 of 23 rats developed moderate to severe liver damage (fatty metamorphosis, focal necrosis, fibrosis, cholestasis, mononuclear cell infiltration). The incidence of hepatic neoplastic nodules and hepatocellular carcinomas combined was 0 of 23, 11 of 27 ($p < .01$), and 1 of 23 at 0, 0.6, and 6.0 mM, respectively (carcinoma: 0 of 23, 2 of 27, 0 of 23, respectively). The incidence of enzyme-altered liver foci, considered to be precursors to neoplasms, was 1 of 23, 23 of 27 ($p < .01$), and 13 of 23 ($p < .01$) at 0, 0.6 and 6.0 mM, respectively. No explanation was offered for the lack of a neoplastic dose-response. Interestingly, the 10 high-dose animals that had severe liver toxicity had no liver neoplasms, but the remaining 13 high-dose rats were found to have hepatocellular carcinomas. The authors state "it is worth noting" that two low-dose rats had urinary bladder papillomas (none in controls or high-dose group) but did not indicate whether they considered these tumors to be treatment related.

In 1991 EPA classified crotonaldehyde as a weight-of-evidence group C (possible human) carcinogen, although a quantitative estimate of the carcinogenic risk from oral exposure was not developed (EPA 2002). EPA classification was based on the increased incidence of hepatic neoplastic nodules and hepatocellular carcinomas (combined) in rats in the Chung et al. (1986) study (despite the lack of a dose-response), a lack of human data, crotonaldehyde genotoxic activity in some of the short-term tests, the anticipated reactivity of croton oil (a known tumor promoter) and aldehyde with DNA, and the fact that crotonaldehyde is a suspected metabolite of the probable human carcinogen *N*-nitrosopyrrolidine (EPA weight-of-evidence classification B2). Based on the

EPA's 1999 Draft Revised Guidelines, the most appropriate cancer classification descriptor for crotonaldehyde would be "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential" (EPA 1999). The ACGIH (1998) has assigned crotonaldehyde to the A3, animal carcinogen, classification. This was based on positive genotoxicity data (caused mutations, clastogenicity, and DNA adducts) and on the Chung et al. (1986) carcinogenicity study in which crotonaldehyde-treated rats developed liver neoplastic lesions and hepatocellular carcinomas.

The IARC (1995), however, noted that the increased incidences of hepatic neoplastic nodules and altered liver-cell foci in rats in the Chung et al. study were not seen at the high dose. IARC therefore concluded that there was inadequate evidence in both humans and experimental animals to establish the carcinogenicity of crotonaldehyde and placed it in group 3 (not classifiable as to its carcinogenicity to humans).

In addition to being a possible metabolite of *N*-nitrosopyrrolidine (Wang et al. 1988), crotonaldehyde is a metabolite of the suspected human carcinogen 1,3-butadiene (Cheng and Ruth 1993; Filser et al. 2001; EPA 2002).

3.7. Summary

In acute lethality studies, rats, mice, guinea pigs, and rabbits were exposed for 1 min to 6 h with crotonaldehyde concentrations ranging from 50 ppm to "saturated" vapor (about 40,000 ppm). Rat LC_{50} values for a given exposure period were about 2-fold lower than those for mice and guinea pigs, although in a second study the rat LC_{50} was comparable to that for the other two species. The differences in response may have been due to the use of nominal versus analytical concentrations. The animals in the acute lethality studies had breathing difficulties, lacrimation, blood-stained nose secretions, pink extremities, and body weight loss. Histological examination revealed ruptured alveolar septa and hemorrhage in the lungs, heart, liver, and kidneys. In a pulmonary function study, animals treated with >16,000 ppm-min died and some had lung edema, and rats exposed to >8,000 ppm-min developed proliferative lesions of the respiratory bronchioles. The respiration rate was reduced by 50% (i.e., RD_{50}) in rats exposed head only for 10 min to 23.2 ppm and in mice exposed head only to 3.53-4.88 ppm.

Crotonaldehyde was mutagenic in *Salmonella typhimurium* TA100 (± metabolic activation), caused induction of the SOS response in *E. Coli* PQ37, induced sex-linked recessive lethals and reciprocal translocations in *Drosophila melanogaster*, inhibited DNA synthesis, induced chromosome aberrations and sister chromatid exchanges, and was shown to bind to DNA in vitro and in vivo. Male rats given 0.6 or 6.0 mM of crotonaldehyde in their drinking water for 113 weeks developed hepatic neoplastic nodules, hepatocellular carcinomas, and altered liver foci, although the incidence was not dose related.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Little information was available regarding the metabolism and disposition of crotonaldehyde following inhalation exposure. One route of human crotonaldehyde excretion is milk: Crotonaldehyde was detected qualitatively in the milk of 1 of 12 lactating women who lived in an urban environment for ≥1 year, although the atmospheric crotonaldehyde levels were not reported (Pellizzari et al. 1982).

Male F344 rats given 2.8 mg/kg of [^{14}C]-crotonaldehyde intravenously excreted 31% of the administered radioactivity as $^{14}CO_2$ and 37% as urinary metabolites within 6 h of dosing. Elimination of crotonaldehyde increased to 40% in expired air and 50% in the urine after 72 h (NTP 1985). Essentially all the crotonaldehyde was metabolized, as <1% of the ^{14}C in the urine was parent compound. There was no significant radioactivity in any tissues or in the feces, suggesting that neither the parent compound nor its metabolites accumulated in the body.

[^{14}C]-Crotonaldehyde administered by gavage to adult male F344 rats at 0.7, 3, or 35 mg/kg was largely absorbed from the gastrointestinal tract: 60-78% was excreted in the breath and urine within 12 h of dosing, and after 72 h, this increased to 82-86% (NTP 1985). Approximately 7% of the administered radioactivity was eliminated in the feces.

Crotonaldehyde can be conjugated with glutathione with or without glutathione S-transferase activity (Esterbauer et al. 1991). Male albino and black-hooded rats injected subcutaneously with 0.75 mmol/kg (53 mg/kg) of crotonaldehyde in olive oil had 3-hydroxyl-1-methylpropyl and 2-carboxyl-1-methylpropyl-mercapturic acids in their urine (collected over 24 h), which represented 6-15% of the given dose (Gray and Barnsley 1971). Smaller amounts of 2-carboxy-1-methylethylmercapturic acid also were occasionally detected. Because crotonaldehyde caused rapid sulfhydryl depletion in an *in vitro* reaction with glutathione in buffer, Gray and Barnsley (1971) proposed that the thiol group of glutathione was adding to the double bond of crotonaldehyde, which was then hydrolyzed to form these metabolites in the rat.

4.2. Mechanism of Toxicity

Crotonaldehyde is a well-recognized severe eye and respiratory irritant, although little information regarding its mechanism of toxicity was available. It appears to be primarily a locally acting irritant; systemic effects were seen only after exposure to extremely high doses (i.e., which caused death within 2 h). Crotonaldehyde is a deep lung irritant, apparently acting at the level of the bronchioles (Rinehart 1967).

It has been suggested that depletion of reduced glutathione in cells is involved in cellular toxicity caused by crotonaldehyde (reviewed in ACGIH 1998). Human polymorphonuclear leukocytes (PMNLs) had a dose-related decrease in surface sulfhydryls and soluble sulfhydryls after in vitro treatment with crotonaldehyde (Witz et al. 1987) and a dose-dependent inhibition of PMNL adherence (assayed with nylon fiber columns) and chemotaxis (Bridges et al. 1980).

Crotonaldehyde caused ciliostasis in chicken tracheal organ cultures incubated for 5 min with 5 mM of crotonaldehyde (Pettersson et al. 1982). Since the basic mechanism of ciliated epithelia are likely similar in all organisms, including humans, Pettersson et al. suggested that the respiratory toxicity of inhaled crotonaldehyde may be due in part to its inhibition of ciliary movement.

4.3. Structure-Activity Relationships

Steinhagen and Barrow (1984) evaluated the sensory irritation potential of inhaled aldehydes in B6C3F1 and Swiss-Webster mice by comparing the concentrations that caused a 50% reduction in the respiration rate (RD_{50}). Saturated aliphatic aldehydes with ≥ 2 carbons (acetaldehyde, propionaldehyde, butyraldehyde, isobutyraldehyde, valeraldehyde, isovaleraldehyde, caproaldehyde, and 2-ethylbutyraldehyde) were the least irritating, with RD_{50} values of 750-4,200 ppm. Cyclic aldehydes (2-furaldehyde, cyclohexane carboxaldehyde, 3-cyclohexane-1-carboxaldehyde, and benzaldehyde) had RD_{50} values of 60-400 ppm. Unsaturated aliphatic aldehydes (formaldehyde, acrolein, and crotonaldehyde) were the most irritating, having RD_{50} values of 3.2/4.90, 1.03/1.41, and 3.53/4.88 ppm, respectively (in Swiss-Webster/B6C3F1 mice). The two strains of mice had similar RD_{50} values for any given chemical. Crotonaldehyde was thus shown to be a far more potent irritant than the cyclic or saturated aliphatic aldehydes, a less potent than acrolein, and a similarly potent irritant as formaldehyde in Swiss-Webster and B6C3F1 mice.

Skog (1950) compared the inhalation LC_{50} of several aldehydes, including formaldehyde, acetaldehyde, propionaldehyde, and butyraldehyde, acrolein, and crotonaldehyde. He found that for the saturated hydrocarbon aldehydes studied, the toxicity decreased with increased molecular weight (this also held true when administration was by injection). The unsaturated aldehydes—acrolein (the most toxic) and crotonaldehyde—were more acutely toxic than their saturated analogs propionaldehyde and butyraldehyde and were the most acutely toxic of the aldehydes tested. Crotonaldehyde, formaldehyde, and acrolein primarily caused lung and respiratory tract irritation and lung injury and had a mild narcotic effect, whereas the narcotic effect was the primary sign resulting from acetaldehyde, propionaldehyde, and butyraldehyde exposure.

Groups of 50 mice, 20 guinea pigs, and five rabbits were exposed to vapor and/or aerosols of acrolein, crotonaldehyde, formaldehyde, acetaldehyde, propi-

onaldehyde, and isomers of butyraldehyde until death ensued or up to 10 h (Salem and Cullumbine 1960). The results indicated that the unsaturated aldehydes (acrolein and crotonaldehyde) were more potent (in terms of mean fatal dose) than the saturated aldehydes and that increased chain length was associated with decreased toxicity. At necropsy all animals displayed severe alveolar lung damage: hemorrhage, distended alveoli, ruptured alveolar septa, and pleural edema. Toxicity of the compounds was similar whether they were in aerosol or vapor form.

4.4. Other Relevant Information

4.4.1. Species Variability

LC_{50} values for several species varied by a factor of ≤ 2.5 for several exposure durations, indicating that interspecies variability was minor. For example, a 15-min LC_{50} of 809 ppm (analytical) was obtained for rats by Rinehart (1967), whereas Smyth (1966) obtained a 15-min LC_{50} of 2,000 ppm (nominal). For 30-min exposures, LC_{50} values of 1,400 ppm (nominal) and 593 ppm (analytical) were obtained for rats (Skog 1950; Rinehart 1967) and an LC_{50} of 1,000 ppm (nominal) was obtained for guinea pigs (Smyth 1966). Mouse 2-h LC_{50} values of 200 ppm (unknown if nominal) and 530 ppm (analytical) are reported (Voronii et al. 1982; Trofimov 1962), and although rat 2-h LC_{50} values are not available, the mouse LC_{50} values are roughly consistent with rat 1-h LC_{50} values of 391 ppm (analytical; Rinehart 1967) and 4-h LC_{50} values of 70 ppm (unknown if nominal) and 88 ppm (analytical; Voronii et al. 1982; Rinehart 1967).

4.4.2. Susceptible Populations

No populations uniquely susceptible to crotonaldehyde exposure were identified.

4.4.3. Concentration-Exposure Duration Relationship

ten Berge et al. (1986) determined that the concentration-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranged from 0.8 to 3.5, and n ranged from 1 to 3 for 90% of the chemicals examined. The value of $n = 1.2$ was determined by ten Berge et al. by linear regression analysis of the Rinehart (1967) rat LC_{50} data and was used to perform scaling across time for AEGL-3 values.

For the calculation of AEGL-2 values, the end point was impaired pulmonary function and the NOAEL for proliferative lesions of the respiratory bronchioles at 8,000 ppm-min. A value of $n = 1$ was used to scale across time, based

on the fact that in this study there was a general dose response for increasing exposure levels, but individual concentrations and exposure times were not given (exposure was 5 min to 4 h for 10-580 ppm). Concentration and time were roughly equally important for toxicity. AEGL-2 values were therefore calculated by dividing 8,000 ppm-min by 10, 30, 60, 240, or 480 min.

No data were available from which to determine the concentration-time relationship for crotonaldehyde AEGL-1 effects (mild eye irritation). The n values used for AEGL-2 and AEGL-3 effects (n = 1.2 or n = 1) did not appear to be appropriate for predicting human sensory irritation based on a comparison of two human studies (Sim and Pattle 1957; Fannick 1982). In these studies, irritation was much greater for shorter exposure durations than for longer exposure durations yielding comparable Ct (concentration × time) values: 4.1-ppm exposure for 10 min ($C^1 \times t = 41$ ppm-min) was highly irritating to the upper respiratory tract and caused lacrimation, whereas exposure to 0.56 ppm for (up to) 8 h ($C^1 \times t = 269$ ppm-min) caused only mild eye irritation. It was thus considered more appropriate to use the same exposure concentration (0.56 ppm) for 10 min to 8 h since mild irritant effects generally do not vary greatly over time.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

Two human studies were located in which concentrations of crotonaldehyde were measured and exposure durations were of appropriate length for deriving AEGL-1 values. In one study, 12 healthy males were exposed for 15 min to 4.1 ppm of crotonaldehyde vapor (and cigarette smoke) in a 100-m^3 chamber. The men found it to be highly irritating to the nose and upper respiratory tract and lacrimated after about 30 s (Sim and Pattle 1957). In a second study, workers in a chemical plant who were exposed to a mean of 0.56 ppm for <8 h/day complained of occasional minor eye irritation (Fannick 1982). In the Fannick (1982) study, <0.35-1.1 ppm (mean = 0.56 ppm) was measured in eight stationary area samples and two personal samples worn by the hygienists were 0.66 and 0.73 ppm (limit of quantitation [LOQ] = 0.35 ppm). Both studies had the drawback that the subjects were likely exposed simultaneously to other chemicals (although crotonaldehyde was likely the most irritating). These concentrations (0.56 and 4.1 ppm) are above the generally reported odor detection threshold of 0.035-0.2 ppm (Amoore and Hautala 1983; Verschueren 1996).

Other studies in which humans were exposed to crotonaldehyde were not useful for AEGL derivation because the exposure time was too brief (≤1 min) or was not specified. These studies were compromised in that insufficient descriptions of the analytical method of crotonaldehyde concentration measurement were given.

5.2. Summary of Animal Data Relevant to AEGL-1

The threshold concentrations of crotonaldehyde that were irritating to the mucosa of rabbits and cats were reported as 17.5 ppm and 3.15 ppm, respectively (Trofimov 1962).

5.3. Derivation of AEGL-1

AEGL-1 values were derived from a Health Hazard Evaluation conducted by NIOSH at a U.S. chemical plant where some workers who were exposed to approximately 0.56 ppm of crotonaldehyde reported occasional minor eye irritation (Fannick 1982). It is possible that some of the workers had become adapted (inurred) to crotonaldehyde, but there was insufficient information to quantitate the effect of this phenomenon (which is commonly experienced with other aldehydes, e.g., formaldehyde). The workers were co-exposed to several other airborne chemicals, although available mouse (RD_{50}) irritation data and occupational reports indicated that crotonaldehyde was the most irritating. Exponential scaling across time was not performed (see Section 4.4.2 for discussion); rather, it was considered more appropriate to adopt the same exposure concentration for 10 min to 8 h since the critical end point (ocular irritation) generally does not vary greatly over time. A total uncertainty factor of 3 was applied to account for intraspecies variability, because the eye irritation is a direct surface-contact effect not subject to pharmacokinetic differences between individuals. The resulting AEGL-1 values are shown in Table 5-7; calculations are detailed in Appendix A.

The AEGL-1 values are consistent with the RD_{50} values of 3.53 and 4.88 ppm that were obtained for crotonaldehyde using male Swiss-Webster and B6C3F1 mice, respectively (Steinhagen and Barrow 1984). According to Alarie (1981), 0.1 of the RD_{50} (i.e., 0.35 or 0.49 ppm) for several hours to days should result in some sensory irritation in humans, whereas $0.01 \times RD_{50}$ (0.035 or 0.049 ppm) should cause no sensory irritation.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No human data were located that were appropriate for derivation of AEGL-2 levels.

TABLE 5-7 AEGL-1 Values for Crotonaldehyde

10 min	30 min	1 h	4 h	8 h
0.19 ppm ($0.55 mg/m^3$)	0.19 ppm ($0.55 mg/m^3$)	0.19 ppm ($0.55 mg/m^3$)	0.19 ppm ($0.55 mg/m^3$)	0.19 ppm ($0.55 mg/m^3$)

6.2. Summary of Animal Data Relevant to AEGL-2

Only one animal study presented an end point consistent with the AEGL-2 definition and provided sufficient experimental details for AEGL derivation. In this pulmonary performance study, rats displayed concentration-related reductions in the rates of ether and CO absorption compared to preexposure levels (see Table 5-6). Rats exposed to >8,000 ppm-min (product of concentration and time, individual values not provided) developed proliferative lesions of the respiratory bronchioles, but exposures above 16,000 ppm-min induced pulmonary edema and the animals died (Rinehart 1967).

Several animal studies described end points potentially within the scope of the AEGL-2 definition, although sufficient experimental detail was not provided for the studies to be useful for AEGL derivation. In one study the respiration rate and heart rate of male rabbits were significantly decreased after inhalation of 5 ppm of crotonaldehyde for <10 min (Ikeda et al. 1980). Nasopharyngeal mucosal morphological changes were found in rats exposed for 30 min to ≥0.45 ppm, although the nature of the changes and the analytical methods used were not described (Tepikina et al. 1997).

6.3. Derivation of AEGL-2

AEGL-2 values were derived from the pulmonary performance study in which rats exposed to 8,000 ppm-min had reduced rates of gas absorption. This exposure was near the threshold for developing proliferative lesions of the respiratory bronchioles. Because the individual concentrations and exposure times were not given (exposure was 5 min to 4 h to 10-580 ppm), only the concentration × time (Ct) values, and it appeared from the overall data that concentration and time were roughly equally important for toxicity [this is also supported by n = 1.2 derived from the LC_{50} study by Rinehart (1967)], AEGL-2 values were calculated by dividing 8,000 ppm-min by 10, 30, 60, 240, or 480 min. A total uncertainty factor of 30 was used: 10 for interspecies uncertainty (because the actual exposure concentration and time were not known for the key study and there was a lack of supporting animal studies) and 3 for intraspecies uncertainty [although human variability to crotonaldehyde toxicity is not well defined, a greater uncertainty factor was judged inappropriate because it yields 4- and 8-h AEGL-2 concentrations that caused only mild irritation in workers exposed for up to 8 h (Fannick 1982)]. The resulting AEGL-2 values are shown in Table 5-8; calculations are shown in Appendix A.

A cancer inhalation slope factor was derived for crotonaldehyde and used to estimate the 10^{-4} excess cancer risk from a single 30-min to 8-h exposure, as shown in Appendix D. Crotonaldehyde concentrations associated with a 10^{-4} excess cancer risk were 25-fold greater than the toxicity-based AEGL-2 values

TABLE 5-8 AEGL-2 Values for Crotonaldehyde

10 min	30 min	1 h	4 h	8 h
27 ppm (77 mg/m^3)	8.9 ppm (26 mg/m^3)	4.4 ppm (13 mg/m^3)	1.1 ppm (3.2 mg/m^3)	0.56 ppm (1.6 mg/m^3)

for 30 to 480 min. The noncarcinogenic end points were considered more appropriate for AEGL-2 derivation because (1) there is insufficient evidence that inhalation is a route that results in crotonaldehyde-induced liver lesions or neoplasia at concentrations comparable to the AEGL-2 values; (2) the data used to derive the cancer slope factor were very weak (the key study had only one dose and one control group; the high dose was excluded due to lack of fit), and most of the neoplastic changes were benign; (3) AEGL values are applicable to rare events or single once-in-a-lifetime exposures, and the data indicate that TNM neoplasms resulted from lifetime treatment; and (4) a direct comparison of estimated TNM cancer risk and AEGL values is not appropriate due to large differences in the methodologies used to obtain these numbers.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No quantitative information on lethal crotonaldehyde exposure in humans was located.

7.2. Summary of Animal Data Relevant to AEGL-3

The most comprehensive lethality study was conducted by Rinehart (1967), where LC_{50} values were obtained for male Wistar rats exposed for 5, 10, 15, 30, 60, or 240 min. The mortality incidences were clearly concentration related for each exposure duration. The rats displayed obvious respiratory distress and a lowered respiratory rate during exposure and lost up to 25% of their body weight within the first 3 days. These animals had clear or slightly blood-stained nasal discharge; the rats that died within a day had terminal convulsions. Necropsy showed that a few animals had pulmonary congestion; other organs were grossly normal. Chamber exposure concentrations of crotonaldehyde were measured analytically.

A number of animal studies in which LC_{50} values were determined for a single exposure time can potentially be used to calculate AEGL-3 values, extrapolating to the necessary exposure times and applying appropriate uncertainty factors. These studies include (1) a 30-min exposure of rats in which an LC_{50} of 1,400 ppm (nominal) was obtained (Skog 1950); the rats gasped and had closed eyes, lacrimation, heavy nose secretion, hyperemia, and hemorrhage in the

lungs, heart, liver, and kidneys; no edema was evident in the lungs; (2) an LC_{50} of 70 ppm was reported for a 4-h exposure of white rats (no other details reported; Voronii et al. 1982); (3) white mice exposed to crotonaldehyde for 2 h had an LC_{50} of 530 ppm (measured); the animals rubbed their faces with their paws and displayed respiratory distress, a period of intense excitation, convulsions, and lung hemorrhage, and edema in the lungs and brain (Trofimov 1962); (4) a 2-h LC_{50} of 200 ppm was obtained for white mice (no other details given; Voronii et al. 1982); (5) guinea pigs exposed to 1,000 ppm for 30 min had 50% mortality (further experimental details not provided; Smyth 1966).

7.3. Derivation of AEGL-3

The rat study conducted by Rinehart, in which LC_{50} values were obtained for exposures from 5 min to 4 h, was considered the most relevant for derivation of AEGL-3 values. The Rinehart protocol was an extensive study in which air crotonaldehyde concentrations were measured and 30-60 animals were used for each of the six exposure periods. The Rinehart study was used by ten Berge et al. (1986) to develop the value of n = 1.2 for scaling across time in the relationship $C^n \times t = k$.

The AEGL-3s for 10 min, 30 min, 1 h, and 4 h were obtained directly from the 10-min, 30-min, 1-h, and 4-h LC_{01} values (440, 268, 138, and 26 ppm, respectively) calculated by probit analysis from the mortality data. The 8-h AEGL-3 values were extrapolated from the 4-h LC_{01} (26 ppm) using the relationship $C^{1.2} \times t = k$. A total uncertainty factor of 10 was applied: 3 for interspecies uncertainty because interspecies variability was small (LC_{50} values for rats, mice, and guinea pigs were within a factor of 2.5, and these studies yield similar or higher AEGL-3 values) and 3 for intraspecies uncertainty because great human variability in unlikely given the homogeneity of the animal data, and a larger uncertainty factor yields 8-h AEGL-3 concentrations that caused only mild irritation in workers exposed for up to 8 h (Fannick 1982). The AEGL-3 values are shown in Table 5-9; calculations are shown in Appendix A.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

A summary of the AEGL values for crotonaldehyde (*trans* isomer and commercial *cis-trans* mixture) and their relationships are shown is Table 5-10.

AEGL-1 values were derived from a Health Hazard Evaluation conducted by NIOSH in which workers who were exposed to approximately 0.56 ppm of crotonaldehyde for <8 h reported occasional minor eye irritation (Fannick 1982). Exponential scaling across time was not performed (see Section 4.4.2 for discus-

TABLE 5-9 AEGL-3 Values for Crotonaldehyde

10 min	30 min	1 h	4 h	8 h
44 ppm (130 mg/m^3)	27 ppm (77 mg/m^3)	14 ppm (40 mg/m^3)	2.6 ppm (7.4 mg/m^3)	1.5 ppm (4.3 mg/m^3)

TABLE 5-10 Summary of AEGL Values for Crotonaldehyde

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	0.19 ppm (0.55 mg/m^3)	0.19 ppm (0.55 mg/m^3)	0.19 ppm (0.55 mg/m^3)	0.19 ppm (0.55 mg/m^3)	0.19 ppm (0.55 mg/m^3)
AEGL-2 (disabling)	27 ppm (77 mg/m^3)	8.9 ppm (26 mg/m^3)	4.4 ppm (13 mg/m^3)	1.1 ppm (3.2 mg/m^3)	0.56 ppm (1.6 mg/m^3)
AEGL-3 (lethal)	44 ppm (130 mg/m^3)	27 ppm (77 mg/m^3)	14 ppm (40 mg/m^3)	2.6 ppm (7.4 mg/m^3)	1.5 ppm (4.3 mg/m^3)

sion); rather, it was considered more appropriate to adopt the same exposure concentration for 10 min to 8 h since the critical end point (eye irritation) was mild and mild irritant effects generally do not vary greatly over time. A total uncertainty factor of 3 was applied to account for intraspecies variability because the eye irritation is a direct surface-contact effect not subject to pharmacokinetic differences between individuals.

AEGL-2 values were derived from the pulmonary performance study in which rats exposed to >8,000 ppm-min (individual concentrations and exposure times were not given) had lower rates of ether and CO absorption and were a NOAEL for proliferative lesions of the respiratory bronchioles. Because the available data suggested that concentration and time were roughly equal contributors to crotonaldehyde toxicity [this is also supported by n = 1.2 derived from the LC_{50} study by Rinehart (1967)], AEGL-2 values were calculated by dividing 8,000 ppm-min by 10, 30, 60, 240, or 480 min. A total uncertainty factor of 30 was used: 10 for interspecies uncertainty because the actual exposure concentration and time were not known for the key study and there was a lack of supporting animal studies and 3 for intraspecies uncertainty because, although human variability to crotonaldehyde toxicity is not well defined, a greater uncertainty factor was judged inappropriate because it yields 4- and 8-h AEGL-2 concentrations that caused only mild irritation in workers exposed for up to 8 h (Fannick 1982).

The comprehensive study conducted by Rinehart, in which rat LC_{50} values were obtained for exposures from 5 min to 4 h, was used to derive AEGL-3 values. The AEGL-3s for 10 min, 30 min, 1 h, and 4 h were obtained directly from the 10-min, 30-min, 1-h, and 4-h LC_{01} values (440, 268, 138, and 26 ppm, respectively) calculated by probit analysis from the mortality data. The 8-h AEGL-3 values were extrapolated from the 4-h LC_{01} using the relationship $C^{1.2} \times t = k$. A total uncertainty factor of 10 was applied: 3 for interspecies uncer-

tainty because interspecies variability was small (LC_{50} values for rats, mice, and guinea pigs were within a factor of 2.5, and these studies yield similar or higher AEGL-3 values) and 3 for intraspecies uncertainty because great human variability is unlikely given the homogeneity of the animal data, and a larger uncertainty factor yields 8-h AEGL-3 concentrations that caused only mild irritation in workers exposed for up to 8 h (Fannick 1982).

A cancer inhalation slope factor was derived for crotonaldehyde and used to estimate the 10^{-4} excess cancer risk from a single 30-min to 8-h exposure. Crotonaldehyde concentrations associated with a 10^{-4} excess cancer risk were 25-fold greater than the toxicity-based AEGL-2 values for 30 to 480 min. The noncarcinogenic end points were considered more appropriate for AEGL-2 derivation, as detailed in Appendix D.

8.2. Comparison with Other Standards and Guidelines

The existing standards and guidelines for crotonaldehyde (in all cases for both the *cis* and *trans* isomers) are summarized in Table 5-11.

TABLE 5-11 Extant Standards and Guidelines for *cis*- and *trans*-Crotonaldehyde (values in ppm)

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	0.19	0.19	0.19	0.19	0.19
AEGL-2	27	8.9	4.4	1.1	0.56
AEGL-3	44	27	14	2.6	1.5
ERPG-1 (AIHA)[a]			2		
ERPG-2 (AIHA)			10		
ERPG-3 (AIHA)			50		
PEL-TWA (OSHA)[b]					2
IDLH (NIOSH)[c]		50			
REL-TWA (NIOSH)[d]					2
TLV-Ceiling (ACGIH)[e]	0.3				
MAK (Germany)[f]					—[f]
MAC (The Netherlands)[g]					2

[a]ERPG (emergency response planning guidelines, American Industrial Hygiene Association (AIHA 2004; values under review; documented 9/1/87). 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-1 for crotonaldehyde is based on odor threshold data (Amoore and Hautala 1983; Verschueren 1996) and human exposure studies (Sim and Pattle 1957; Rinehart 1967). ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed

(Continued)

TABLE 5-11 Continued

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 protective action. The ERPG-2 for crotonaldehyde is based on human acute exposure studies (Sim and Pattle 1957; Rinehart 1967) and the rat pulmonary function study of Rinehart (1967). 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. The ERPG-3 for crotonaldehyde is based on the Rinehart (1967) acute exposure studies, and concentrations exceeding the ERPG-3 "may be expected to produce severe health effects, such as pulmonary edema and possible mortality, in a heterogenous human population" (AIHA 2004; documented 9/1/87).

[b]OSHA PEL-TWA (Occupational Health and Safety Administration, permissible exposure limit–time weighted average) (OSHA 2005) is the time-weighted average concentration for exposures of no more than 10 h/day, 40 h/week, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[c]IDLH (immediately dangerous to life and health, National Institute of Occupational Safety and Health) (NIOSH 1994) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects. The IDLH for crotonaldehyde is based on acute inhalation toxicity data for humans and animals (Rinehart 1967).

[d]NIOSH REL-TWA (National Institute of Occupational Safety and Health, recommended exposure limit–time-weighted average) (NIOSH 1994, 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.

[e]ACGIH TLV-C (Threshold Limit Value ceiling) (adopted 1997; ACGIH 1998, 2004) is defined as the concentration that should not be exceeded during any part of the working exposure.

[f]MAK (maximale arbeitsplatzkonzentration [maximum workplace concentration]) (DFG 2002) [Deutsche Forschungs-Gemeinschaft [German Research Association]) is defined analogously to the ACGIH-TLV-TWA. No MAK values were established for crotonaldehyde. Crotonaldehyde was placed in carcinogenicity category 3B because in vitro or animal studies yielded evidence of carcinogenic effects that were insufficient to classify the substance in one of the other categories. A skin designation was also established because it appears that dermal absorption can make a significant contribution to a person's body burden.

[g]MAC (maximaal aanvaaarde concentratie [maximal accepted concentration]) (SDU Uitgevers 2000 [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands) is defined analogous to the ACGIH TLV-TWA.

The OSHA PEL and NIOSH REL (8-h TWA exposure limit) for crotonaldehyde is 2 ppm (6 mg/m^3) to prevent eye and respiratory irritation (NIOSH 1994, 2002; OSHA 2005). The TLV applies to both the *trans* isomer (123-73-9) and the *cis*-*trans* mixture (4170-31-3) (IARC 1995; OSHA 2005). The same occupational exposure limits (2 ppm TLV-TWA) are used in Australia, Belgium, Denmark, Finland, France, Italy, the Philippines, Switzerland, and the United Kingdom (IARC 1995; RTECS 2005).

The ACGIH had recommended a TLV-TWA of 2 ppm (5.7 mg/m^3) for both isomers (with certain defined permitted excursions above 2 ppm) from 1967 to 1997 but in 1998 omitted the TLV-TWA and adopted a TLV ceiling of 0.3 ppm (ACGIH 1998). This reduction was based on a reevaluation of the available human data of Sim and Pattle (1957; respiratory and eye irritation from 4.1 ppm crotonaldehyde; lacrimation within about 30 s), Rinehart (1967; 15 ppm for 15 min [Rinehart's stated exposure ≤30 s] strong but not intolerable), and the mouse RD_{50} study of Steinhagen and Barrow (1984). The TLV committee concluded that the mouse RD_{50} data were consistent with the Sim and Pattle (1957) but not the Rinehart (1967) data and suggested that the discrepancy between the two sets of data was due to "analysis errors between the two methods used." Additionally, since crotonaldehyde was a "rapidly acting irritant," had an RD_{50} similar to that of formaldehyde (which is structurally and functionally related to crotonaldehyde), and an extensive body of evidence supported the TLV ceiling of 0.3 ppm for formaldehyde, the TLV committee concluded that the occupational exposure limit of crotonaldehyde should be consistent with that of formaldehyde (ACGIH 1998).

8.3. Data Quality and Research Needs

The human and animal data available to derive AEGL-1 and AEGL-2 values were limited, and further investigations are warranted. In many of the LC_{50} studies, air crotonaldehyde concentrations were nominal and not measured, and comparisons of obtained LC_{50} values with other studies were not as meaningful.

Limited human data were available but were sufficient to develop AEGL-1 values. The key study (Fannick 1982) was from a site investigation conducted by NIOSH, and crotonaldehyde concentrations were measured analytically. The actual exposure time and the associated air crotonaldehyde concentrations were not provided, although this was not critical for the AEGL-1 calculations because the same value (based on ocular irritation) was adopted across all time points. A possible confounding factor was the simultaneous exposure of the workers to several other airborne chemicals, although it is likely that crotonaldehyde was the most acutely irritating of all the airborne chemicals used in the plant.

Only one rigorous animal study with an end point within the scope of the definition of AEGL-2 was located. The rat pulmonary function study of Rinehart (1967), from which the AEGL-2 values were derived, was well conducted and crotonaldehyde air concentrations were measured, although the actual concentrations and exposure times were not presented ($C \times t$ values were listed).

The database for AEGL-3 derivation was considered adequate, primarily due to the availability of the comprehensive single-exposure rat acute lethality study by Rinehart. In this study, 30-60 animals were tested at five to seven crotonaldehyde concentrations for six different exposure times, and a clear concentration response (for mortality) was seen for each exposure time. Similar or

higher AEGL-3 values could be derived from other rat LC_{50} studies as well as from mouse and guinea pig LC_{50} studies.

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APPENDIX A

Derivation of AEGL-1 Values

Key study:	Fannick 1982. Human occupational exposure to a mean concentration of 0.56 ppm crotonaldehyde during a workday caused occasional eye irritation; exposure time not given but was <8 h.
Toxicity end point:	Ocular irritation.
Scaling:	None: 0.56 ppm = k; the critical end point (eye irritation) was mild, and mild irritant effects generally do not vary greatly over time.
Uncertainty factors:	Total uncertainty factor: 3
Interspecies:	Not applicable
Intraspecies:	3, for intraspecies variability because the eye irritation is a direct surface-contact effect not subject to pharmacokinetic differences between individuals.
Calculations:	
10-min AEGL-1:	0.56 ppm/3 = 0.19 ppm (0.55 mg/m^3)
30-min AEGL-1:	0.56 ppm/3 = 0.19 ppm (0.55 mg/m^3)
1-h AEGL-1:	0.56 ppm/3 = 0.19 ppm (0.55 mg/m^3)
4-h AEGL-1:	0.56 ppm/3 = 0.19 ppm (0.55 mg/m^3)
8-h AEGL-1:	0.56 ppm/3 = 0.19 ppm (0.55 mg/m^3)

Derivation of AEGL-2 Values

Key study:	Rinehart 1967. Rat pulmonary function study. Rats had lower rates of ether and CO absorption and those exposed to >8,000 ppm-min (product of concentration and time; individual concentrations and exposure times were not given) developed proliferative respiratory bronchiole lesions.

Toxicity end point:	Moderate pulmonary impairment and NOAEL for proliferative lesions of the respiratory bronchioles.
Scaling:	$C^1 \times t = k$ (concentration and time were approximately equally important for toxicity)
Uncertainty factors:	Total uncertainty factor: 30
Interspecies:	10: The actual exposure concentration and time were not known for the key study, and there was a lack of supporting animal studies.
Intraspecies:	3: Although human variability to crotonaldehyde toxicity is not well defined, a greater uncertainty factor was judged inappropriate because it yields 4- and 8-h AEGL-2 concentrations that caused only mild irritation in workers exposed for up to 8 h (Fannick 1982).
Calculations:	$(\text{Concentration})^1$ (30-480 min) = k = 8,000 ppm-min Apply the total UF of 30-8,000 ppm-min and get k = 267 ppm-min
10-min AEGL-2:	$C^1 \times 10$ min = 267 ppm-min 10 min AEGL-2 = 267 ppm-min/10 min = 27 ppm (77 mg/m^3)
30-min AEGL-2:	$C^1 \times 30$ min = 267 ppm-min 30-min AEGL-2 = 267 ppm-min/30 min = 8.9 ppm (26 mg/m^3)
1-h AEGL-2:	$C^1 \times 60$ min = 267 ppm-min 1 h AEGL-2 = 267 ppm-min/60 min = 4.4 ppm (13 mg/m^3)
4-h AEGL-2:	$C^1 \times 240$ min = 267 ppm-min 4-h AEGL-2 = 267 ppm-min/240 min = 1.1 ppm (3.2 mg/m^3)
8-h AEGL-2:	$C^1 \times 480$ min = 267 ppm-min 8-h AEGL-2 = 267 ppm-min/480 min = 0.56 ppm (1.6 mg/m^3)

Derivation of AEGL-3 Values

Key study:	Rinehart 1967. Rat 5-min to 4-h exposure inhalation LC_{50} study. Most deaths occurred by 4 days after exposure, and the animals had clear or slightly blood-tinged nasal exudate; rats that died within 1 day also had terminal convulsions. Autopsy showed that a few rats had pulmonary congestion.
Toxicity end point:	Lethality NOELs, estimated from LC_{01} values obtained by probit analysis: 10-min LC_{01} = 440 ppm (standard error = 153) 30-min LC_{01} = 268 ppm (standard error = 50) 1-h LC_{01} = 138 ppm (standard error = 71) 4-h LC_{01} = 26 ppm (standard error = 7.8); used to derive 8-h values
Scaling:	$C^{1.2} \times t = k$ (Rinehart 1967 LC_{50} data; ten Berge et al. 1986)
Uncertainty factors:	Total uncertainty factor: 10
Interspecies:	3, Interspecies variability was small (LC_{50} values for rats, mice, and guinea pigs were within a factor of 2.5; these studies yield similar or higher AEGL-3 values).
Intraspecies:	3, Great human variability is unlikely given the homogeneity of the animal data, and a larger uncertainty factor yields 8-h AEGL-3 concentrations that caused only mild irritation in workers exposed for up to 8 h (Fannick 1982).

Calculations for 10, 30, 60, and 240 min:

10-min AEGL-3:	10-min LC_{01} = 440 ppm 10-min AEGL-3 = 440/10 = 44 ppm (130 mg/m^3)
30-min AEGL-3:	30-min LC_{01} = 268 ppm 30-min AEGL-3 = 268/10 = 27 ppm (77 mg/m^3)
1-h AEGL-3:	1-h LC_{01} = 138 ppm 1-h AEGL-3 = 138/10 = 14 ppm (40 mg/m^3)
4-h AEGL-3:	4-h LC_{01} = 26 ppm 4-h AEGL-3 = 26/10 = 2.6 ppm (7.4 mg/m^3)

Calculations for 8 h:

$$\frac{\text{Concentration}}{\text{UF}} \quad \frac{26 \text{ ppm}^{1.2}}{10} \times \text{time (240 min)} = k = 755.4 \text{ ppm-min}$$

8-h AEGL-3 $C^{1.2} \times 480 \text{ min} = 755.4 \text{ ppm-min}$

8-h AEGL-3 $C = 1.5 \text{ ppm } (4.3 \text{ mg/m}^3)$

APPENDIX B

Derivation of the Level of Distinct Odor Awareness (LOA)

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 responders in assessing public awareness of exposure due to odor perception. The LOA derivation follows the guidance given by van Doorn et al. (2002).

An odor detection threshold (OT_{50}; i.e., concentration at which 50% of the odor panel observed an odor without necessarily recognizing it) of 0.069 ppm was reported for the *trans* isomer and 0.063-0.20 ppm for the *cis* isomer of crotonaldehyde. The value of 0.069 was used for the LOA calculations because commercial crotonaldehyde (tested in the animal studies) is a mixture of the two isomers consisting of >95% *trans* isomer.

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:

$$3 = 2.33 \times \log (C / 0.069) + 0.5, \text{ which can be rearranged to}$$
$$\log (C / 0.069 = (3 - 0.5) / 2.33 = 1.07 \text{ and results in}$$
$$C = (10^{1.07}) \times 0.069 = 0.81 \text{ ppm}$$

The resulting concentration is multiplied by an empirical field correction factor. It takes into account that in everyday life factors such as sex, age, sleep, smoking, upper-airway infections, and allergies, 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 s), which leads to the perception of

concentration peaks. Based on current knowledge, a factor of 1/3 is applied to adjust for peak exposure. Adjustment for distraction and peak exposure leads to a correction factor of 4/3 = 1.33.

$$\text{LOA} = \text{C} \times 1.33 = 0.81 \text{ ppm} \times 1.33 = 1.1 \text{ ppm}$$

The LOA for crotonaldehyde is 1.1 ppm.

APPENDIX C

Category Plot for Crotonaldehyde

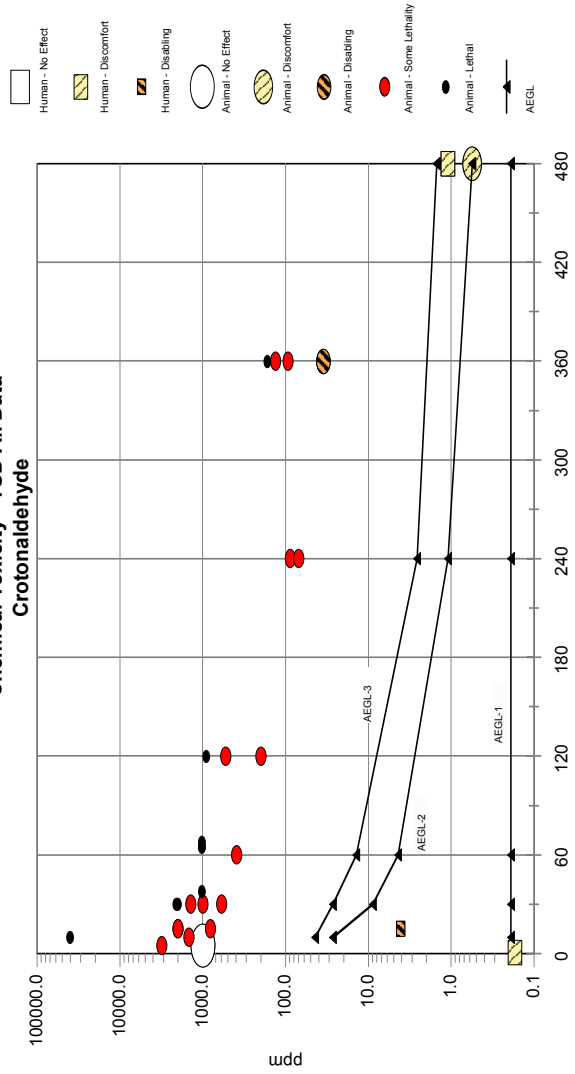

FIGURE 5-1 Category plot of human and animal toxicity data compared with AEGL values.

APPENDIX D

CARCINOGENICITY ASSESSMENT

Preliminary Cancer Assessment of Crotonaldehyde

A preliminary cancer assessment of crotonaldehyde was performed using data from Chung et al. (1986). In this study, male F344 rats were treated with 0, 0.6, or 6.0 mM of crotonaldehyde in their drinking water for 113 weeks. The high-dose group had approximately 10% lower body weight gain starting at week 8. The incidence of hepatic neoplastic nodules and hepatocellular carcinomas (combined) was 0/23, 11/27*, and 1/23 at 0, 0.6, and 6.0 mM, respectively (*$p < .01$; carcinoma: 0/23, 2/27, 0/23, respectively).

The oral dose can be extrapolated to an air concentration that results in an equivalent human inhaled dose when assuming 100% lung absorption (NRC 1993). The extrapolation uses a rat intake of 2.06 mg of crotonaldehyde/day from the drinking water at the low dose (0.049 L/day (default) × 0.6 mmol/L × 70.09 g/mol crotonaldehyde), default body weights (BW) of 70 kg for humans and 0.35 kg for rats, and an inhalation rate of 20 m^3/day for humans. The calculation is performed as follows:

Human equivalent concentration =

$$\frac{\text{2.06 mg crotonaldehyde/day} \times \text{70 kg body weight}}{\text{20 m}^3\text{ air/day} \times \text{0.35 kg of body weight}} = 20.6\ \text{mg/m}^3.$$

This yields air concentrations of 20.6 mg/m^3 (7.2 ppm) and 206 mg/m^3 (72 ppm), respectively, for 0.6 and 6.0 mM crotonaldehyde in water. Using the linearized multistage model (GLOBAL86 program; Howe et al. 1986), the inhalation unit risk (or slope factor; i.e., q_1*) was calculated to be 0.0327 per (mg/m^3). Note that the high dose was excluded from the unit risk calculation by the GLOBAL86 program due to lack of fit.

For a lifetime theoretical cancer risk of 10^{-4}, crotonaldehyde air concentration is $^{10-4}/0.0327\ (\text{mg/m}^3)^{-1} = 3.06 \times 10^{-3}$ mg/m^3. To convert a 70-year exposure to a 24-h exposure:

$$(3.06 \times 10^{-3}\ \text{mg/m}^3)\ 25{,}600\ \text{days} = 78.34\ \text{mg/m}^3$$
$$\text{(risk)}\quad 70\text{-year life.}$$

An additional adjustment factor of 6 is applied to account for uncertainty regarding the stages of the carcinogenic process at which TNM or its metabolites may act (Crump and Howe 1984):

$$78.34 \text{ mg/m}^3 \div 6 = 13.1 \text{ mg/m}^3 \text{ or } 4.6 \text{ ppm.}$$

For exposures of less than 24 h, the fractional exposure (f) becomes $1/f \times 24$ h (NRC 1985). (Extrapolation to 10 min was not calculated due to unacceptably large inherent uncertainty; see Section 4.4.3.)

Exposure Duration	AEGL-2 Values (ppm) Based on Toxicity End Points	Crotonaldehyde Exposure Concentrations (ppm) with an Excess Cancer Risk of		
		10^{-4}	10^{-5}	10^{-6}
½ h	8.9	221	22	2.2
1 h	4.4	110	11	1.1
4 h	1.1	28	2.8	0.28
8 h	0.56	14	1.4	0.14

Because animal doses were converted to an air concentration that results in an equivalent human inhaled dose for the derivation of the cancer slope factor, no reduction of exposure levels is applied to account for interspecies variability.

Crotonaldehyde concentrations associated with a 10^{-4} excess cancer risk for a single 30- to 480-min exposure were 25-fold greater than the toxicity-based AEGL-2 values for 30-480 min. The noncarcinogenic end points were considered to be more appropriate for AEGL-2 derivation because (1) there is insufficient evidence that inhalation is a route that results in crotonaldehyde-induced liver lesions or neoplasia at concentrations comparable to the AEGL-2 values (liver effects were mentioned in two inhalation studies: Skog (1950) reported hyperemia in multiple organs, including the liver, at unspecified exposure concentrations, and Salem and Cullumbine (1960) found that livers appeared enlarged in animals exposed to concentrations that killed all animals within 86 min); (2) the data used to derive the cancer slope factor were very weak (the key study had only one dose and one control group; the high dose was excluded due to lack of fit), and most of the neoplastic changes were benign; (3) multiple worst-case assumptions were made in extrapolating from the oral route to the inhalation route and in the derivation of the cancer slope factor; and (4) AEGL values are applicable to rare events or single, once-in-a-lifetime exposures and the neoplasms resulted from lifetime treatment.

APPENDIX E

ACUTE EXPOSURE GUIDELINE LEVELS FOR CROTONALDEHYDE

Derivation Summary for Crotonaldehyde AEGLS (CAS Nos. 123-73-9 and 4170-30-3)

AEGL-1 VALUES

10-min	30-min	1-h	4-h	8-h
0.19 ppm	0.19 ppm	0.19 ppm	0.19 ppm	0.19 ppm

Key reference: Fannick, N. 1982. Sandoz Colors and Chemicals, East Hanover, New Jersey. Health Hazard Evaluation Report No. HETA-81-102-1244. National Institute for Occupational Safety and Health, Hazard Evaluations and Technical Assistance Branch, Cincinnati, OH.

Test species/Strain/Sex/Number: Humans; number not specified but likely <10.

Exposure route/Concentrations/Durations: Inhalation for <8 h to 0.56 ppm; highest measured air concentration was 1.1 ppm.

Effects: Slight eye irritation.

End point/Concentration/Rationale: Workers exposed to 0.56 ppm for a portion of their 8-h work shift occasionally had mild eye irritation.

Uncertainty factors/Rationale:
Uncertainty factors: Total uncertainty factor: 3
Interspecies: Not applicable
Intraspecies: 3: for intraspecies variability because the eye irritation is a direct surface-contact effect not subject to pharmacokinetic differences between individuals.

Modifying factor: None.

Animal to human dosimetric adjustment: Not necessary

Time scaling: The same value is adopted for 10-min to 8-h exposures because the critical end point (eye irritation) was mild and mild irritant effects generally do not vary greatly over time. Human exposure studies suggested that scaling across time was not appropriate (the degree of irritation was much greater at shorter time periods than at longer time periods for the same Ct).

Data adequacy: Database of appropriate studies was limited but included human data. The key study was conducted by NIOSH, and crotonaldehyde concentrations were measured analytically. A possible confounding factor was co-exposure of the workers to several other airborne chemicals, although mouse irritation data indicate that crotonaldehyde was the most irritating of the chemicals present.

AEGL-2 VALUES

10-min	30-min	1-h	4-h	8-h
27 ppm	8.9 ppm	4.4 ppm	1.1 ppm	0.56 ppm

Key reference: Rinehart, W. 1967. The effect on rats of single exposures to crotonaldehyde vapor. Am. Ind. Hyg. Assoc. J. 28:561-566.

Test species/Strain/Sex/Number: Male Sprague-Dawley rats; 12-16 per Ct (concentration × time) range

Exposure route/Concentrations/Durations: Inhalation for 5 min to 4 h of 10-580 ppm; individual concentrations and exposure times were not given.

Effects: Decreased pulmonary function at ≥ 2,000 ppm-min, manifest as a 5-50% reduction in CO and ether uptake rates compared to preexposure values. Proliferative lesions of the respiratory bronchioles occurred at >8,000 ppm-min.

End point/Concentration/Rationale: Decreased pulmonary function and NOAEL for proliferative lesions of the respiratory bronchioles at 8,000 ppm-min.

Uncertainty factors/Rationale: Total uncertainty factor: 30
Interspecies: 10: The actual exposure concentration and time were not known for the key study, and there was a lack of supporting animal studies.

Intraspecies: 3: Although human variability to crotonaldehyde toxicity is not well defined, a greater uncertainty factor was judged inappropriate because it yields 4- and 8-h AEGL-2 concentrations that caused only mild irritation in workers exposed for up to 8 h (Fannick 1982).

Modifying factor: None.

Animal to human dosimetric adjustment: Not applied

Time scaling: Concentration and time appeared to be roughly equally important for toxicity; i.e., $C^1 \times t = k$, which is also supported by n = 1.2 derived from an LC_{50} study by Rinehart (1967). AEGL-2 values were calculated by dividing 8,000 ppm-min by 10, 30, 60, 240, or 480 min.

Data adequacy: The database of appropriate studies was small. The key study was well conducted and crotonaldehyde air concentrations were measured, although the actual concentrations and exposure times were not given (only Ct values).

AEGL-3 VALUES

10-min	30-min	1-h	4-h	8-h
44 ppm	27 ppm	14 ppm	2.6 ppm	1.5 ppm

Key reference: Rinehart, W. 1967. The effect on rats of single exposures to crotonaldehyde vapor. Am. Ind. Hyg. Assoc. J. 28:561-566.

Test species/Strain/Sex/Number: Male Sprague-Dawley rats; 5-12/concentration (see below)

(Continued)

AEGL-3 VALUES Continued

10-min	30-min	1-h	4-h	8-h
44 ppm	27 ppm	14 ppm	2.6 ppm	1.5 ppm

Exposure route/Concentrations/Durations: Inhalation: see below for exposure times and concentrations.

Effects: Most deaths occurred by 4 days after exposure, and the animals had clear or slightly blood-tinged nasal exudate (rats that died within 1 day also had terminal convulsions); some had pulmonary congestion.

5-min ppm–mortality	10-min ppm–mortality	15-min ppm–mortality	30-min ppm–mortality	60 min ppm–mortality	240-min ppm–mortality
1,920 – 0/5	800 – 1/12	550 – 0/10	370 – 0/10	370 – 4/10	50 – 1/10
2,420 – 1/5	1,110 – 4/12	680 – 2/10	420 – 2/10	400 – 6/10	60 – 2/10
2,680 – 1/5	1,380 – 6/12	750 – 5/10	530 – 4/10	490 – 7/10	70 – 4/10
3,180 – 3/5	1,820 – 7/12	850 – 7/10	675 – 6/10	590 – 7/10	100 – 6/10
4,160 – 4/5	2,050 – 9/12	980 – 7/10	800 – 8/10	640 – 10/10	120 – 8/10
4,640 – 5/5	LC_{50} = 1480	1,090 – 8/10	890 – 9/10	LC_{50} = 391	200 – 9/10
LC_{50} = 3132	LC_{01} = 440	1,290 – 10/10	LC_{50} = 593	LC_{01} = 138	LC_{50} = 88
LC_{01} = 1492		LC_{50} = 809	LC_{01} = 268		LC_{01} = 26
		LC_{01} = 419			

End point/Concentration/Rationale: LC_{01} values, representing the NOEL for lethality, were obtained by probit analysis and used to obtain the 10-, 30-, 1-h, and 4-h AEGL-3 values. The 8-h values were derived from the 4-h LC_{01} by exponential time scaling and using n = 1.2.

Uncertainty factors/Rationale: Total uncertainty factor: 10
Interspecies: 3: Interspecies variability was small (LC_{50} values for rats, mice, and guinea pigs were within a factor of 2.5, and these studies yielded similar or higher AEGL-3 values).
Intraspecies: 3: Great human variability in unlikely given the homogeneity of the animal data, and a larger uncertainty factor yields 8-h AEGL-3 concentrations that caused only mild irritation in workers exposed for up to 8 h (Fannick 1982).

Modifying factor: None.

Animal to human dosimetric adjustment: Not applied

Time scaling: Performed only for 8-h time point by exponential scaling; i.e., $C^n \times t = k$, where n = 1.2 was derived by ten Berge et al. (1986) from the Rinehart (1967) rat LC_{50} data.

Data adequacy: Database quality was considered adequate, and the key study was well conducted: 30-60 animals were tested per exposure time at five to seven crotonaldehyde concentrations, and a clear dose-response was obtained. Similar or higher AEGL-3 values could be obtained with mice, rats, and guinea pigs.

6

Dimethylhydrazine[1]

Acute Exposure Guideline Levels

UPDATE OF DIMETHYLHYDRAZINE AEGLS

In Volume 1 of the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2000), AEGL values were developed for 30 minutes (min), and 1, 4, and 8 hours (h). Since that time AEGL values have also been developed for 10-min exposures. This document updates Volume 1 to include 10-min values. The summary below is from Volume 1, with additional discussion to address the development of 10-min values.

SUMMARY

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

[1]This document was prepared by AEGL Development Team member Richard Thomas of the National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances (NAC) and Robert Young of the Oak Ridge National Laboratory. The NAC reviewed and revised the document, which was then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC Committee concludes that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NAC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

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

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

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

Both isomers of dimethylhydrazine have been shown to be carcinogenic in rodents following oral exposure, and 6-month inhalation to 1,1-dimethylhydrazine resulted in an increased tumor response in mice, although these findings are compromised by the contaminant dimethylnitrosamine. U.S. Environmental Protection Agency (EPA) inhalation slope factors are currently unavailable for dimethylhydrazine.

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

Behavioral changes and muscle fasciculations in dogs exposed for 15 min to 360 ppm of 1,1-dimethylhydrazine (Weeks et al. 1963) served as the basis for deriving AEGL-2 values. Available lethality data in dogs and rats indicated a near-linear temporal relationship (n = 0.84 and 0.80 for dogs and rats, respectively). For temporal scaling ($C^1 \times t = k$) to derive values for AEGL-specific exposure durations, a linear concentration-response relationship, n = 1, was used. (C = exposure concentration, t = exposure duration, and k = a constant). An uncertainty factor of 3 for interspecies variability was applied because the

toxic response to dimethylhydrazine was similar across the species tested. This was especially true for lethality responses (LC_{50} values for various time periods ranging from 5 min to 4 h) among rats, mice, dogs, and hamsters. A comparison of LC_{50} values for the same exposure durations in these species did not vary by more than 3-fold. An uncertainty factor of 10 was retained for intraspecies variability, however, based primarily on the varied toxic responses observed in dogs, from extremely severe (vomiting, tremors, convulsions, and death) to no observable effects. Additionally, Weeks et al. indicated that dogs that had been previously stressed (auditory stimuli) may have potentiated their response to dimethylhydrazine. Based on these data, it was assumed that humans may be equally divergent in their response to dimethylhydrazine as a result of similar stresses.

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

Verified inhalation and oral slope factors were unavailable from EPA for dimethylhydrazine. A cancer assessment based on the carcinogenic potential (withdrawn cancer slope factors) of dimethylhydrazine revealed that AEGL values for a 10^{-4} carcinogenic risk exceeded the AEGL- 2 values that were based on noncancer end points. Because the cancer risk for dimethylhydrazine was estimated from nonverified cancer estimates, and because AEGLs are applicable to rare events or single once-in-a-lifetime exposures to a limited geographic area and small population, the AEGL values based on noncarcinogenic end points were considered more appropriate. A summary of AEGL values is shown in Table 6-1.

TABLE 6-1 Summary of AEGL Values for 1,1- and 1,2-Dimethylhydrazines

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR	NR	NR	NR	NR	Not recommended due to insufficient data; concentration-response relationships suggest little margin between exposures causing minor effects and those resulting in serious toxicity.[a]
AEGL-2 (disabling)	18 ppm (44 mg/m^3)	6 ppm (14.7 mg/m^3)	3 ppm (7.4 mg/m^3)	0.75 ppm (2 mg/m^3)	0.38 ppm (1 mg/m^3)	Behavioral changes and muscle fasciculations in dogs exposed to 360 ppm for 15 min (Weeks et al. 1963).
AEGL-3 (lethal)	65 ppm (159 mg/m^3)	22 ppm (54 mg/m^3)	11 ppm (27 mg/m^3)	2.7 ppm (6.6 mg/m^3)	1.4 ppm (3.4 mg/m^3)	Lethality threshold of 327 ppm for 1 h estimated from 1-h LC_{50} in dogs (Weeks et al. 1963).

[a]Refer to AEGL-1 for hydrazine if hydrazine is also present.

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

REFERENCES

NRC (National Research Council). 2000. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 1. Washington, DC: National Academy Press.

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

7

Iron Pentacarbonyl[1]

Acute Exposure Guideline Levels

PREFACE

Under the authority of the Federal Advisory Committee Act (P.L. 92-463) of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances has been established to identify, review, and interpret relevant toxicologic and other scientific data and develop acute exposure guideline levels (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). AEGL-2 and AEGL-3 levels, and AEGL-1 levels as appropriate, will be developed for each of five exposure periods (10 min, 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 parts per million [ppm] or milligrams per cubic meter [mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including sus-

[1]This document was prepared by AEGL Development Team member Robert Young of Oak Ridge National Laboratory and Ernest Falke (Chemical Manager) of the National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances (NAC). The NAC reviewed and revised the document, which was 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 data reviewed by the NRC and are consistent with the NRC guideline reports (NRC 1993, 2001).

ceptible 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 unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Iron pentacarbonyl is one of several iron carbonyls. It is formed by the interaction of carbon monoxide with finely divided iron. Iron pentacarbonyl is used in the manufacture of powdered iron cores for electronic components, as a catalyst and reagent in organic reactions, and as an antiknock agent in gasoline. Iron pentacarbonyl is pyrophoric in air (50 C auto ignition point), burning to ferric oxide.

Quantitative toxicity data and odor detection data for humans are unavailable. Qualitative descriptions of the signs and symptoms of iron pentacarbonyl exposure include giddiness and headache and occasionally dyspnea and vomiting. With the exception of dyspnea, these signs and symptoms are alleviated upon removal from exposure, but fever, cyanosis, and coughing may occur 12-36 h after exposure. This information could not be validated, and additional details were unavailable.

Animal data are limited to lethality findings in rats, mice, and rabbits. Based on the limited data available, the rat appears to be the most sensitive species as determined by the 30-min LC_{50} of 118 ppm and a 4-h LC_{50} of 10 ppm relative to the 30-min LC_{50} of 285 ppm for the mouse. For mice a 1.35-fold increase in the LC_{50} exposure concentration resulted in near 100% mortality for the same exposure duration, suggesting a steep exposure-response relationship for this species above the lethality threshold. Similarly, a 2.8-fold increase in exposure concentration (from 86 to 244 ppm) resulted in an increased mortality rate in rats from 4/12 to 11/12. No reproductive/developmental toxicity, genotoxicity, or carcinogenicity data are available for iron pentacarbonyl.

Data were unavailable for determining the exponent n. 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 1 to 3.5 (ten Berge et al. 1986). In the absence of chemical-specific data, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points.

Data consistent with AEGL-1 effects were limited to labored breathing and signs of irritation in rats exposed to 5.2 ppm for 4 h and no observable effects in rats exposed for 6 h/day to 1 ppm for 28 days. However, analysis of the overall dataset for iron pentacarbonyl indicated a very steep exposure-response curve with little margin between exposures producing no observable effects and those resulting in lethality. No AEGL-1 values were recommended.

Limited data in rats revealed that there is only a small margin between exposures causing little or no toxicity and those causing more severe effects and death. No effect was observed following exposure of rats to 1 ppm, for 6 h/day for up to 28 days, while a single exposure to 2.91 ppm for 6 h/day caused notable signs of toxicity and 10% mortality. The occurrence of deaths in laboratory species several days following cessation of exposure was considered in the derivation of the AEGL-2 values. In the absence of exposure-response data for serious and/or possibly irreversible effects, AEGL-2 values were developed by a 3-fold reduction in the AEGL-3 values. This 3-fold reduction was justified by the steep exposure-response relationship in rats, where there appears to be about a 3-fold difference between exposures that produce no lethality and those resulting in 50-100% lethality. The AEGL-2 values also reflect the application of an uncertainty factor of 3 for both interspecies variability and intraspecies variability as described for the development of AEGL-3 values.

Animal data consistent with the definition of AEGL-3 were limited to 30-min LC_{50} values for rats (118 ppm) and mice (285 ppm), a 45.5-min LC_{lo} value for rabbits (250 ppm), and a 4-h LC_{50} in rats (10 ppm). In addition to a 4-h LC_{50} value for rats, Biodynamics (1988) provided a 4-h LC_{16} estimate of 6.99 ppm and an estimated lethality threshold (4 h) of 5.2 ppm for male and female rats. Data from a study by BASF (1995), however, showed that a single 6-h exposure to 2.91 ppm resulted in 10% (1/10 rats) mortality and that a second exposure resulted in 50% mortality. Remaining rats, however, survived an additional 26 six-h exposures, while rats exposed to 1.0 ppm exhibited no clinical signs of toxicity. Using benchmark dose (BMD) analysis of the BASF data, a 6-h exposure to 1.0 ppm was selected as the point of departure for AEGL-3 derivation. A total uncertainty factor of 10 was applied. An uncertainty factor of 3 was applied to account for interspecies variability and is justified by the 2- to 3-fold variance observed for rats and mice and uncertainties in extrapolating to humans. An additional factor of 3 was applied to account for uncertainties regarding individual variability in the toxic response to iron pentacarbonyl. Additionally, iron pentacarbonyl exhibits a steep exposure-response relationship with little margin between minimal and lethal effects and little individual variability in the response of test animals. The AEGL values for iron pentacarbonyl are presented in Table

7-1. The AEGL-3 values are defensible when compared to the absence of a toxic response in rats following multiple exposures (6 h/day at 1 ppm for 28 days).

Neither quantitative nor qualitative data are available regarding the potential carcinogenicity of iron pentacarbonyl by any route of exposure. Therefore, a quantitative assessment of potential risk is not possible. Genotoxicity tests in several strains of *Salmonella typhimurium* were negative.

1. INTRODUCTION

Iron pentacarbonyl is one of several iron carbonyls. It is formed by the interaction of carbon monoxide with finely divided iron, as shown below (Brief et al. 1967):

$$\text{Fe (finely divided)} + 5\text{CO} \leftrightarrow \text{Fe(CO)}_5$$

The reaction rate is proportional to the square of the carbon monoxide partial pressure. The presence of oxygen, carbon dioxide, and oxidizing gases retards the formation of iron pentacarbonyl.

TABLE 7-1 Summary of AEGL Values for Iron Pentacarbonyl

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR	NR	NR	NR	NR	Not recommended; insufficient data.
AEGL-2 (disabling)	0.077 ppm 0.61 mg/m^3	0.077 ppm 0.61 mg/m^3	0.060 ppm 0.48 mg/m^3	0.037 ppm 0.30 mg/m^3	0.025 ppm 0.20 mg/m^3	Based on a 3-fold reduction in the AEGL-3 values.
AEGL-3 (lethal)	0.23 ppm 1.8 mg/m^3	0.23 ppm 1.8 mg/m^3	0.18 ppm 1.4 mg/m^3	0.11 ppm 0.88 mg/m^3	0.075 ppm 0.60 mg/m^3	Estimated lethality threshold in rats (1.0 ppm determined by BMD analysis (BASF 1995). n = 1 or 3; uncertainty factor = 10 (3 for both interspecies variability, and individual variability).

Note: NR: not recommended. Numerical values for AEGL-1 are not recommended (1) because of the lack of available data and (2) because an inadequate margin of safety exists between the derived AEGL-1 and the AEGL-2. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects. Under ambient atmospheric conditions, iron pentacarbonyl may undergo photochemical decomposition to iron nonacarbonyl and carbon monoxide or burn to ferric oxide.

Iron pentacarbonyl is used in the manufacture of powdered iron cores for electronic components, as a catalyst and reagent in organic reactions, and as an antiknock agent in gasoline (Sunderman et al. 1959; Budavari et al. 1989). Iron pentacarbonyl is pyrophoric in air (–15°C flashpoint; 50°C autoignition temperature), burning to ferric oxide (ACGIH 2001). It is also light sensitive, decomposing to iron nonacarbonyl and carbon monoxide (ACGIH 1991). Exposure of the general population to iron pentacarbonyl probably would be limited to pressurized releases at manufacturing sites utilizing this chemical intermediate.

Information regarding odor threshold is unavailable. Chemical and physical data for iron pentacarbonyl are shown in Table 7-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Information regarding the lethal toxicity of iron pentacarbonyl is limited to statements by Stokinger (1994) that death may occur 4-11 days following exposure (exposure terms not provided). Pathologic findings may include pulmonary hepatization, vascular injury, and degeneration of the central nervous system. No further details are available regarding these qualitative descriptions.

TABLE 7-2 Chemical and Physical Data

Property	Descriptor or Value	Reference
Synonyms	Iron carbonyl; pentacarbonyl iron	
Common name	Iron pentacarbonyl	ACGIH 2001; Budavari et al. 1989
Chemical formula	$Fe(CO)_5$	Budavari et al. 1998
Molecular weight	195.90	Budavari et al. 1998
CAS Registry No.	13463-40-6	Budavari et al. 1998
Physical state	Liquid	Budavari et al. 1998
Solubility	Insoluble in water and dilute acids, soluble in most organic solvents	ACGIH 2001; Budavari et al. 1998
Vapor pressure	35 torr at 25°C 40 mm Hg at 30.3°C	ACGIH 2001; Brief et al. 1967
Density	1.46-1.52 at 20°C	ACGIH 2001
Boiling/melting point	103°C/–20°C	ACGIH 2001
Conversion factors in air	1 mg/m^3 = 0.13 ppm 1 ppm = 8.0 mg/m^3	ACGIH 2001

2.2. Nonlethal Toxicity

Information on the nonlethal toxicity of iron pentacarbonyl in humans is limited to qualitative descriptions provided by Stokinger (1994). Stokinger noted that the signs and symptoms of iron pentacarbonyl exposure are similar to those for nickel carbonyl and include giddiness and headache and occasionally dyspnea and vomiting, these effects being similar to those associated with metal fume fever. With the exception of dyspnea, these signs and symptoms are alleviated upon removal from exposure, but fever, cyanosis, and coughing may occur 12-36 h after exposure. No source was provided for validation of this information, and no further details were available.

2.2.1. Epidemiologic Studies

No epidemiologic studies of iron pentacarbonyl toxicity are available.

2.3. Reproductive/Developmental Toxicity

Data regarding the reproductive/developmental toxicity of iron pentacarbonyl in humans are not available.

2.4. Genotoxicity

No human genotoxicity data for iron pentacarbonyl are currently available.

2.5. Carcinogenicity

Information regarding the potential carcinogenicity of iron pentacarbonyl in humans is not available.

2.6. Summary

Information regarding the toxicity of iron pentacarbonyl in humans is limited to unverifiable qualitative statements regarding signs and symptoms of exposure. Exposure terms relating to lethal or nonlethal effects are not available.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Acute lethality data are available for several laboratory species but are lim-

ited to only a few older studies. These studies tend to lack details on the analytical techniques used for determining exposure concentrations.

3.1.1. Rats

Sunderman et al. (1959) conducted toxicity studies in which male and female Wistar rats (130-180 g) were exposed for 30 min to iron pentacarbonyl at concentrations of 1.57, 2.08, 2.98, or 3.62 mg/L (equivalent to 204, 270, 387, or 470 ppm). There was no description of analytical methods regarding measurement of exposure atmospheres. A total of 20 rats were used in each exposure; three or four rats were exposed at a time. The exposure chamber consisted of an 11-L desiccator. Iron pentacarbonyl was dissolved in ethyl ether and injected into the desiccator via a Vigreux column and a motor-driven syringe. Airflow was set at 11 L/min. Mortality ratios were determined at 3 and 5 days postexposure and are shown in Table 7-3. The investigators estimated the 30-min LC_{50} as 0.91 mg/L (118 ppm) with a 95% confidence interval of 0.73-1.14 mg/L (95-148 ppm). There was no mention of test animal deaths occurring during or immediately following exposure.

Gage (1970) reported the results of inhalation studies on groups of four male and four female rats exposed to iron pentacarbonyl. Two 5.5-h exposures (on consecutive days) to 15 ppm produced lethargy, respiratory difficulty, 0.2-0.4% carboxyhemoglobin, and four deaths 3-4 days following exposure. Necropsy revealed pulmonary edema and congestion in the dead rats. One 5.5-h exposure to 33 ppm resulted in lethargy, respiratory difficulty, 4% carboxyhemoglobin, and three deaths one day following exposure. Necropsy findings again included pulmonary edema and congestion. The experiments utilized dynamic atmospheres (i.e., continuously generated and passed through the exposure chamber). The iron pentacarbonyl atmosphere was generated by injecting liquid test article (in petroleum ether) at a known rate into a metered stream of air. The iron pentacarbonyl test atmospheres were not verified by analytical techniques.

In an acute inhalation study conducted by Biodynamics for International Specialty Products, groups of 10 CD Sprague-Dawley rats (five/sex/exposure) were exposed to iron pentacarbonyl (0,5.2, 17, 28, or 60 ppm; 99.5% purity) for 4 h (Biodynamics 1988). A group of 10 rats exposed to clean air served as controls. Impinger samples of chamber air were taken every hour for 1 min and analyzed colorimetrically. For each exposure group, chamber concentrations varied (see Table 7-4), but the response was 100% lethality at analytical concentrations at or above 14 ppm and no lethality at or below 6.6 ppm. The results of this experiment are summarized in Table 7-4. The investigators calculated a 4-h LC_{50} of 10 ppm (both sexes combined, 95% confidence interval of 8.5-13 ppm). No deaths occurred at 5.2 ppm, but 100% mortality was observed for the remaining exposure groups. Deaths occurred at 1-8 days postexposure. For the 60-, 28-,

TABLE 7-3 Lethal Toxicity of Iron Pentacarbonyl in Rats Exposed for 30 min

Exposure Concentration (ppm)	Mortality at 3 Days	Mortality at 5 Days
244	11/12	11/12
195	12/18	15/18
160	12/18	13/18
118	3/12	6/12
86	1/12	4/12

Source: Sunderman et al. 1959. Reprinted with permission; copyright 1959, American Medical Association.

TABLE 7-4 Mortality in Rats Exposed for 4 h to Iron Pentacarbonyl

Concentration (ppm)		Mortality (Number Dead/Number Exposed)		
Nominal	Analytical (range)	Males	Females	Combined
Control	—	0/5	0/5	0/10
7.5	5.2 (4.1-6.6)	0/5	0/5	0/10
24	17 (14-20)	5/5	5/5	10/10
38	28 (19-38)	5/5	5/5	10/10
80	60 (55-64)	5/5	5/5	10/10

Source: Biodynamics 1988.

17-, and 5.2-ppm groups, the respective mortality ratios at postexposure day 5 were 6/10, 7/10, 9/10, and 0/10. Carboxyhemoglobin increased in a dose-related fashion (up to 11.6% increase in the high-dose group relative to controls) but was unaffected in the low-dose group. A lethality versus concentration plot provided in the study indicated that the 5.2-ppm concentration was near a lethality threshold. Gross pathology of rats that died spontaneously revealed red discoloration in several tissues (not specified) and pulmonary edema. The study authors indicated that this was consistent with animals that are not exsanguinated upon death and, therefore, could not be unequivocally considered treatment related.

A 28-day exposure study (consistent with good laboratory practice [GLP] and Organisation for Economic Co-operation and Development [OECD] guidelines) was conducted by BASF Aktiengesellschaft (BASF 1995) in which male and female Wistar rats (five/sex/exposure group) were exposed for 6 h/day, 5 days/week, to iron pentacarbonyl (99.5% purity) at concentrations of 0.1, 0.3, 1, 3, or 10 ppm (0, 0.1, 0.3, 1, 2.91, and 9.85 ppm analytical). A group of 10 rats exposed to clean air only served as controls. All of the rats in the 10-ppm exposure group died within 4 days of the first and only 6-h exposure (see Table 7-5). Prior to death, these rats exhibited clinical signs of piloerection, lassitude, red discharge (confirmed as blood) around the nostrils, and labored respiration. Five of 10 rats in the 3-ppm group were dead within 4 days after only two 6-h ex-

TABLE 7-5 Mortality in Rats Exposed to Iron Pentacarbonyl for 6 h/Day for Up to 28 Days

Concentration (ppm)		Results	
Test Group[a]	Analytical	Mortality (Number Dead/Number Exposed)	Comments
0 control	–	0/10	No clinical signs
4	0.1 (0.1 ± 0.01)	0/10	No clinical signs
E	0.3 (0.3 ± 0.01)	0/10	No clinical signs
1	1 (1.00 ± 0.02)	0/10	No clinical signs
2	3 (2.91 ± 0.01)	5/10	One death after first exposure; 50% after two exposures; death occurred within 4 days
3	10 (9.85)	10/10	Dead or terminated in extremis after one exposure; deaths occurred within 3 days

[a]Group designators as reported in BASF 1995.

posures. On days 4 and 5 the surviving rats exhibited piloerection and accelerated respiration, and on days 6 through 9 they still exhibited accelerated respiration. From day 10 to the end of the study, the rats exhibited no abnormal clinical signs. Moribund animals also exhibited impaired respiration and bloody discharge from the nostrils. Necropsy of these animals revealed severe pulmonary damage as well as damage to the spleen. None of the rats in the 0.1-, 0.3-, or 1-ppm groups exhibited any clinical signs even after 4 weeks of exposure, although some rats in the 1.0-ppm group were found (upon necropsy) to have increased absolute and relative lung weights. The investigators stated that this could possibly be treatment related. The mortality and exposure-response reported in this study are consistent with those of the previously described acute inhalation study by Biodynamics. The data from these studies suggest a steep exposure-response relationship and a lethality threshold of ~3-5 ppm for exposures of 4-6 h in duration.

3.1.2. Mice

Sunderman et al. (1959) also conducted lethality studies using Swiss albino mice (18-20 g; gender not specified) using the same exposure system as described for the rat studies (se Section 3.1.1). Exposure concentrations over the 30-min exposure period were 1.57, 2.08, 2.98, and 3.62 mg/L (204, 270, 387, and 470 ppm). The investigators estimated the 30-min LC_{50} as 2.19 mg/L (285 ppm) with a 95% confidence interval of 1.91-2.51 mg/L (248-326 ppm). Results of this experiment are shown in Table 7-6.

TABLE 7-6 Lethal Toxicity of Iron Pentacarbonyl in Mice Exposed for 30 min

Exposure Concentration (ppm)	Mortality at 3 Days	Mortality at 5 Days
470	16/20	20/20
387	15/20	17/20
270	8/20	9/20
204	5/20	5/20

Source: Sunderman et al. 1959. Reprinted with permission; copyright 1959, American Medical Association.

In addition to the experiments conducted to estimate an LC_{50}, experiments were conducted to assess the effectiveness of antidotes (dithiocarb, dimercaprol, penicillamine, and $CaNa_2EDTA$). For these experiments, groups of 10 albino Swiss mice (gender not specified) were exposed to 3.0 mg of iron pentacarbonyl/L (390 ppm) for 30 min. Lethality was assessed at 3 and 5 days postexposure. At 3 days postexposure, mice not receiving an antidote exhibited 50-90% mortality (Table 7-5). At 5 days postexposure, mice not given any antidote and exposed for 30 min to 390 ppm, exhibited 70-100% lethality (see Table 7-7). These data and the data from the LC_{50} experiments suggest a steep exposure-response curve (≈1.35-fold increase in the LC_{50} produces near 100% mortality) for this strain of mouse. Preliminary data indicated that $CaNa_2EDTA$ may have provided some protection against iron pentacarbonyl-induced toxicity.

3.1.3. Rabbits

Armit (1908) reported that a 45.4-min exposure of rabbits (age, number, strain, and gender not specified) to 0.025 volume percent (≈250 ppm) of iron pentacarbonyl resulted in fatality. No further information is available regarding this finding. Stokinger (1981) cited an oral LD_{50} of 18 mg/kg and a dermal LD_{50} of 240 mg/kg for rabbits.

TABLE 7-7 Lethal Toxicity of Iron Pentacarbonyl (390 ppm) in Six Groups of Mice Exposed for 30 min

Mortality at 3 Days	Mortality at 5 Days
8/10	9/10
5/10	7/10
10/10	10/10
9/10	10/10
9/10	9/10
9/10	9/10

Source: Sunderman et al. 1959. Reprinted with permission; copyright 1959, American Medical Association.

3.2. Nonlethal Toxicity

Data on the nonlethal toxicity of iron pentacarbonyl in animals are limited to two unpublished studies regarding pathology in dead rats.

3.2.1. Rats

Gage (1970) reported the results of inhalation studies on groups of four male and four female rats exposed to iron pentacarbonyl. One group receiving eighteen 5.5-h exposures to 7 ppm exhibited no overt signs of toxicity and necropsy findings were unremarkable. Exposures to higher concentrations (15 and 33 ppm) were lethal. As previously described, the experiments utilized dynamic atmospheres (i.e., continuously generated and passed through the exposure chamber) generated by injecting liquid test article (in petroleum ether) at a known rate into a metered stream of air. Iron pentacarbonyl concentrations were not verified by analytical techniques.

In a 4-h inhalation study reported by Biodynamics (1988), groups of five male and five female Sprague-Dawley CD rats were exposed (whole body) to iron pentacarbonyl at concentrations of 5.2, 17, 28, or 60 ppm (analytical concentration). A control group was exposed to clean air. With the exception of the 5.2-ppm group, all exposures resulted in 100% lethality within 9 days after exposure (mortality ratios at day 5 are noted in Section 3.1.1). Clinical signs during exposure were limited to decreased activity, closing of the eyes, and labored breathing. At 1-2 h postexposure, however, clinical observations for all treatment groups included labored breathing (not for the 5.2-ppm group), lacrimation, mucoid and bloody nasal discharge, salivation, hypothermia (60-ppm group only), and ano-genital staining. A slight exposure-related increase in carboxyhemoglobin levels was observed in males, especially at 1 h into the exposure, but tended to return to normal by the end of the exposure. Even rats in the 5.2-ppm group exhibited a slight increase in carboxyhemoglobin relative to unexposed controls [males: 3.7% (1 h) and 3.5% (4 h) versus 3.2% (1 h) and 3.3% (4 h) for controls; females: 3.0% (1 h) and 2.5% (4 h) versus 2.6% (1 h) and 3.2% (4 h) for controls]. Neurological examinations (gait, muscle tone, reflexes) revealed no findings in the 5.2-ppm group rats. At 1-2 h postexposure, rats in the 5.2-ppm group exhibited lacrimation, nasal discharge, and salivation at incidences similar to those of unexposed controls. Although gross pathology findings at terminal necropsy (postexposure day 15) of rats in the 5.2-ppm group revealed red lungs in a few rats and red turbinates in one male, the study authors indicated the treatment relationship of these findings to be equivocal.

In a 28-day inhalation exposure study (BASF 1995), groups of SPF-Wistar rats (five males and five females per group) were exposed (whole body) to iron pentacarbonyl (0, 0.1, 0.3, 1, 3, or 10 ppm), 6 h/day, for up to 28 days (analytical concentrations were 0, 0.1, 0.3, 1, 2.91, and 9.85 ppm). Although 50% and 100% lethality occurred in the 3-ppm and 10-ppm groups, respectively, no rats

died in the lower (0.1-, 0.3-, and 1.0-ppm) groups, nor were there any clinical signs or findings reported for the 0.1-, 0.3-, and 1-ppm groups over the treatment period.

3.3. Developmental/Reproductive Toxicity

No data are available regarding the developmental/reproductive toxicity of iron pentacarbonyl in animals.

3.4. Genotoxicity

BASF (1988) conducted mutagenicity (Ames test) studies using *Salmonella typhimurium* strains TA1535, TA100, TA1537, and TA98 and iron pentacarbonyl concentrations of 20-5,000μg/plate. There was no evidence of genotoxicity (with or without S9) and no bacteriotoxic effects.

3.5. Carcinogenicity

No data are available regarding the carcinogenic potential of iron pentacarbonyl in animals.

3.6. Summary of Toxicity Data in Animals

Limited data are available indicating that 4-h exposure of rats to 5.2 ppm was without serious toxicologic effect, but analysis of lethality data suggests that this exposure may be approaching a lethality threshold. Exposure of rats to 1 ppm for 6 h/day for 28 days was without notable toxicity, as were eighteen 5.5-h exposures to 7 ppm. Lethal toxicity data are available for rats, mice, and rabbits. Based on the limited data available, the rat appears to be the most sensitive species as determined by the 30-min LC_{50} of 118 ppm relative to the 30-min LC_{50} of 285 ppm for the mouse. Additionally, a single 5.5-h exposure to 33 ppm or two 5.5-h exposures to 17 ppm resulted in 19% and 25% mortality, respectively, within 1-2 days. A 45.4-min exposure to 250 ppm caused death in rabbits, and a 4-h LC_{50} of 10 ppm was also reported for rats. For mice a 1.35-fold increase in the LC_{50} resulted in near 100% mortality for the same exposure duration, suggesting a steep exposure-response relationship for this species (see Section 3.1.2). Similarly, a 2.8-fold increase in exposure concentration (from 86 to 244 ppm) increased the mortality rate in rats from 4/12 to 11/12 (5 days postexposure; see Table 7-3). In calculating a 4-h LC_{50} of 10 ppm for rats, Biodynamics (1988) estimated a lethality threshold of ~5.2 ppm for 4 h, and BASF (1995) reported 50% mortality in rats following only two 6-h exposures to 3 ppm.

Data regarding the nonlethal effects of iron pentacarbonyl in animals are limited to data from rat studies showing inconsequential effects (similar to responses observed for control groups) or evidence of pulmonary involvement (congestion and edema) at exposure also associated with up to 25% mortality (Gage 1970; Biodynamics 1988; BASF 1995).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Data on the metabolism and disposition of iron pentacarbonyl are not currently available.

4.2. Mechanism of Toxicity

The specific mechanism of toxicity for iron carbonyl following inhalation exposure has not been elucidated. Data from inhalation studies with animals suggest that the chemical acts as a pulmonary and an airway irritant and that portal-of-entry effects are the most notable. Data from these studies indicate that lethality likely results from pulmonary damage.

4.3. Structure-Activity Relationships

Toxicity data for other iron carbonyls are not available. Limited data suggest that nickel carbonyl is more toxic than iron pentacarbonyl (Armit 1908; Sunderman et al. 1959) and that dimercaprol and sodium diethyldithiocarbamate, both of which are effective antidotes for nickel carbonyl, are ineffective for iron pentacarbonyl (Sunderman et al. 1959).

Iron pentacarbonyl should not be confused with carbonyl iron, which is particulate iron (CAS No. 7439-89-6) formed by heating gaseous iron pentacarbonyl ($Fe[CO]_5$). This process deposits metallic iron as submicroscopic crystals that form microscopic spheres (Huebers et al. 1986). In the case of carbonyl iron, the "carbonyl" refers to the process and not the composition of the material (Huebers et al. 1986). Studies are available that investigated the toxicity of inhaled carbonyl iron (Warheit et al. 1991) in rats and orally administered carbonyl iron in humans (Gordeuk et al. 1987; Devasthali et al. 1991). In both studies, carbonyl iron was not found to be especially toxic.

4.4. Other Relevant Information

4.4.1. Species Variability

The limited lethality data suggest minor species variability as shown by the somewhat lower 30-min LC_{50} value for rats relative to mice and rabbits.

4.4.2. Concurrent Exposure Issues

No concurrent exposure issues have been identified that would directly impact the derivation of AEGL values for iron pentacarbonyl.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

Quantitative data regarding AEGL-1 level effects of inhaled iron pentacarbonyl in humans are not available. Qualitative data are limited to nonverifiable descriptions of signs and symptoms of exposure. Specifically, Stokinger (1981) reported giddiness and headache as signs and symptoms of iron pentacarbonyl exposure but provided no exposure terms or data references with which to verify these findings. Information regarding odor detection is not available.

5.2. Summary of Animal Data Relevant to AEGL-1

Findings consistent with AEGL-1 end points were available from a 4-h inhalation study reported by Biodynamics (1988) in which groups of five male and five female Sprague-Dawley CD rats were exposed (whole body) to iron pentacarbonyl at concentrations of 5.2, 17, 28, or 60 ppm (analytical concentration). A control group was exposed to clean air. Although all rats in the 17-, 28-, and 60-ppm groups died, rats in the 5.2-ppm group exhibited only labored breathing and a slight increase in carboxyhemoglobin relative to unexposed controls. Neurological examinations (gait, muscle tone, reflexes) revealed no findings in the 5.2-ppm rats. At 1-2 h postexposure, rats in the 5.2-ppm group exhibited lacrimation, nasal discharges, and salivation at incidences similar to those of unexposed controls. Data from a 28-day inhalation exposure study (BASF 1995) in rats showed that exposure (6 h/day) to a concentration of 1 ppm resulted in no significant clinical signs or findings over the treatment duration.

5.3. Derivation of AEGL-1

Data consistent with AEGL-1 end points are limited to two studies in rats demonstrating that acute exposure to 5.2 ppm for 4 h (Biodynamics 1988) or exposure to 1 ppm for 6 h/day for 28 days (BASF 1995) produced minor irritation or no observable effects, respectively. However, analysis of lethality data by Biodynamics (1988) suggests that the 5.2 ppm exposure may be near a lethality threshold (see Section 7.3), and therefore this exposure would be inappropriate for development of AEGL-1 values. The findings from the BASF study indicated that even a 28-day exposure to 1 ppm for 6 h/day was without discernable

effect in rats. Although this exposure represents a no-adverse-effect-level (NOAEL), the utility and validity for AEGL-1 derivation are questionable. This exposure, representing a no-effect level, does not meet the criteria for AEGL-1 category effects. Based on the available data from laboratory species, it is difficult to identify an exposure causing notable irritation that does not approach an exposure causing severe effects or death. Therefore, AEGL-1 values are not recommended (see Table 7-8).

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Quantitative data consistent with AEGL-2 level effects in humans following exposure to iron pentacarbonyl are unavailable. Qualitative data are limited to nonverifiable descriptions of signs and symptoms of exposure; no quantitative exposure terms are available. Stokinger (1981) reported dyspnea, fever, and cyanosis as signs and symptoms of iron pentacarbonyl exposure but provided no exposure values or verification.

6.2. Summary of Animal Data Relevant to AEGL-2

Quantitative data consistent with AEGL-2 level effects in animals following exposure to iron pentacarbonyl are unavailable. The reports by Biodynamics (1988) and BASF (1995) provide some information regarding nonlethal effects (i.e., lassitude, pulmonary and airway irritation, labored respiration, carboxyhemoglobin formation, gross pathology and histopathology findings in the lungs) in rats exposed to iron pentacarbonyl, but the effects were not consistent with AEGL-2 severity (i.e., they were not of great severity and were not irreversible). Signs of more severe effects (e.g., pulmonary damage, hypothermia) were associated with single 6-h exposure of rats to 3 ppm (2.91 ppm analytical; BASF 1995), but this exposure also resulted in lethality (10% after one exposure, 50% after only two 6-h exposures). Although these data demonstrate effects that could be considered consistent with AEGL-2 effects, the 6-h exposure to 3 ppm

TABLE 7-8 AEGL-1 Values for Iron Pentacarbonyl

AEGL Level	1 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR	NR	NR	NR	NR

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

appears to also represent a threshold for lethality. A definitive estimate of the lethality threshold determination is complicated by the fact that lethality may be delayed up to several days following exposure (Sunderman et al. 1959; Biodynamics 1988; BASF 1995).

6.3. Derivation of AEGL-2

Data from the BASF (1995) study were considered for the derivation of AEGL-2 values. Exposure of rats to a concentration of 1 ppm for 6 h/day for up to 28 days caused no significant effects, and therefore this exposure is not appropriate for deriving AEGL-2 values. Exposure of rats to 2.91 ppm for 6 h/day caused notable signs of toxicity and 10% (1 of 10 rats) mortality after only one exposure and significant mortality (50%) after an additional exposure. In a study reported by Gage (1970), multiple 5.5-h exposures of rats to 7 ppm produced no toxic effects, whereas two 5.5-h exposures to 15 ppm resulted in 100% mortality 3-4 days following exposure. These findings indicate that for rats exposed to iron pentacarbonyl there is only a small margin between exposures causing little or no toxicity and those causing more severe effects and death. The deaths in laboratory species several days after cessation of exposure are also considered in the derivation of AEGL-2 values.

In the absence of exposure-response data consistent with AEGL-2 effects, the AEGL-2 values were derived by a 3-fold reduction in the AEGL-3 values. Such an approach results in values that are clearly below the threshold for lethality or severe toxic responses and is justified for a chemical exhibiting a steep exposure-response curve. The resulting AEGL-2 values are shown in Table 7-9 and Appendix A.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

Quantitative data consistent with AEGL-3 level effects in humans following exposure to iron pentacarbonyl are unavailable. Qualitative data are limited to nonverifiable descriptions of signs and symptoms of exposure. Although Stokinger (1981) reported that death may occur 4-11 days after a lethal exposure, no exposure concentration terms or reference sources were provided.

7.2. Summary of Animal Data Relevant to AEGL-3

Animal data consistent with the AEGL-3 definition are limited to a 30-min LC_{50} of 118 ppm for rats, a 4-h LC_{50} of 10 ppm for rats, a 30-min LC_{50} of 285

TABLE 7-9 AEGL-2 Values for Iron Pentacarbonyl[a]

AEGL Level	10 min	30 min	1 h	4 h	8 h
AEGL-2 (disabling)	0.077 ppm	0.077 ppm	0.060 ppm	0.037 ppm	0.025 ppm

[a]Under ambient atmospheric conditions, iron pentacarbonyl may undergo photochemical decomposition to iron nonacarbonyl and carbon monoxide or burn to ferric oxide if an ignition source is present.

ppm for mice, and a 45.5-min lethality value (250 ppm) for rabbits. The 30-min LC_{50} values for rats and mice come from well-conducted experiments reported by Sunderman et al. (1959), but the report lacks details regarding analytical techniques for measuring the exposure concentrations used in the experiments. The 4-h LC_{50} of 10 ppm for rats comes from a well-conducted study by Biodynamics (1988) with analytically determined exposure concentrations. Additionally, this report provided a 4-h LC_{16} of 6.99 ppm and analysis of lethality data that indicated 5.2 ppm to be an estimate of the lethality threshold. In a study reported by Gage (1970), two 5.5-h exposures of rats to 15 ppm resulted in 100% mortality at 3-4 days following exposure, and a single 5.5-h exposure to 33 ppm killed three of four rats 1 day postexposure. Lethality data were also available from a 28-day study by BASF (1995), showing 100% lethality in rats following a single 6-h exposure to 10 ppm (9.85 ppm analytical) and 50% lethality in rats following two 6-h exposures to 3 ppm (2.91 ppm analytical).

7.3. Derivation of AEGL-3

Because of the availability of analytically determined exposure concentrations and overall study quality, data from the BASF (1995) study were used to derive AEGL-3 values. In this study a single 6-h exposure to 2.91 ppm resulted in the death of one of 10 rats, while a second exposure produced 50% mortality. The remaining five rats survived 26 additional 6-h exposures. Exposure of rats to 1.0 ppm for 6 h/day for 28 days resulted in no clinical signs of toxicity.

Because a latency period is associated with iron pentacarbonyl-induced lethality, it was not possible to determine whether the four additional animals that died would have done so from only the first exposure or if the second exposure was necessary. Given this uncertainty, a log-probit benchmark dose analysis was performed (U.S. Environmental Protection Agency [EPA] software V 1.3.1) for two different possibilities, and the results are presented in Table 7-10. In one case it was assumed that only one of 10 animals would have died from one exposure, and in the other case it was assumed that five of 10 animals would have died from a single exposure.

Because the data do not permit any distinction among the hypotheses that one exposure would have killed one, two, three, four, or five animals, the worst-

TABLE 7-10 Log-Probit Benchmark Dose Analysis of BASF (1995) Rat Data Using EPA Software V 1.3.1

	Number of Animals Dying at 2.91 ppm for 6 h	
Benchmark	1 of 10	5 of 10
MLE LC_{01}	2.4 ppm	1.9 ppm
BMCL LC_{05}	1.7 ppm	0.80 ppm

case scenario that one exposure would have killed five animals was assumed. The benchmark dose analysis of this scenario provided an maximum likelihood estimate (MLE) LC_{01} of 1.9 ppm and a BMCL LC_{05} of 0.80 ppm. Due to insufficient data differentiating the MLE LC_{01} from the BMCL $LC_{05,}$ the more conservative lower one-sided confidence limit on the benchmark concentration (BMCL) LC_{05}, value of 0.80 ppm would normally have been selected as the point of departure for the AEGL-3 estimation. However, because no deaths resulted from a 28-day exposure to 1 ppm, 1 ppm was considered a more reasonable point of departure than 0.8 ppm.

In the absence of human data, and because there is some variability among the laboratory species tested, some uncertainty exists regarding species variability. However, Sunderman et al. (1959) provided data for rats and mice tested in a comparable manner (see Tables 7-4 and 7-5). Generally, the rat appears to be about two to three times more sensitive than the mouse (see Figure 7-1).

Because the most sensitive species was used (rat) and conservative experimental results were used for the AEGL-3 point of departure, an interspecies uncertainty factor (UF) of 3 is supportable. The uncertainty adjustment for intraspecies variability (UF of 3) was supported by several points. The available toxicity data indicate that acute inhalation exposure to iron pentacarbonyl results in portal-of-entry effects (i.e., airway and lungs) rather than systemic effects, and therefore variability in response due to dosimetric factors may be limited. Additionally, lethality in rats following acute inhalation exposure to iron pentacarbonyl exhibits a steep exposure-response relationship with little margin between minimal and lethal effects and little individual variability in the response of test animals (Biodynamics 1988). Finally, the total UF of 10 resulted in AEGL-3 values that were consistent with the acute exposure data and the data from multiple-exposure animal studies.

The available data for rats and mice suggest that the exposure-response curve for iron pentacarbonyl is steep. Exposure-response data for the same toxicity end point over multiple time periods are limited (30-min LC_{50} and 4-h LC_{50}) for iron pentacarbonyl. Data were unavailable for a definitive mathematical determination of the time scaling factor, n, for the equation $C^n \times t = k$ (see Appendix C). 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.

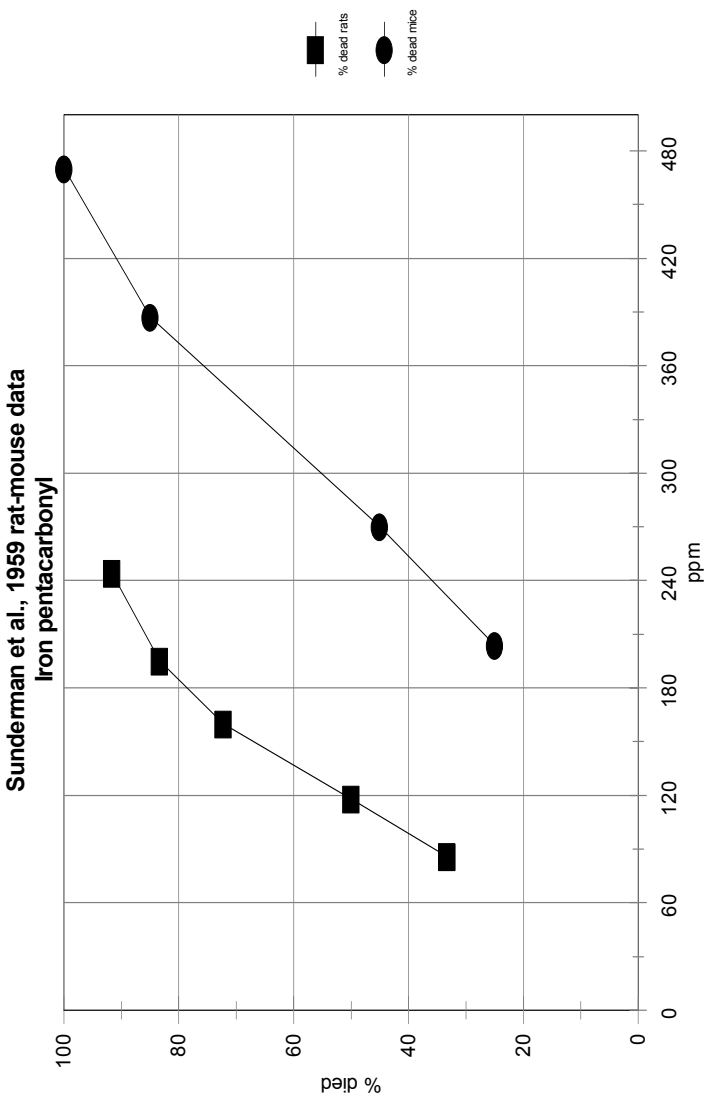

FIGURE 7-1 Lethal response of rats and mice following 30-min inhalation exposure to iron pentacarbonyl. Source: Sunderman et al. 1959 (rate mouse data iron pentacarbonyl).

It was considered reasonable to extrapolate the data back to 10 min based on a benchmark dose analysis of the Sunderman et al. (1959) data on rats exposed for 30 min. One caveat to the Sunderman data is that the animals were observed for only 5 days; however, the data are probably reasonable because in the BASF (1995) study rats died within 4 days of exposure at the lowest dose. These data were analyzed using a log probit model (EPA Benchmark Dose software V 1.31). The 30-min LC_{01} MLE was calculated to be 45 ppm, and the lower 95% confidence limit of the LC_{05} was 17 ppm. Choosing the lower value of 17 ppm and applying a total UF of 10, the 30-min value of 1.7 ppm calculated from the Sunderman et al.data affirms the protectiveness of the extrapolated AEGL-3 value of 0.23 ppm. Because the point-of-departure for AEGL-3 derivation was of 6-h duration, the 30-min AEGL-3 value was adopted as the 10-min value (NRC 2001).

These values are reasonable when viewed against all of the data on iron pentacarbonyl and well below any lethal concentrations in animals (see Appendix D). Use of a larger total UF would drive AEGL-3 values far below any observed levels of concern.

The draft AEGL-3 values for iron pentacarbonyl are shown in Table 7-11, and their derivation is presented in Appendix A.

8. SUMMARY OF AEGL VALUES

8.1. AEGL Values and Toxicity End Points

Due to the lack of exposure-response data consistent with AEGL-1 end points and the subsequent inability to define realistic exposures for such end points, AEGL-1 values are not recommended. AEGL-2 values are based on a 3-fold reduction in the AEGL-3 values. The point of departure for deriving AEGL-3 values was an estimated lethality threshold of 1.0 ppm for a 6-h exposure as determined by BMC analysis of rat lethality data. Available data for rodents suggest there is little margin between exposures void of notable effects and those causing death. Uncertainty factors were applied to account for this observation. The relationships of the AEGL values to one another and to available data are shown in the category plot in Appendix D.

8.2. Comparison with Other Standards and Guidelines

Other standards and guidelines for iron pentacarbonyl are presented in Table 7-12. No other values are currently available.

8.3. Data Adequacy and Research Needs

The animal lethality data were sufficient for the development of AEGL-3 values. The findings from these lethality studies also suggested an exposure-

TABLE 7-11 AEGL-3 Values for Iron Pentacarbonyl[a]

AEGL Level	10 min	30 min	1 h	4 h	8 h
AEGL-3 (lethal)	0.23 ppm	0.23 ppm	0.18 ppm	0.11 ppm	0.075 ppm

[a]Under ambient atmospheric conditions, iron pentacarbonyl may undergo photochemical decomposition to iron nonacarbonyl and carbon monoxide or burn to ferric oxide if an ignition source is present.

TABLE 7-12 Extant Standards and Guidelines for Iron Pentacarbonyl

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.077 ppm	0.077 ppm	0.060 ppm	0.037 ppm	0.025 ppm
AEGL-3	0.23 ppm	0.23 ppm	0.18 ppm	0.11 ppm	0.075 ppm
ERPG-1 (AIHA)[a]	—	—	—	—	—
ERPG-2 (AIHA)[a]	—	—	—	—	—
ERPG-3 (AIHA)[a]	—	—	—	—	—
EEGL (NRC)[b]	—	—	—	—	—
PEL-TWA (OSHA)[c]	—	—	—	—	0.1 ppm
PEL-STEL (OSHA)[d]	—	—	—	—	0.2 ppm
IDLH (NIOSH)[e]	—	—	—	—	—
REL-TWA (NIOSH)[f]	—	—	—	—	0.1 ppm
REL-STEL (NIOSH)[g]	—	—	0.2 ppm	—	—
TLV-TWA (ACGIH)[h]	—	—	—	—	0.1 ppm
STEL/ceiling (ACGIH)[i]	—	—	—	—	0.2 ppm
MAK (Germany)	—	—	—	—	0.1 ppm
MAK Spitzenbegrenzung (Germany)[k]	—	—	—	—	1 ppm
Einstaztolermanzwert (Germany)[l]	—	—	—	—	—

[a]ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association) (AIHA 1994). 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 protective 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]EEGL (Emergency Exposure Guidance Levels, National Research Council) (NRC 1985). The EEGL is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace but avoids death, other severe acute effects, and long-term or chronic injury.

(Continued)

TABLE 7-12 Continued

[c]OSHA PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits–Time Weighted Average) (OSHA 1993) is defined analogous to the ACGIH TLV-TWA but is for exposures of no more than 10 h/day, 40 h/week.
[d]OSHA PEL-STEL (Permissible Exposure Limits–Short-Term Exposure Limit) (OSHA 1993) is defined analogous to the ACGIH TLV-STEL.
[e]IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health) (NIOSH 2003) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms or any irreversible health effects. By concurrence with OSHA PEL, no IDLH was established.
[f]NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits–Time Weighted Average) (NIOSH 2003) is defined analogous to the ACGIH TLV-TWA.
[g]NIOSH REL-STEL (Recommended Exposure Limits–Short-Term Exposure Limit) (NIOSH 2003) is defined analogous to the ACGIH-TLV-STEL.
[h]ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value–Time Weighted Average) (ACGIH 2001) 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]ACGIH TLV-STEL (Threshold Limit Value–Short-Term Exposure Limit) (ACGIH 2001) is defined as a 15-min TWA exposure which should not be exceeded at any time during the workday even if the 8-h TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 min and should not occur more than four times per day. There should be at least 60 min between successive exposures in this range.
[j]MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration], Deutsche Forschungs-Gemeinschaft [German Research Association], Germany) (DFG 1999) is defined analogous to the ACGIH-TLV-TWA.
[k]MAK Spitzenbegrenzung (Kategorie II,2) (Peak Limit Category II,2) (DFG 1999) constitutes the maximum concentration to which workers can be exposed for a period up to 30 min, with no more than two exposure periods per work shift; total exposure may not exceed 8-h MAK.
[l]Einsatztoleranzwert (Action Tolerance Levels) (Vereinigung zur Förderung des deutschen Brandschutzes e.V. [Federation for the Advancement of German Fire Prevention]) constitutes a concentration to which unprotected firemen and the general population can be exposed to for up to 4 h without any health risks.
Note: NR: not recommended. Numerical values for AEGL-1 are not recommended (1) because of the lack of available data or (2) because an inadequate margin of safety exists between the derived AEGL-1 and the AEGL-2. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects. Under ambient atmospheric conditions, iron pentacarbonyl may undergo photochemical decomposition to iron nonacarbonyl and carbon monoxide or burn to ferric oxide.

response relationship for which there appeared to be little margin between exposures producing little or no toxicity and those resulting in lethal responses. The available studies also showed that the respiratory tract may be a primary target for the lethality of this chemical following inhalation exposure. Information re-

garding the human experience was limited to inadequately validated qualitative descriptions of nonspecific responses.

The most notable research need is to provide definitive exposure-response data for nonlethal effects, thereby allowing for a more precise description of the exposure-response profile for iron pentacarbonyl, particularly in terms of AEGL-2 effects. AEGL-1 are not recommended due to the absence of data specific to response end points consistent with the AEGL-1 definition. Furthermore, available data suggest that there is little margin between these levels, thereby rendering development of AEGL-1 values tenuous and of questionable utility. Although LC_{50} data are available for two species, the overall database is insufficient to definitively determine the magnitude of species variability in the lethal response to inhaled iron pentacarbonyl.

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APPENDIX A

Derivation of AEGL-1 Values

Quantitative data regarding responses consistent with the AEGL-1 definition were not available for acute inhalation exposure of humans or test animals to iron pentacarbonyl. Because of the lack of appropriate data, reliable AEGL-1 values could not be determined. Additionally, the exposure-response relationship and apparent extreme toxicity of iron pentacarbonyl following inhalation exposure in animals suggest little margin between exposures with little or no apparent effect and those causing lethality. Therefore, AEGL-1 values are not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 concentration is without adverse effects.

Derivation of AEGL-2 Values

Key study:	AEGL-2 values were derived by a 3-fold reduction in the AEGL-3 and therefore are also based on the data reported by BASF (1995).
Toxicity end point:	The AEGL-3 values were reduced by a factor of 3 as a threshold estimate for serious and/or irreversible effects. Comparison of the resulting values with available animal data affirms that the resulting values would be below those causing a lethal response and that they are consistent with the steep exposure-response relationship indicated by the animal data.
Scaling:	As per AEGL-3 development.
Uncertainty factors:	3 for uncertainties regarding interspecies variability as per AEGL-3 development. 3 for intraspecies variability as per AEGL-3 development.

Derivation of AEGL-3 Values

Key study:	BASF 1995.
Toxicity end point:	10% lethality following a single 6-h exposure of male and female rats to 2.91 ppm; 50% mortality following

two 6-h exposures to 2.91 ppm. Data from an independent study (Biodynamics 1988) provided a 4-h LC_{50} of 10 ppm, a 4-h LC_{16} of 6.99 ppm, and an estimated 4-h lethality threshold of 5.2 ppm. The AEGL-3 point of departure (NOAEL for lethality) was estimated to be 1.0 ppm (6-h exposure) based on BMD analysis and evaluation of the available data (see Section 7.3).

Scaling: Data were unavailable for determining the exponent "n." 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 1 to 3.5 (ten Berge et al. 1986). In the absence of chemical-specific data, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points.
$(1.0 \text{ ppm})^1 \times 6 \text{ h} = 6 \text{ ppm•h}$
$(1.0 \text{ ppm})^3 \times 6 \text{ h} = 6 \text{ ppm•h}$

Uncertainty factors: 3 for uncertainties regarding interspecies variability. Lethality data suggest some variability (approximately 2 to 3 fold based on data from Sunderman et al. 1959) among the laboratory species tested. Definitive data regarding a lethality threshold for humans exposed to iron pentacarbonyl are not available.

3 for intraspecies variability. The adjustment for this area of uncertainty was limited to 3 because the available toxicity data indicate that acute inhalation exposure to iron pentacarbonyl results in port-of-entry effects (i.e., airway and lungs) rather than systemic effects, and therefore variability in response due to dosimetric factors may be limited. Additionally, lethality in rats following acute inhalation exposure to iron pentacarbonyl exhibits a steep exposure-response relationship with little margin between minimal and lethal effects and little individual variability in the response of test animals.

10-min AEGL-3: Due to uncertainties in extrapolating from a 6-h experimental time point to a 10-min AEGL-specific du-

ration, the 30-min AEGL-3 has been adopted as the 10-min AEGL-3.

10-min AEGL-3 = 0.23 ppm (1.8 mg/m^3)

30-min AEGL-3: $C^3 \times 0.5$ h = 6.0 ppm•h
C = 2.28 ppm
30-min AEGL-3 = 2.28 ppm/10 = 0.23 ppm
(1.8 mg/m^3)

1-h AEGL-3: $C^3 \times 1$ h = 6.0 ppm•h
C = 1.82 ppm
1-h AEGL-3 = 1.82 ppm/10 = 0.18 ppm
(1.4 mg/m^3)

4-h AEGL-3: $C^3 \times 4$ h = 6.0 ppm•h
C = 1.14 ppm
4-h AEGL-3 = 1.14 ppm/10 = 0.11 ppm
(0.88 mg/m^3)

8-h AEGL-3: $C \times 8$ h = 6.0 ppm•h
C = 0.75 ppm
8-h AEGL-3 = 0.75 ppm/10 = 0.075 ppm
(0.60 mg/m^3)

APPENDIX B

Time Scaling for Iron Pentacarbonyl AEGLs

The relationship between dose and time for any given chemical is a function of the physical and chemical properties of the substance and its unique toxicological and pharmacological properties. Historically, the relationship according to Haber (1924), commonly called Haber's law or Haber's rule (i.e., $C \times t = k$, where C = exposure concentration, t = exposure duration, and k = a constant) has been used to relate exposure concentration and duration to effect (Rinehart and Hatch 1964). This concept states that exposure concentration and exposure duration may be reciprocally adjusted to maintain a cumulative exposure constant (k) and that this cumulative exposure constant will always reflect a specific quantitative and qualitative response. This inverse relationship of concentration and time may be valid when the toxic response to a chemical is equally dependent on the concentration and the exposure duration. However, an assessment by ten Berge et al. (1986) of LC_{50} data for certain chemicals revealed chemical-

specific relationships between exposure concentration and exposure duration that were often exponential. This relationship can be expressed by the equation $C^n \times t = k$, where n represents a chemical-specific, and even a toxic end point-specific, exponent. The relationship described by this equation is basically the form of a linear regression analysis of the log-log transformation of a plot of C versus t. ten Berge et al. (1986) examined the airborne concentration (C) and short-term exposure duration (t) relationship relative to death for approximately 20 chemicals and found that the empirically derived value of n ranged from 0.8 to 3.5 among this group of chemicals. Hence, the value of the exponent (n) in the equation $C^n \times t = k$ quantitatively defines the relationship between exposure concentration and exposure duration for a given chemical and for a specific health effect end point. Haber's rule is the special case where n = 1. As the value of n increases, the plot of concentration versus time yields a progressive decrease in the slope of the curve.

Data were not available to derive an exposure concentration-exposure duration relationship (n) for propargyl alcohol. 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 (NRC 2001).

Although exposure-response data for the same toxicity end point over multiple time periods were limited to several LC_{50} values, these data suggested a near-linear relationship. Therefore, the value of n was set at unity for the exponential temporal scaling equation, $C^1 \times t = k$.

APPENDIX C

ACUTE EXPOSURE GUIDELINES FOR IRON PENTACARBONYL

Derivation Summary for Iron Pentacarbonyl AEGLS

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Key reference: Not applicable.				
Test species/Strain/Number: Not applicable.				
Exposure route/Concentrations/Durations: Not applicable.				
Toxicity end point: Data unavailable for defining AEGL-1-specific end points.				
Time scaling: Not applicable.				
Concentration/Time selection/Rationale: Not applicable.				
Uncertainty factors/Rationale: Not applicable.				

(Continued)

AEGL-1 VALUES Continued

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

Modifying factor: Not applicable.

Animal-to-human dosimetric adjustments: Not applicable.

Comments: NR: not recommended. Numerical values for AEGL-1 are not recommended (1) because of the lack of available data, and (2) because an inadequate margin of safety exists between the derived AEGL-1 and the AEGL-2 values. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 concentration is without adverse effects.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.077 ppm	0.077 ppm	0.060 ppm	0.037 ppm	0.025 ppm

Key reference: Not applicable; see AEGL-3.

Test species/Strain/Number: Rat/Wistar/5 males and 5 females per exposure group.

Exposure route/Concentrations/Durations: Not applicable; see AEGL-3.

Toxicity end point: 3-fold reduction in AEGL-3 values.

Time scaling: $C^n \times t = k$, where n =1 or 3; as per AEGL-3 values.

Concentration/Time selection/Rationale: See procedure/rationale for AEGL-3.

Uncertainty factors/Rationale
Total Uncertainty Factor: 10 (as per AEGL-3 values).

Modifying factor: None applied

Animal-to-human dosimetric adjustments: None.

Data adequacy: Although definitive data were unavailable that described effects consistent with the AEGL-2 definition, a 3-fold reduction in AEGL-3 values was considered appropriate for development of AEGL-2 values. This approach is consistent with the available data demonstrating a steep exposure-response curve. Under ambient atmospheric conditions, iron pentacarbonyl may undergo photochemical decomposition to iron nonacarbonyl and carbon monoxide or burn to ferric oxide.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
0.23 ppm	0.23 ppm	0.18 ppm	0.11 ppm	0.075 ppm

Key reference: BASF. 1995. Study on the inhalation toxicity of eisenpentacarbonyl as a vapor in rats—28 day test. BASF Department of Toxicology. EPA/OTS Doc # 89-950000244.

(Continued)

AEGL-3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
0.23 ppm	0.23 ppm	0.18 ppm	0.11 ppm	0.075 ppm

Test species/Strain/Number: Rat/Wistar/5 males and 5 females per exposure group.

Exposure route/Concentrations/Durations: 6-h inhalation exposure

Test Group	*Exposure Concentration (ppm analytical)*
0	clean air control
4	0.1 (0.1 ± 0.01)
E	0.1 (0.1 ± 0.01)
1	1 (1.00 ± 0.02)
2	3 (2.91 ± 0.01)
3	10 (9.85)

Toxicity end point: 10% mortality after one 6-h exposure to 2.91 ppm; 50% mortality following two 6-h exposures. A benchmark dose analysis of the BASF (1995) data provided an MLE LC_{01} of 1.9 ppm and a BMDL LC_{05} of 0.80 ppm.

Time scaling: $C^n \times t = k$, where n =1 or 3. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by C^n x t = k, where the exponent n ranges from 1 to 3.5 (ten Berge et al. 1986). In the absence of chemical-specific data, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points. Due to uncertainties in extrapolating from the 6-h point of departure to 10 min, the 30-min AEGL-3 was adopted as the 10-min value.

Concentration/Time selection/Rationale: A benchmark dose analysis of the BASF (1995) data provided an MLE LC_{01} of 1.9 ppm and a BMCL LC_{05} of 0.80 ppm. Due to insufficient data differentiating the MLE LC_{01} from the BMCL LC_{05}, the more conservative BMCL LC_{05} value of 0.80 ppm would normally have been selected as the point of departure for the AEGL-3 estimation. However, because no deaths resulted from a 28-day exposure to 1 ppm, 1 ppm was considered a more reasonable point of departure than 0.8.

Uncertainty factors/Rationale:
Total uncertainty factor: 10

Interspecies: 3 to account for data deficiencies in species variability in the toxic response to iron carbonyl and for possible variability in toxicodynamics; exposures causing lethality in rats and mice varied by 2- to 3-fold.

Intraspecies: 3 to account for possible individual variability in the sensitivity to iron pentacarbonyl-induced toxicity. Adjustment of the AEGL-3 values by application of greater uncertainty was not considered necessary because the total uncertainty factor of 10 resulted in AEGL-3 values that were reasonable compared to the available acute exposure data and data from multiple-exposure

(Continued)

AEGL-3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
0.23 ppm	0.23 ppm	0.18 ppm	0.11 ppm	0.075 ppm

animal studies. Additionally, lethality of rats following acute inhalation exposure to iron pentacarbonyl exhibits a steep exposure-response relationship with little margin between minimal and lethal effects and little individual variability in the response (Biodynamics 1988).

Modifying factor: None.

Animal-to-human dosimetric adjustments: None.

Data adequacy: The AEGL-3 values have been developed based on an estimate of the lethality threshold as determined by data available from a well-conducted GLP study. Under ambient atmospheric conditions, iron pentacarbonyl may undergo photochemical decomposition to iron nonacarbonyl and carbon monoxide or burn to ferric oxide.

APPENDIX D

Category Plot for Iron Pentacarbonyl AEGLS

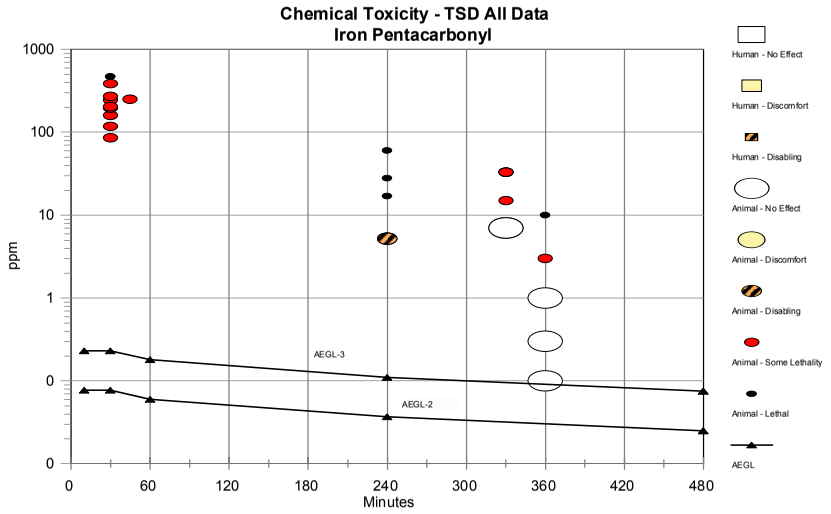

FIGURE 7-2 Category plot of animal toxicity data compared to AEGL values. Note that the above plot includes multiple exposure studies for which a single exposure was input into the plot (5.5 h/d for two days in rats (Gage 1970); 6h/d, 5d/wk for 28 days in rats (BASF 1995). No effect = No effect or mild discomfort. Discomfort = Notable transient discomfort/irritation consistent with AEGL-1 level effects. Disabling = Irreversible/long-lasting effects or an impaired ability to escape. Some lethality = Some, but not all, exposed animals died. Lethal = All exposed animals died.

8

Monomethylhydrazine[1]

Acute Exposure Guideline Levels

UPDATE OF MONOMETHYLHYDRAZINE AEGLS

In Volume 1 of the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2000), acute exposure guideline level (AEGL) values were developed for 30 minutes (min) and 1, 4, and 8 hours (h). Since that time AEGL values have also been developed for 10-min exposures. This document updates Volume 1 to include 10-min values. The summary below is from Volume 1, reference with additional discussion to address the development of 10-min values.

SUMMARY

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

Human volunteers exposed to 90 ppm of monomethylhydrazine for 10 min reported minor irritation as the only effect (MacEwen et al. 1970).

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

[1]This document was prepared by AEGL Development Team member Richard Thomas of the National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances (NAC) and Robert Young of the Oak Ridge National Laboratory. The NAC reviewed and revised the document, which was then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC Committee concludes that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NAC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

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

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

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

For AEGL-3, lethality data (1-h LC_{50} of 82 ppm) for squirrel monkeys (Haun et al. 1970) were downwardly adjusted by a factor of 3 to estimate a lethality threshold (27.3 ppm). Temporal scaling to obtain time-specific AEGL values was described by $C^1 \times t = k$ (where C = exposure concentration, t = exposure duration, and k = a constant). The lethality data for the species tested indicated a near-linear relationship between concentration and time (n = 0.97 and 0.99 for monkeys and dogs, respectively). The derived exposure values were adjusted by a total uncertainty factor of 10. An uncertainty factor of 3 was applied for interspecies variability with the following justification. One-hour LC_{50}s were determined for the monkey, dog, rat, and mouse. The LC_{50} values ranged from 82 ppm in the squirrel monkey to 244 ppm in the mouse, differing by a factor of approximately 3. The squirrel monkey data (1-h LC_{50} = 82 ppm) were used to determine the AEGL-3 because this species appeared to be the most sensitive to monomethylhydrazine toxicity and because it was the species most closely related to humans. An uncertainty factor of 3 for protection of sensitive individuals was applied to reflect individual variability of less than an order of magnitude. Although the mechanism of toxicity is uncertain and sensitivity among individuals may vary, the exposure-response relationship for each spe-

cies tested is very steep, suggesting limited variability in the toxic response to monomethylhydrazine. Furthermore, it is likely that acute toxic responses are, at least initially, a function of the extreme reactivity of monomethylhydrazine. Interaction of the highly reactive monomethylhydrazine with tissues (e.g., pulmonary epithelium) is not likely to vary greatly among individuals.

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

Inhalation or oral slope factors were not available for monomethylhydrazine. A cancer assessment based on the carcinogenic potential of dimethylhydrazine revealed that AEGL values for a 10^{-4} carcinogenic risk exceeded the AEGL-3 values that were based on noncancer end points. Furthermore, the available data for hydrazine and its methylated derivatives suggest that the tumorigenic response observed for these compounds results from long-term, repeated exposures that cause repetitive tissue damage. Because AEGLs are applicable to rare events or single once-in-a-lifetime exposures to a limited geographic area and small population, the AEGL values based on noncarcinogenic end points were considered more appropriate. The AEGL values and toxicity end points are summarized in Table 8-1.

TABLE 8-1 Summary of AEGL Values for Monomethylhyrazine[a]

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1	NR	NR	NR	NR	NR	Not recommended due to inadequate data; concentration-response relationships suggest little margin between exposures that cause minor effects and those that result in serious toxicity.[b]
AEGL-2	5.3 ppm (10 mg/m^3)	1.8 ppm (3.4 mg/m^3)	0.90 ppm (1.7 mg/m^3)	0.23 ppm (0.43 mg/m^3)	0.11 ppm (0.21 mg/m^3)	3-fold reduction in AEGL-3
AEGL-3	16 ppm 30 mg/m^3	5.5 ppm 10.3 mg/m^3	2.7 ppm 5.1 mg/m^3	0.68 ppm 1.3 mg/m^3	0.34 ppm 0.64 mg/m^3	1-h LC_{50} of 82 ppm reduced 3-fold to estimate a lethality threshold; uncertainty factor = 10

[a]Each uncertainty factor of 3 is the geometric mean of 10, which is 3.16; hence, 3.16 × 3.16 = 10.
[b]Refer to AEGL-1 for hydrazine if hydrazine is also present.

(Continued)

TABLE 8-1 Continued

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

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9

Nickel Carbonyl[1]

Acute Exposure Guideline Levels

PREFACE

Under the authority of the Federal Advisory Committee Act (P.L. 92-463) of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances has been established to identify, review, and interpret relevant toxicologic and other scientific data and develop acute exposure guideline levels (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). AEGL-2 and AEGL-3 levels, and AEGL-1 levels as appropriate, will be developed for each of five exposure periods (10 min, 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 parts per million [ppm] or milligrams per cubic meter [mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

[1]This document was prepared by AEGL Development Team member Robert Young of Oak Ridge National Laboratory and Ernest Falke (Chemical Manager) of the National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances (NAC). The NAC reviewed and revised the document, which was 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 data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993; 2001).

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

SUMMARY

Nickel carbonyl, formed by the reaction of carbon monoxide with metallic nickel, is used in nickel refining, in the synthesis of acrylic and methacrylic esters, and for other organic synthesis. In air, nickel carbonyl rapidly decomposes to metallic nickel and carbon monoxide with a 50% decomposition at room temperature and total decomposition at 150-200 C. Its decomposition is inversely proportional to the concentration of carbon monoxide; in the absence of carbon monoxide, decomposition may occur in approximately 1 min. Thus, potential exposure to the parent nickel carbonyl is limited by its rapid conversion to airborne metallic nickel.

Human data are limited to case reports, primarily of nickel workers, that affirm the extreme toxicity of the compound. Definitive exposure terms are lacking in these reports. Available information suggests that there are very limited or no warning properties associated with exposure to nickel carbonyl. Significant signs and symptoms of toxicity are known to occur in the absence of recognizable odor. Human case studies have shown that a latency period often occurs between initial signs of toxicity and subsequent serious effects that may progress to death. The primary target of nickel carbonyl-induced acute toxicity appears to be the lungs, although extra pulmonary involvement also has been reported. The specific mechanism of toxicity is unclear but appears to involve damage to pulmonary tissue.

Animal data are limited to lethality and developmental toxicity. Lethality values (LC_{50}) are available for rats, mice, cats, and rabbits. Thirty-minute LC_{50}

values for these species range from 33.6 to 266 ppm. These lethality data indicate notable species variability in the lethal response to inhaled nickel carbonyl; smaller species are generally more sensitive. Developmental toxicity has been demonstrated in rats and hamsters following single 30-min (11.2-42 ppm, rats) or 15-min (8.4 ppm, hamsters) exposures of dams during gestation. In hamsters, developmental toxicity was observed in dams following lethal or near-lethal exposures. In rats, developmental toxicity was observed in offspring of dams that were exposed to nonlethal concentrations of nickel carbonyl. Because information on the health status of the rat dams was not provided, it was not possible to determine the relative maternal versus fetal sensitivity to nickel carbonyl challenge.

Epidemiologic data do not support the contention that inhalation of nickel carbonyl is carcinogenic to humans. Studies of respiratory tract cancer in nickel workers suggest that nickel dusts, nickel sulfide, and nickel subsulfide may be more relevant than nickel carbonyl and that nickel carbonyl is not a likely causative agent in the carcinogenicity observed in nickel refinery workers. Limited data for rats have provided equivocal evidence of pulmonary carcinogenicity following acute or long-term exposure to nickel carbonyl. Data are unavailable for a quantitative assessment of the carcinogenic potential of nickel carbonyl in humans or animals.

Exposure-response data over multiple time periods are unavailable for nickel carbonyl, and empirical derivation of a temporal scaling factor (n) was not possible. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived exponent (n), temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points.

Neither human nor animal data are available for deriving AEGL-1 values. Both human and animal data affirm the extreme toxicity of nickel carbonyl. Published accounts of human exposures indicate that symptoms of toxicity can occur in the absence of olfactory or other sensory detection. Severe pulmonary edema and hemorrhage can follow initial asymptomatic exposures by as much as 12 h after exposure. Therefore, AEGL-1 values are not recommended.

Teratogenicity and fetotoxicity findings in rats and hamsters following lethal or near-lethal exposures have been reported. No human data are available that specifically identify effects consistent with AEGL-2.

AEGL-2 values for nickel carbonyl were developed based on a 30-min exposure of mice to 2.17 ppm (Kincaid et al. 1953). A concentration-dependent lethal response was observed for exposures to 6.51-12.6 ppm, but the lowest concentration (2.17 ppm) resulted in no deaths. Exposure to 6.51 ppm resulted in the deaths of two of 15 mice, and a 30-min LC_{50} of ~9.4 ppm was estimated by the investigators. Although no histopathology examinations were performed on the mice in the 2.17-ppm group, Kincaid et al. and Barns and Denz (1951) reported findings of pleural effusion, severe pulmonary congestion, and pulmo-

nary edema for rats that died following exposure to nickel carbonyl. Therefore, the 30-min exposure to 2.17 ppm was considered a reasonable estimate of an exposure that might cause pulmonary damage in the mouse (the most sensitive species tested) but not result in irreversible adverse effects. As shown by the multiple-exposure studies of Kincaid et al., repeated exposures of mice to this or greater concentrations did not result in a lethal response. Pulmonary damage appears to be a component in the continuum of the toxic response to nickel carbonyl and an appropriate critical effect for AEGL-2 development. The available lethality data suggest that the mouse represents a sensitive species. Based on this and the analysis conducted by Kincaid et al. indicating an inverse relationship between lethality and body size, the interspecies uncertainty factor of 3 appears to be justified. Although intraspecies variability is difficult to assess based on available data, an uncertainty factor of 3 was applied with the assumption that neither the effects of nickel carbonyl on pulmonary tissues nor dosimetry would vary greatly among individuals. Occupational exposure data suggest that the AEGL-2 values are sufficiently protective. A modifying factor of 3 was applied in the development of the AEGL-2 values to account for data deficiencies regarding AEGL-2 specific effects and the possibility of developmental toxicity.

AEGL-3 values were derived based on an estimated lethality threshold in mice (3.17 ppm) exposed to nickel carbonyl for 30 min (Kincaid et al. 1953). Lethality data were available for several species (rats, mice, rabbits, and cats). A total uncertainty adjustment of 10 was applied (each uncertainty factor of 3 is the approximate logarithmic mean of 10, which is 3.16; hence, $3.16 \times 3.16 = 10$). Analysis of the available data indicated that the mouse was the most sensitive species and that larger species tended to be less sensitive. Because data from the most sensitive species were used and because the available LC_{50} values vary approximately 8-fold, the total uncertainty adjustment of 10 is weighted toward the uncertainty in individual sensitivity to nickel carbonyl exposure. Data are unavailable to definitively apportion the uncertainty adjustment between inter- and intraspecies.

Limited data suggest the development of pulmonary tumors in rats inhaling nickel carbonyl. There are equivocal findings suggestive of a tumorigenic response following a single massive exposure of rats to nickel carbonyl. However, a valid quantitative cancer risk assessment is not currently feasible for a single acute exposure. Although some nickel compounds (nickel subsulfide and nickel refinery dust) are considered human carcinogens based on animal data and epidemiological studies, other nickel compounds including nickel carbonyl are considered potential human carcinogens based on limited animal data. The human carcinogen classification is based on animal data and evaluations of epidemiologic data showing an increased risk of pulmonary and sinonasal cancers in nickel refinery workers with exposure to nickel refinery dust, which is primarily nickel subsulfide (EPA 1991). No quantitative carcinogen risk assessment has been conducted for nickel carbonyl due to deficiencies in the available data. Evaluations of epidemiological studies by Doll (1984) and CEC (1990) concluded that nickel carbonyl was an unlikely contributor to the increased risk

of sinonasal cancers in the nickel refinery workers. Therefore, cancer risk was not the basis for AEGL development. The AEGL values and toxicity end points are summarized in Table 9-1.

1. INTRODUCTION

Nickel carbonyl, formed by the reaction of carbon monoxide with metallic nickel, is used in nickel refining, in the synthesis of acrylic and methacrylic esters, and for other organic syntheses (Antonsen 1978; Budavari et al. 1996). Additionally, the compound is used in vapor deposition plating to increase the durability of injection molds for automotive parts (EPA 2002). Although frequently listed as a site-limited intermediate, on-site storage by some users have listed up to 900 pounds of nickel carbonyl (EPA 2002). Upon heating to 200° C, nickel carbonyl decomposes to pure nickel and carbon monoxide, a reaction referred to as the Mond process (Goyer 1991). In air at room temperature, 50% of nickel carbonyl rapidly decomposes to nickel and carbon monoxide. At temperatures of 150-200°C, 100% degradation may occur (Vuopola et al. 1970). The rate of decomposition is inversely dependent on the carbon monoxide concentration; in the absence of carbon monoxide, nickel carbonyl will completely decay in about 1 min (Stedman et al. 1980). An odor threshold of 0.5-3 ppm has been reported for humans but not validated (AIHA 1989). Some inhaled nickel carbonyl is eliminated via expired air, the remainder may dissociate to Ni^0, subsequently oxidized to Ni (II) and released into the blood serum, where it may bind to albumin and nickel-binding substances and be cleared via the kidneys. Nickel carbonyl will, however, damage Type I and Type II alveolar cells of the lungs and may induce pulmonary edema and chemical pneumonitis. Physicochemical data for nickel carbonyl are shown in Table 9-2.

TABLE 9-1 Summary of AEGL Values for Nickel Carbonyl (ppm [mg/m^3])

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR	NR	NR	NR	NR	NR
AEGL-2 (disabling)	0.10 (0.69)	0.072 (0.50)	0.036 (0.25)	0.0090 (0.063)	0.0045 (0.031)	NOAEL for severe pulmonary damage in mice; 2.17 ppm, 30 min (Kincaid et al. 1953).
AEGL-3 (lethal)	0.46 (3.2)	0.32 (2.2)	0.16 (1.1)	0.040 (0.27)	0.020 (0.14)	Estimated mouse lethality threshold (LC_{01} of 3.17 ppm; (Kincaid et al. 1953).

Note: Numerical values for AEGL-1 are not recommended because of the lack of available data. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.
Abbreviations: NR, not recommended; NOAEL, no-observed-adverse-effect level.

TABLE 9-2 Physical and Chemical Data

Property	Descriptor or Value	Reference
Synonyms	Nickel tetracarbonyl	Budavari et al. 1996
Common name	Nickel carbonyl	
Chemical formula	C_4NiO_4	Budavari et al. 1996
Molecular weight	170.73	Budavari et al. 1996
CAS Registry No.	13463-39-3	Budavari et al. 1996
Physical state	Liquid	Budavari et al. 1996
Vapor pressure	28.7 kPa at 20°C 400 mm at 25.8°C	Antonsen 1978 Sax and Lewis 1989
Density	1.318 at 17°C	Budavari et al. 1996
Boiling/melting point	43°C/–19.3°C	Budavari et al. 1996
Solubility	Miscible with organic solvents, soluble to about 5,000 parts in water.	Antonsen 1978; Budavari et al. 1996
Conversion factors in air	1 mg/m^3 = 0.14 ppm 1 ppm = 6.9 mg/m^3	

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Nickel carbonyl is known to exhibit extreme toxicity in humans following acute exposure (Antonsen 1978; Budavari et al. 1996; Sunderman 1989; Goyer 1991). Nickel carbonyl is generally considered the most toxic form of nickel (Ellenhorn 1997) and upon inhalation produces both respiratory tract and systemic effects (Shi 1994a). Individuals poisoned by acute exposure to nickel carbonyl exhibit immediate and delayed effects (Kincaid et al. 1953). The acute lethality of nickel carbonyl in humans is well documented (Sunderman 1989; Kurta et al. 1993; Ellenhorn 1997). Lethality appears to be attributed to neurologic and respiratory effects (Sunderman 1989; Kurta et al. 1993).

Several reports are available that document lethal exposure to nickel carbonyl. Sunderman (1989) reported on the exposure of over 100 workers to nickel carbonyl at a Port Arthur, Texas, petroleum refining facility. Thirty-one experienced acute signs and symptoms of toxicity (headache, sternal and epigastric pain, nausea, vomiting, chest constriction, shortness of breath, hacking and unproductive cough, extreme weakness, fatigue), and two subsequently died. Case-specific data were not reported, but pneumonitis, respiratory difficulties (cough, shortness of breath, chest constriction) and neurological signs (convulsions, confusion) were associated with those individuals with severe or lethal

poisoning. It was noted that the signs and symptoms of poisoning could be categorized as immediate or delayed (latency of 1-5 days). The onset of severe symptoms varied from 10 h to 6 days. Convalescence was protracted and the administration of 2,3-dimercaptopropanol was attributed with saving the lives of some of the victims. Kincaid et al. (1956) estimated the human LC_{50} as 3 ppm, and Vuopola et al. (1970) noted that atmospheric concentrations of 30 ppm of nickel carbonyl are probably immediately fatal to humans.

The limited acute lethality values for inhalation exposure of humans to nickel carbonyl are summarized in Table 9-3.

2.2. Nonlethal Toxicity

Shi (1986) reported on 179 cases of nonlethal occupational exposure to nickel carbonyl. Exposure times varied from <30 min to >2 h. The report was primarily a qualitative analysis of the documented exposures. No specific exposure concentration or exposure duration data were provided regarding the signs and symptoms discussed, and therefore there were no data useful for derivation of AEGL values. Exposures were categorized as mild, moderate, or severe based on many clinical signs and symptoms. The onset of signs and symptoms varied from a few minutes to several hours to as long as a week following exposure and included respiratory system, nervous system, digestive tract, and cardiovascular effects. In analyzing the toxic responses in the 179 cases, Shi (1994a) found that there was an immediate stage lasting 4-5, followed by a remission of approximately 12 h that may extend to 2-3 days. The immediate phase was characterized by neurologic disorders and upper-airway irritation, while the delayed phase was generally characterized by chest pain, cough and dyspnea, palpitation, fever, leukocytosis, and some X-ray abnormalities (irregular linear shadow, expansion and increased density of the hilus, diffuse irregular nodular mottling or patchy shadows). The delayed onset of toxicity is consistent with what is observed in animal models.

Sunderman (1992) provided information on the results of a study involving 156 male workers accidentally exposed to nickel carbonyl at the Toa Gosei Chemical plant in Nagoya, Japan. Of the workers exposed, 137 exhibited symptoms of poisoning, but no fatalities occurred, due in part to treatment of the workers with Antabuse and Dithiocarb (diethyldithiocarbamate). Exposure terms were unavailable, but the report served to identify major medical findings for the exposed workers. These included abnormal liver function, renal insufficiencies, skin lesions, abnormal densities in pulmonary x-rays, and symptoms of encephalopathy.

An acute case of nickel carbonyl poisoning involving inhalation and dermal exposure was reported by Kurta et al. (1993). Although exposure terms were unavailable, the report provided a clinical picture of nickel carbonyl poisoning and its outcome following antidote therapy with disulfiram and diethyl-

TABLE 9-3 Acute Lethality of Nickel Carbonyl in Humans

Acute Lethality Value	Reference
30-min LC_{50}: 3 ppm (Estimated)	Kincaid et al. 1956
30 ppm: Immediately Fatal (Estimated)	Vuopola et al. 1970

dithiocarbamate. Twenty-four hours after the exposure, urinary nickel levels were 172 µg/dL (normal is <5 µg/dL). The 46-year-old subject initially experienced headache, chest pains, shortness of breath, and weakness. The subject was aggressively treated with oxygen and other supportive and prophylactic therapy (e.g., antibiotics) as well as disulfiram and diethyldithiocarbamate. An 18-day hospital stay was required, but upon discharge pulmonary function was still moderately impaired.

In a report by Sunderman (1990) on clinical management of nickel carbonyl poisoning with Dithiocarb, reference was made to the inability of human subjects to detect low concentrations of nickel carbonyl. Results of experiments in which six human subjects smelled "whiffs" of 0-5 ppm of nickel carbonyl (no specific exposure durations were provided) were highly variable, with some individuals acknowledging detection of the compound and others being unaware of any odor. The results suggested that nickel carbonyl is unlikely to be detected at low concentrations, especially by those unfamiliar with it.

2.2.1. Epidemiologic Studies

Shi et al. (1986) conducted a study in which serum monoamine oxidase (SMAO) activity and electroencephalograms (EEGs) were evaluated in male and female nickel carbonyl workers. Group A contained 42 workers (average age, 36.2) with 10-20 years of work; Group B had 36 individuals (average age, 29.1) with 2-8 years of work; and Group C included 40 individuals (average age, 28.4) with no possible exposure to nickel carbonyl. It was noted that the average concentration of nickel carbonyl in the work area was 0.007-0.52 mg/m^3 (equivalent to 0.0009-0.073 ppm). Results of the study revealed statistically significant (t-test) decreases in SMAO activity with longer exposure durations. Incidences of abnormal EEGs were significantly increased with longer exposure durations. Although these findings demonstrate nonlethal effects following long-term, low-level exposure to nickel carbonyl, extrapolation to acute exposure situations would be uncertain.

More recently, Shi (1994b) conducted a study of lung function in workers occupationally exposed to nickel carbonyl for 2-20 years. The study groups included workers exposed to nickel carbonyl over 18.6 years (men), 16.6 years (women), 2.5 years (men), or 3.8 years (women). The nickel carbonyl concentration at the workplace, as determined by gas chromatography, ranged from 0.007 to 0.52 mg/m^3 (0.00098-0.072 ppm). Unexposed workers served as controls. For

male workers exposed for more than 14 years and for female workers exposed for more than 10 years, statistically significant ($p < .05$ to $p < .001$) alterations in several lung function measures were noted. For those workers exposed for lesser durations, considerably fewer parameters were altered. Although inadequate for the derivation of AEGL values, the results of this study show that long-term exposure to nickel carbonyl at concentrations of 0.00098-0.072 ppm may affect respiratory function but are not life threatening.

2.3. Reproductive/Developmental Toxicity

Data regarding the reproductive/developmental toxicity of nickel carbonyl in humans were not available.

2.4. Genotoxicity

Decheng et al. (1987) analyzed data from workers occupationally exposed to nickel carbonyl and found no increase in the frequency of chromosomal aberrations but that nickel carbonyl appeared to act synergistically with cigarette smoke in increasing the frequency of sister chromatid exchange in peripheral lymphocytes.

Cytogenetic measurements were evaluated by Shi (1992) in 64 workers (19-48 years old) exposed to nickel carbonyl (0.0043-0.026 mg/m^3; 0.0006-0.0036 ppm) over a period of 10 years. Compared to unexposed workers, the incidences of chromosomal anomalies in peripheral lymphocytes were significantly increased ($p < .01$ to $p < .05$). Anomalies included "teratogenized" cells, chromatic aberrations, chromosomal aberrations, breakage and deletion, sister chromatid exchanges, and increased micronuclei frequency. An increase in dyskaryotic cells in the sputum was also found to be significant ($p < .01$) in workers exposed to nickel carbonyl compared to unexposed workers.

2.5. Carcinogenicity

In an unpublished study (cited in Morgan 1992) using data from the Clydach, Wales, refinery, pulmonary cancer deaths in a group of 69 men occupationally exposed to nickel carbonyl vapor did not exceed those of unexposed workers based on an age-specific status (see Table 9-4). It was not specified if the analysis was adjusted for cigarette smoking or other confounding factors, and definitive exposure data were not available.

IARC (1987) considers nickel and nickel compounds as Group 1 carcinogens (sufficient evidence in humans and animals) and U.S. Environmental Protection Agency (EPA) has classified both nickel subsulfide and nickel refinery

TABLE 9-4 Mortality Data for 69 Workers Occupationally Exposed to Nickel Carbonyl (1933-1964)

Disease Group	Expected	Observed	SMR[a]
All causes	35.8	38	106
Pulmonary cancer	3.9	6	152

[a]Standard mortality ratio; $p > .05$.

dust as human carcinogens (EPA 1991). These assessments are based primarily on epidemiologic data showing an increased risk of pulmonary and sinonasal cancers in nickel refinery workers exposed to nickel refinery dust (which is primarily nickel subsulfide). Nickel carbonyl is considered a potential human carcinogen, although a quantitative assessment has not been conducted due to insufficient data (EPA 1991). However, Doll (1984) and CEC reported that nickel carbonyl was considered an unlikely contributor to the increased risk of sinonasal cancers in the nickel refinery workers. The CEC (1990) concluded that "the available epidemiological studies suggest that the toxicologic properties of nickel tetracarbonyl do not include the potential to cause cancer."

2.6. Summary

The human health effects of inhaled nickel carbonyl have been summarized by Sunderman (1989) and Shi (1994a). Nickel carbonyl is generally considered to be one of the most toxic industrial chemicals. A thorough assessment of the exposure response to nickel carbonyl is complicated by the often asymptomatic delay between initial, mild toxic effects and delayed serious effects that may result in fatal outcomes. Sunderman and co-workers summarized the various signs and symptoms of 350 individuals poisoned by nickel carbonyl. Immediate effects that usually resolved upon removal from exposure included headache, dizziness, sternal and epigastric pain, nausea, and vomiting. Effects that followed a 1- to 5-day latency included chest constriction, chills, shortness of breath, muscle pains, weakness, gastrointestinal disorders, convulsions, delirium, and death. Although some forms of nickel are known and suspected carcinogens, the carcinogenic potential of nickel carbonyl in humans is equivocal and no quantitative data are currently available.

Although specific exposure response data for human health effects are not available, the severity of acute nickel carbonyl poisoning paralleled increases in urinary nickel (Shi 1994a), and correlations between urinary nickel and exposure severity have been determined (Sunderman and Sunderman (1958). For mild, moderately severe, and severe exposures, initial 8-h urinary nickel values were <10 µg/100 mL, >10 µg/100 mL but <50 µg/100 mL, and >50 µg/100 mL, respectively.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Inhalation lethality data are available for several species. Although data from some reports were only semiquantitative and lacked detail, other reports provided definitive data from well-conducted studies.

3.1.1. Rats

In experiments with rats, Barnes and Denz (1951) examined the lethality of nickel carbonyl exposure and the effects of subsequent treatment with 2,3-dimercaptopropanol (British Anti-Lewisite). In this study, groups of 10-76 albino rats (sex and strain not specified) were exposed to nickel carbonyl for periods of 5-30 min (ct of 17×10^3 to 70×10^3 mg•min/m^3; equivalent to 2,380-9,800 ppm•min). Nickel carbonyl concentrations were estimated by chemical analysis and, although capable of detecting nickel concentrations of 1-2 μg, may lack the precision of later reports in which concentrations were determined by gas chromatographic techniques. Only a range of exposure periods and ct values were provided by the authors ($17\text{-}23 \times 10^3$, $29\text{-}38 \times 10^3$, $43\text{-}58 \times 10^3$, and 70×10^3 mg•min/m^3; equivalent to 2,380-3,220, 4,060-5,200, 6,020-8,120, and 9,800 ppm•min, respectively). Mortality in these four exposure groups was 65%, 77%, 84%, and 100%, respectively. Exposed rats exhibited initial postexposure inactivity, followed by apparent recovery. At about 12 h postexposure, the condition of the rats deteriorated, followed by death 18-150 h after exposure. Necropsy findings revealed marked pleural effusion and extensive pulmonary edema. The concentrations reported in this study appear to be extremely high when compared to other experimental data.

Kincaid et al. (1953) conducted acute lethality studies in several species, including rats. In these experiments, groups of 6-21 Wistar rats (gender not specified) were exposed to nickel carbonyl vapor at concentrations of 0.17, 0.20, 0.38, 0.45, or 0.50 mg/L for 30 min (equivalent to 23.8, 28.0, 53.2, 63.0, and 70 ppm, respectively). The report provided detailed information regarding the exposure protocol as well as generation and measurement of the experimental atmosphere. Adjustments were made to account for decomposition of the nickel carbonyl. Results of the experiment with rats are shown in Table 9-5. Using probit analysis, a 30-min LC_{50} of 0.24 mg/L (33.6 ppm) was estimated. The rats were observed for 0.2 h to 6 days after exposure. It was reported that deaths usually occurred 2-3 days after termination of exposure. Animals that died immediately exhibited severe pulmonary congestion and pulmonary edema. In rats that survived for several days, extensive pneumonitis was observed.

In experiments to study the efficacy of dimercaprol in the treatment of nickel carbonyl poisoning, control rats (those not receiving the dimercaprol) were exposed for 30 min to nickel carbonyl at concentrations of 0.20, 0.40, or

0.60 mg/L (equivalent to 28, 56, and, 84 ppm, respectively; Kincaid et al. 1953). The mortality incidences for these exposures were 9/18, 7/9, and 9/9, respectively. Dimercaprol (3-day dosing regimen of 10, 8, and 3.8 mg/kg) reduced the incidences to 0/18, 3/9, and 8/9, respectively.

Sunderman (1964) conducted studies in rats to evaluate the effectiveness of Dithiocarb as an antidote for nickel carbonyl poisoning. Groups of Wistar rats (sex not specified) were exposed by 30-min inhalation to nickel carbonyl at concentrations of 67, 105, 168, or 266 ppm. Chamber concentrations were determined by chemical analysis capable of detecting nickel carbonyl concentrations in the parts per billion ranges. Survival ratios were determined 5 days after the exposure. Results for the control groups (nickel carbonyl exposed with no antidote administration) are shown in Table 9-6. The data show that 30-min exposures of rats to nickel carbonyl concentrations ≥67 ppm produced significant mortality approaching or attaining 100%. All rats (30 per group) receiving the Dithiocarb intraperitoneally were alive at 5 days postexposure, although orally administered Dithiocarb was not as effective (60-90% mortality was still observed following 30-min exposure to 266 ppm nickel carbonyl).

TABLE 9-5 Lethal Response of Rats Exposed to Nickel Carbonyl for 30 min

Exposure Concentration, mg/L (ppm)	Number Dead/ Number Exposed	Probit
0.17 (23.8)	0/6	3.27
0.20 (28.0)	9/18	5.00
0.38 (53.2)	17/21	5.88
0.45 (63.0)	15/18	5.97
0.50 (70.0)	12/12	6.75

Source: Kincaid et al. 1953. Reprinted with permission; copyright 1953, American Medical Association.

TABLE 9-6 Lethality in Rats Following 30-min Inhalation Exposure to Nickel Carbonyl

Nickel Carbonyl Concentration (ppm)	Number Surviving/ Number Exposed	Mortality (%)
67	11/30	63
67	1/10	90
105	6/30	80
168	0/30	100
266	0/30	100
266	0/10	100

Source: Sunderman 1964. Reprinted with permission; copyright 1964, *Journal of New Drugs*.

In carcinogenicity assays, Sunderman and Donnelly (1965) reported that 214 of 285 rats died within 3 weeks of a single 30-min inhalation exposure to nickel carbonyl (80 ppm). None of the 19 control rats died during this time period.

Baselt et al. (1977) tested groups of 8-33 female Fischer-344 rats exposed for 15 min to nickel carbonyl at concentrations of 1.4 (196 ppm) or 4.2 mg/L (588 ppm). Measurement of exposure concentrations was by gas chromatography. Results are shown in Table 9-7. Necropsies were apparently not performed. Separate groups of 20 female F-344 rats were exposed for 15 min to nickel carbonyl at 0.14, 0.28, 0.72, or 1.43 mg/L (19.6, 39.2, 100.8, or 200.2 ppm). The lethality ratios for the 19.6-, 39.2-, 100.8-, and 200.2-ppm exposures were 5/20, 7/20, 12/20, and 15/20, respectively, but no further details were provided. A 15-min LC_{50} of 0.58 mg/L (81.2 ppm) was calculated by the study authors.

In a study by Baselt and Hanson (1982), female Fischer rats (four rats/group) were exposed to nickel carbonyl (1.4- or 1.7- mg/L; 196 or 238 ppm) for 15 min and observed for 1 week after exposure. The mortality ratio for rats not given the chelating agents was 6/14 and 7/8, respectively, for the 1.4 and 1.7 mg/L groups. Specific time-to-death data were not provided. Mortality was limited in rats receiving the chelating agents. Rats given D-penicillamine and diethyldithiocarbamate in the higher-exposure groups exhibited mortality ratios of 4/4 and 1/4, respectively, for the 1.4- and 1.7-mg/L nickel carbonyl groups. Rats receiving disulfiram in the 1.4-mg/L group had a mortality ratio of 1/6 and 3/4 at disulfiram doses of 125 and 1,500 mg/kg (three doses of 500 mg/kg at hourly intervals).

3.1.2. Mice

In the research reported by Kincaid et al. (1953), groups of 10-29 albino mice were exposed to nickel carbonyl vapor at concentrations of 0.0155, 0.0465, 0.056, 0.062, 0.070, 0.078, or 0.090 mg/L for 30 min (equivalent to 2.17, 6.51, 7.84, 8.68, 9.80, 10.9, and 12.6 ppm, respectively). The report provided detailed information regarding the exposure protocol as well as generation and measurement of the experimental atmosphere. Adjustments were made to account for decomposition of the nickel carbonyl. The results of the experiment are shown in Table 9-8. Using probit analysis, a 30-min LC_{50} of 0.067 ± 0.003 mg/L (~9.4 ppm) was calculated. Similar to the experiments with rats, deaths in mice occurred 2-3 days after termination of exposure.

In experiments intended to evaluate the effectiveness of edathamil calcium-disodium (calcium disodium EDTA) as a treatment for nickel carbonyl poisoning, West and Sunderman (1958) exposed four groups of 20 mice (strain and sex not specified) for 30 min to 0.06 mg of nickel carbonyl per liter of air (equivalent to 60 mg/m^3 [8.4 ppm]). Ten mice from each group were also given the chelating agent. The 3-day postexposure mortality ratios for the groups of 10

TABLE 9-7 Lethality in Rats Following 15-min Exposure to Nickel Carbonyl

Exposure Concentration (ppm)	Mortality Ratio	Time-to Death (Days)
588	33/33	<1-2
196	19/26	2-5
196	17/26	1-6
196	3/8	4-6

Source: Baselt et al. 1977. Reprinted with permission; copyright 1977, *Research Communications in Chemical Pathology and Pharmacology*.

TABLE 9-8 Lethal Response of Mice Exposed to Nickel Carbonyl for 30 min

Exposure Concentration mg/L (ppm)	Number Dead/ Number Exposed	Probit
0.0155 (2.17)	0/12	2.98
0.0465 (6.51)	2/15	3.89
0.056 (7.84)	3/10	4.48
0.062 (8.68)	10/29	4.60
0.070 (9.80)	10/20	5.00
0.078 (10.9)	12/22	5.11
0.090 (12.6)	10/10	6.96

Source: Kincaid et al. 1953. Reprinted with permission; copyright 1953, American Medical Association.

mice not given the chelating agent are shown in Table 9-9. The edathamil calcium-disodium treatment was ineffective in reducing lethality.

Sunderman (1964) conducted studies in mice to evaluate the effectiveness of sodium dithiocarbamate (Dithiocarb) as an antidote for nickel carbonyl poisoning. In these experiments, groups of C-57 mice (sex not specified) were exposed by 30-min inhalation to nickel carbonyl at concentrations of 6, 8, 10, 16, or 24 ppm. The exposure concentrations were determined by chemical analysis previously shown to be sensitive in the parts per billion ranges (Kincaid et al. 1956). Survival ratios were determined 5 days after the exposure. The results for the control groups (nickel carbonyl exposed with no antidote administration) are shown in Table 9-10. From these experiments it is apparent that 30-min exposures to nickel carbonyl concentrations as low as 6 ppm resulted in substantial mortality. Additionally, the large number of test animals in the 10-ppm exposure group affirms this exposure as being near 100% lethal. No deaths were observed in the Diothiocarb-treated mice.

TABLE 9-9 Mortality Ratio for Mice 3 Days Following 30-min Exposure to Nickel Carbonyl (8.4 ppm)

Experimental Group	Exposure	Mortality Ratio
Group 1	0.06 mg/L (8.4 ppm)	6/10
Group 2	0.06 mg/L (8.4 ppm)	10/10
Group 3	0.06 mg/L (8.4 ppm)	9/10
Group 4	0.06 mg/L (8.4 ppm)	8/10

Source: West and Sunderman 1958.

TABLE 9-10 Lethality in Mice Following 30-min Inhalation Exposure to Nickel Carbonyl

Nickel Carbonyl Concentration (ppm)	Number Surviving/ Number Exposed	Mortality (%)
6	6/30	80
8	0/30	100
10	2/30	99
16	0/30	100
24	0/30	100

Source: Sunderman 1964. Reprinted with permission; copyright 1964, *Journal of New Drugs*.

3.1.3 Rabbits

In addition to studies with rats, Barnes and Denz (1951) examined the effects of nickel carbonyl and subsequent BAL treatment on rabbits. Similar to the previously described experiments in rats, the exposures were reported only as ct values (i.e., 10-37 $\times$ 10^3 mg·min/m^3; equivalent to 1,400-5,180 ppm·min). The mortality in rabbits exposed to nickel carbonyl but not given BAL was 18/23 (62%), with an average survival of 3.3 days.

3.1.4. Cats

With regard to determination of a 30-min LC_{50} for cats in the Kincaid et al. (1953) study, data were less conclusive (see Table 9-11). With the exception of using a larger exposure chamber, the exposure protocol and techniques were the same as for mice and rats, but only a limited number of animals were used (i.e., 1-3). The small sample size precluded an exposure-probit analysis. Because

TABLE 9-11 Lethal Response of Cats Exposed to Nickel Carbonyl for 30 min

Exposure Concentration mg/L (ppm)	Number Dead/Number Exposed	Time to Death (h)
0.19 (26.6)	0/1	–
0.50 (70.0)	0/1	–
1.24 (173.6)	1/1	216
1.94 (271.6)	0/2	–
2.00 (280.0)	3/3	56, 96, 142
2.11 (295.4)	3/3	36, 72, 96
2.43 (340.2)	1/1	40

Source: Kincaid et al. 1953. Reprinted with permission; copyright 1953, American Medical Association.

only one cat died following exposure to <2.00 mg nickel carbonyl/L (280 ppm) and 3/3 died following exposure to 2.11 mg/L (295.4 ppm), it was concluded that the 30-min LC_{50} for cats was <2.00 mg/L (280 ppm). Both cats exposed to 1.94 mg/L (271.6 ppm) survived; therefore, the 30-min LC_{50} was estimated as 1.9 mg/L (266 ppm).

3.1.5. Summary of Lethal Toxicity in Animals

Acute lethality values for nickel carbonyl are summarized in Table 9-12. There appears to be considerable species variability in the lethal response to inhaled nickel carbonyl, and, as noted by Kincaid et al. (1953), the acute lethality of nickel carbonyl appears to be inversely related to body mass. Based on the lethality data for rats, mice, and cats, Kincaid et al. found that the LC_{50} values were proportional to the 2/3 power of the body mass; specifically, $LC_{50} = 0.009 (\text{body mass})^{2/3}$.

3.2. Nonlethal Toxicity

Data regarding nonlethal toxicity of nickel carbonyl in animals are limited. The acute toxicity of nickel carbonyl and the progression of systemic toxicity to lethality limit the identification of critical effects consistent with AEGL-2 end points.

3.2.1. Rats

Kincaid et al. (1953) conducted pathologic evaluations on a series of rats following various exposure protocols. One rat, exposed for 30 min to 0.08 mg

TABLE 9-12 Acute Lethality of Nickel Carbonyl in Animal Species

Species	Acute Lethality Value	Reference
Rat	30-min LC_{50}: 56 ppm	Kincaid et al. 1953; Barnes and Denz 1951[a]
Rat	30-min LC_{50}: 33.6 ppm	Kincaid et al. 1953
Rat	30-min LC_{75}: 80 ppm	Sunderman and Donnelly 1965
Rat	15-min LC_{50}: 81.2 ppm	Baselt et al. 1977
Mouse	30-min LC_{50}: 9.38 ppm	Kincaid et al. 1953
Rabbit	30 min LC_{50}: 42-168 ppm	Kincaid et al. 1953; Barnes and Denz 1951[a]
Cat	30-min LC_{50}: ≈266 ppm[b]	Kincaid et al. 1953

[a]50% mortality value determined by Kincaid et al. (1953) using probit analysis and multiple exposure time data of Barnes and Denz (1951).
[b]Value estimated by authors based on 100% (3/3) mortality at 280 ppm for 30 min but no mortality (0/2) at 271.6 ppm for 30 min.

nickel carbonyl/L (11.2 ppm), survived to 144 h postexposure, whereupon it was killed and examined. Although the rat survived to 144 h, the pathologic findings (pulmonary congestion and edema, extensive pneumonitis) were reportedly similar to those of other rats that died as a result of nickel carbonyl exposure.

Exposure of rats to nickel carbonyl induced transient hyperglycemia, the severity of which was concentration dependent (Horak et al. 1978). In this study, female F-344 rats were exposed to nickel carbonyl at concentrations of 0, 1.2, 3.5, or 6.4 μmoles/L (equivalent to 0, 28.67, 83.66, and 152.97 ppm) for 15 min. The nickel carbonyl concentrations were determined by gas chromatography. Compared to untreated controls, rats of all three nickel carbonyl groups exhibited a significant ($p < .01$, F-test) hyperglycemic response at 0.5-1 h but returned to normal 2 h after the onset of exposure. Plasma glucose was also significantly ($p < .01$; test) increased in the high-exposure (6.4 μmoles/L) group at 30 min and 1 h after initiation of the 15-min exposure. Although these effects per se are indicative of nonlethal responses to nickel carbonyl exposure, the ultimate fate of the exposed rats was not stated. Considering that the two highest exposure concentrations exceed the reported 15-min LC_{50} value for rats (Baselt et al. 1977), it is likely that these exposures would result in fatality.

3.2.2. Mice

In the research reported by Kincaid et al. (1953), groups of 10-29 albino mice were exposed to nickel carbonyl vapor at concentrations of 0.0155, 0.0465, 0.056, 0.062, 0.070, 0.078, or 0.090 mg/L for 30 min (equivalent to 2.17, 6.51, 7.84, 8.68, 9.80, 10.9, and 12.6 ppm, respectively). As noted in Section 3.1.2,

Kincaid et al. provided detailed information regarding the exposure protocol as well as generation and measurement of the experimental atmosphere. Adjustments were made to account for decomposition of the nickel carbonyl. Although the experiments were primarily an assessment of lethality, there were no deaths in the lowest concentration group. Histopathologic examinations were not reported for these mice. In another phase of the study, the potential tolerance to nickel carbonyl poisoning was examined, wherein groups of five mice were exposed to increasingly higher levels of the compound (10 30-min exposures over 48 days. The exposure concentrations ranged from 0.016 to 0.19 mg/L (2.24-26.6 ppm). The results of this experiment revealed no deaths until after the tenth exposure, even though the sixth and seventh exposures (9.9 ppm and 9.5 ppm) were equivalent to the LC_{50}.

3.2.3. Summary of Nonlethal Toxicity in Animals

Data regarding nonlethal exposure of laboratory species to nickel carbonyl are extremely limited. A hyperglycemic response was documented for rats but involved exposure concentrations approaching or equivalent to LC_{50} values. The well-documented latency in the lethal response complicates the identification of exposures inducing serious, irreversible effects but not causing death.

3.3. Developmental/Reproductive Toxicity

Sunderman et al. (1980) showed that inhalation of nickel carbonyl is teratogenic and embryotoxic in Syrian hamsters. Groups of pregnant Syrian hamsters were exposed by inhalation to nickel carbonyl (0.06 mg/L [60 mg/m^3; 8.4 ppm]) for 15 min/day on either day 4, 5, 6, 7, or 8 of gestation. Nickel carbonyl concentrations in the exposure chamber were determined by gas chromatography. The dams were killed on day 15 of gestation, and the fetuses were examined for malformations. The statistically significant findings of this experiment (see Table 9-13), showed increased incidences of malformations resulting from exposures on gestation days 4 and 5. In order to study postnatal survival, pregnant Syrian hamsters were exposed similarly but only on day 5 of gestation. Developmental toxicity has been demonstrated in rats and hamsters following single 30-min (11.2-42 ppm, rats) or 15-min (8.4 ppm, hamsters) exposures of dams during gestation. In hamsters, developmental toxicity was observed in dams following lethal or near-lethal exposures. Five of 14 hamsters exposed to 8.4 ppm died by gestation day 16. All 14 dams in the control group (five died by gestation day 16) delivered their litters, and the offspring were observed for 10 weeks. Although there was no significant difference in the average number of live births between the controls and the nickel carbonyl-exposed group, neonatal mortality was significantly increased ($p < .01$) in the nickel carbonyl group by

postpartum day 4 (7.6 ± 1.5 and 9.7 ± 1.8 live pups/litter for the treated and control groups, respectively). Additionally, serous cavity hemorrhage (peritoneal, pleural, pericardial, and subdural spaces) was observed in the fetuses of the treated dams but not the untreated controls.

The teratogenic potential of inhaled nickel carbonyl in rats was evaluated by Sunderman et al. (1979). In this study, pregnant Fischer-344 rats were exposed for 15 min to nickel carbonyl vapor (0.08 mg/L, equivalent to 11.2 ppm) on gestation day 7, 8, or 9 (day 0 determined by sperm in vaginal smear). Groups of pregnant rats were exposed to 0.16 or 0.30 mg nickel carbonyl/L (equivalent to 22.4 and 42 ppm) on gestation days 8 and 7, respectively. Concentrations of nickel carbonyl in chamber air were determined by gas chromatography. Sham-exposed (ambient air) rats and a separate group of pregnant rats exposed to carbon monoxide (0.5%) also were included in the protocol. For the first phase of the study, fetuses were removed by cesarean section on gestation day 20 and examined. Ocular malformations were observed in 22 of 78 (28%) of the fetuses from nickel carbonyl-exposed dams. An exposure-response relationship was observed between the incidences of malformations and the nickel carbonyl exposure concentration (see Table 9-14). The mean body weight of fetuses was significantly reduced ($p < .01$) in all but the lowest exposure group, and the number of live fetuses per conceptuses was significantly reduced ($p <$ .05 to 0.01) in all nickel carbonyl groups and the carbon monoxide groups. No malformations were observed in fetuses of dams exposed on day 9 of gestation, the sham-exposed group, or the carbon monoxide exposure group, indicating that the teratogenic effects were due to nickel carbonyl and not a carbon monoxide biotransformation product. In another phase of the study, dams exposed to

TABLE 9-13 Embryotoxic Effects of Nickel Carbonyl Inhalation (8.4 ppm, 15 min/day) in Pregnant Syrian Hamsters

Parameter	Control	$Ni(CO)_4$-Treated
Total malformations[a]	0% (0/9)	
Day 4 exposure		5.5% (8/146)[b]
Day 5 exposure		5.8% (10/171)[b]
Proportion of litters with malformed fetuses	0% (0/9)	
Day 4 exposure		33% (4/12)[b]
Day 5 exposure		24% (4/17)[b]
Serous cavity hemorrhage	0% (0/9)	
Day 4 exposure		18% (26/146)[b]
Day 5 exposure		25% (42/171)[b]

[a]Included nine fetuses with cystic lungs, seven fetuses with exencephaly, one fetus with exencephaly plus fused rib, and 1 fetus with anophthalmia plus cleft palate; for fetuses of dams exposed on days 6 or 7, there were one fetus with fused ribs and two fetuses with hydronephrosis.

[b]Significantly different from controls ($p < .05$).

Source: Sunderman et al. 1980. Reprinted with permission; copyright 1980, *Teratogenesis, Carcinogenesis and Mutagenesis*.

TABLE 9-14 Malformations in Rats Following 15-min Exposure to Nickel Carbonyl During Gestation

Observation	Treatment Groups						
Exposure (mg/L)	Sham	CO	0.16	0.30[a]	0.08	0.16	0.16
Surviving dams; day 20	12/12	22/22	14/14	10/19**	16/16	13/15	13/13
Exposure day	8	7	7	7	8	8	9
Live fetuses/litter	9.2 ± 2.1	8.3 ± 2.6	8.1 ± 2.6	9.1 ± 1.6	7.6 ± 3.6	8.3 ± 2.6	7.4 ± 4.8
Live fetuses/ conceptuses	110/114	187/215**	113/135**	91/100*	121/134*	108/120*	96/112*
Mean fetus weight (g)	3.4 ± 0.2	3.1 ± 0.7	3.0 ± 0.3**	3.0 ± 0.4**	3.3 ± 0.5	3.1 ± 0.3**	3.2 ± 0.3**
Litters with malformed fetuses	0/12	0/22	9/14***	9/10***	2/16	9/13***	0/13
Total malformations[b]	0	0	15***	29***	2	19***	0

[a]Ten of 19 dams survived to day 20; clinical signs of toxicity were not specified.
[b]Ocular malformations: bilateral anophthalmia, unilateral anophthalmia, bilateral microphthalmia, unilateral microphthalmia, anophthalmia, and microphthalmia; only one incidence each in Group C and Group D was categorized as other than ophthalmic anomalies. * $p < .05$; ** $p < .01$; *** $p < .001$.
Source: Adapted from Sunderman et al. 1979. Reprinted with permission; copyright 1979, Science Magazine.

nickel carbonyl (0.30 mg/L [42 ppm]) for 15 min on gestation day 7 were allowed to deliver and nurse the pups for 4 weeks. The progeny were then observed for 16 weeks after birth. Results of this experiment revealed an increased incidence of total malformations (1/87 and 22/78 in controls and treated rats, respectively; $p < .001$), a significant reduction ($p < .001$) in live pups per litter (10.9 ± 2.5 versus 8.7 ± 2.6), and significantly increased incidence ($p < .001$) of litters with malformed pups (0/8 versus 6/9 in controls and treated rats, respectively). With the exception of increased mortality in some treatment groups, no additional information was provided regarding health effects in the dams. The study authors stated that the observed teratogenic response is likely specific to inhaled nickel carbonyl because such responses were not observed following exposures to divalent nickel salts or parenterally administered nickel carbonyl. The investigators hypothesized that the relatively low absorption of nickel salts from the gastrointestinal tract (compared to inhalation) and consequent lower dose to the fetus, or the conversion to a less active form following gastrointestinal absorption, are plausible explanations for this observation.

Results of a dominant lethal mutation test were reported by Sunderman et al. (1983). In this experiment, 10 male Fischer-344 rats were exposed to 0.05 mg/L (equivalent to 7 ppm) of nickel carbonyl for 15 min and subsequently caged with mature females each week during the following 2-6 weeks. Compared to unexposed controls, there were no significant effects on fertilization rate, live fetuses/litter, live fetuses/corpora lutea/dam, dead fetuses/implants, or dead fetuses/implants/litter.

3.4. Genotoxicity

Both IARC (1987) and EPA (1986) reviewed the genotoxicity of nickel and nickel compounds. In vivo chromosomal aberration studies generally showed a lack of clastogenic activity (EPA 1986), although some studies were equivocal. Bacterial mutagenesis studies revealed nickel compounds to lack mutagenic activity or to be only weakly mutagenic (EPA 1986). Nickel carbonyl, however, was not among the nickel compounds tested.

3.5. Carcinogenicity

Results of two studies by Sunderman and co-workers have shown a carcinogenic response in male Wistar rats following various exposure protocols involving inhalation of nickel carbonyl. These protocols included a single 30-min exposure to a high concentration (80 ppm) and lifetime exposures (30-min, three times/week) to lower concentrations (4 ppm) of nickel carbonyl.

Sunderman et al. (1959) reported on a study wherein groups of 32-64 rats (gender and strain not specified) were exposed three times per week for 1 year to nickel carbonyl concentrations of 0.0, 0.03, or 0.06 mg/L (equivalent to 0.0, 4.2, and 8.4 ppm). Another group of 80 rats was given a single (presumably 30-min exposure, although not specifically stated) to 0.25 mg of nickel carbonyl/L (equivalent to 35 ppm; noted by the investigators as approximately the LD_{50}). Within 1 week, 52 of the 80 rats in the single-exposure group had died; only eight rats survived to 8 months and only three survived to 24 months. At 2 years after the exposure, 3/41, 5/64, and 3/32 rats survived in the control, 4.2-, and 8.4-ppm groups, respectively. Among these survivors, pulmonary tumors were found in one rat each in the 4.2- and 8.4-ppm groups, and two rats of the single-exposure (8.4-ppm) group. None of the three surviving control rats exhibited pulmonary tumors. Although the study authors concluded from these results that nickel carbonyl caused pulmonary tumors in rats, the number of rats remaining alive in each group is insufficient for a statistically and biologically meaningful analysis. Additionally, no time-to-tumor data were provided.

Sunderman and Donnelly (1965) conducted experiments in which various exposure protocols were used to assess the carcinogenic potential of inhaled nickel carbonyl in male Wistar rats. Of relevance to AEGLs was the fact that a single 30-min exposure to 80 ppm was found to induce pulmonary tumors in 3 of the 71 rats that survived beyond 2 years. The tumor types, all of which also involved metastases to the kidneys and liver, included anaplastic carcinomas in two rats and an adenocarcinoma in the third rat. The lesions were found between 24 and 27 months after exposure. Malignant lymphomas were also observed in the nickel carbonyl-treated rats, but because of similar incidences in control rats the investigators concluded that these lesions were not due to nickel carbonyl exposure.

3.6. Summary of Animal Toxicity Data

Experiments in animals have confirmed the extreme toxicity of nickel carbonyl following acute inhalation exposure. Animal data also reflect the latency of severe or lethal effects observed in humans exposed to nickel carbonyl. Data describing nonlethal effects in test animals are limited to the demonstration of a nickel carbonyl-induced hyperglycemia in rats following 15-min inhalation exposure to nickel carbonyl at or near LC_{50} values. Lethality data are available for several species, including rats (30-min LC_{50} values of 33.6 and 56 ppm and a 30-min LC_{75} of 80 ppm), mice (30-min LC_{50} of 9.38 ppm), rabbits (30-min LC_{50} values ranging from 42 to 168 ppm), and cats (estimated 30-min LC_{50} of 266 ppm). Nickel carbonyl has been shown to be teratogenic in rats and hamsters exposed during gestation to concentrations of 22.4 ppm and 8.4 ppm, respectively. In rats the health status of the dams was uncertain, thereby disallowing a definitive determination of the relative maternal versus fetal sensitivity to nickel carbonyl challenge. A single gestational exposure of hamsters (15-min exposure to 8.4 ppm on gestation day 5) resulted in increased neonate mortality by postpartum day 4 but was also maternally toxic. There are limited, equivocal data showing the development of pulmonary tumors in rats exposed chronically to nickel carbonyl and equivocal data suggestive of a tumorigenic response following a single massive exposure of rats to nickel carbonyl.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Following inhalation and oral exposure to most nickel compounds, absorbed nickel is excreted primarily via the urine and feces (summarized in Sunderman 1989). In studies with dogs exposed to nickel carbonyl, Sunderman and co-workers noted that the excretion route varied with the exposure route; fecal excretion accounted for 90% and urinary excretion about 10% following ingestion, while the reverse was found for inhalation exposure. This finding attests to the poor absorption of nickel carbonyl from the gastrointestinal tract. It was also found that urinary excretion of nickel increased sharply immediately after exposure and prior to any signs of toxicity. Results of studies with radiolabeled nickel carbonyl administered to rats have shown that the compound will, upon inhalation, cross the alveolar membrane unchanged (reviewed in Sunderman et al. 1979; NAS 1975). The biologic half-life for nickel carbonyl in the rat is about 0.5 h. Although a substantial amount of nickel carbonyl may be eliminated via the lungs (≈36% in the rat within 4 h), the remainder reportedly undergoes dissociation to nickel nickel and carbon monoxide within erythrocytes and other tissues (NAS 1975). The nickel is subsequently oxidized to Ni (II) and released into the blood serum where it may bind to albumin and nickel-binding substances (nickeloplasmin, an α_2-macroglobulin) and is cleared via the kidneys.

Sunderman (1964) also studied nickel balance in 50 nickel carbonyl-exposed workers. These workers experienced severe exposures (concentrations not provided) that likely would have been fatal without treatment with Dithiocarb. The urinary concentration of nickel was monitored in the 13 most severe exposures. In several subjects (all treated with Dithiocarb), urinary excretion was 100-200 µg/mL for up to 4 days postexposure. A comparison of nickel burden in tissues of humans not exposed to nickel carbonyl (values are the mean of four individuals) and an individual dying from acute nickel carbonyl exposure revealed considerably elevated nickel content in the lung (1.59 µg/100 g versus 17.3 µg/100 g) and liver (0.87 µg/100 g versus 5.3 µg/100 g) (Sunderman 1989).

Using urinary nickel as an index of exposure severity, Sunderman and Sunderman (1958) categorized nickel carbonyl exposure as mild, moderately severe, or severe if urinary nickel concentrations at 18 h were 60-100 µg/L, 100-500 µg/L, or >500 µg/L, respectively. There are currently no reliable correlations between air concentrations of nickel carbonyl and nickel levels in the body fluids or tissues of exposed individuals.

In a time-course analysis with rats exposed by inhalation to nickel carbonyl, Barnes and Denz (1951) reported a rapid uptake of nickel carbonyl. Immediately after a 30-min exposure, nickel was found in the liver and brain, with the liver tissue containing the greatest amounts. The lungs contained very little nickel, indicating exhalation of inhaled nickel carbonyl and/or rapid uptake. Barnes and Denz found that rabbits exhibited very little accumulation of nickel in the brain following lethal exposure to nickel carbonyl. However, Tjälve et al. (1984) found that 1 h after inhalation exposure of mice to radiolabeled nickel carbonyl, the highest $^{63}Ni^{2+}$ levels were found in the lung. High levels were also detected in the brain, heart, and diaphragm.

4.2. Mechanism of Toxicity

In a review of nickel toxicology, Sunderman (1981) summarized research findings conducted with his co-workers on the pathologic reaction of laboratory species to nickel carbonyl. These investigators found that the pulmonary parenchyma was consistently the principal target for nickel carbonyl insult, regardless of the route of exposure. Both Type I and Type II alveolar cells were affected by nickel carbonyl, although the former were reportedly the primary target (Hackett and Sunderman 1968). It has also been shown that pulmonary edema and chemical pneumonitis are characteristic of severe nickel carbonyl poisoning (Shi 1994b). Shi reported impairment of some respiratory functions (spirometric indices) in workers with long-term exposures to low levels (0.00098-0.072 ppm) of nickel carbonyl.

Although carbon monoxide is a biotransformation product of nickel carbonyl, it is not considered responsible for the pronounced toxicity of nickel carbonyl (Sunderman et al. 1979).

4.3. Structure-Activity Relationships

The physicochemical properties of nickel carbonyl are sufficiently different from other nickel compounds to preclude the use of structure-activity relationships in the derivation of AEGL values for the title compound.

4.4. Other Relevant Information

4.4.1. Species Variability

Generally, the lethality values presented in Section 3.1 for various species suggest that smaller species may be more sensitive to the lethal effects of nickel carbonyl. Based on data for rats, mice, and cats, Kincaid et al. (1953) determined that the lethality of nickel carbonyl was directly proportional to the 2/3 power of the body weight. Using this relationship, Kincaid et al. projected an LC_{50} (no duration specified) of 15 mg/L (2,100 ppm) for a 70-kg human.

4.4.2. Concurrent Exposure Issues

No concurrent exposure issues of special concern have been identified that influence the derivation of AEGL values for nickel carbonyl.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

Quantitative data pertinent to AEGL-1 effects in humans are not available. Many of the reports describing human exposures to nickel carbonyl involved serious health effects of a severity above and beyond that consistent with the AEGL-1. Human poisonings in the absence of detection also have been documented. Furthermore, nickel carbonyl poisoning characteristically exhibits a latency period, which may be asymptomatic, between the initial exposure and subsequent severe effects that may be lethal.

5.2. Summary of Animal Data Relevant to AEGL-1 Values

Neither quantitative nor qualitative data in animals were available that were consistent with AEGL-1 effects.

5.3. Derivation of AEGL-1

Qualitative data are limited, and quantitative data consistent with AEGL-1 effects are unavailable. Odor detection does not appear to be a valid end point for derivation of AEGL-1 values for nickel carbonyl because toxic effects have occurred in subjects unaware of its presence (Sunderman 1990). Available data also indicate that severe toxicity (i.e., lethality) may occur days after exposures that are initially suggestive of little or no toxicity. Therefore, AEGL-1 values are not recommended for nickel carbonyl (see Table 9-15). This contention is justified by findings from a previous accidental exposure in which more than 100 workers were exposed to nickel carbonyl (some as long as 12 h) with no knowledge of its presence until there were severe signs and symptoms of illness (Kincaid et al. 1956).

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Quantitative data regarding AEGL-2 level effects in humans following acute exposures were unavailable.

6.2. Summary of Animal Data Relevant to AEGL-2

Animal data regarding serious but nonlethal effects of acute inhalation exposure to nickel carbonyl were limited to studies examining the developmental toxicity of nickel carbonyl in Syrian hamsters (Sunderman et al. 1980) and F-344 rats (Sunderman et al. 1979), and to nonlethal effects in the lower exposure groups of lethality experiments (Kincaid et al. 1953). Exposure of pregnant Syrian hamsters to nickel carbonyl (0.06 mg/L equivalent to 8.4 ppm) for 15 min per day on gestation days 4 or 5 killed four of five dams and resulted in a significant ($p < .05$) increase in the number of litters with malformed fetuses and serous cavity hemorrhage compared to unexposed controls (Sunderman et al. 1980; see Table 9-13). A significant increase ($p < .01$) in neonate mortality was also observed on postpartum day 4 in an experiment in which the dams were permitted to deliver and nurse their pups. These data indicate that these exposure conditions were embryotoxic in the Syrian hamster under conditions that produced concomitant overt maternal toxicity.

In the study reported by Sunderman et al. (1979), a significant increase ($p < .001$) in the numbers of litters with malformed offspring of rats exposed to concentrations as low as 0.16 mg/L nickel carbonyl (equivalent to 22.4 ppm) for 15-min on gestation day 7 was observed. An additional group of dams were exposed to 0.3 mg/L (42 ppm) for 15 min but were allowed to deliver and nurse

TABLE 9-15 AEGL-1 for Nickel Carbonyl

AEGL Level	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR	NR	NR	NR	NR

Note: NR, not recommended. Numerical values for AEGL-1 are not recommended because of the lack of available data. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 concentration is without adverse effects.

their pups for 4 weeks. Litters from the nickel carbonyl-treated dams had a significant decrease ($p < .001$) in live pups per litter. There was a significantly increased incidence of ocular malformations ($p < .001$) in these litters and significantly lower pup weight ($p < .001$) at 4 and 16 weeks. Nine of 19 dams exposed to 0.3 mg of nickel carbonyl/L and 9 of 14 dams exposed for 15 min to 0.06 mg/L died.

In the lethality experiments reported by Kincaid et al. (1953), none of the 15 mice in the lowest exposure group (2.17 ppm for 30 min) died, whereas two of 15 mice exposed to 6.51 ppm died. Although no pathologic examinations were reported, these investigators and Barnes and Denz (1951) reported that rats killed by inhalation of nickel carbonyl exhibited pleural effusion, severe pulmonary congestion, and edema. It may be assumed that the mice receiving nonlethal exposures were likely to have some level of pulmonary damage that would be consistent with a critical effect appropriate for AEGL-2 development.

6.3. Derivation of AEGL-2

The development of the AEGL-2 values for nickel carbonyl is based on the toxic response of mice following 30-min inhalation exposures at seven concentrations: 2.17, 6.51, 7.84, 8.68, 9.80, 10.9, or 12.6 ppm (Kincaid et al. 1953). A concentration-dependent lethal response was observed for exposures to 6.51-12.6 ppm, but the lowest exposure (2.17 ppm) resulted in no deaths. Exposure to 6.51 ppm resulted in the deaths of two of 15 mice. A 30-min LC_{50} of ~9.4 ppm was estimated by the investigators. Although no histopathology examinations were performed on the mice in the 2.17-ppm group, Kincaid et al. (1953) and Barns and Denz (1951) reported findings of pleural effusion, severe pulmonary congestion, and pulmonary edema in rats that died following exposure to nickel carbonyl. Therefore, the 30-min exposure to 2.17 ppm was considered a reasonable estimate of an exposure that may cause pulmonary damage in the mouse (most sensitive species tested) but not result in irreversible adverse effects. As shown by the multiple-exposure studies of Kincaid et al. (1953), repeated exposures of mice to this or greater concentrations did not result in a lethal response. Pulmonary damage appears to a component in the continuum of the toxic response to nickel carbonyl and an appropriate critical effect for AEGL-2 development. The 30-min exposure to 2.17 ppm was considered a point-of-departure

representative of a no-observed-adverse-effect level (NOAEL) for AEGL-2 effects.

Exposure-response data over multiple time periods were unavailable for nickel carbonyl, and therefore empirical derivation of a scaling factor (n) was not possible. 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 an empirically derived exponent, and to obtain conservative and protective AEGL values, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points. A total uncertainty factor adjustment of 10 was applied. An uncertainty factor of 3 was applied to account for interspecies variability. The available lethality data, however, do suggest that the mouse represents a sensitive species. Based on available lethality data and the analysis conducted by Kincaid et al. (1953) indicating an inverse relationship between lethality and body size (see Section 4.4.1.), the interspecies uncertainty factor of 3 appears to be justified. Although intraspecies variability is difficult to assess based on available data, an uncertainty factor of 3 was applied with the assumption that neither the effects of nickel carbonyl on pulmonary tissues nor dosimetry would vary greatly among individuals. The occupational exposure data reported by Shi et al. (1994b) suggest that the AEGL-2 values are sufficiently protective. The overall dataset for nickel carbonyl is deficient regarding nonlethal effects of nickel carbonyl inhalation. Therefore, a modifying factor of 3 was applied in the development of the AEGL-2 values to account for these deficiencies and the possibility of developmental toxic effects reported by Sunderman and colleagues. The resulting AEGL-2 values are shown in Table 9-16 and their derivations in Appendix A.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

Quantitative data regarding human lethality following inhalation exposure to nickel carbonyl are unavailable. The available data on human exposures qualitatively define initial effects of varying severity often followed by an asymptomatic latency prior to the onset of more serious effects and possible lethal response. Kincaid et al. (1956) estimated a 30-min LC_{50} of 3 ppm for humans, and Vuopola et al. (1970) estimated that exposure to 30 ppm would be immediately fatal. These estimates do not appear to have been quantitatively derived.

7.2. Summary of Animal Data Relevant to AEGL-3

Lethality data are available for rats, mice, rabbits, and cats. Based on comparison of 30-min LC_{50} values, the mouse appears to be the most sensitive

TABLE 9-16 AEGL-2 Values for Nickel Carbonyl

AEGL Level	10 min	30 min	1 h	4 h	8 h
AEGL-2 (disabling)	0.10 ppm	0.072 ppm	0.036 ppm	0.0090 ppm	0.0045 ppm

species: 9.38 ppm for mice, 33.6 and 56 ppm for rats, 42-168 ppm for rabbits, and 266 ppm for cats (Kincaid et al. 1953). A developmental toxicity study in Syrian hamsters showed that a single 15-min exposure to 0.06 mg/L (8.4 ppm) during gestation resulted in teratogenic effects and increased neonate mortality (Sunderman et al. 1980). Data defining a lethality threshold or those that could be used to estimate a lethality threshold were not available. Lethality data for varying exposure durations were also deficient for defining a temporal extrapolation function.

7.3. Derivation of AEGL-3 Values

As previously noted, lethality data are available for several species but are limited to LC_{50} determinations. Kincaid et al. (1953) suggest that sensitivity to nickel carbonyl may be a function of body mass, and as a result, lethal exposures for humans have been estimated. Based on data from mice, rats, and cats, these investigators estimated that the lethality of nickel carbonyl was directly proportional to body weight to the 2/3 power. Human exposure reports suggest a wide range of nonlethal responses to acute exposure to nickel carbonyl as well as a characteristic latency period between initial exposure and subsequent, more serious effects.

The mouse represents the most sensitive species, and therefore a lethality threshold (LC_{01}) was estimated from the mouse data of Kincaid et al. (1953) (Appendix A). The lethality threshold was estimated using the method of Litchfield and Wilcoxon (1949). This value was determined to be 3.17 ppm for 30 min (Appendix D). Exposure response data over multiple time periods are unavailable for nickel carbonyl, and therefore temporal scaling to AEGL-specific exposure durations necessitated the assumption of default values for n in the exponential temporal scaling equation, $C^n \times t = k$. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of chemical-specific data and to obtain protective AEGL values, temporal scaling was performed using n = 3 when extrapolating to shorter time periods and n = 1 when extrapolating to longer time periods. A total uncertainty factor of 10 has been applied for developing the AEGL-3 values. Lethality data from the smallest and, according to Kincaid et al. (1953), the most sensitive species were used for development of the AEGL-3. In the Kincaid et al. report, a body mass-based extrapolated plot was provided for hu-

man lethality that predicted an LC_{50} two orders of magnitude greater than the experimentally derived LC_{50} for mice. For this reason, and because the available LC_{50} values vary approximately 8-fold, the total uncertainty adjustment of 10 is weighted toward the uncertainty in individual sensitivity to nickel carbonyl exposure. Data are unavailable to definitively apportion uncertainty adjustment between inter- and intraspecies. The resulting AEGL-3 values are summarized in Table 9-17.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

Only AEGL-2 and AEGL-3 values have been derived for nickel carbonyl. Neither human nor animal data were available for the derivation of AEGL-1 values, and therefore they are not recommended. Data consistent with AEGL-2 effects were limited to developmental toxicity data in rats and hamsters and absence of lethal effect in mice and rats (and evidence for tolerance) following multiple exposures. Significant fetotoxicity and teratogenicity following single 15-min gestational exposures at 0.16 mg/L (22.4 ppm) in rats and 8.4 ppm in Syrian hamsters have been reported, but absence of maternal toxicity data precludes a definitive determination of the relative maternal/fetal sensitivity. Data for rats were also inconclusive regarding nickel carbonyl as a selective developmental toxicant following a single exposure during pregnancy. These exposures were also associated with neonate lethality and for the hamsters represented lethal or near-lethal exposures for the dams. The AEGL-2 values were developed to account for possible (and often latently occurring) pulmonary damage. Lethality data were available for four animal species. Analysis of these data also suggested that the larger species were somewhat less sensitive regarding the lethal response to nickel carbonyl following acute inhalation exposure. The AEGL-3 values were derived from mouse lethality data, the most sensitive species tested.

Category plots depicting the relationship of the AEGL values to one another and to the available data are shown in Appendix E. Because most of the available data were generated from exposure durations of 30 min or less, a plot with an expanded lower timeframe is included for clarity.

The available evidence does not support a definitive assessment of cancer risk in humans for a single once-in-a-lifetime acute exposure. Epidemiologic data do not support the contention that inhalation of nickel carbonyl is carcinogenic to humans. Based on inadequate human data and limited data in animals, the EPA (2003) categorizes nickel carbonyl as B2 (potential human carcinogen), while IARC (1987) specifically stated that nickel carbonyl was considered unlikely to be involved in causing cancers among nickel refinery workers.

8.2. Comparison with Other Standards and Criteria

Several organizations have developed standards and criteria for nickel carbonyl (see Table 9-18). Most values are expressed as nickel equivalents. The occupational exposure standard (OES) for the United Kingdom. is 0.1 ppm for 10 min (Morgan and Usher 1994). There are currently no ERPG values, Dutch MAC values, or German MAK values for nickel carbonyl.

Cancer risk estimates have not been developed for nickel carbonyl (ATSDR 2005).

TABLE 9-17 AEGL-3 Values for Nickel Carbonyl

AEGL Level	10 min	30 min	1 h	4 h	8 h
AEGL-3 (Lethality)	0.46 ppm	0.32 ppm	0.16 ppm	0.040 ppm	0.020 ppm

TABLE 9-18 Extant Standards and Guidelines for Nickel Carbonyl

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.10 ppm	0.072 ppm	0.036 ppm	0.0090ppm	0.0045 ppm
AEGL-3	0.46 ppm	0.32 ppm	0.16 ppm	0.040 ppm	0.020 ppm
ERPG-1 (AIHA)[a]	-	-	-	-	-
ERPG-2 (AIHA)	-	-	-	-	-
ERPG-3 (AIHA)	-	-	-	-	-
EEGL (NRC)[b]	-	-	-	-	-
PEL-TWA (OSHA)[c]	-	-	-	-	0.001 ppm[m]
PEL-STEL (OSHA)[d]	-	-	-	-	-
IDLH (NIOSH)[e]	-	2 ppm[m]	-	-	-
REL-TWA (NIOSH)[f]	-	-	-	-	0.001 ppm[m]
REL-STEL (NIOSH)[g]	-	-	-	-	-
TLV-TWA (ACGIH)[h]	-	-	-	-	0.05 ppm[m]
TLV-STEL (ACGIH)[i]	-	-	-	-	-
MAK (Germany)[j]	-	-	-	-	-
MAK Spitzenbegrenzung (Germany)[k]	-	-	-	-	Cat. III
Einsaztoleranzwert (Germany)[l]	-	-	-	-	-

[a]ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association) (AIHA 1994). 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

(Continued)

TABLE 9-18 Continued

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 protective 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]EEGL (Emergency Exposure Guidance Levels, National Research Council) (NRC 1985) is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace but avoids death, other severe acute effects, and long-term or chronic injury.

[c]OSHA PEL-TWA (Occupational Safety and Health and Administration, Permissible Exposure Limits–Time-Weighted Average) (OSHA 1993) is defined analogous to the ACGIH-TLV-TWA but is for exposures of no more than 10 h/day, 40 h/week.

[d]OSHA PEL-STEL (Permissible Exposure Limits–Short-Term Exposure Limit) (OSHA 1993) is defined analogous to the ACGIH TLV-STEL.

[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 irreversible health effects. The revised IDLH for nickel carbonyl is 2 ppm based on being 2,000 times the current OSHA permissible exposure limit (PEL) of 0.001 ppm. (2,000 is an assigned protection factor for respirators; only the most reliable respirators are recommended above 2,000 times the OSHA PEL). NIOSH recommends, as part of its carcinogen policy, that the most protective respirator be worn for nickel carbonyl at concentrations above 0.001 ppm.

[f]NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits–Time-Weighted Average) (NIOSH 1994) is defined analogous to the ACGIH-TLV-TWA.

[g]NIOSH REL-STEL (Recommended Exposure Limits–Short-Term Exposure Limit) (NIOSH 1994) is defined analogous to the ACGIH TLV-STEL.

[h]ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value–Time-Weighted Average) (ACGIH 1997) is the time-weighted average concentration for a normal 8-h workday and a 40-h work week, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[i]ACGIH TLV-STEL (Threshold Limit Value–Short-Term Exposure Limit) (ACGIH 1997) is defined as a 15-min TWA exposure that should not be exceeded at any time during the workday even if the 8-h TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 min and should not occur more than four times per day. There should be at least 60 min between successive exposures in this range.

[j]MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration], Deutsche Forschungsgemeinschaft [German Research Association], Germany) (DFG 1999) is defined analogous to the ACGIH-TLV-TWA.

[k]MAK Spitzenbegrenzung (Kategorie II,2) (Peak Limit Category II,2) (DFG 1999) constitutes the maximum average concentration to which workers can be exposed for a period up to 30 min, with no more than two exposure periods per work shift; total exposure may not exceed 8-h MAK. Category III indicates possible significant contribution to cancer risk.

TABLE 9-18 Continued

[l]Einsatztoleranzwert (Action Tolerance Levels) (Vereinigung zur Förderung des deutschen Brandschutzes e.V. [Federation for the Advancement of German Fire Prevention]) constitutes a concentration to which unprotected firemen and the general population can be exposed to for up to 4 h without any health risks.
[m]As nickel.
Note: NR: not recommended. Numerical values for AEGL-1 are not recommended because of the lack of available data. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

8.3. Data Adequacy and Research Needs

There were insufficient data to develop of AEGL-1 values. Lethality studies in four species and developmental toxicity studies in two rodent species provided data that were sufficient for the development of AEGL-2 and AEGL-3 values. Human data indicated the extreme toxicity of nickel carbonyl but lacked definitive exposure terms with which to develop AEGL values. Both human and animal data affirm the progressive toxicity of nickel carbonyl following a single exposure and the inherent asymptomatic latency between initial exposure and more severe and often lethal effects. Analysis of occupational exposure data based on area samples of workers exposed to nickel carbonyl indicated that minor respiratory effects (altered spirometric indices) were associated with long-term low-level (up to 0.07 ppm) exposure. Data were lacking for evaluating species variability and individual variability in the nonlethal toxic response to nickel carbonyl.

Data limitations regarding nonlethal exposure responses may be due to the extreme toxicity of the compound, whereby manifestation of any signs and symptoms of toxicity is indicative of exposures great enough to induce lethal effects. The latency period between what initially appear to be relatively mild effects and subsequent lethality also contributes to the difficulty in developing AEGL values, especially for AEGL-1 and AEGL-2 levels. Lethality data currently imply that the mouse is the most sensitive species (the lowest 30-min LC_{50} is for the mouse), but no developmental toxicity studies or other toxicity assays have been reported for this species; therefore, it is uncertain whether this sensitivity is also reflected in nonlethal end points. More definitive information on mechanism of action would be useful for understanding the toxic responses to nickel carbonyl.

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APPENDIX A

Derivation of AEGL-1 Values

Quantitative data regarding responses consistent with the AEGL-1 definition were not available for acute inhalation exposure to nickel carbonyl. Available data indicate that toxic effects in humans may occur in the absence of detection. Because of the lack of appropriate data, AEGL-1 values could not be determined and, due to the extreme toxicity of nickel carbonyl and the documented latency between relatively asymptomatic exposures and severe toxicity, are not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 concentration is without adverse effects.

Derivation of AEGL-2 Values

Key study:	Kincaid et al. 1953.
Toxicity end point:	Estimated threshold for pulmonary damage in mice exposed to 2.17 ppm for 30 min.
Scaling:	Exposure-response data over multiple time periods are unavailable for nickel carbonyl, and empirical derivation of a scaling factor (n) was not possible. 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 an empirically derived exponent (n), and to obtain conservative and protective AEGL values, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points. $(2.17 \text{ ppm})^1 \times 0.5 \text{ h} = 1.09 \text{ ppm h}$ $(2.17 \text{ ppm})^3 \times 0.5 \text{ h} = 5.1 \text{ ppm}^3 \text{ h}$
Uncertainty factors:	3 for interspecies variability. The available lethality data suggest that the mouse represents a sensitive species. Based on available lethality data and the analysis conducted by Kincaid et al. (1953) indicating an inverse relationship between lethality and body size (see Section 4.4.1.), the interspecies uncertainty factor of 3 appears to be justified.

	3 for intraspecies variability. Although intraspecies variability is difficult to assess based on available data, an uncertainty factor of 3 was applied with the assumption that neither the effects of nickel carbonyl on pulmonary tissues nor dosimetry would vary greatly among individuals. Additionally, the occupational exposure data reported by Shi et al. (1994b) suggest that the AEGL-2 values are sufficiently protective.
Modifying factor:	A modifying factor of 3 was applied to account for data deficiencies regarding AEGL-2 specific effects and to account for the possible developmental toxic effects.
10-min AEGL-2:	$C^3 \times 0.167$ h = 5.1 ppm^3·h C = 3.1 ppm 10-min AEGL-2 = 3.1 ppm/30 = 0.10 ppm (0.69 mg/m^3)
30-min AEGL-2:	$C^1 \times 0.5$ h = 1.09 ppm·h C = 2.17 ppm 30-min AEGL-2 = 2.17 ppm/30 = 0.072 ppm (0.50 mg/m^3)
1-h AEGL-2:	$C^1 \times 1$ h = 1.09 ppm·h C = 1.03 ppm 1-h AEGL-2 = 1.09 ppm/30 = 0.036 ppm (0.25 mg/m^3)
4-h AEGL-2	$C^1 \times 4$ h = 1.09 ppm·h C = 0.27 ppm 4-h AEGL-2 = 0.27 ppm/30 = 0.0090 ppm (0.063 mg/m^3)
8-h AEGL-2:	$C^1 \times 8$ h = 1.09 ppm·h C = 0.136 ppm 8-h AEGL-2 = 0.136 ppm/30 = 0.0045 ppm (0.031 mg/m^3)

Derivation of AEGL-3 Values

Key study:	Kincaid et al. 1953
Toxicity end point:	Estimated 30-min lethality threshold in mice: 3.17 ppm, using the mouse lethality data from Sunderman et al. (1980) and the method of Litchfield and Wilcoxon (1949) (see Appendix D).
Scaling:	$C^n \times t = k$ (ten Berge 1986). Data were unavailable for determining the exponent n. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent *n* ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived exponent (n), and to obtain conservative and protective AEGL values, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points. $(3.17 \text{ ppm})^1 \times 0.5 \text{ h} = 1.58 \text{ ppm}\cdot\text{h}$ $(3.17 \text{ ppm})^3 \times 0.5 \text{ h} = 15.93 \text{ ppm}^3\cdot\text{h}$
Uncertainty factors:	Total uncertainty adjustment of 10 (each uncertainty factor of 3 is the logarithimic mean of 10, which is 3.16; hence, 3.16. × 3.16 = 10). Lethality data from the smallest and, according to Kincaid et al. (1953), the most sensitive species was used for development of the AEGL-3. For this reason, and because the available LC_{50} values vary approximately 8-fold, the total uncertainty adjustment of 10 is weighted toward the uncertainty in individual sensitivity to nickel carbonyl exposure. Data are unavailable to definitively apportion adjustment between inter- and intraspecies uncertainty.
10-min AEGL-3:	$C^3 \times 0.5 \text{ h} = 15.93 \text{ ppm}^3\cdot\text{h}$ C = 4.57 ppm 10-min AEGL-3 = 4.57 ppm/10 = 0.46 ppm (3.2 mg/m^3)

30-min AEGL-3: $C^1 \times 0.5$ h = 1.58 ppm·h
C = 3.17 ppm
30-min AEGL-3 = 3.17 ppm/10 = 0.32 ppm
(2.2 mg/m^3)

1-h AEGL-3: $C^1 \times 1$ h = 1.58 ppm·h
C = 1.58 ppm
1-h AEGL-3 = 1.58 ppm/10 = 0.16 ppm (1.1 mg/m^3)

4-h AEGL-3: $C^1 \times 4$ h = 1.59 ppm·h
C = 0.398 ppm
4-h AEGL-3 = 0.398 ppm/10 = 0.040 ppm
(0.27 mg/m^3)

8-h AEGL-3: $C^1 \times 8$ h = 1.59 ppm·h
C = 0.198 ppm
8-h AEGL-3 = 0.198 ppm/10 = 0.020 ppm
(0.14 mg/m^3)

APPENDIX B

CARCINOGENICITY ASSESSMENT FOR NICKEL CARBONYL

CANCER ASSESSMENT OF NICKEL CARBONYL

Quantitative data regarding the carcinogenicity of nickel carbonyl in humans and laboratory species are unavailable, and therefore neither a cancer slope factor nor unit risk can be derived. The available evidence does not support a definitive assessment of cancer risk in humans for a single once-in-a-lifetime acute exposure. Epidemiologic data do not support the contention that inhalation of nickel carbonyl is carcinogenic to humans. Based on inadequate human data and limited data in animals, EPA (2003) categorizes nickel carbonyl as B2 (potential human carcinogen), while the IARC (1987) specifically states that nickel carbonyl was considered unlikely to be involved in causing cancers among nickel refinery workers.

APPENDIX C

DETERMINATION OF LETHALITY THRESHOLDS

Mouse lethality data: Kincaid et al. (1953) (see Table 9-8).

Dose (ppm)	Mortality	Observed, %	Expected, %	Observed	Expected Chi-Square
2.170	0/12	0 (0.30)	0.21	0.09	0.0004
6.510	2/15	13.33	16.46	–3.13	0.0071
7.840	3/10	30.00	29.83	0.17	0.0000
8.680	10/29	34.48	39.30	–4.82	0.0097
9.800	10/20	50.00	51.68	–1.68	0.0011
10.900	12/22	54.55	62.41	–7.86	0.0264
12.600	10/10	100 (92.20)	75.14	17.06	0.1558

Values in parentheses are corrected for 0 or 100 percent. Total = 0.2005.
LC_{50} = 9.642(8.609 – 10.800)*
Slope = 1.49(1.37 – 1.63)*
*These values are 95 percent confidence limits.
Total animals = 118. Total doses = 7. Animals/dose = 16.86.
Chi-square = total chi-square × animals/dose = 3.3800.
Table value for Chi-square with 5 degrees of freedom = 11.0700.
LC_{84} = 14.398. LC_{16} = 6.457

Expected Lethal Concentration Values (ppm)	
$LC_{0.1}$	1.814
$LC_{1.0}$	3.174
$LC_{5.0}$	4.731
LC_{10}	5.668
LC_{25}	7.392
LC_{50}	9.642
LC_{75}	12.577
LC_{90}	16.404
LC_{99}	29.296

Rat lethality data: Kincaid et al. (1953) (see Table 9-6).

Dose (ppm)	Mortality	Observed, %	Expected, %	Observed Expected	Chi-Square
67.000	19/30	94.00	89.13	4.87	0.0245
67.000	9/10	90.00	89.13	0.87	0.0008
105.000	24/30	80.00	90.66	–10.66	0.1342
168.000	30/30	100 (94.30)	92.05	2.25	0.0069
266.000	30/30	100 (94.30)	93.22	1.08	0.0018
266.000	10/10	100 (94.30)	93.22	1.08	0.0018

Values in parentheses are corrected for 0 or 100 percent: Total = 0.1700.
LC_{50} = 0.246(0.057 – 1.062)*
Slope = 82.91(0.00 – 450639439.54)*.
*These values are 95 percent confidence limits.
Total animals = 140. Total doses = 6. Animals/dose = 23.33.
Chi-square = Total chi-square × animals/dose = 3.9672.
Table value for chi-square with 4 degrees of freedom = 9.4900.
LC_{84} = 20.398: LC_{16} = 0.003

Expected Lethal Concentration Values (ppm)	
$LC_{0.1}$	0.000
$LC_{1.0}$	0.000
$LC_{5.0}$	0.000
LC_{10}	0.000
LC_{25}	0.013
LC_{50}	0.246
LC_{75}	4.596
LC_{90}	85.860
LC_{99}	511.48

APPENDIX D

ACUTE EXPOSURE GUIDELINE LEVELS FOR NICKEL CARBONYL

Derivation Summary for Nickel Carbonyl AEGLS

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
NR	NR	NR	NR	NR

Key reference: NA

Test species/Strain/Number: NA

Exposure route/Concentrations/Durations: NA

Toxicity end point: NA

Time scaling: NA

Concentration/Time selection/Rationale: NA

Uncertainty factors/Rationale
Total uncertainty factor: NA

Modifying factor: NA

Animal to human dosimetric adjustments: NA

Data adequacy: Quantitative data regarding responses consistent with the AEGL-1 definition were not available for acute inhalation exposure to nickel carbonyl, and therefore AEGL-1 values are not recommended (NR). Available data indicate that toxic effects in humans may occur in the absence of detection. Because of the lack of appropriate data, AEGL-1 values could not be determined and, due to the extreme toxicity of nickel carbonyl and the documented latency between relatively asymptomatic exposures and severe toxicity, are not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 concentrations are without adverse effects.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.10 ppm	0.072 ppm	0.036 ppm	0.0090 ppm	0.0045 ppm

Key reference: Kincaid, J.F., J.S. Strong, and F.W. Sunderman. 1953. Nickel poisoning. 1. Experimental study of the effects of acute and subacute exposure to nickel carbonyl. Arch. Ind. Hyg. Occup. Med. 8:48-60.

Test species/Strain/Number: albino mice; gender and strain not specified

Exposure route/Concentrations/Durations: inhalation, 2.17 ppm 30 min

Toxicity end point: Exposure to 2.17 ppm for 30 min caused no deaths and was considered a NOAEL for severe damage pulmonary tissue. Exposure to 6.51 ppm resulted in the death of 2/15 mice. Although no pathology examinations were performed on the mice, lethal exposure of rats to nickel carbonyl caused

(Continued)

AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
0.10 ppm	0.072 ppm	0.036 ppm	0.0090 ppm	0.0045 ppm

Toxicity end point *(continued)*: severe pulmonary edema, pulmonary congestion, and pleural effusion. It is assumed that mice (most sensitive species) exposed to 2.17 ppm for 30 min would exhibit some effects on pulmonary tissue. Pulmonary damage appears to be a component in the continuum of the toxic response to nickel carbonyl and an appropriate critical effect for AEGL-2 development. The 30-min exposure to 2.17 ppm was considered a point-of-departure representative of a NOAEL for AEGL-2 effects.

Time scaling: Exposure-response data over multiple time periods are unavailable for nickel carbonyl, and empirical derivation of a scaling factor (n) was not possible. 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 an empirically derived exponent n, and to obtain conservative and protective AEGL values, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points.

Concentration/Time selection/Rationale: Groups of 15 mice exposed for 30 min to 2.17, 6.51, 7.84, 8.68, 9.80, 10.9, or 12.6 ppm. A concentration-dependent lethal response was observed for exposures to 6.51-12.6 ppm, but the lowest exposure (2.17 ppm) resulted in no deaths. Exposure to 6.51 ppm resulted in the death of 2/15 mice. The 2.17 ppm exposure for 30 min was considered a NOAEL for severe damage to pulmonary tissue.

Uncertainty factors/Rationale:
Total uncertainty: 10

- Interspecies: An uncertainty factor of 3 was applied to account for interspecies variability. The available lethality data suggest that the mouse represents a sensitive species. Based on available lethality data and the analysis conducted by Kincaid et al. (1953) indicating an inverse relationship between lethality and body size (see Section 4.4.1.), the interspecies uncertainty factor of 3 appears to be justified.
- Intraspecies: An uncertainty factor of 3 was applied with the assumption that neither the effects of nickel carbonyl on pulmonary tissues nor dosimetry would vary greatly among individuals. The occupational exposure data reported by Shi et al. (1994b) suggest that the AEGL-2 values are sufficiently protective.

Modifying factor: 3; the overall dataset for nickel carbonyl is deficient regarding nonlethal effects of nickel carbonyl inhalation. Therefore, a modifying factor of 3 was applied in the development of the AEGL-2 values to account for these

(Continued)

AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
0.10 ppm	0.072 ppm	0.036 ppm	0.0090 ppm	0.0045 ppm

Modifying factor *(continued)*: deficiencies and the possibility of developmental toxic effects reported by Sunderman and colleagues.

Animal to human dosimetric adjustments: None applied; insufficient data.

Data adequacy: Data regarding AEGL-2 specifics effects are lacking. The AEGL-2 is based on an estimated threshold for severe pulmonary damage with considerations based on selection of a sensitive species and a critical effect and point of departure appropriate for AEGL-2 development. The data deficiencies have been acknowledged by application of a modifying factor.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
0.46 ppm	0.32 ppm	0.16 ppm	0.040 ppm	0.020 ppm

Key reference: Kincaid et al. 1953.

Test species/Strain/Number: 10-20 albino mice (age, gender and strain not specified)

Exposure route/Concentrations/Durations: Inhalation (whole-body exposure) exposure to 2.17, 6.51, 7.84, 8.68, 9.80, 10.9, or 12.6 ppm for 30 min

Toxicity end point: Lethality; LC_{01} estimated by method of Litchfield and Wilcoxon (1949)

Concentration (ppm)	Response (Number Dead/Number Exposed)
2.17	
6.51	
7.84	
8.68	
9.80	
10.9	
12.6	

0-min LC_{01} estimated at 3.17 ppm was used as the determinant of AEGL-3.

Time scaling: Exposure-response data over multiple time periods are unavailable for nickel carbonyl, and empirical derivation of a scaling factor (n) was not possible. 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 an empirically derived exponent n, and to obtain conservative and protective AEGL values, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation (ten Berge et al. 1986).

Concentration/Time selection/Rationale: Estimated 30-min LC_{01} (3.17 ppm)

(Continued)

AEGL-3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
0.46 ppm	0.32 ppm	0.16 ppm	0.040 ppm	0.020 ppm

Uncertainty factors/Rationale:
Total Uncertainty Factor: 10 (Each uncertainty factor of 3 is the approximate logarithmic mean of 10, which is 3.16; hence, 3.16. × 3.16 = 10. Lethality data from the smallest and the most sensitive species were used for development of the AEGL-3. For this reason, and because the available LC_{50} values vary approximately 8-fold, the total uncertainty adjustment of 10 is weighted toward the uncertainty in individual sensitivity to nickel carbonyl exposure. Data are unavailable to definitively apportion adjustment between inter- and intraspecies uncertainty.

Modifying factor: None.

Animal to human dosimetric adjustments: None applied; insufficient data.

Data adequacy: The AEGL-3 values were based on a reasonable estimate of the lethality threshold in a sensitive species. The key study was properly designed and conducted.

APPENDIX E

CATEGORY PLOT FOR NICKEL CARBONYL AEGLS

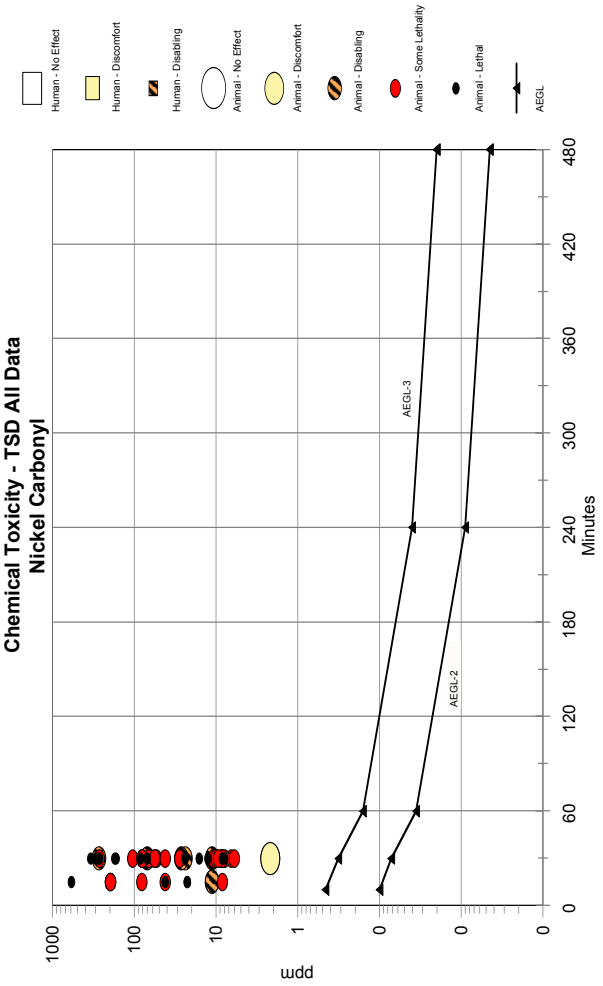

FIGURE 9-1 Chemical toxicity; TSD all data, nickel carbonyl.

10

Phosphine and Eight Metal Phosphides[1,2]

Acute Exposure Guideline Levels

PREFACE

Under the authority of the Federal Advisory Committee Act (P.L. 92-463) of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances has been established to identify, review, and interpret relevant toxicologic and other scientific data and develop Acute Exposure Guideline Levels (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 min to 8 h. AEGL-2 and AEGL-3, and AEGL-1 levels as appropriate, will be developed for each of five exposure periods (10 min, 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 susceptible. The three AEGLs have been defined as follows:

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[1]This document was prepared by AEGL Development Team member Cheryl Bast of Oak Ridge National Laboratory and Ernest Falke (Chemical Manager) of the National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances (NAC). The NAC reviewed and revised the document, which was then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC Committee concludes that the AEGLs developed in this document are scientifically valid conclusions based on data reviewed by the NRC and are consistent with the NRC guideline reports (NRC 1993, 2001).

[2]After an earlier version of this document was released in 2007, the committee evaluated AEGLs that were developed for eight metal phosphides: aluminum phosphide, potassium phosphide, sodium phosphide, zinc phosphide, calcium phosphide, magnesium phosphide, strontium phosphide, and magnesium aluminum phosphide. Because their acute toxicity results from the phosphine generated from hydrolysis of the metal phosphides, their AEGL values are likewise based upon phosphine AEGLs. AEGL values for the eight metal phosphides have been added as Appendix D of this document, Appendix 10.

AEGL-1 is the airborne concentration [expressed as parts per million (ppm) or milligrams per cubic meter (mg/m^3)] of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

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

SUMMARY

Phosphine is a colorless gas used as a fumigant against insects and rodents in stored grain. The pesticide is usually applied as a metal phosphide and reacts with moisture to liberate phosphine gas. Phosphine is also used in the semiconductor industry. Information concerning human exposure to phosphine is of limited use in the derivation of AEGL values since exposure durations and concentrations are not precisely reported. Appropriate animal data are more abundant; however, data consistent with the definition of AEGL-1 values are not available. Therefore, due to insufficient data, AEGL-1 values were not derived.

The AEGL-2 was based on red mucoid nasal discharge in Fischer 344 rats exposed to 10 ppm phosphine for 6 h (Newton et al. 1993). An uncertainty factor (UF) of 3 was applied to account for interspecies variability since time-to-death lethality data from 45 min to 30 h for rats, mice, rabbits, and guinea pigs suggest little species variability (see Figure 10-2). A UF of 10 was applied to account for intraspecies variability since the human data suggest that children may be more sensitive than adults when exposed to presumably similar phosphine concentrations (total UF = 30). The concentration-exposure time rela-

tionship 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). For scaling the AEGL values for phosphine for the 30-min, 1-, 4-, and 8-h time points, the empirically derived value of 1 was used as the exponent n. The exponent n was derived from rat lethality data ranging from 1 to 6 h. The 30-min AEGL-2 was also adopted as the 10-min value due to the added uncertainty of extrapolating from a 6-h time point to 10 min.

The AEGL-3 was based on a concentration causing no deaths (18 ppm) in Sprague Dawley rats exposed to phosphine for 6 h. An uncertainty factor of 3 was applied to account for interspecies variability since lethality data from rats, mice, rabbits, and guinea pigs suggest little species variability. An uncertainty factor of 10 was applied to account for intraspecies variability since human data suggest that children may be more sensitive than adults when exposed to presumably similar phosphine concentrations (total UF = 30). 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). For scaling the AEGL values for phosphine for the 30-min, 1-, 4-, and 8-h time points, the empirically derived value of 1 was used as the exponent n. The exponent n was derived from rat lethality data ranging from 1 to 6 h. The 30-min AEGL-3 was also adopted as the 10-min value due to the added uncertainty of extrapolating from a 6-h time point to 10-min. The calculated values are listed in the Table 10-1.

AEGL values for the eight metal phosphides are presented in Appendix D.

1. INTRODUCTION

Phosphine is a colorless gas used as a fumigant against insects and rodents in stored grain. Paper sachets containing aluminum phosphide are added to grain and the grain is then sealed. The aluminum phosphide reacts with moisture in the grain to produce the phosphine gas. Phosphine is also used as a doping agent to treat silicon crystals in the semiconductor industry and is a byproduct of metallurgical reactions (Hryhorczuk et al. 1992). Pure phosphine is odorless at concentrations up to 200 ppm (IPCS 1988); however, technical-grade phosphine contains impurities (up to 5% higher phosphines and substituted phosphines) that may be responsible for a garlic-like odor that can be detected at 1.5-3 ppm (Hryhorczuk et al. 1992). A concentration of 7.58 ppm has been reported as "irritating" to humans; however, no data to support this claim were provided (Ruth 1986). Naturally occurring phosphine is rare. It may occur transiently in marsh gas and other areas of anaerobic degradation of materials containing phosphorus. Phosphine is produced by the hydrolysis of aluminum phosphide or the electrolysis of phosphorus in the presence of hydrogen. The physicochemical data for phosphine are given in Table 10-2.

TABLE 10-1 Summary of AEGL Values for Phosphine

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Appropriate data not available
AEGL-2 (Disabling)	4.0 ppm (5.6 mg/m^3)	4.0 ppm (5.6 mg/m^3)	2.0 ppm (2.8 mg/m^3)	0.50 ppm (0.71 mg/m^3)	0.25 ppm (0.35 mg/m^3)	Red mucoid nasal discharge in rats exposed to 10 ppm of phosphine for 6 h (Newton et al. 1993)
AEGL-3 (Lethality)	7.2 ppm (10 mg/m^3)	7.2 ppm (10 mg/m^3)	3.6 ppm (5.1 mg/m^3)	0.90 ppm (1.3 mg/m^3)	0.45 ppm (0.63 mg/m^3)	Concentration causing no death in rats exposed to 18 ppm of phosphine for 6 h (Newton 1991)

Note: The AEGL-2 and AEGL-3 values for phosphine are only 1.8-fold different from one another. This closeness of AEGL tiers is reflective of the very steep concentration-response curve observed for phosphine toxicity.
NR: not recommended. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

TABLE 10-2 Physical and Chemical Data

Property	Descriptor or Value	Reference
Synonyms	Hydrogen phosphide, phosphorus trihydride, phosphoretted hydrogen, phosphane	
CAS Registry No.	7803-51-2	IPCS 1989
Chemical formula	PH_3	IPCS 1989
Molecular weight	34.00	Budavari et al. 1989
Physical state	Gas	IPCS 1988
Vapor pressure	41.3 atm at 20°C	Braker and Mossman 1980
Vapor density	1.17	IPCS 1988
Melting/boiling point	–133.5°C/–87.4°C	IPCS 1988
Solubility in water	2.5% v/v at 20°C	IPCS 1989
Conversion factors in air	1 mg/m^3 = 0.71 ppm 1 ppm = 1.41 mg/m^3	IPCS 1989

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

2.1.1. Case Reports

Numerous case reports concerning human lethality from phosphine exposure were located; however, exposure time and concentrations were not specified in most of the reports. Two siblings, 2 and 4 year old, weighing 11 and 17 kg, respectively, died within 18 h of playing on fumigated wheat for 1 h (Heyndrickx et al. 1976). The wheat had been treated with pyrethrum and malathion (120 kg/2,000 tons of grain) and aluminum phosphide tablets (1 kg/2,000 tons of grain). Analysis of wheat samples taken the morning after the children were exposed yielded 0.95 mg/100 g to 1.6 mg/100 g malathion (1.3 mg/100 g average) and 0.02-0.5 ppm phosphine (0.2 ppm average). Two days after the children played on the wheat 1 ppm of phosphine was detected in several places just above the grain. Postmortem examinations suggested that the deaths were due to acute intoxication, most likely from phosphine, although malathion exposure may have been a contributing factor. The lungs of both children were congested and had atelectatical areas. Ethanol, commonly formed postmortem in both blood and tissues, also was detected in both children.

In another report, two deaths were reported in fumigated boxcars (MMWR 1994). Four males—12, 35, 39, and 52 years old—were discovered in a boxcar containing loose bulk lima beans that had been fumigated with aluminum phosphide. The men had been in the car for approximately 16 h and had periodically opened the hatch for fresh air as needed. When discovered, the 12-year-old was dead and the three men were ill, suggesting that children may be more susceptible than adults. The three survivors reported nausea, vomiting, headache, and abdominal discomfort. In another incident the body of a 23-year-old man was discovered in a rice-filled boxcar during unloading. The rice had been fumigated with aluminum phosphide 12 days prior to unloading, and autopsy results showed phosphine in tissue samples. No phosphine concentrations were reported in either incident.

Aluminum phosphide fumigation aboard a grain freighter on September 24, 1978, resulted in acute illness in two female children and 29 of 31 crew members (Wilson et al. 1980). Phosphine gas escaped from the holds of the ship through a cable housing located near the ship's ventilation intake and around hatch covers on the forward deck; illness was associated with living or working on the forward deck. Phosphine concentrations were measured on September 30, 1978, 1-4 days after the onset of illness. The highest concentration of 20-30 ppm was detected in a void space of the main deck adjacent to the air ventilation intake. Concentrations between 7.5 and 10 ppm were measured around a hatch on the forward deck, while 0.5 ppm of phosphine was measured in some living quarters. Concentrations were measured with a Drager tube and are estimates of phosphine levels at that time. Wilson et al. stated that phosphine levels reach

peak concentrations in 4-5 days. They note that there was an association between severity of illness and living or working amid ships on the forward deck (phosphine was not detected in the rear crew cabins). Measurements were made shortly after peak exposures are likely to have occurred. Phosphine levels and exposure durations to those peak levels cannot be estimated from the data provided. Exposures were probably continuous for a period of days to levels above a range of 0.5-20 or 30 ppm. One of the two exposed children died (age 2), and postmortem examination revealed congestive heart failure, focal myocardial necrosis with mononuclear infiltrates and fragmented fibers, inflamed mitral and aortic valves, pulmonary edema, pleural effusion, desquamated respiratory epithelium with alveoli thickened by hemolyzed red cells, congested capillaries, an enlarged spleen, and aspirated gastrointestinal contents. The surviving child (age 4 years, 9 months) exhibited nausea, vomiting, dizziness, epigastric pain, and fatigue. An electrocardiogram (ECG) revealed tachycardia with ST depression, and an echocardiogram 24 h later showed dilation and poor function of the left ventricle. A transient increase in the myocardial band (MB) fraction of creatinine phosphokinase (CPK) was also observed. Clinical signs and symptoms resolved within 18 h, and ECG, echo, and CPK abnormalities resolved within 72 h. Crew members exhibited shortness of breath, cough, sputum production, nasal drainage, nausea, jaundice, vomiting, diarrhea, fatigue, headache, drowsiness, paresthesias, tremor, and weakness. Abnormal urinalyses and increased liver enzyme activities were observed in approximately 10% of exposed crew members compared to normal human values.

A 16-year-old male who was employed as an acetylene generator operator for approximately 1 month died from apparent phosphine poisoning (Harger and Spolyar 1958). The subject had experienced periods of dizziness while filling generator hoppers with calcium carbide and became unconscious on two occasions. On a third occasion he was found with his face near an open hopper, where the measured phosphine concentration was 75-95 ppm. On this occasion he could not be aroused and later died. Autopsy revealed lividity of the head and shoulder, bloody exudate from the nose and mouth, edematous lungs, and frothy exudate in the bronchioles and bronchi. Samples of air over the generators contained concentrations of phosphine between 1 and 14 ppm and <3 ppm arsine. The cause of death was reported to be acute pulmonary edema from inhalation of phosphine gas.

Garry et al. (1993) reported the accidental death of a 24-year-old woman who was 7 months pregnant. The victim's home was located approximately 30 yards from a large bunker-type grain storage facility. The storage facility was topographically more than 5 feet higher than the home and was routinely fumigated with 49,000-82,950 aluminum phosphide pellets. Residents in the area complained of odor and dust coming from the grain, particularly in the evenings. On the afternoon of the fatal exposure there was a rain shower, followed by clear skies and wind of 5 mph in the direction of the patient's home. She went outside between 8 and 9 p.m. and commented that the odor was "real strong." At approximately 10:30 p.m. she was tachycardiac and vomiting, and clear frothy

sputum was coming from her nose and mouth. She suffered cardiac arrest shortly after midnight and died. The autopsy revealed pulmonary edema and aluminum concentrations of 713 ng/mL in the blood and >200 ppm in alveolar macrophages. The tachycardia and pulmonary edema noted are consistent with phosphine poisoning. The authors stated that because the phosphine generated from the metal phosphide is highly reactive and unstable, quantitative analysis of aluminum in blood and tissues was used as a marker of exposure to test for possible fumigant intoxication.

Shadnia et al. (2008) reported the accidental poisoning of a woman (age 35 years), her daughter (age 18 years), and son (age 6 years) from phosphine inhalation. The phosphine was released from 20 aluminum phosphide tablets stored in 15 bags of rice. The boy died 2-days postexposure; he had received no medical attention. The other two victims were admitted to the hospital 48 h postexposure and presented with metabolic acidosis, electrocardiogram abnormalities, and hypotension. The patients were discharged after 3 days.

Poisoning from ingestion of aluminum phosphide tablets for attempted suicides has also been reported (Misra et al. 1988a). Eight people (three females, five males; ages 14-25 years) ingested 0.5-20 aluminum phosphide tablets each. Gastritis, drowsiness/dizziness/coma, and peripheral vascular failure were observed in all patients, while cardiac arrhythmia was seen in three cases, and jaundice and kidney failure were observed in one case each. Six of the patients died, and autopsies of two revealed pulmonary edema, gastrointestinal mucosal congestion, petechial hemorrhage on liver and brain surfaces, desquamation of bronchiole epithelium, vacuolar degeneration of hepatocytes, and dilation and engorgement of hepatic central veins and sinusoids.

2.2. Nonlethal Toxicity

2.2.1. Case Reports

Case reports concerning human phosphine exposure were available; however, exposure times and concentrations were not specified in most of the reports.

Sixty-seven male grain fumigators in New South Wales were occupationally exposed to phosphine concentrations ranging from 0.4 to 35 ppm (measured in the breathing zone; Jones et al. 1964). Exposure durations were described as "intermittent." Symptoms occurred immediately in some workers, while the onset of symptoms were delayed from several hours to 2 days in others. Symptoms included diarrhea (82%), nausea (73%), epigastric pain (65%), vomiting (29%), chest tightness (52%), breathlessness (34%), chest pain (29%), palpitations (27%), severe retrosternal pain (6%), headache (83%), dizziness (35%), and staggering gait (12%). There was no evidence of cumulative effects and no tendency to develop immunity.

Zaebst et al. (1988) reported odor but no adverse effects in grain fumigant workers exposed to >50 ppm phosphine for 2-5 min.

Verma et al. (2007) reported acute pancreatitis and myocarditis in a man after ingestion of aluminum phosphide pellets.

Twenty-two fumigation workers 24 to 60 years old (mean age 48) were evaluated for possible phosphine-related toxicity (Misra et al. 1988b). The mean duration of employment using aluminum phosphide was 11.1 years (range 0.5-29 years) and phosphine concentrations ranged from 0.17 to 2.11 ppm. The workers had also been exposed to malathion, hexachlorocyclohexane, and ethylene dibromide; however, during the study and for 4 weeks preceding the study, the workers were exposed only to phosphine. The following effects were reported: cough (18.2%); dyspnea (31.8%); chest tightness (27.3%); headache (31.8%); giddiness, numbness, lethargy (13.6% each); irritability (9.1%); anorexia and epigastric pain (18.2%); nausea (9.1%); and dry mouth (13.6%). Sensory and motor nerve conduction velocities were normal.

In another case, a 53-year-old man used a pesticide powder containing 28% calcium phosphide to poison moles in his garden (Schoonbroodt et al. 1992). He worked for approximately 2 h in rainy weather, and 18 h later experienced fever (40°C), dry cough, weakness, myalgia, headache, dizziness and nausea. Upon hospital admission he was anxious and cyanotic and complained of severe nasal obstruction. He had interstitial infiltrates of the left upper and right lower lobes of the lungs, sinus tachycardia, left anterior fascicular block, leucocyturia, and necrosis of the nasal mucosa. Despite antibiotic treatment, symptoms progressed and the patient developed pulmonary edema, left pleural effusion, and pericardial effusion. He was placed on a ventilator for 18 days and was discharged on day 32; one month after discharge his clinical profile was unremarkable.

Five workers were reportedly exposed to 0.01-0.001 ppm of phosphine during corn fumigation (Modrzejewski and Myslak 1967). However, no validation of analytical methods and no exposure times were reported, and there was no mention of probable occupational exposure to other pesticides. Vertigo, headache, nausea, and vomiting were observed in all subjects. Four workers exhibited dyspnea and bronchial inflammation; three had fever; and one had an enlarged liver, bilirubinemia, and jaundice. In another occupational exposure, three grain inspectors were instantaneously exposed to approximately 159-2,029 ppm of phosphine (no analytical validation provided) while inspecting railroad cars (Feldstein et al. 1991). Immediately after the exposures they experienced facial numbness and tingling, dizziness, nausea, shortness of breath, headache, disorientation, diaphoresis, despondency, and a "sense of doom."

2.2.2. Epidemiologic Studies

Epidemiologic studies regarding human exposure to phosphine were not available.

2.3. Developmental/Reproductive Toxicity

No developmental/reproductive toxicity data concerning phosphine were identified in the available literature.

2.4. Genetic Toxicology

Barbosa and Bonin (1994) observed no increase in clastogenicity or aneuploidy in lymphocytes of 31 long-term phosphine fumigators compared to a group of 21 matched controls. Sporadic phosphine exposure ranged from 0.1 to 2 ppm for an average of 11.6 years. Specific chromosome aberrations associated with occupational pesticide exposure are discussed in Section 2.5.

2.5. Carcinogenicity

Epidemiologic data suggest that farm and grain industry workers have an increased incidence of non-Hodgkin's lymphoma; however, because these workers are generally exposed to myriad pesticides and solvents throughout their working lives, it is difficult to use the data to determine whether there is an association between increased cancer incidence and exposure to a particular pesticide (Garry et al. 1992).

Several studies of chromosomal analysis of male pesticide applicators suggest that occupational exposure to phosphine or mixed exposure to phosphine and other pesticides may contribute to an increased incidence of aberrations (Garry et al. 1989, 1990, 1992). Although dose-related stable (translocations) and unstable (gaps and chromatid deletions) aberrations have been identified in the lymphocytes of phosphine applicators (Garry et al. 1989, 1990), the most convincing link between phosphine exposure and non-Hodgkin's lymphoma is observed in molecular analyses of the stable aberrations (Garry et al. 1992). A group of 18 pesticide appliers exposed to phosphine or to phosphine and a mixture of other chemicals had an increased incidence of stable aberrations (1.3% of cells with aberrations) compared to five appliers who had ceased phosphine application for 8 months or 26 control subjects (0.2% cells with aberrations). There were four bands with an excess of breaks (over what would be expected on band length alone) in the exposed group and no breaks in the control group. These breaks were also not observed in the group that had ceased phosphine application. Each of these breaks is in a protooncogene region associated with non-Hodgkin's lymphoma as follows: 1p13 (NRAS), 2p23 (NMYC), 14q32 (ELK2), and 21q22 (ETS-2). More breaks than expected were also observed in 1q32, 3p14, 7p15, and 14q11; however, these breaks are likely not due to pesticide exposure since increases were observed in both exposed and control subjects.

2.6. Summary

Reports of occupational exposures and attempted suicides are numerous; however, data on exposure durations and concentrations are limited. Common clinical signs are headache, nausea, vomiting, coughing, shortness of breath, paresthesia, weakness, tremors, and jaundice. Pulmonary congestion, pleural effusion, and congestive heart failure may be observed upon postmortem examination. Fumigation workers exposed long term to phosphine have a higher incidence of both stable and less stable chromosomal aberrations. Molecular analysis of these lesions suggests that the breakpoints are near protooncogenes involved in non-Hodgkin's lymphoma, possibly contributing to the increased incidence of lymphomas in pesticide workers. No reproductive or developmental data were available.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

A 4-h LC_{50} of 11 ppm (15.5 mg/m^3) phosphine was reported for male Charles River-CD rats (Waritz and Brown 1975). The phosphine was analyzed by scrubbing samples of the chamber atmosphere through H_2SO_4 and analyzing the resulting solution for phosphorus. One sample was taken during each exposure. Signs of respiratory irritation, including salivation, lacrimation, face pawing, and dyspnea, were observed. Hyperemia of the ears also was observed. No effects attributable to phosphine exposure were observed at necropsy.

Newton (1991) reported a combined 6-h LC_{50} of 28 ppm (39.5 mg/m^3) for male and female Sprague-Dawley rats. No deaths occurred in rats exposed to 18 ppm of phosphine for 6 h, suggesting a steep concentration-response curve. This study is discussed in further detail in Section 3.2.1.

Muthu et al. (1980) exposed groups of six adult female albino rats to varying concentrations of phosphine for 1, 4, 6, or 8 h and observed the animals for up to 4 weeks. The gas was generated by dropping aluminum phosphide pellets into distilled water in a beaker in the middle of the exposure chamber. By varying the number of aluminum phosphide pellets and the exposure times, different concentration-time products were obtained. Rats were exposed in a wire mesh cage that was placed in an "insulated aluminum paneled gas-tight atmospheric vault" with a volume of 5,943 L. Phosphine concentrations were measured every hour during the exposure periods with a "phosphine detector tube" developed by the study authors. No other study details were reported. A 1-h LC_{50} of 134 ppm and a 5.2-h LC_{50} of 28 ppm were calculated. LC_{95} values of 45 ppm and 33.3 ppm were calculated for 6.2-h and 8.8 h, respectively.

Groups of four male F344 rats were exposed to 0, 1, 5, or 10 ppm of phosphine for 6 h/day for up to 4 days. All rats died by the end of the third exposure to 10 ppm (Morgan et al. 1995). Deaths were not observed in rats exposed to 1 or 5 ppm, suggesting a steep concentration-response curve.

Neubert and Hoffmeister (1960) exposed groups of eight rats constantly to phosphine concentrations ranging from 71 to 3,294 ppm. Survival times ranged from 16 through 600 min. No further data were provided.

3.1.2. Mice

Omae et al. (1996) exposed groups of 10 male ICR mice to 17.2, 25.1, 31.7, 41.6, or 59.2 ppm of phosphine for 1-h or to 22.5, 26.5, 33.4, 45.5, or 66.9 ppm for 4 h. The source gas was 99.995% pure phosphine (used in semiconductor manufacturing) diluted with purified nitrogen. It was supplied at a constant rate, mixed with filtered room air, and introduced into the whole-body 550-L exposure chamber. Phosphine concentrations were measured via gas chromatography every 12 min during exposure. The oxygen concentration in the chamber was measured simultaneously with a digital oximeter. The 1-h LC_{50} was >59.2 ppm, whereas the 4-h LC_{50} was between 26.5 and 33.4 ppm. In all of the 1-h exposed animals, the mice exhibited face-washing movements and were very active in the initial exposure period. No adverse signs were noted during the 3-day observation period after exposure. In the 4-h exposed mice, the initial observations were similar to those of the 1-h group. However, 3 h after the start of exposure at 33.4 ppm and above, the mice became slower in response to tapping on the chamber glass and supine posture was observed. After the completion of exposure at 22.5 ppm and above, slight tremor and piloerection were observed. At 33.4 ppm and above, mild loss of spontaneous motor activity and piloerection were observed, and at 45.4 ppm and above, complete loss of motor activity, ocular cloudiness, and moribundity were noted.

A 2-h LC_{L0} of 270 ppm (380 mg/m^3) phosphine was reported for an unspecified strain of mice (NIOSH 1994, 2005). No further experimental details were provided.

3.1.3. Guinea Pigs

A 4-h LC_{L0} of 100 ppm (141 mg/m^3) phosphine was reported for an unspecified strain of guinea pigs (NIOSH 1994, 2005). No further experimental details were provided.

3.1.4. Cats

A 2-h LC_{L0} of 50 ppm (70.5 mg/m^3) of phosphine was reported for an unspecified strain of cat (NIOSH 1994, 2005). In another report an unspecified

strain of cats survived exposure to 170 ppm (240 mg/m^3) for 2 h (IPCS 1988). No further experimental details were provided for either report.

3.1.5. Rabbits

A 20-min LC_{L0} of 2,500 ppm (3,525 mg/m^3) phosphine was reported for an unspecified strain of rabbit (NIOSH 1994, 2005). In another report an unspecified strain of rabbits survived exposure to 50 ppm (70 mg/m^3) for 10 min; however, exposure to 100 ppm (140 mg/m^3) was fatal to all exposed animals in 2.5-3 h, and 500 ppm (700 mg/m^3) was fatal in 25-30 min (IPCS 1988). No further experimental details were provided for either study.

3.2. Nonlethal Toxicity

3.2.1. Rats

Groups of five Sprague-Dawley rats/sex were exposed to target phosphine concentrations of 0, 1, 5, or 26 ppm (actual concentrations 0, 1.3, 6.0, or 28 ppm, respectively) for 6 h, while additional groups of 10 male Sprague-Dawley rats were exposed to target concentrations of 0, 3, 12, or 18 ppm (actual concentrations 0, 3.1, 10, or 18 ppm, respectively) for 6 h (Newton 1991). Actual exposure concentrations were determined hourly by gas chromatography, and particle size distribution for any possible background aerosol was measured with a TSI aerodynamic particle sizer. Actual exposure concentrations and mortality data are presented in Table 10-3. Postexposure observations were unremarkable except for the surviving 26-ppm animals. Hunched appearance, coarse tremors, decreased activity, and cold to touch were observed and resolved by the following day. Mean body-weight data were generally unremarkable. Body-weight

TABLE 10-3 Exposure Concentration and Mortality of Rats Exposed to Phosphine for 6 h

Target Exposure Concentration (ppm)	Actual Mean Concentration (ppm)	Mortality		
		Male	Female	Total
0	0	0/5	0/5	0/10
1.0	1.3	0/5	0/5	0/10
5.4	6.0	0/5	0/5	0/10
26	28	3/5	2/5	5/10
0	0	0/10	–	0/10
3.0	3.1	0/10	–	0/10
12	10	0/10	–	0/10
18	18	0/10	–	0/10

Source: Newton 1991. Reprinted with permission; copyright 1991, Huntingdon Life Sciences.

decreases of approximately 10% were observed on day 2 in surviving animals from the 12-, 18-, and 2-6-ppm groups. The decreases were not statistically significant.

Dose-related statistically significant increases in mean hemoglobin, hematocrit, and red blood cell levels were observed in the 10- and 18-ppm males (hematology values were measured only in the 0-, 3.1-, 10-, and 18-ppm males). However, these increases, possibly the result of dehydration, are of questionable biologic significance since they are generally within normal historical ranges for Sprague-Dawley rats (Charles River Laboratories 1984). No Heinz Bodies were observed in control or treated animals. Hematology data are presented in Table 10-4.

Results from chromosomal analyses of exposed rats are given in a separate report (Hazleton Laboratories 1991). Statistically significant increases in stable chromosomal aberrations were observed only in male rats exposed to 3.1, 6.0, and 18 ppm of phosphine. Although some aberrations were observed in treated females and in males treated with 10 or 28 ppm, the incidence was not statistically significant. Due to the lack of a clear dose response in males and the small magnitude of response in females, the increase in aberrations is of questionable toxicologic significance.

In another study, Newton et al. (1993) exposed 15 Fischer 344 rats/sex/group to 0, 2.5, 5, or 10 ppm (0, 3.5, 7, or 14 mg/m^3) phosphine for 6 h. No animals died during the study. During the exposure period, red mucoid nasal discharges were observed at all exposure concentrations; however, these effects resolved during the 14-day recovery period. There was no effect on body weight, and there were no abnormal findings during postmortem examinations.

Newton et al. also conducted a subchronic study, exposing groups of 30 male and 30 female Fischer 344 rats to 0, 0.37, 1.0, or 3.1 ppm of phosphine 6 h/day, 5 days/week, for 13 weeks. Ten animals/sex/group were killed after 4 and 13 weeks of exposure and after 4 weeks of recovery. A satellite group of 10 animals/sex/concentration (0 or 10-ppm exposure) was added after animals were killed after the 4-weeks of exposure because no effects were observed in the 3.1-ppm group. However, 4/10 females (10 ppm) died after three exposures. Thus, the 10-ppm exposures were stopped and satellite groups at target concentrations of 0 or 5 ppm were added; all of these animals survived until they were killed 13 days later. Statistically significant decreases in body weights, accompanied by significant decreases in feed consumption, were observed in males and females exposed to 1 ppm and higher. Statistically significant ($p < .05$), although biologically questionable, hematologic and clinical chemistry parameters were affected only in male animals at 3.1 ppm and above. All previously described effects were reversible. Treatment-related lung congestion and kidney lesions (coagulative necrosis of proximal convoluted tubular epithelia) were observed in both males and females exposed to 10 ppm. The kidney pathology was more severe in males than in females. No pathology was observed at 3.1 or 1 ppm.

TABLE 10-4 Mean Hematology Values for Male Rats Exposed to Phosphine for 6 h

Target Exposure Concentration (ppm)	Actual Mean Concentration (ppm)	Hematology Values (mean ± SD)		
		HBG (g/dl)	HCT (%)	RBC (10^6/µl)
Historical control range[a]		13-21	39-51	4.2-6.2
0	0	13.1 ± 0.6	39 ± 1	6.47 ± 0.24
3.0	3.1	13.2 ± 0.4	39 ± 1	6.45 ± 0.3
12	10	14.2 ± 0.6[b]	42 ± 2[b]	6.88 ± 0.34[b]
18	18	14.7 ± 0.7[b]	43 ± 2[b]	7.11 ± 0.4[b]

[a]Charles River Laboratories 1984.
[b]$p < .05$.
Source: Newton 1991. Reprinted with permission; copyright 1991, Huntingdon Life Sciences.

Morgan et al. (1995) exposed 18 F344 rats/sex/group to 0, 1.25, 2.5, or 5 ppm of phosphine 6 h/day, 5 days/week, for 2 weeks. None of the rats died as a result of phosphine exposure. Male rats exposed to 5 ppm had decreased (21-29%) lung weights after 2 weeks, and female rats exposed to 5 ppm had increased (16-27%) heart weights after 2 weeks. The significance of these data appear somewhat equivocal in that no microscopic evidence of treatment-related effects were found in any of the tissues examined from rats or mice exposed to 5 ppm for 2 weeks.

3.2.2. Mice

Groups of four male B6C3F1 mice were exposed to 0, 1, 5, or 10 ppm of phosphine for 6 h/day for 4 days (Morgan et al. 1995). All mice were killed moribund after the fourth exposure. Pathology data were collected, and there were no treatment-related effects observed in mice exposed to 1 or 5 ppm. Anemia, decreased leukocyte counts, increased serum ALT and SDH activities, increased urine nitrogen, degeneration and necrosis of renal tubule epithelium, myocardial degeneration, and liver foci and degeneration were observed in the 10-ppm group. In a follow-up study, Morgan et al. exposed 18 mice/sex/group to 0, 1.25, 2.5, or 5 ppm of phosphine for 6 h/day, 5 days/week, for 2 weeks. None of the mice died as a result of the phosphine exposure. Male mice exposed to 5 ppm had decreased (21-29%) lung weights after 2 weeks, and female mice exposed to 5 ppm had increased (16-27%) heart weights after 2 weeks.

3.3. Developmental/Reproductive Toxicity

Groups of 18 pregnant F344 rats were exposed to 0, 0.03, 3.0, 5.0, or 7.5 ppm of phosphine for 6 h/day during days 6-15 of gestation (Newton et al.

1993). Fourteen females exposed to 7.5 ppm died after 3-10 days of exposure. No maternal deaths were observed at lower concentrations, suggesting a steep concentration response with regard to lethality. Due to excessive the mortality, the remaining animals in the 7.5-ppm group were terminated. No adverse treatment-related effects were observed in maternal body weight and feed consumption, maternal physical observations, or uterine implantation. There was a statistically significant increase in the mean number of resorption sites and the mean resorption/implantation ratio in the 0.03-ppm group. However, in the absence of similar observations at the higher concentrations of phosphine, these effects are not considered toxicologically relevant. No treatment-related effects were observed during maternal postmortem examinations. No treatment-related effects were observed on mean fetal weights or fetal sex ratio. No external, visceral, or skeletal malformations were observed in the fetuses.

Kligerman et al. (1994a) exposed 50 male B6C3F1 mice to 5 ppm of phosphine for 6 h/day for 10 days over a 12-day period. The treated males were then mated to groups of untreated females (two females/male) on each of six consecutive 4-day mating intervals. None of the females had a significant increase in percent resorptions, and there was no difference in pregnancy rates between control and treated animals.

3.4. Genetic Toxicology

Kligerman et al. (1994b) exposed male CD-1 mice to 0, 5, 10, or 15 ppm of phosphine for 6 h. No increase in the incidence of chromosome aberrations was observed in cultured splenocytes, and no increase in micronuclei incidence was observed in bone marrow smears. In another study, Kligerman et al. (1994a) exposed groups of male F344/N rats and male B6C3F1 mice to 0, 1.25, 2.5, or 5 ppm of phosphine for 6 h/day for 9 days over an 11-day period. No increase in cytogenetic end points was observed over controls in cultured lymphocytes or in bone marrow smears. Barbosa et al. (1994) observed an increased incidence of micronuclei in mice exposed to 4.5 ppm of phosphine for 6 h/day, 5 days/week, for 13 weeks, but no increase was seen in mice exposed similarly to 0.3 or 1.0 ppm.

3.5. Carcinogenicity

No data concerning the carcinogenicity of phosphine from inhalation exposure were identified in the available literature.

3.6. Summary

A 4-h LC_{50} of 11 ppm of phosphine was reported for male Charles River-CD rats (Waritz and Brown 1975). Newton (1991) defined a 6-h LC_{50} of 28 ppm

for male and female Sprague-Dawley rats. Muthu et al. (1980) calculated a 5.2-h LC_{50} of 28 ppm and LC_{95} values of 45 ppm and 33.3 ppm for 6.2-h and 8.8 h, respectively, in female albino rats. Signs of respiratory irritation, including hyperemia of the ears, salivation, lacrimation, face pawing, and dyspnea, were observed in rats. Omae et al. (1996) determined a 1-h LC_{50} >59.2 ppm (the highest concentration tested), and a 4-h LC_{50} was between 26.5 and 33.4 ppm in male Institute for Cancer Research (ICR) mice. Clinical signs in mice included face-washing movements, increased activity in the initial exposure period, followed by a slowing in response to tapping on the chamber glass, supine posture, slight tremor, piloerection, mild loss of spontaneous motor activity progressing to complete loss of motor activity, ocular cloudiness, and moribundity. Selected mortality data are presented in Table 10-5. The concentration × time products from these data are relatively constant across species except for the Waritz and Brown (1975) data, which appear to be an outlier.

Exposure to phosphine affected multiple end points in rats and mice. Rats exposed for 6 h exhibited increased hematology values at 12 and 18 ppm; decreased body weight at 12, 18, and 26 ppm; and tremors, hunched appearance, decreased activity, and death at 26 ppm (Newton 1991). Rats exposed to 2.5, 5.0, or 10 ppm of phosphine for 6 h exhibited a red nasal discharge (Newton et al. 1993). Repeated exposures resulted in decreased lung weight and increased heart weight in rats and mice (Morgan et al. 1995) and reversible body-weight and feed-consumption decreases and lung and kidney histopathology in rats (Newton et al. 1993). Mice repeatedly exposed to 10 ppm exhibited anemia; decreased white-blood-cell counts; increased serum liver enzymes; and kidney, heart, and liver pathology (Morgan et al. 1995). Phosphine was not a developmental or reproductive toxicant in rats (Newton et al. 1993) or mice (Kligerman et al. 1994a). Carcinogenicity data were not available. Although several genotoxicity studies reported negative results, the results concerning micronuclei incidence were equivocal.

TABLE 10-5 Selected Lethality Data from Animals Exposed to Phosphine

End Point	Species	Concentration (ppm)[a]	Time (h)	C × T (ppm-h)	Reference
LC_{50}	Rat	11	4	44	Waritz and Brown 1975
LC_{50}	Rat	134	1	134	Muthu et al. 1980
LC_{50}	Rat	28	5.2	146	Muthu et al. 1980
LC_{50}	Rat	28	6	168	Newton 1991
LC_{50}	Mouse	26.5-33.4	4	106-134	Omae et al. 1996
LC_{95}	Rat	45	6.2	279	Muthu et al. 1980
LC_{95}	Rat	33.3	8.8	293	Muthu et al. 1980

[a]1 ppm = 1.41 mg/m3.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

A report of the International Programme on Chemical Safety indicated that inhaled phosphine is readily absorbed through the lungs and is primarily distributed to the blood, nervous system, and liver (IPCS 1988). The report also indicated that phosphide has been detected in the kidneys of fatal poisoning cases. In rats, phosphine not excreted in expired air is oxidized and is excreted in urine as hypophosphite and phosphite. The fact that phosphine is incompletely oxidized and the fact that the proportion of an administered dose that is eliminated as expired phosphine increases with dose suggest that the oxidative pathway is slow (IPCS 1988).

4.2. Mechanism of Toxicity

In vitro, phosphine reacts with cytochrome c and cytochrome c oxidase, thereby inhibiting mitochondrial oxygen uptake (Chefurka et al. 1976; IPCS 1988). In vitro studies have shown that phosphine can react with the heme moiety of hemoglobin in the presence of oxygen (Chefurka et al. 1976). In rabbits treated with zinc phosphide, increases in serum glutamic-pyruvic and glutamic-oxaloacetic transaminases, leucine aminopeptidase, aldolase, alkaline phosphatase, and albumin were observed. Hepatic fat metabolism was also disturbed. Cell death and loss of cell membrane integrity accounted for the increased liver enzymes, bronchiolytic effects, cloudy swelling of renal tubular epithelia, and hemorrhagic myocardial lesions (IPCS 1988). Phosphine and arsine are often described as chemically similar. However, no explanation exists as to why hemolysis does not occur as a result of phosphine poisoning.

4.3. Structure-Activity Relationships

Phosphine may be successively alkylated, oxygenated, and esterified to yield phosphates or phosphites, phosphine oxide, phosphinic acid esters or phosphinates, and phosphoric acid esters or phosphonates. These compounds may contain alkyl or aryl groups (Bisesi 1994). Toxicologic properties of these compounds vary as follows: (1) central nervous system (CNS) damage with secondary paralysis, (2) CNS stimulation or convulsion with anesthetic action, (3) true or pseudocholinesterase inhibition, (4) irritation of dermal or respiratory system, and (5) no effect. Alkyl and aryl phosphates exhibit relatively high toxicity, and phosphonates are moderately to highly toxic, with toxicity lowest for alkyl derivatives and rising with increasing aromatization and further increasing with halogenation or nitro- group substitution. The toxicologic properties of organophosphites are similar to those of the phosphonates (Bisesi 1994). Since

these metabolites cause primarily neurologic symptoms, as opposed to the symptoms seen from phosphine toxicity, they are likely not the cause of death from phosphine exposure.

Four-hour LC_{50} values for Charles River-CD male rats were 11 ppm for phosphine, 38 ppm for phenylphosphine, and 8,865 ppm for triphenylphosphine (Waritz and Brown 1975). The dose-response curves were parallel, and all caused clinical signs associated with mild respiratory irritation. Additionally, triphenylphosphine caused severe weight loss immediately following exposure, followed by a normal rate of weight gain. Phosphine and phenylphosphine caused mild weight loss, followed by a normal rate of weight gain.

4.4. Other Relevant Information

4.4.1. Species Variability

Klimmer (1969) exposed groups of rats, rabbits, guinea pigs, and rabbits to phosphine concentrations ranging from 5.3 to 400 ppm for over 800 h. When Gehring et al. (1991) plotted exposure concentration against average time to death for these data, the values for all four species fell along the same log concentration-log time curve, suggesting little species variability (see Figure 10-1).

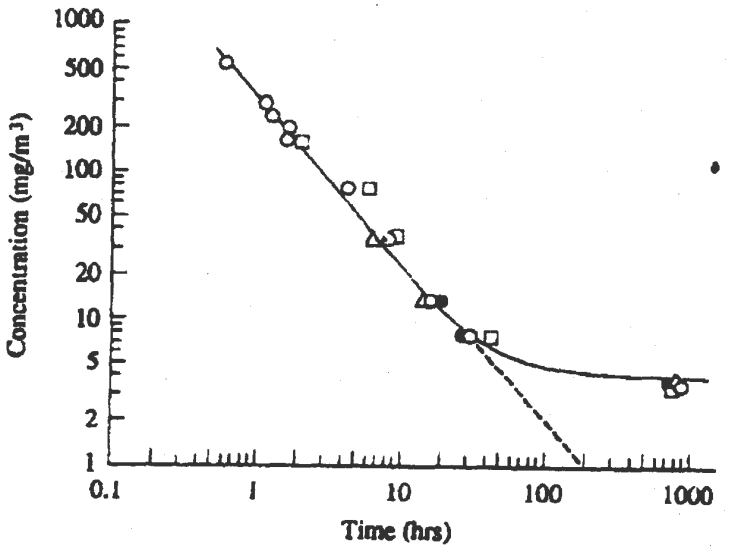

FIGURE 10-1 Phosphine concentration versus average time to death of rats (o), rabbits (Δ), guinea pigs (●), and cats. Source: Gehring et al. (1991) from analysis of the data of Klimmer (1969).

4.4.2. Concurrent Exposure Issues

In an occupational setting, phosphine is likely to be encountered in conjunction with other pesticides. No definitive data were located concerning the potential synergy of combinations of pesticides or of the relative toxic potential of phosphine in mixtures.

4.4.3. Derivation of the Exponent n

The concentration-exposure time relationship for many irritant and systemically acting vapors and gases has been described by the relationship $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). When rat LC_{50} data (from Table 10-5) ranging from 1- to 6-h exposure duration are utilized, an n value of 0.98 is derived (see Figure 10-2).

5. RATIONALE FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No human data are available for the derivation of AEGL-1 for phosphine. Nonlethal effects observed were more severe than those defined by AEGL-1; furthermore, no reliable exposure parameters were available.

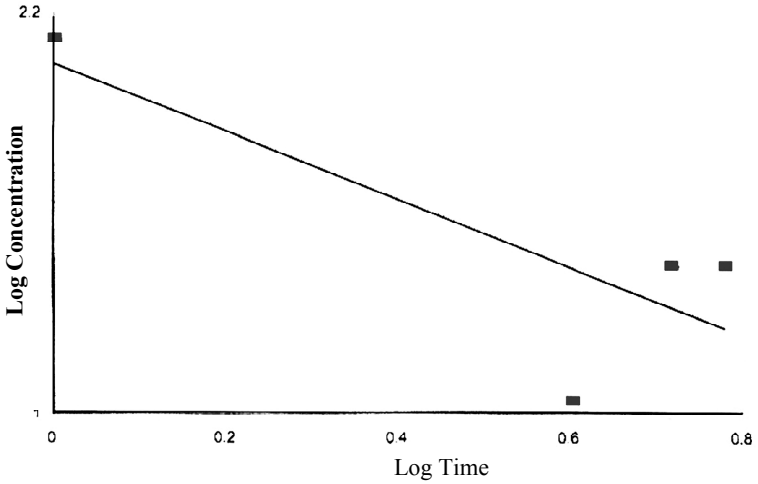

FIGURE 10-2 Best-fit concentration (ppm phosphine) × time (exposure duration in hours) curve. Linear regression of rat lethality data.

5.2. Summary of Animal Data Relevant to AEGL-1

Animal data from exposure to phosphine relevant to the derivation of AEGL-1 are not available.

5.3. Derivation of AEGL-1

Appropriate data were not available for derivation of AEGL-1 values for phosphine. No human or animal data are consistent with the effects defined by AEGL-1. The fact that lethality has been observed in animals exposed to phosphine concentrations below the odor threshold (1.5-200 ppm, dependent on impurities) also supports this recommendation. Therefore, AEGL-1 values for phosphine are not recommended (see Table 10-6.)

6. RATIONALE FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No human data are available for the derivation of AEGL-2 for phosphine. Although effects such as headache, nausea, vomiting, coughing, shortness of breath, weakness, and paresthesia have been observed, the studies are not appropriate for the derivation since the descriptions of concentration, exposure time, and effects are not well defined.

6.2. Summary of Animal Data Relevant to AEGL-2

A red mucoid discharge was observed in rats exposed to 10 ppm of phosphine for 6 h (Newton et al. 1993). In another experiment no pulmonary lesions or renal congestion were observed in rats exposed to 3.1 ppm for 6 h/day, 5 days/week, for 13 weeks.

6.3. Derivation of AEGL-2

The red mucoid nasal discharge observed in rats exposed to 10 ppm of phosphine for 6 h (Newton et al. 1993) is used as the basis for the calculation of the AEGL-2. Although this effect does not meet the definition of AEGL-2, it is being utilized since no other relevant effect is observed in a single-exposure study. Since red mucoid nasal discharge by itself is less severe than the effects defined by AEGL-2 (irreversible or severe long-lasting effects), the resulting values should be protective. An uncertainty factor of 3 was applied to account

TABLE 10-6 AEGL-1 for Phosphine

AEGL Level	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR

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

for interspecies variability since time-to-death lethality data from 45 min to 30 h for rats, mice, rabbits, and guinea pigs suggest little species variability (see Figure 10-1). An uncertainty factor of 10 will be applied to account for intraspecies variability since the human data suggest that children may be more sensitive than adults when exposed to presumably similar phosphine concentrations. For example, in both the MMWR (1994) and Wilson et al. (1980) reports, exposed children died, but exposed adults survived. 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). When rat lethality data of 1-6-h are utilized in the derivation of the exponent for phosphine, a value of 1 is obtained. For scaling the AEGL values for phosphine for the 30-min, 1-, 4-, and 8-h time points, this empirically derived value of 1 was used as the exponent n. The 30-min AEGL-2 was also adopted as the 10-min value due to the added uncertainty of extrapolating from a 6-h time point to 10 min. The values for AEGL-2 are given in Table 10-7.

These AEGL-2 values are considered protective since no effects defined by AEGL-2 were observed in rats repeatedly exposed to 3.1 ppm of phosphine for 6 h/day, 5 days/week, for 13 weeks (Newton et al. 1993) and only a 10% decrease in body weight was observed in rats exposed to 10 ppm for 6 h (Newton 1991).

7. RATIONALE FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

Human data from exposure to phosphine are not appropriate for the derivation of AEGL-3, since the descriptions of concentration and exposure times are not well documented.

7.2. Summary of Animal Data Relevant to AEGL-3

Waritz and Brown (1975) reported a 4-h LC_{50} for phosphine of 11 ppm in Charles River-CD rats, and Newton (1991) observed hunched appearance, coarse tremors, decreased activity, and death in Sprague-Dawley rats exposed to 28 ppm for 6 h. This study also points to a steep concentration-response curve

TABLE 10-7 AEGL-2 for Phosphine (ppm [mg/m^3])

AEGL Level	10 min	30 min	1 h	4 h	8 h
AEGL-2	4.0 (5.6)	4.0 (5.6)	2.0 (2.8)	0.50 (0.71)	0.25 (0.35)

since no deaths were seen in groups of 10 rats exposed to 18 or 10 ppm of phosphine for 6 h. Muthu et al. (1980) calculated a 5.2-h LC_{50} of 28 ppm and LC_{95} values of 45 ppm and 33.3 ppm for 6.2-h and 8.8-h exposures, respectively, in female albino rats. Omae et al. (1996) determined a 1-h LC_{50} >59.2 ppm, and a 4-h LC_{50} was between 26.5 and 33.4 ppm in male ICR mice.

7.3. Derivation of AEGL-3

The highest concentration yielding no deaths in rats (18 ppm) for 6 h is used as the basis for the calculation of the AEGL-3 (Newton 1991). This study is selected because 10 animals per dose group were used and data were for exposures over a range of phosphine concentrations. The Waritz and Brown (1975) study included a small number of animals per dose group and were incompletely reported. Additionally, the Waritz and Brown data seem to be an outlier to the database (see Table 10-5). A rat study was chosen instead of mouse data since the exponent n was derived from rat data. An uncertainty factor of 3 was applied to account for interspecies variability since time-to-death lethality data from 45 min to 30 h for rats, mice, rabbits, and guinea pigs suggest little species variability (see Figure 10-1). An uncertainty factor of 10 is applied to account for intraspecies variability since the human data suggest that children may be more sensitive than adults when exposed to presumably similar phosphine concentrations. For example, in both the MMWR (1994) and Wilson et al. (1980) reports, exposed children died, but exposed adults survived. 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). When rat lethality data of 1-6-h are utilized in the derivation of the exponent for phosphine, a value of 1 is obtained. For scaling the AEGL values for phosphine for the 30-min, 1-, 4-, and 8-h time points, this empirically derived value of 1 was used as the exponent n. The 30-min AEGL-3 was also adopted as the 10-min value due to the added uncertainty of extrapolating from a 6-h time point to 10 min. The values for AEGL-3 are given in Table 10-8.

These values are considered protective since workers were repeatedly exposed for "brief" periods of time to phosphine concentrations up to 35 ppm with no life-threatening effects (Jones et al. 1964) and workers exposed to >50 ppm for 2-5 min experienced only odor (Zaebst et al. 1988).

8. SUMMARY OF AEGL VALUES

8.1. AEGL Values and Toxicity End Points

The derived AEGL values for various levels of effects and durations of exposure are summarized in Table 10-9. Appropriate data are not available for derivation of AEGL-1. AEGL-2 values were based on a red mucoid nasal discharge in rats exposed to phosphine for 6 h. A concentration causing no deaths in rats exposed to phosphine for 6 h was used for AEGL-3 calculation. It should be noted that the AEGL-2 and AEGL-3 values for phosphine are very close (AEGL-2; AEGL-3 ratio = 1.8). This reflects an extremely steep concentration-response curve for phosphine; there is little margin between nonlethal effects and death.

8.2. Comparison with Other Standards and Criteria

Several organizations have developed standards and criteria for phosphine (see Table 10-10).

8.3. Data Adequacy and Research Needs

Appropriate data from human studies are not available for phosphine. There appears to be little species variability with regard to lethality. With regard to nonlethal end points, data are equivocal and in many cases lack a concentration response-relationship.

TABLE 10-8 AEGL-3 for Phosphine (ppm [mg/m^3])

AEGL Level	10 min	30 min	1 h	4 h	8 h
AEGL-3	7.2 (10)	7.2 (10)	3.6 (5.1)	0.90 (1.3)	0.45 (0.63)

TABLE 10-9 Relational Comparison of AEGL Values for Phosphine (ppm [mg/m3])[a]

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	4.0 (5.6)	4.0 (5.6)	2.0 (2.8)	0.50 (0.71)	0.25 (0.35)
AEGL-3 (Lethality)	7.2 (10)	7.2 (10)	3.6 (5.1)	0.90 (1.3)	0.45 (0.63)

[a]The AEGL-2 and AEGL-3 values for phosphine are only 1.8-fold different from one another This closeness of AEGL tiers is reflective of the very steep concentration-response curve observed for phosphine toxicity.
NR: not recommended Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

TABLE 10-10 Extant Standards and Guidelines for Phosphine

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	4.0 ppm	4.0 ppm	2.0 ppm	0.50 ppm	0.25 ppm
AEGL-3	7.2 ppm	7.2 ppm	3.6 ppm	0.90 ppm	0.45 ppm
ERPG-1[a]			NR		
ERPG-2[a]			0.5 ppm		
ERPG-3[a]			5 ppm		
NIOSH IDLH[b]	50 ppm				
NIOSH REL[c]	0.3 ppm				
NIOSH STEL[c]	1.0 ppm				
OSHA PEL-TWA[d]					0.28 ppm
ACGIH TLV-TWA[e]					0.3 ppm
ACGIH TLV-STEL[e]	1.0 ppm				
German MAK-TWA[f]					0.1 ppm
German MAK-Peak[f]					1 ppm
Dutch MAC[g]	1.0 ppm (15 min)				0.3 ppm (8 hr)

[a]ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association) (AIHA 2002). 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-2 for phosphine is based on human experience. 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. The ERPG-3 for phosphine is based on animal lethality data and human experience.

[b]IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health) (NIOSH 2002, 2005) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms or any irreversible health effects. The IDLH for phosphine is based on acute inhalation toxicity data in humans.

[c]NIOSH REL-STEL (Recommended Exposure Limits–Short-Term Exposure Limit) (NIOSH 2002, 2005) is defined analogous to the ACGIH TLV-TWA.

[d]OSHA PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits–Time-Weighted Average) (29 CFR 1910.1000 [2002]) is defined analogous to the ACGIH-TLV-TWA but is for exposures of no more than 10 h/day, 40 h/week.

[e]ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value–Time Weighted Average) (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.

(Continued)

TABLE 10-10 Continued

[e]ACGIH TLV-STEL (American Conference of Governmental Industrial Hygienists, Threshold Limit Value–Short-Term Exposure Limit) (ACGIH 2002) is for a 15-min exposure.
[f]MAK (Maximale Argeitsplatzkonzentration [Maximum Workplace Concentration]) (DFG 2000) is defined analogous to the ACGIH-TLV-TWA.
[g]MAC (Maximaal Aanvaaarde Concentratie [Maximal Accepted Concentration]) (SDU Uitgevers 2000) is defined analogous to the ACGIH TLV-TWA.

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APPENDIX A

Derivation of AEGL-1 Values

Quantitative data regarding responses consistent with the AEGL-1 definition were not available for acute inhalation exposure to phosphine. Because of the lack of appropriate data, AEGL-1 values could not be determined. Data showing lethality in animals exposed to phosphine at concentrations below the odor threshold (1.5-200 ppm, depending on impurities) supports this decision. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 concentration is without adverse effects.

Derivation of AEGL-2 Values

Key study:	Newton et al. 1993
Toxicity end point:	Red nasal mucoid discharge in rats exposed to 10 ppm phosphine for 6 h
Scaling:	$C^1 \times t = k$ (30 min; 1, 4, and 8 h) 10 ppm × 6 h = 60 ppm·h
Uncertainty factors:	3 for interspecies variability 10 for intraspecies variability
10-min AEGL-2:	4.0 ppm (30-min value adopted as 10-min value)
30-min AEGL-2:	C × 0.5 h = 60 ppm·h C = 120 ppm 30-min AEGL-2 = 120 ppm/30 = 4.0 ppm
1-h AEGL-2:	C × 1 h = 60 ppm·h C = 60 ppm 1-h AEGL-2 = 60 ppm/30 = 2.0 ppm
4-h AEGL-2:	C × 4 h = 60 ppm·h C = 15 ppm 4-h AEGL-2 = 15 ppm/30 = 0.50 ppm
8-h AEGL-2:	C × 8 h = 60 ppm·h C = 7.5 ppm 8-h AEGL-2 = 7.5 ppm/30 = 0.25 ppm

Derivation of AEGL-3 Values

Key study:	Newton 1991
Toxicity end point:	No-effect level for death (18 ppm) in rats exposed to phosphine for 6 h
Scaling:	$C^1 \times t = k$ (30 min; 1, 4, and 8 h) 18 ppm × 6 h = 108 ppm·h
Uncertainty factors:	3 for interspecies variability 10 for intraspecies variability
10-min AEGL-3:	7.2 ppm (30-min value adopted as 10-min value)
30-min AEGL-3:	C × 0.5 h = 108 ppm·h C = 216 ppm 30-min AEGL-3 = 216 ppm/30 = 7.2 ppm
1-h AEGL-3:	C × 1 h = 108 ppm·h C = 108 ppm 1-h AEGL-3 = 108 ppm/30 = 3.6 ppm
4-h AEGL-3:	C × 4 h = 108 ppm·h C = 27 ppm 4-h AEGL-3 = 27 ppm/30 = 0.90 ppm
8-h AEGL-3:	C × 8 h = 108 ppm·h C = 13.5 ppm 8-h AEGL-3 = 13.5 ppm/30 = 0.45 ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINES FOR PHOSPHINE

Derivation Summary for Phosphine (CAS No. 7803-51-2)

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
Not Recommended	Not Recommended	Not Recommended	Not Recommended	Not Recommended

Reference: Data unavailable.

Test species/Strain/Number: Not applicable.

Exposure route/Concentrations/Durations: Not applicable.

Effects: Not applicable.

End point/Concentration/Rationale: Not applicable.

Uncertainty factors/Rationale: Not applicable.

Modifying factor: Not applicable.

Animal to human dosimetric adjustment: Not applicable.

Time scaling: Not applicable.

Data quality and research needs: Appropriate data were not available for derivation of AEGL-1 values.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
4.0 ppm	4.0 ppm	2.0 ppm	0.50 ppm	0.25 ppm

Reference: Newton, P.E., R.E. Schroeder, J.B. Sullivan, W.M. Busey, and D.A. Banas. 1993. Inhalation toxicity of phosphine in the rat: Acute, subchronic, and developmental. Inhal. Toxicol. 5(2):223-239.

Test species/Strain/Number: F344 rats/ 15/sex/concentration

Exposure route/Concentrations/Durations: Inhalation: 0, 2.5, 5.0, or 10 ppm, 6 h/day

Effects:

2.5 ppm	red mucoid nasal discharge
5.0 ppm	red mucoid nasal discharge
10 ppm	red mucoid nasal discharge (determinant for AEGL-2)

End point/Concentration/Rationale: 10 ppm, exposure was for 6 h; red mucoid nasal discharge.

Uncertainty factors/Rationale:

Total uncertainty factor: 30

Interspecies: 3—Lethality data (45 min to 30 h) for rats, mice, rabbits, and guinea pigs suggest little species variability.

(Continued)

AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
4.0 ppm	4.0 ppm	2.0 ppm	0.50 ppm	0.25 ppm

Uncertainty factors/Rationale: *(Continued)*

Intraspecies: 10—Children appear to be more sensitive than adults to the effects of phosphine. There were two case reports in which exposed children died, but adults exposed under similar conditions survived.

Modifying factor: Not applicable.

Animal to human dosimetric adjustment: None; insufficient data.

Time scaling: $C^n \times t = k$, where n = 1; empirically derived from rat lethality data from 1 to 6 h. Time scaling was employed for the 30-min, 1-, 4-, and 8-h time points. The 30-min AEGL-2 was also adopted as the 10-min value due to the added uncertainty of extrapolating from a 6-h time point to 10 min.

Data quality and research needs: Data for effects defined by AEGL-2 are limited.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
7.2 ppm	7.2 ppm	3.6 ppm	0.90 ppm	0.45 ppm

Reference: Newton, P.E. 1991. Acute Inhalation Exposures of Rats to Phosphine. Project No. 90-8271. East Millstone, NJ: Bio/Dynamics, Inc.

Test species/Strain/Sex/Number: Sprague-Dawley rats, 5/sex/concentration or 10 males/concentration.

Exposure route/Concentrations/Durations: Inhalation: 0, 1.3, 6.0, or 28 ppm for 6 h (5/sex/group); 0, 3.1, 10, or 18 ppm for 6 h (10 males/group).

Effects: Exposure was for 6 h

Concentration	Mortality
0 ppm	0/10
1.3 ppm	0/10
3.1 ppm	0/10
6.0 ppm	0/10
10 ppm	0/10
18 ppm	0/10 (determinant for AEGL-3)
28 ppm	5/10

LC_{50}: 28 ppm

End point/Concentration/Rationale: Threshold for lethality; 18 ppm, 6 h. This study was chosen because 10 animals per dose group were used and data were for exposures over a range of phosphine concentrations.

(Continued)

AEGL-3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
7.2 ppm	7.2 ppm	3.6 ppm	0.90 ppm	0.45 ppm

Uncertainty factors/Rationale:

Total uncertainty factor: 30

Interspecies: 3—Lethality data (45 min to 30 h) for rats, mice, rabbits, and guinea pigs suggest little species variability.

Intraspecies: 10—Children appear to be more sensitive than adults to the effects of phosphine. There were two case reports in which exposed children died, but adults exposed under similar conditions survived.

Modifying factor: Not applicable.

Animal to human dosimetric adjustment: Insufficient data

Time scaling: $C^n \times t = k$ where $n = 1$; empirically derived from rat lethality data from 1 to 6 h. Time scaling was employed for the 30-min, 1-, 4-, and 8-h time points. The 30-min AEGL-3 was also adopted as the 10-min value due to the added uncertainty of extrapolating from a 6-h time point to 10 min.

Data quality and research needs: Study is considered appropriate for AEGL-3 derivation since exposures are over a wide range of phosphine concentrations and utilize a sufficient number of animals.

APPENDIX C

Category Plot for Phosphine

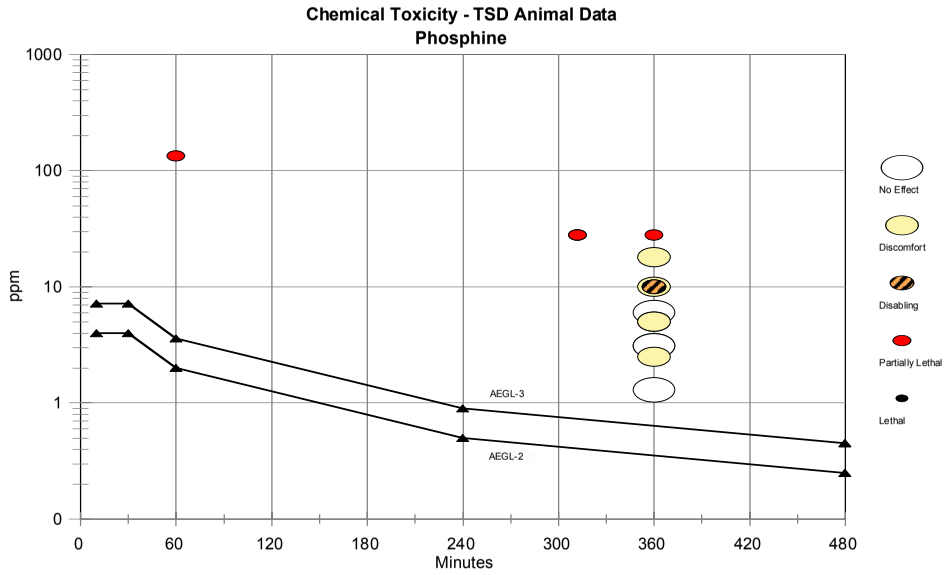

FIGURE 10-3 Category plot of animal toxicity data compared to AEGL values. Reprinted with permission; copyright 1991, Huntingon Life Sciences.

APPENDIX D

AEGL Values for Selected Metal Phosphides
Aluminum Phosphide (AlP)
Potassium Phosphide (K_3P)
Sodium Phosphide (Na_3P)
Zinc Phosphide (Zn_3P_2)
Calcium Phosphide (Ca_3P_2)
Magnesium Phosphide (Mg_3P_2)
Strontium Phosphide (Sr_3P_2)
Magnesium Aluminum Phosphide (Mg_3AlP_3)

SUMMARY

Metal phosphides are solids and are typically used as fumigants against insects and rodents in stored grain. The metal phosphides react rapidly with water and moisture in the air or stored grain to produce phosphine gas. It is the phosphine gas that is responsible for acute toxicity, and the rate of phosphine generation is dependent on ambient temperature and humidity and the chemical structure of the phosphide (Anger et al. 2000).

In the absence of appropriate chemical-specific data for the metal phosphides considered in this appendix, the AEGL-2 and AEGL-3 values for phosphine were used to obtain AEGL-2 and AEGL-3 values, respectively, for the metal phosphides. The use of phosphine as a surrogate for the metal phosphides is deemed appropriate because qualitative (clinical signs) and quantitative (phosphine blood level) data suggest that the phosphine hydrolysis product is responsible for acute toxicity from metal phosphides. The phosphine AEGL-2 and AEGL-3 values were used as target values for calculating the concentrations of metal phosphide needed to generate the phosphine AEGL values.

Because AEGL-1 values for phosphine are not recommended (due to insufficient data), AEGL-1 values for the metal phosphides considered in this appendix are also not recommended. The calculated values are listed in Table D-1 below.

D.I. INTRODUCTION

Metal phosphides are solids and are typically used as fumigants against insects and rodents in stored grain. The metal phosphides react rapidly with water and moisture in the air or stored grain to produce phosphine gas. It is the phosphine gas which is responsible for acute toxicity, and the rate of phosphine generation is dependent on ambient temperature and humidity and the chemical structure of the phosphide (Anger et al. 2000).

TABLE D-1 AEGL Values for Metal Phosphides[a]

Compound	Classification	10-min	30-min	1-hr	4-hr	8-hr
Aluminum Phosphide	AEGL-1	NR	NR	NR	NR	NR
	AEGL-2	9.5 mg/m^3	9.5 mg/m^3	4.7 mg/m^3	1.2 mg/m^3	0.59 mg/m^3
	AEGL-3	17 mg/m^3	17 mg/m^3	8.5 mg/m^3	2.1 mg/m^3	1.1 mg/m^3
Potassium Phosphide	AEGL-1	NR	NR	NR	NR	NR
	AEGL-2	24 mg/m^3	24 mg/m^3	12 mg/m^3	3.0 mg/m^3	1.5 mg/m^3
	AEGL-3	44 mg/m^3	44 mg/m^3	22 mg/m^3	5.5 mg/m^3	2.7 mg/m^3
Sodium Phosphide	AEGL-1	NR	NR	NR	NR	NR
	AEGL-2	16 mg/m^3	16 mg/m^3	8.2 mg/m^3	2.0 mg/m^3	1.0 mg/m^3
	AEGL-3	29 mg/m^3	29 mg/m^3	15 mg/m^3	3.7 mg/m^3	1.8 mg/m^3
Zinc Phosphide	AEGL-1	NR	NR	NR	NR	NR
	AEGL-2	21 mg/m^3	21 mg/m^3	11 mg/m^3	2.6 mg/m^3	1.3 mg/m^3
	AEGL-3	38 mg/m^3	38 mg/m^3	19 mg/m^3	4.8 mg/m^3	2.4 mg/m^3
Calcium Phosphide	AEGL-1	NR	NR	NR	NR	NR
	AEGL-2	15 mg/m^3	15 mg/m^3	7.5 mg/m^3	1.9 mg/m^3	0.93 mg/m^3
	AEGL-3	27 mg/m^3	27 mg/m^3	13 mg/m^3	3.4 mg/m^3	1.7 mg/m^3
Magnesium Phosphide	AEGL-1	NR	NR	NR	NR	NR
	AEGL-2	11 mg/m^3	11 mg/m^3	5.5 mg/m^3	1.4 mg/m^3	0.69 mg/m^3
	AEGL-3	20 mg/m^3	20 mg/m^3	9.9 mg/m^3	2.5 mg/m^3	1.2 mg/m^3
Strontium Phosphide	AEGL-1	NR	NR	NR	NR	NR
	AEGL-2	27 mg/m^3	27 mg/m^3	13 mg/m^3	3.3 mg/m^3	1.7 mg/m^3
	AEGL-3	48 mg/m^3	48 mg/m^3	24 mg/m^3	6.0 mg/m^3	3.0 mg/m^3
Magnesium Aluminum Phosphide	AEGL-1	NR	NR	NR	NR	NR
	AEGL-2	11 mg/m^3	11 mg/m^3	5.3 mg/m^3	1.3 mg/m^3	0.66 mg/m^3
	AEGL-3	19 mg/m^3	19 mg/m^3	9.5 mg/m^3	2.4 mg/m^3	1.2 mg/m^3

[a]These airborne concentrations will produce the equivalent AEGL values for phosphine.
Note: Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.
NR, not recommended.

Aluminum Phosphide (CAS No. 20859-73-8), Potassium Phosphide (CAS No. 20770-41-6), and Sodium Phosphide (CAS No. 12058-85-4): One mole of aluminum phosphide, potassium phosphide, or sodium phosphide will react rapidly with water or moisture to produce a maximum of 1 mole of phosphine gas as follows:

$$AlP + 3H_2O \rightarrow PH_3 + Al(OH)_3$$

$$K_3P + 3H_2O \rightarrow PH_3 + 3KOH$$

$$Na_3P + 3H_2O \rightarrow PH_3 + 3NaOH$$

Zinc Phosphide (CAS No. 1314-84-7), Calcium Phosphide (CAS No. 1305-99-3), Magnesium Phosphide (CAS No. 10257-74-8), and Strontium Phosphide (CAS No. 12504-13-1): One mole of zinc phosphide, calcium phosphide, magnesium phosphide or strontium phosphide will react rapidly with water or moisture to produce a maximum of 2 moles of phosphine gas as follows:

$$Zn_3P_2 + 6H_2O \rightarrow 2PH_3 + 3Zn(OH)_2$$

$$Ca_3P_2 + 6H_2O \rightarrow 2PH_3 + 3Ca(OH)_2$$

$$Mg_3P_2 + 6H_2O \rightarrow 2PH_3 + 3Mg(OH)_2$$

$$Sr_3P_2 + 6H_2O \rightarrow 2PH_3 + 3Sr(OH)_2$$

Magnesium Aluminum Phosphide (CAS No. None): One mole of magnesium aluminum phosphide will react rapidly with water or moisture to produce a maximum of 3 moles of phosphine gas as follows:

$$Mg_3AlP_3 + 9H_2O \rightarrow 3PH_3 + Al(OH)_3 + 3Mg(OH)_2$$

Aluminum phosphide is a gray or yellow crystalline solid prepared from red phosphorus and aluminum powder (O'Neil et al. 2001). Commercial aluminum phosphide sachets contain 70% aluminum phosphide and 30% aluminum carbonate (Bajaj et al. 1988). Calcium phosphide is a red-brown or gray solid prepared by heating calcium phosphate with aluminum or carbon by passing phosphorus vapors over metallic calcium. In addition to its use as a rodenticide, calcium phosphide is also used in signal fires and pyrotechnics and in the purification of copper and copper alloys (HSDB 2007a). Zinc phosphide is a gray solid and may be produced by passing phosphine through a solution of zinc sulfate (HSDB 2007b). Manufacturing information on the other metal phosphides considered in this appendix was not located. Available physico-chemical data for the metal phosphides are shown in Tables D-2 through D-9.

TABLE D-2 Physicochemical Data for Aluminum Phosphide

Parameter	Description/Value	Reference
Synonyms (commercial product)	Celphos, Phostoxin, Quickphos	O'Neil et al. 2001
CAS Registry No.	20859-73-8	O'Neil et al. 2001
Chemical formula	AlP	O'Neil et al. 2001
Molecular weight	57.96	O'Neil et al. 2001
Physical state	Solid, gray of yellow crystals	O'Neil et al. 2001

(Continued)

TABLE D-2 Continued

Parameter	Description/Value	Reference
Relative density (water = 1)	2.9	IPCS 1989
Melting point	>1350°C	IPCS 1989
Solubility in water	Reactive produces phosphine gas	IPCS 1989

TABLE D-3 Physicochemical Data for Potassium Phosphide

Parameter	Description/Value	Reference
CAS Registry No.	20770-41-6	ChemIDPlus 2005a
Chemical formula	K_3P	ChemIDPlus 2005a
Molecular weight	148.3	ChemIDPlus 2005a

TABLE D-4 Physicochemical Data for Sodium Phosphide

Parameter	Description/Value	Reference
Synonyms	Trisodium phosphide	ChemIDPlus 2005b
CAS Registry No.	12058-85-4	ChemIDPlus 2005b
Chemical formula	Na_3P	ChemIDPlus 2005b
Molecular weight	99.94	Lewis 1996a
Physical state	Solid, red crystals	Lewis 1996a
Melting point	Decomposes	Lewis 1996a
Solubility in water	Reacts violently	Lewis 1996a

TABLE D-5 Physicochemical Data for Zinc Phosphide

Parameter	Description/Value	Reference
Synonym	Trizinc diphosphide	IPCS 1989
CAS Registry No.	1314-84-7	IPCS 1989
Chemical formula	Zn_3P_2	IPCS 1989
Molecular weight	258.1	IPCS 1989
Physical state	Solid, gray powder or crystals	O'Neil et al. 2001
Relative density (water = 1)	4.55	O'Neil et al.2001
Melting point	Sublimes	IPCS 1989
Solubility in water	Insoluble, reacts	IPCS 1989

TABLE D-6 Physicochemical Data for Calcium Phosphide

Parameter	Description/Value	Reference
Synonyms (commercial product)	Calcium photophor, photophor	O'Neil et al. 2001
CAS Registry No.	1305-99-3	O'Neil et al. 2001
Chemical formula	Ca_3P_2	O'Neil et al. 2001

(Continued)

TABLE D-6 Continued

Parameter	Description/Value	Reference
Molecular weight	182.18	O'Neil et al. 2001
Physical state	Solid, red-brown crystals or gray lumps	O'Neil et al. 2001
Relative density (water = 1)	2.51	O'Neil et al. 2001
Melting point	1600°C	O'Neil et al. 2001
Solubility in water	Decomposes	O'Neil et al. 2001

TABLE D-7 Physicochemical Data for Magnesium Phosphide

Parameter	Description/Value	Reference
Synonyms	Trimagnesium diphosphide	IPCS 1989
CAS Registry No.	12057-74-8	IPCS 1989
Chemical formula	Mg_3P_2	IPCS 1989
Molecular weight	134.87	IPCS 1989
Physical state	Solid, gray or bright yellow crystals	IPCS 1989
Relative density (water = 1)	2.1	IPCS 1989
Melting point	>750°C	IPCS 1989
Solubility in water	Moisture sensitive, reacts	IPCS 1989

TABLE D-8 Physicochemical Data for Strontium Phosphide

Parameter	Description/Value	Reference
CAS Registry No.	12504-13-1	Lewis 1996b
Chemical formula	Sr_3P_2	Lewis 1996b
Molecular weight	324.9	Lewis 1996b
Physical state	Solid	Lewis 1996b

TABLE D-9 Physicochemical Data for Magnesium Aluminum Phosphide

Parameter	Description/Value	Reference
CAS Registry No.	None	ChemIDPlus 2005c
Chemical formula	Mg_3AlP_3	ChemIDPlus 2005c
Molecular weight	192.8	—
Physical state	Solid	ChemIDPlus 2005c

D.II. SPECIAL CONSIDERATIONS

Metabolism and Disposition

Solid metal phosphides deposited on moist respiratory tract surfaces may hydrolyze and release absorbable phosphine. However, a more likely scenario would involve atmospheric hydrolysis of metal phosphides to phosphine gas.

Chan et al. (1983) detected phosphine in postmortem stomach, blood, and liver specimens from a 27-year-old man who had ingested aluminum phosphide tablets. The phosphine was released from the samples after acid treatment. Similarly, Anger et al. (2000) identified phosphine in postmortem brain, liver, and kidneys of a 39-year-old man who had committed suicide by ingestion of aluminum phosphide tablets.

Chugh et al. (1996) measured blood phosphine levels in patients with severe (n = 30), mild (n = 10), or minimal (n = 5) toxicity due to aluminum phosphide ingestion. Patients with severe toxicity had ingested "fresh" aluminum phosphide compound and were in a state of shock. Those with mild toxicity had ingested "old" aluminum phosphide compound and presented with hypotension and gastrointestinal symptoms. Patients with minimal toxicity ingested some powder from the aluminum phosphide tablets and presented with only nausea and occasional vomiting. Blood phosphine levels were positively correlated with severity of clinical signs and to dose of pesticide. At admission, blood phosphine levels were 71% higher ($p < 0.001$) in patients in the severe toxicity group than in the mild toxicity group of patients; blood phosphine was not detected in the minimal toxicity group of patients. Blood phosphine levels were also correlated to mortality; patients having blood phosphine levels $\leq 1.067 \pm 0.16$ mg% survived, whereas those with blood phosphine above this apparent threshold died (6 of 30 in the severe toxicity group).

Garry et al. (1993) described a fatality from inhalation of aluminum phosphide aerosol In this case report, blood aluminum concentration was used as a marker of exposure (see Section 2.1.1).

Mechanism of Toxicity

Metal phosphides react rapidly with moisture in air to produce phosphine gas. It is the phosphine gas that is responsible for acute inhalation toxicity from metal phosphide exposure. The rate of phosphine generation is dependent on ambient temperature and humidity (Anger et al. 2000) in addition to the chemical structure of the metal phosphide. The hydrolysis reactions and phosphine evolution rates (OECD 2001) of the metal phosphides considered in this appendix are summarized in Table D-10.

D.III. RATIONALE AND AEGL-1

Summary of Human Data Relevant to AEGL-1

No human data are available for the derivation of AEGL-1 for the metal phosphides considered in this appendix.

TABLE D-10 Hydrolysis of Metal Phosphides

Metal Phosphide	Hydrolysis Reaction	Maximum Number of moles of phosphine produced per mole of metal phosphide hydrolyzed	Phosphine evolution rate at 20°C and 1 atm (mL/kg• min)
Aluminum Phosphide	$AlP + 3H_2O \rightarrow PH_3 + Al(OH)_3$	1	2069.7
Potassium Phosphide	$K_3P + 3H_2O \rightarrow PH_3 + 3KOH$	1	807.6
Sodium Phosphide	$Na_3P + 3H_2O \rightarrow PH_3 + 3NaOH$	1	997.8
Zinc Phosphide	$Zn_3P_2 + 6H_2O \rightarrow 2PH_3 + 3Zn(OH)_2$	2	929.9
Calcium Phosphide	$Ca_3P_2 + 6H_2O \rightarrow 2PH_3 + 3Ca(OH)_2$	2	1274.6
Magnesium Phosphide	$Mg_3P_2 + 6H_2O \rightarrow 2PH_3 + 3Mg(OH)_2$	2	1781.4
Strontium Phosphide	$Sr_3P_2 + 6H_2O \rightarrow 2PH_3 + 3Sr(OH)_2$	2	737.1
Magnesium Aluminum Phosphide	$Mg_3AlP_3 + 9H_2O \rightarrow 3PH_3 + Al(OH)_3 + 3Mg(OH)_2$	3	1865.2

Summary of Animal Data Relevant to AEGL-1

No animal data are available for the derivation of AEGL-1 for the metal phosphides considered in this appendix.

Derivation of AEGL-1

No human or animal data are consistent with the effects defined by AEGL-1. Data were also insufficient for derivation of AEGL-1 values for phosphine; thus phosphine cannot be used as a surrogate. Therefore, AEGL-1 values for the metal phosphides considered in this appendix are not recommended (Table D-11).

D.IV. RATIONALE AND AEGL-2

Summary of Human Data Relevant to AEGL-2

No human data are available for the derivation of AEGL-2 for the metal phosphides considered in this appendix.

TABLE D-11 AEGL-1 Values for Metal Phosphides

Compound	10 min	30 min	1 h	4 h	8 h
Aluminum Phosphide	NR	NR	NR	NR	NR
Potassium Phosphide	NR	NR	NR	NR	NR
Sodium Phosphide	NR	NR	NR	NR	NR
Zinc Phosphide	NR	NR	NR	NR	NR
Calcium Phosphide	NR	NR	NR	NR	NR
Magnesium Phosphide	NR	NR	NR	NR	NR
Strontium Phosphide	NR	NR	NR	NR	NR
Magnesium Aluminum Phosphide	NR	NR	NR	NR	NR

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

Summary of Animal Data Relevant to AEGL-2

No animal data are available for the derivation of AEGL-2 for the metal phosphides considered in this appendix.

Derivation of AEGL-2

In the absence of appropriate chemical-specific data for the metal phosphides considered in this appendix, the AEGL-2 values for phosphine will be used to obtain AEGL-2 values for the metal phosphides. The use of phosphine as a surrogate for the metal phosphides is deemed appropriate because qualitative (clinical signs) and quantitative (phosphine blood level) data suggest that the phosphine hydrolysis product is responsible for acute toxicity from metal phosphides. The phosphine AEGL-2 values will be used as target values for calculating the concentrations of metal phosphide needed to generate the phosphine AEGL values. Calculations were done using the methodology in NRC (2001) and are for 25 degrees C and 760 mm Hg. The metal phosphide values for AEGL-2 are given in Table D-12.

D.V. RATIONALE AND AEGL-3

Summary of Human Data Relevant to AEGL-3

No human data are available for the derivation of AEGL-3 for the metal phosphides considered in this appendix.

Summary of Animal Data Relevant to AEGL-3

No animal data are available for the derivation of AEGL-3 for the metal phosphides considered in this appendix.

TABLE D-12 AEGL-2 Values For Metal Phosphides[a]

Compound	10-min	30-min	1-hr	4-hr	8-hr
Aluminum Phosphide	9.5 mg/m^3	9.5 mg/m^3	4.7 mg/m^3	1.2 mg/m^3	0.59 mg/m^3
Potassium Phosphide	24 mg/m^3	24 mg/m^3	12 mg/m^3	3.0 mg/m^3	1.5 mg/m^3
Sodium Phosphide	16 mg/m^3	16 mg/m^3	8.2 mg/m^3	2.0 mg/m^3	1.0 mg/m^3
Zinc Phosphide	21 mg/m^3	21 mg/m^3	11 mg/m^3	2.6 mg/m^3	1.3 mg/m^3
Calcium Phosphide	15 mg/m^3	15 mg/m^3	7.4 mg/m^3	1.9 mg/m^3	0.93 mg/m^3
Magnesium Phosphide	11 mg/m^3	11 mg/m^3	5.5 mg/m^3	1.4 mg/m^3	0.69 mg/m^3
Strontium Phosphide	27 mg/m^3	27 mg/m^3	13 mg/m^3	3.3 mg/m^3	1.7 mg/m^3
Magnesium Aluminum Phosphide	11 mg/m^3	11 mg/m^3	5.3 mg/m^3	1.3 mg/m^3	0.66 mg/m^3

[a]These airborne concentrations will produce the equivalent AEGL values for phosphine.

Derivation of AEGL-3

In the absence of appropriate chemical-specific data for the metal phosphides considered in this appendix, the AEGL-3 values for phosphine will be used to obtain AEGL-3 values for the metal phosphides. The use of phosphine as a surrogate for the metal phosphides is deemed appropriate because qualitative (clinical signs) and quantitative (phosphine blood level) data suggest that the phosphine hydrolysis product is responsible for acute toxicity from metal phosphides. The phosphine AEGL-3 values will be used as target values for calculating the concentrations of metal phosphide needed to generate the phosphine AEGL values. Calculations were done using the methodology in NRC (2001) and are for 25 degrees C and 760 mm Hg. The metal phosphide values for AEGL-3 are given in Table D-13.

D.VI. Comparison with Other Standards and Criteria

No other exposure criteria or guidelines were located for the metal phosphides.

TABLE D-13 AEGL-3 Values for Metal Phosphides[a]

Compound	10-min	30-min	1-hr	4-hr	8-hr
Aluminum Phosphide	17 mg/m^3	17 mg/m^3	8.5 mg/m^3	2.1 mg/m^3	1.1 mg/m^3
Potassium Phosphide	44 mg/m^3	44 mg/m^3	22 mg/m^3	5.5 mg/m^3	2.7 mg/m^3
Sodium Phosphide	29 mg/m^3	29 mg/m^3	15 mg/m^3	3.7 mg/m^3	1.8 mg/m^3
Zinc Phosphide	38 mg/m^3	38 mg/m^3	19 mg/m^3	4.8 mg/m^3	2.4 mg/m^3
Calcium Phosphide	27 mg/m^3	27 mg/m^3	13 mg/m^3	3.4 mg/m^3	1.7 mg/m^3
Magnesium Phosphide	20 mg/m^3	20 mg/m^3	9.9 mg/m^3	2.5 mg/m^3	1.2 mg/m^3
Strontium Phosphide	48 mg/m^3	48 mg/m^3	24 mg/m^3	6.0 mg/m^3	3.0 mg/m^3
Magnesium Aluminum Phosphide	19 mg/m^3	19 mg/m^3	9.5 mg/m^3	2.4 mg/m^3	1.2 mg/m^3

[a]These airborne concentrations will produce the equivalent AEGL values for phosphine.