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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 11

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Preface

Extremely hazardous substances (EHSs)[2] can be released accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars and trucks transporting EHSs. Workers and residents in communities surrounding industrial facilities where EHSs are manufactured, used, or stored and in communities along the nation's railways and highways are potentially at risk of being exposed to airborne EHSs during accidental releases or intentional releases by terrorists. Pursuant to the Superfund Amendments and Reauthorization Act of 1986, the U.S. Environmental Protection Agency (EPA) has identified approximately 400 EHSs on the basis of acute lethality data in rodents.

As part of its efforts to develop acute exposure guideline levels for EHSs, EPA and the Agency for Toxic Substances and Disease Registry (ATSDR) in 1991 requested that the National Research Council (NRC) develop guidelines for establishing such levels. In response to that request, the NRC published *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* in 1993. Subsequently, *Standard Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Substances* was published in 2001, providing updated procedures, methodologies, and other guidelines used by the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances and the Committee on Acute Exposure Guideline Levels (AEGLs) in developing the AEGL values.

Using the 1993 and 2001 NRC guidelines reports, the NAC—consisting of members from EPA, the Department of Defense (DOD), the Department of Energy (DOE), the Department of Transportation (DOT), other federal and state governments, the chemical industry, academia, and other organizations from the private sector—has developed AEGLs for more than 270 EHSs.

In 1998, EPA and DOD requested that the NRC independently review the AEGLs developed by NAC. In response to that request, the NRC organized within its Committee on Toxicology (COT) the Committee on Acute Exposure Guideline Levels, which prepared this report. This report is the eleventh volume in that series. AEGL documents for bis-chloromethyl ether, chloromethyl

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

methyl ether, chlorosilanes, nitrogen oxides, and vinyl chloride are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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

The five interim reports of the committee that led to this report were reviewed in draft form by individuals selected for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of the five committee interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for bis-chloromethyl ether (interim reports 18 and 19a), chloromethyl methyl ether (interim reports 11, 18, and 19a), chlorosilanes (interim reports 18 and 19a), nitrogen oxides (interim reports 15, 18, and 19a), and vinyl chloride (interim reports 16, 18, and 19a): Deepak Bhalla (Wayne State University), Harvey Clewell (The Hamner Institutes for Health Sciences), Sidney Green, Jr. (Howard University), A. Wallace Hayes (Harvard School of Public Health), Rogene Henderson (Lovelace Respiratory Research Institute [retired]), Sam Kacew (University of Ottawa), James McDougal (Wright State University [retired]), Charles Reinhardt (DuPont Haskell Laboratory [retired]), Andrew Salmon (California Environmental Protection Agency), Joyce Tsuji (Exponent, Inc.), and Judith Zelikoff (New York University).

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of this volume before its release. The review of interim report 11 was overseen by Rakesh Dixit (MedImmune/AstraZeneca Biologics, Inc.), and interim reports 15, 16, 18, and 19a were overseen by Robert Goyer (University of Western Ontario [retired]). Appointed by the NRC, they were responsible for making certain that an independent examination of the interim reports was carried out in accordance with institutional

procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The committee gratefully acknowledges the valuable assistance provided by the following persons: Ernest Falke and Iris A. Camacho (both from EPA) and George Rusch (Risk Assessment and Toxicology Services). The committee also acknowledges Susan Martel, the project director for her work this project. Other staff members who contributed to this effort are James J. Reisa (director of the Board on Environmental Studies and Toxicology), Radiah Rose (manager of editorial projects), Mirsada Karalic-Loncarevic (manager of the Technical Information Center), and Tamara Dawson (program associate). Finally, I 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

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 11

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

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

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

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

As a first step in assisting the LEPCs, EPA identified approximately 400 EHSs largely on the basis of their immediately dangerous to life and health values, developed by the National Institute for Occupational Safety or Health. 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 (NASA) (NRC 1968, 1972, 1984a,b,c,d, 1985a,b, 1986a, 1987, 1988, 1994, 1996a,b, 2000a, 2002a, 2007a, 2008a). COT has also published guidelines for developing emergency exposure guidance levels for military personnel and for astronauts (NRC 1986b, 1992, 2000b). Because of COT's experience in recommending emergency exposure levels for short-term exposures, in 1991 EPA and ATSDR requested that COT develop criteria and methods for developing emergency exposure levels for EHSs for the general population. In response to that request, the NRC assigned this project to the COT Subcommittee on Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. The report of that subcommittee, *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993), provides step-by-step guidance for setting emergency exposure levels for EHSs. Guidance is given on what data are needed, what data are available, how to evaluate the data, and how to present the results.

In November 1995, the National Advisory Committee (NAC)[1] for Acute Exposure Guideline Levels for Hazardous Substances was established to identify, review, and interpret relevant toxicologic and other scientific data and to develop acute exposure guideline levels (AEGLs) for high-priority, acutely toxic chemicals. The NRC's previous name for acute exposure levels—community emergency exposure levels (CEELs)—was replaced by the term AEGLs to reflect the broad application of these values to planning, response, and prevention in the community, the workplace, transportation, the military, and the remediation of Superfund sites.

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

[1]NAC completed its chemical reviews in October 2011. The committee was composed of members from EPA, DOD, many other federal and state agencies, industry, academia, and other organizations. From 1996 to 2011, the NAC discussed over 300 chemicals and developed AEGLs values for at least 272 of the 329 chemicals on the AEGLs priority chemicals lists. Although the work of the NAC has ended, the NAC-reviewed technical support documents are being submitted to the NRC for independent review and finalization.

sure periods (10 min, 30 min, 1 h, 4 h, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as ppm [parts per million] or mg/m^3 [milligrams per cubic meter]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

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

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

As described in *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993) and the NRC guidelines report *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals* (NRC 2001a), the first step in establishing AEGLs for a chemical is to collect and review all relevant published and unpublished information. Various types of evidence are assessed in establishing AEGL values for a chemical. These include information from (1) chemical-physical characterizations, (2) structure-activity relationships, (3) in vitro toxicity studies, (4) animal toxicity studies, (5) controlled human studies, (6) observations of humans involved in chemical accidents, and (7) epidemiologic studies. Toxicity data from human studies are most applicable and are used when available in preference to data from animal studies and in vitro studies. Toxicity data from

inhalation exposures are most useful for setting AEGLs for airborne chemicals because inhalation is the most likely route of exposure and because extrapolation of data from other routes would lead to additional uncertainty in the AEGL estimate.

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

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

REVIEW OF AEGL REPORTS

As NAC began developing chemical-specific AEGL reports, EPA and DOD asked the NRC to review independently the NAC reports for their scientific validity, completeness, and consistency with the NRC guideline reports (NRC 1993, 2001a). The NRC assigned this project to the COT Committee on Acute Exposure Guideline Levels. The committee has expertise in toxicology, epidemiology, occupational health, pharmacology, medicine, pharmacokinetics, industrial hygiene, and risk assessment.

The AEGL draft reports were initially prepared by ad hoc AEGL development teams consisting of a chemical manager, chemical reviewers, and a staff scientist of the NAC contractors—Oak Ridge National Laboratory and subsequently Syracuse Research Corporation. The draft documents were then reviewed by NAC and elevated from "draft" to "proposed" status. After the AEGL documents were approved by NAC, they were published in the *Federal Register* for public comment. The reports were 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 committee 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 ten reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009, 2010a,b, 2011). This report is the eleventh volume in that series. AEGL documents for bis-chloromethyl ether, chloromethyl methyl ether, chlorosilanes, nitrogen oxides, and vinyl chloride are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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Appendixes

1

bis-Chloromethyl Ether[1]

Acute Exposure Guideline Levels

PREFACE

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

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, 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 or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory

[1]This document was prepared by the AEGL Development Team composed of Sylvia Milanez (Oak Ridge National Laboratory), Mark Follansbee (Syracuse Research Corporation), and Chemical Manager Ernest V. Falke (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 guidelines reports (NRC 1993, 2001).

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

SUMMARY

bis-Chloromethyl ether (BCME) is a synthetic chemical that is a severe respiratory, eye, nose, and skin irritant that can lead to pulmonary edema and congestion, corneal necrosis, dyspnea, and death. Chronic occupational exposure has caused small-cell lung carcinoma, which has a histology distinct from smoking-associated lung cancer and a shorter latency period. The U.S. Environmental Protection Agency (EPA) classifies BCME as a human carcinogen based on sufficient human carcinogenicity data, and the Occupational Safety and Health Administration (OSHA) federal regulations limit its use, storage, and handling to controlled areas.

AEGL-1 values were not recommended for BCME because effects exceeding the severity of AEGL-1 occurred at concentrations that did not produce sensory irritation in humans or animals.

The AEGL-2 was based on a study in which rats were exposed for 7 h to BCME at a concentration of 0.7, 2.1, 6.9, or 9.5 ppm and hamsters were exposed for 7 h to BCME at 0.7, 2.1, 5.6, or 9.9 ppm, followed by lifetime observation (Drew et al. 1975). All groups of treated rats had increased lung-to-body weight ratios, indicative of respiratory lesions, which were considered irreversible because they were seen after lifetime observation. There also was an increased incidence of tracheal epithelial hyperplasia in rats and of pneumonitis in hamsters at 0.7 ppm, and both species had increased mortality and lung lesions

at ≥2.1 ppm. The lowest concentration tested was a lowest-observed-adverse-effect level (LOAEL) for irreversible respiratory-tract lesions, and an adjustment factor of 3 was applied to estimate a no-observed-adverse-effect level (NOAEL) of 0.23 ppm. This point-of-departure is supported by two other experiments by Drew et al. (1975) that had similar LOAELs for irreversible or serious lung lesions. No data were available from which to determine the BCME concentration-time relationship to derive AEGL-2 values for time periods other than 7 h. ten Berge et al. (1986) showed that the concentration-time relationship for many irritant and systemically acting vapors and gases can be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. To obtain protective AEGL-2 values, scaling across time was performed using n = 3 when extrapolating to shorter time points than 7 h and n = 1 when extrapolating to longer time points than 7 h. The 10-min values were not extrapolated because of unacceptably large inherent uncertainty; the 30-min value were adopted for the 10-min value to be protective of human health. A total uncertainty factor of 10 was used. An uncertainty factor of 3 was applied for interspecies extrapolation because BCME caused a similar toxic response in two species at the same test concentration in the key study and is expected to cause toxicity similarly in human lung. An uncertainty factor of 3 was applied for intraspecies variability as recommended by NRC (2001) for chemicals with a steep dose-response relationship, because the effects are unlikely to vary greatly among humans. Using the intraspecies default uncertainty factor of 10 would reduce the 4- and 8-h AEGL-2 values to below 0.010 ppm, which was shown to be a no-effect level from 129 exposures in rats and mice (Leong et al. 1981).

AEGL-3 values were derived from the single-exposure scenario of a study in which rats and hamsters were received 1, 3, 10, or 30 six-hour exposures to BCME at 1 ppm, and observed for a lifetime (Drew et al. 1975). After one exposure, rats and hamsters had slightly increased incidences of lung lesions, whereas three exposures produced lung lesions and increased mortality. This study was chosen because it had the highest BCME concentration that caused no mortality after lifetime observation. Because no data were available from which to determine the BCME concentration-time relationship, scaling across time was performed as for AEGL-2 values, using n = 3 and n = 1 for durations shorter and longer, respectively, than 6 h. The 10-min values were set equal to the 30-min values to be protective of human health. A total uncertainty factor of 10 was used. An uncertainty factor of 3 was applied for interspecies extrapolation because the no-observed-effect level (NOEL) for lethality was the same in two species in the key study, and lethality is expected to occur by a similar mode of action in humans and animals. An uncertainty factor of 3 was applied for intraspecies variability as recommended by NRC (2001) for chemicals with a steep dose-response relationship, as the effects are unlikely to vary greatly among humans. AEGLs values are summarized in Table 1-1 below.

An inhalation cancer slope factor for BCME was derived by EPA (2002). It was used to calculate the concentration of BCME associated with a 1×10^{-4} cancer risk from a single exposure for 10 min to 8 h, as shown in Appendix B,

and in Table 1-2 below. The concentrations are similar to the AEGL-2 values for exposures ≤1 h, but are up to 5-fold lower than AEGL-2 values for exposures of 4-8 h. The carcinogenic end points were not considered appropriate for AEGL derivation because the data did not show that tumor formation could result from a single exposure. Additionally, a direct comparison of BCME cancer risk and AEGL values is of unknown validity because the two sets of numbers are calculated using different methodologies (the cancer risk calculation involves a linear extrapolation from 25,600 days to 0.5 to 8 h whereas the calculation of AEGL values involves extrapolation from a single 7-h exposure using either n = 3 or n = 1, and different uncertainties are addressed by the two methods). The estimated cancer risks associated with the AEGL-2 and AEGL-3 values are shown in Table 1-2.

TABLE 1-1 Summary of AEGL Values for bis-Chloromethyl Methyl Ether

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR[a]	NR	NR	NR	NR	
AEGL-2 (disabling)	0.055 ppm (0.26 mg/m^3)	0.055 ppm (0.26 mg/m^3)	0.044 ppm[b] (0.21 mg/m^3)	0.028 ppm[b] (0.13 mg/m^3)	0.020 ppm[b] (0.095 mg/m^3)	NOAEL for irreversible lung lesions in rats and hamsters (Drew et al. 1975)
AEGL-3 (lethal)	0.23 ppm[b] (1.1 mg/m^3)	0.23 ppm[b] (1.1 mg/m^3)	0.18 ppm[b] (0.86 mg/m^3)	0.11 ppm[b] (0.52 mg/m^3)	0.075 ppm[b] (0.36 mg/m^3)	Lethality NOEL for rats and hamsters (Drew et al. 1975)

[a]Not recommended (effects exceeding the severity of AEGL-1 effects occurred at concentrations that did not produce sensory irritation in humans or animals).
[b]These concentrations are estimated to have a cancer risk greater than 1×10^{-4}, on the basis of an inhalation cancer slope factor derived by EPA (2002).

TABLE 1-2 Estimated Cancer Risks Associated with a Single Exposure to bis-Chloromethyl Ether

Exposure	10 min	30 min	1 h	4 h	8 h
BCME concentration:	Not calculated	0.069 ppm	0.035 ppm	0.0086 ppm	0.0043 ppm
Estimated cancer risk:		1.0×10^{-4}	1.0×10^{-4}	1.0×10^{-4}	1.0×10^{-4}
AEGL-2 value:	0.055 ppm	0.055 ppm	0.044 ppm	0.028 ppm	0.020 ppm
Estimated cancer risk:	Not calculated	8.0×10^{-5}	1.3×10^{-4}	3.3×10^{-4}	4.7×10^{-4}
AEGL-3 value:	0.23 ppm	0.23 ppm	0.18 ppm	0.11 ppm	0.075 ppm
Estimated cancer risk:	Not calculated	3.3×10^{-4}	5.1×10^{-4}	1.3×10^{-3}	1.7×10^{-3}

1. INTRODUCTION

BCME is a colorless, flammable liquid with a "suffocating" and irritating odor (O'Neil et al. 2001; NTP 2011). It is used industrially as a chloromethylating agent in the manufacture of ion-exchange resins, bactericides, pesticides, dispersing agents, water repellants, solvents for industrial polymerization reactions, and flame-proofing agents (O'Neil et al. 2001; NTP 2011). BCME is a contaminant (≤10%) of the related and similarly used chemical, chloromethyl methyl ether (CMME) (Langner 1977). BCME does not occur naturally, and human exposure by inhalation is limited to occupational settings. BCME is produced by saturating a paraformaldehyde solution with cold sulfuric acid and hydrochloric acid (HCl) (IARC 1974). A low yield (~0.01-0.001%) of BCME has been shown to form spontaneously from the commonly used chemicals HCl and formaldehyde; for example, mixtures of 500-5,000 ppm each of HCl and formaldehyde produced BCME at <0.5-179 ppb (Kallos and Solomon 1973; Frankel et al. 1974; Albert et al. 1982; Sellakumar et al. 1985).

BCME is hydrolyzed to HCl and formaldehyde upon contact with water, where it is believed to exist in equilibrium with its hydrolysis products, with about 20% of the original compound (Van Duuren et al. 1972). The BCME half-life in water is 10-60 seconds (sec) at 20°C (Van Duuren et al. 1972; Tou and Kallos 1974). In humid air, at ambient temperature and 81% relative humidity, BCME is more stable, having a half-life of 7-25 h depending on the surface coating of the container (Tou and Kallos 1974). Collier (1972) reported that BCME at 10 and 100 ppm was stable for at least 18 h in air with 70% relative humidity. Frankel et al. (1974) also found BCME was stable for 18 h in a Saran bag containing moist air (40% relative humidity, 24°C).

BCME vapor is a severe respiratory, eye, nose, and skin irritant, and has caused pulmonary edema and congestion, corneal necrosis, dyspnea, and blood-stained sputum in humans (O'Neil et al. 2001). BCME is an alkylating agent and has been shown to react in vitro with guanine and adenine of calf thymus DNA (Goldschmidt et al. 1975). BCME and CMME were recognized as potent human respiratory carcinogens in the early 1970s, prompting facilities to develop hermetically isolated systems for their use (Travenius 1982; Collingwood et al. 1987). In 1973, BCME and CMME were listed by OSHA as part of the first group of chemicals to be restricted by federal regulations because of their human carcinogenicity. The use, storage, and handling of preparations containing BCME at ≥0.1% (by weight or volume) must be in a controlled area (29 CFR 1910.1008 [1996]). BCME is classified as a human carcinogen by EPA, the American Conference of Governmental Hygienists (ACGIH), the International Agency for the Research on Cancer (IARC), and the National Institute of Occupational Safety and Health (NIOSH).

As of 1982, BCME is no longer produced as a commercial product in the United States. Small amounts may be produced or repackaged as a chemical intermediate or laboratory chemical, and it might be inadvertently released

during industrial operations (HSDB 2005). Five U.S. suppliers and three non-U.S. suppliers of BCME were identified in 2005 (ChemSources 2005). Selected chemical and physical properties of BCME are listed in Table 1-3.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Exposure to BCME at 100 ppm for 1-2 min might produce fatal lung injury, whereas a concentration of 100 ppm would incapacitate a person in a few seconds (Flury and Zernik 1931).

Thiess et al. (1973) reported a case of a chemical laboratory worker who died after being splashed from an explosive reaction formed when aluminum chloride was added to a reactor that contained BCME in methylene chloride. The worker developed severe conjunctival irritation, corneal opacity, facial-skin irritation, and second and third degree burns on parts of his body within hours of exposure. His optic nerve atrophied and he developed double pneumonia which progressed into pulmonary fibrosis that resulted in death. BCME concentrations were not measured.

TABLE 1-3 Chemical and Physical Data for bis-Chloromethyl Ether

Parameter	Value	Reference
Synonyms	BCME; bis-CME; chloromethyl ether; dichlorodimethyl ether; oxybis(chloromethane); dichloromethyl ether	NIOSH 2005
CAS registry no.	542-88-1	NIOSH 2005
Chemical formula	$(CH_2Cl)_2O$	NIOSH 2005
Structure	O(CCl)CCl	NIOSH 2005
Molecular weight	114.96	O'Neil et al. 2001
Physical state	Colorless liquid	O'Neil et al. 2001
Melting point	-41.5°C	HSDB 2005
Boiling point	106°C	O'Neil et al. 2001
Density (water = 1)	1.315 at 20/4°C	O'Neil et al. 2001
Vapor density	4.0 (air = 1)	HSDB 2005
Solubility in water	Decomposes to HCl and formaldehyde	O'Neil et al. 2001
Vapor pressure	30 mm Hg at 22°C	HSDB 2005
Flammability limits (volume % in air)	Flash point <23°C; estimated lower explosives limit = 6.5%; estimated upper explosives limit = 21.9%	AIHA 2000; NIOSH 2005
Conversion factors	1 mg/m^3 = 0.21 ppm; 1 ppm = 4.75 mg/m^3	HSDB 2005

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold and Awareness

BCME has a "suffocating" odor (O'Neil et al. 2001). A several-hour exposure to a concentration of BCME (specified only as <3 ppm) did not reach the threshold of perception, but caused severe eye damage several hours after exposure ceased (Travenius 1982). Leong et al. (1971) stated that BCME is a health risk at concentrations that do not produce sensory irritation.

Travenius (1982) reported that the highest tolerable concentration of BCME in air is 5 ppm. BCME was found to be distinctly irritating at 3 ppm (Flury and Zernik 1931).

The data were not adequate to derive a level-of-distinct-odor awareness according to the guidance of van Doorn et al. (2002).

2.2.2. Occupational Exposure

Thirteen accidental exposures to unknown concentrations of BCME occurred from leaking pipes or vessels in a German chemical plant (Thiess et al. 1973). Two of the exposures resulted in severe chemical burns of the cornea that did not completely heal, and some local skin burning. The other 11 exposures were milder, resulting in short-term irritation of the upper respiratory tract, headaches, and nausea. It was not reported whether there was simultaneous exposure to other airborne chemicals.

An overall 8-h time-weighted average concentration for BCME of 0.34 ppb (quarterly range of 0.01-3.1 ppb) was measured for seven workers in an anion exchange plant between 1972 and 1975 (Langner 1977). CMME containing up to 10% BCME was used in closed systems of the plant. No cases of oat-cell respiratory cancer were reported in workers at the plant over its 27 years of operation.

Unwin and Groves (1996) detected BCME at concentrations of 0.03-15.4 ppb at three industrial plants in the United Kingdom. Air samples were taken near reaction vessels where BCME formation was anticipated, and from the continuous online air sampling system. No irritation or other toxicity were reported in the workers, although health effects were not specifically addressed in the study.

Studies in which BCME exposure was associated with respiratory cancer are described in Section 2.5.

2.3. Neurotoxicity

No studies reporting neurotoxic effects of BCME in humans were found.

2.4. Developmental/Reproductive Effects

No developmental or reproductive human studies with BCME were found.

2.5. Genotoxicity

The incidence of chromosomal aberrations was greater in the peripheral lymphocytes of workers exposed to BCME during the manufacture of ion-exchange resins than in control workers (Sram et al. 1983, 1985). The frequency of aberrations was not related to the years of exposure (1-10 years), but was related to the calculated BCME exposure during the last 3 months.

An 11-fold increase in the frequency of transformed cells occurred in human lung WI-38 cells cultured with BCME at 0.008-25 milligrams per milliliter (mg/mL) in the presence of exogenous activation (Styles 1978). Human neonatal foreskin fibroblasts had a 3-14 fold increase in anchorage-independent cells after incubation with BCME at 0.1-8 micrograms per milliliter (μg/mL) (Kurian et al. 1990).

DNA repair was increased in human skin fibroblasts exposed to BCME at ≥0.16 μg/mL, although the quantitative response was not provided (Agrelo and Severn 1981).

2.6. Carcinogenicity

BCME is classified as a human carcinogen by EPA, ACGIH, IARC, and NIOSH. EPA (2002) places BCME in classification A ("human carcinogen") on the basis of sufficient human carcinogenicity data. ACGIH (1991) places BCME in group A1 ("confirmed human carcinogen"), IARC (1987) places it in Group I ("sufficient evidence of carcinogenicity in humans"), and NIOSH (2005) states that BCME is a carcinogen, with no further classification.

2.6.1. Case Reports

Reznik et al. (1977) reported a case of a chemist who developed bronchial adenocarcinoma and died 12 years after over 2 years of work on an experiment in which BCME and CMME were reaction byproducts. Air concentrations of BCME or CMME were unknown but the chemical reaction with triphenyl hydroxymethyl phosphonium chloride was conducted "on a scale of 1-2 mol."

Three workers from a small BCME manufacturing facility in the United Kingdom died from lung cancer (Roe 1985). The exposure concentrations and the total number of men exposed were not given, but it was stated that "between 5 and 8 individuals were employed at any one time on a process involving a chloromethylation stage." The ages of the men at diagnosis were 35-40 years.

Two of the 3 men had oat-cell carcinoma, and the third had anaplastic squamous-cell carcinoma.

Two cases of small-cell lung cancer were attributed to BCME exposure in a Japanese manufacturing facility (Fujio et al. 1986). BCME concentration was not reported. Each case involved a male smoker of approximately 50 years old. One worker was exposed to BCME for 2 years and the other for 8 years. The latter worker died within a year after diagnosis despite treatment with radiation and chemotherapy; the other worker seemingly recovered.

2.6.2. Epidemiologic Studies

In 1972, four workers at a California chemical plant (Diamond Shamrock Co., Redwood City) with 100-200 workers exposed to BCME from anion-exchange resin production died from lung cancer, and two more workers developed lung cancer (Donaldson and Johnson 1972; Fishbein 1972). The ages of the workers at death were 31-48. The concentration of BCME in the air was not reported. One of the workers that died, a 32-year old man, worked at the plant only 2 years. Subsequent cytologic analysis of exfoliated cells in the sputum of 125 current white male employees found a significant association between abnormal cytology (metaplasia and atypia) and exposure to BCME for more than 5 years (34% of anion-exchange workers vs. 11% of controls), whereas there was no difference between in-plant workers not involved in anion-exchange resin production and controls (Lemen et al. 1976). In concert with this cytology survey, a retrospective cohort study of 136 men who worked in the plant for 5 or more years between Jan. 1, 1955 and Mar. 31, 1972 (mean exposure was 10 years) was conducted. During this 17-year period, nine workers died: five from heart disease, one from lymphosarcoma, and three from bronchogenic cancer. Two more workers were diagnosed with bronchogenic cancer. The five cases among 136 workers represented a 9-fold increase in lung cancer from the expected mortality rate of 0.54 cases in white, age-matched men from Connecticut. The histologic type of carcinoma in four of five cases was small-cell undifferentiated carcinoma (the fifth case was large-cell undifferentiated carcinoma). The mean latency period was 15 years and the mean age of the cancer patients was 47 years, the majority of whom were smokers. The majority (>60%) of the workers were followed for less than 10 years after exposure, suggesting that the actual cancer incidence might have been greater.

Five of 32 workers exposed to unreported concentrations of BCME in a Japanese dyestuff factory for 4-7 years during 1955-1970 died of lung cancer, compared with the expected incidence of 0.024 (Sakabe 1973). One of the five cases was confirmed as being of the oat-cell carcinoma type. The latency period was 8-14 years after initial exposure. The men were smokers and their ages were 37-47 at the time of death. A subsequent epidemiologic study of this and a second Japanese dyestuff factory where BCME was manufactured and used

between 1960 and 1968, found a total of 13 cases of lung cancer among 35 exposed men at the two factories (Nishimura et al. 1990). The overall mean exposure period was 7.2 years, the latency period was 13.5 years, and age at death was 46.1 years. The histologic types of the eight cases not previously described by Sakabe (1973) were: small-cell carcinoma in five cases, adenoma in three cases, and large-cell carcinoma in one case.

In a retrospective study for years 1956-1962, Thiess et al. (1973) reported that six of 18 testing facility workers and two of 50 production workers developed lung cancer after 6-9 years of exposure to BCME at unknown concentrations. Most of the workers were smokers. The tumor latency period was 8-16 years. Five of the eight cases were diagnosed as oat-cell carcinomas.

Air concentrations of BCME, but not CMME, were measured in a factory in Chauny, France, that used CMME to produce anion exchange resins (because BCME is more stable) (Gowers et al. 1993). This study is described in greater detail in the technical support document for CMME (see Chapter 2 of this report). For 1979-1984, mean yearly concentrations of BCME were found to be 0.6-4.4 ppb (1.7 ppb, overall weighted average) by mass spectrometry of personal and stationary air samples (n = 96-175 per year). Workers exposed previously to much higher BCME concentrations had an increased incidence of lung cancer with small-cell histology relative to nonexposed workers.

Xue et al. (1988) reported the results of an epidemiologic investigation of lung cancer incidence in a cohort of 915 workers (534 men, 381 women) in 11 plants in China that produced or used "chloromethylether (CME)." It was not clear whether exposure was to BCME or CMME or both. The concentration of chloromethyl in the air was not measured. Between 1958 and 1981, there were 32 mortalities, 15 from lung cancer. Of the 11 cases evaluated histologically, eight were undifferentiated cell carcinoma and three were squamous cell carcinoma. The average age at death was 49.7 (32-64), and the mean interval from beginning of exposure to diagnosis was 9.86 years (2-20). Calculation of standard mortality ratios using various reference cohorts showed that the excess of deaths from all causes and all cancers were from increased lung cancer mortality. The number of lung cancer cases increased with exposure severity, which was estimated from the degree of irritation, job description, and duration of exposure. Heavy smoking was associated with increased lung cancer.

2.7. Summary

No quantitative human studies of BCME were found in which the exposure duration, concentration, and corresponding observed effects were reported. BCME caused severe eye damage and workers developed lung tumors from exposure concentrations that did not produce sensory irritation. The lung cancers had a shorter latency period and histology distinct from tumors from cigarette smoking. BCME is one of the most potent known human (and animal) carcinogens, and is classified as a human carcinogen by EPA, ACGIH, IARC,

and NIOSH. No human developmental or reproductive toxicity studies of BCME were found. An increased incidence of chromosomal aberrations was found in peripheral lymphocytes of workers exposed to BCME, and BCME induced cell transformation and DNA repair in vitro. A summary of semi-quantitative inhalation exposure studies of BCME is provided in Table 1-4.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

In a range-finding study, a 4-h exposure to a nominal concentration of BCME at 7.8 ppm caused death in one of six male albino rats on day 14, and 15.6 ppm caused deaths in all six test rats on days 2, 4, and 7 (Union Carbide 1968; Smyth et al. 1969). The LC_{50} (lethal concentration, 50% lethality) was reported to be 10.26 ppm. Animals that died had lung hemorrhage and blood in the intestines, and survivors had morphologic lung changes described as "consolidated" or "greatly enlarged" areas. Exposure to "substantially" saturated vapor (~40,000 ppm at saturation) caused irritation and prostration by 3 min, and killed six of six rats within 8 min (Union Carbide 1968).

TABLE 1-4 Summary of Human Exposure Data with Defined Concentrations to bis-Chloromethyl Ether

Exposure Concentration	Exposure Duration	Results (Reference)
0.01-3.1 ppb	≤27 years	No effects from occupational exposure (Langner 1977)
0.03-15.4 ppb	Years	No effects reported at three industrial plants (Unwin and Groves 1996)
0.6-4.4 ppb	Years	No sensory effects reported; workers developed oat-cell carcinoma but were previously exposed to much higher BCME levels (Gowers et al. 1993)
<3 ppm	Unknown (short-term)	Did not reach the threshold of perception but caused severe eye damage several hours after exposure ceased (Travenius 1982)
3 ppm	Unknown (short-term)	Distinctly irritating (Flury and Zernik 1931)
5 ppm	Unknown (momentary)	Highest "tolerable" concentration (Travenius 1982)
100 ppm	Few seconds	Would incapacitate a person (Flury and Zernik 1931)
100 ppm	1-2 min	Might produce fatal lung injury (Flury and Zernik 1931)

In another study, all 12 test rats died after 3 min of inhaling air saturated with BCME (~40,000 ppm) (Zeller and Hoffmann 1973). The animals had mucous membrane irritation, milky opacity of the cornea, narcosis, and dyspnea.

Drew et al. (1975) conducted three sets of experiments to evaluate the inhalation toxicity of BCME in male Sprague-Dawley rats. The acute lethality of BCME was determined using ~8-week old rats (10/concentration). Rats were exposed for 7 h to BCME at 0.94-74 ppm and observed for 14 days. BCME vapor was generated by bubbling air through or passing it over liquid BCME before it was introduced into 128-L or 1.3-m^3 exposure chambers; air concentrations of BCME were measured every half-hour spectrophotometrically after coupling with 4-(*p*-nitrobenzyl) pyridine. Lungs were removed from each animal and damage was measured as an increase of three standard deviations in the lung-to-body weight ratio. The ratio for controls was approximately 0.6. A value of 0.9 was considered elevated for rats. (Previous studies with irritants in the same laboratory showed that this ratio was an objective indicator of lung damage.) As shown in Table 1-5, the 14-day LC_{50} was estimated graphically to be ~7 ppm. All animals given BCME at ≥9 ppm died within 14 days, most on the first post-exposure day. The rats had extensive lung damage, including congestion, edema, and hemorrhage and a dose-related increase in the incidence of lung-to-body weight ratio.

In a related experiment, Drew et al. (1975) examined the long-term effects of a single 7-h exposure to BCME at 0.7, 2.1, 6.9, or 9.5 ppm in rats (25/concentration; 50 controls) observed for their lifetimes. Results were reported in terms of percentage of findings per number of observations, as shown in Table 1-6, although it was not clear how the "number of observations" was determined, relative to the original 25 or 50 animals per dose group. At concentrations of 2.1 ppm and greater, rats had severe life shortening (first death during week 2), weight loss, and elevated lung-to-body weight ratios, and as lung edema, congestion, and hemorrhage. Histopathologic findings included increased incidences of tracheal and bronchial hyperplasia (often with nuclear atypia) and squamous metaplasia compared with controls. Animals exposed to BCME at 0.7 ppm had respiratory pathologic changes similar to those of controls, although there was an increase in the incidence of tracheal epithelial hyperplasia (67% vs. 36% in controls) and increased lung-to-body weight ratios.

In their third experiment, Drew et al. (1975) subjected groups of 50 rats to 1, 3, 10, or 30 six-hour exposures to BCME at 1 ppm. Results were reported in terms of percentage of findings per number of observations, as shown in Table 1-7. All groups that received 3, 10, or 30 exposures had increased mortality compared with controls and dose-related increases in the incidence of tracheal and bronchial hyperplasia and squamous metaplasia. Additional findings in rats that received 1 or 10 exposures included bronchoalveolar squamous metaplasia (incidences of 1/29 and 5/43, respectively), cuboidal transformation of the alveolar epithelium (4/29 and 7/43, respectively), and alveolar squamous metaplasia (0/29 and 3/43, respectively). One rat that died 570 days after three exposures had an ulcerating squamous skin cell carcinoma. Central nervous

system effects and extreme irritability were seen after 10 or 30 exposures: subarachnoid hemorrhage was seen microscopically in 24% of the rats given 30 exposures, and in 17% of the rats given 10 exposures.

TABLE 1-5 Mortality, Lung-to-Body Weight Ratio, and Estimated LC_{50} in Rats after Single 7-Hour Exposure to bis-Chloromethyl Ether

Concentration (ppm)	Mortality at 14 d (%)	Rats with increased lung-to-body weight ratio (%)[a]	Estimated LC_{50}[b]
74	100	100	7 ppm
19	100	100	
9	100	100	
7.3	60	90	
6.2	30	100	
4.6	0	100	
0.94	0	40	

[a]Relative lung weight is greater than the control mean plus 3 standard deviations.
[b]LC_{50} value was estimated graphically by the study authors.
Source: Adapted from Drew et al. 1975.

TABLE 1-6 Median Lifespan, Lung-to-Body Weight Ratio, and Histopathologic Findings in Rats after Single 7-Hour Exposure to bis-Chloromethyl Ether

Concentration (ppm)	Median Lifespan (d)	Increased Lung-to-Body Weight Ratio[a] (%)	Histopathologic Findings in Lung Mucosa (%) (based on number observations [obs])[b]
9.5	2	93	Specific lesions not quantified; respiratory lesions similar to those at 2.1 ppm but with higher incidence; seen only in rats that survived >2 d
6.9	2	88	
2.1	36	100	Tracheal [obs = 6]: hyperplasia (100), squamous metaplasia (17) Broncheal [obs = 13]: hyperplasia (100), with atypia (28); squamous metaplasia (62)
0.7	420	96	Increased tracheal epithelial hyperplasia (67% vs. 36% in controls;[c] incidence not stated)
Control	462	0	Tracheal [obs = 35]: hyperplasia (31)[c], squamous metaplasia (11); Broncheal [obs = 48]: hyperplasia (50), with atypia (6); squamous metaplasia (27)

[a]Relative lung weight is greater than the control mean plus 3 standard deviations.
[b]Report does not state how the "number of observations" was determined, relative to the original 25 animals per dose group and 50 controls.
[c]The incidence of epithelial hyperplasia in controls is reported by Drew et al. (1975) as 36% on page 66 and as 31% on page 64 (see Table 3) of the reference.
Source: Adapted from Drew et al. 1975.

TABLE 1-7 Median Lifespan and Histopathologic Findings in Rats after Multiple 6-Hour Exposures to bis-Chloromethyl Ether at 1 ppm

Number Exposures	Median Lifespan (d)	Histopathologic Findings in the Lung Mucosa (%) (based on number of observations [obs])[a]
30	23	Tracheal [obs = 35]: hyperplasia (89), with atypia (11); squamous metaplasia (37); Broncheal [obs = 41]: hyperplasia (95), with atypia (27); squamous metaplasia (66), with atypia (7)
10	21	Tracheal [obs = 23]: hyperplasia (70), with atypia (52); squamous metaplasia (13) Broncheal [obs = 45]: hyperplasia (80), with atypia (47); squamous metaplasia (58)
3	168	Tracheal [obs = 23]: hyperplasia (52), with atypia (22) squamous metaplasia (26); Broncheal [obs = 34]: hyperplasia (62), with atypia (26); squamous metaplasia (41), with atypia (3)
1	457	Tracheal [obs = 22]: hyperplasia (27), with atypia (18) Broncheal [obs = 39]: hyperplasia (41), with atypia (5); squamous metaplasia (23)
Control	462	Tracheal [obs = 35]: hyperplasia (31), squamous metaplasia (11); Broncheal [obs = 48]: hyperplasia (50), with atypia (6); squamous metaplasia (27)

[a]Report does not state how the "number of observations" was determined, relative to the original 50 animals per dose group.
Source: Adapted from Drew et al. 1975.

An RD_{50} (50% decrease in the respiratory rate) value of 145 ppm for BCME was calculated in 8-week old male Crl-CD rats treated head-only for 15 min (Gardner et al. 1985). The BCME exposure concentrations and corresponding mean decreases in respiration rate were 14.4 ppm (14%), 32.5 ppm (16%), 49.8 ppm (37%), 82.8 ppm (55%), 125 ppm (47%), and 233 ppm (62%). The rats (4/dose) were exposed in a body plethysmograph and each rat was its own control. The maximal respiratory inhibition was achieved after 4 min of exposure. During the 5-min post-exposure period, the respiration rate improved but did not return to pretreatment rates. All rats exhibited lacrimation after exposure, and the rats exposed to BCME at 125 and 233 ppm had red nasal discharge. During the 48-h post-treatment observation period, severe weight loss and mortality occurred at ≥82.8 ppm (mortality: 2/4, 2/4, and 1/4 at 82.8, 125, and 233 ppm, respectively). Gardner et al. (1985) also evaluated the respiratory inhibition caused by seven other tumorigens to determine if there was a correlation between sensory irritation potential and nasal tumorigenic potential; no correlation was found.

3.1.2. Mice

Strain A/Heston male mice exposed for 6 h to BCME at 2.7-10.6 ppm had a 14-day LC_{50} of 5.3 ppm (95% confidence limit: 3.7-7.6 ppm) but no respiratory tract irritation (Leong et al. 1971). No further details of the study were provided.

3.1.3. Hamsters

Drew et al. (1975) examined the inhalation toxicity of BCME using male Syrian golden hamsters (~6 weeks old). The generation and measurement of BCME vapor, as well as the evaluation of lung damage was conducted as in the rat studies (see Section 3.1.1.), except that a lung-to-body weight ratio of 0.8 was considered elevated for hamsters. In an acute lethality experiment, hamsters (10/concentration) were exposed for 7 h to BMCE at 0.94-74 ppm and observed for 14 days. Mortality was increased at ≥4.6 ppm, and the 14-day LC_{50} was 7 ppm. All animals given BCME at ≥9 ppm died within 14 days. Animals had concentration-dependent increases in relative lung weights and damaged lungs (congestion, edema, and hemorrhage). The results are summarized in Table 1-8.

TABLE 1-8 Mortality, Lung-to-Body Weight Ratio, and Estimated LC_{50} in Hamsters Exposed to bis-Chloromethyl Ether for 7 Hours

Concentration (ppm)	Mortality at 14 d (%)	Increased Lung-to-Body Weight Ratio[a] (%)	Estimated LC_{50}[b]
74	100	100	7 ppm
19	100	100	
9	100	100	
7.3	60	90	
6.2	10	90	
4.6	10	100	
0.94	0	10	

[a]Relative lung weight is greater than the control mean plus 3 standard deviations.
[b]LC_{50} values were estimated graphically by the study authors.
Source: Adapted from Drew et al. 1975.

The long-term effect of single 7-h exposures to BCME at 0.7, 2.1, 5.6, or 9.9 ppm was examined in hamsters (25/concentration) by Drew et al. (1975). The animals were observed for their lifetimes. The study results were reported in terms of percentage of findings per number of observations, as shown in Table 1-9. At concentrations of ≥2.1 ppm, animals had severe life shortening (first death during week 4), weight loss, and high lung-to-body weight ratios, as well as lung edema, congestion, and hemorrhage and tracheal and bronchial hyperplasia (often atypical). The incidence of the mucosal histopathologic changes was tabulated for only the 2.1-ppm exposure group, although the study also reported that four of five hamsters exposed at 5.6 ppm had squamous metaplasia of the tracheal epithelium. Animals exposed to BCME at 0.7 ppm had respiratory pathologic changes similar to those of controls, although there was an increase in the incidence of pneumonitis (67% vs. 23% in controls), and a few animals had bronchial hyperplasia (two animals with atypia), alveolar squamous metaplasia, and bronchoalveolar metaplasia.

TABLE 1-9 Median Lifespan, Lung-to-Body Weight Ratio, and Histopathoglogic Findings in Hamsters Exposed to bis-Chloromethyl Ether for 7 Hours

Concentration (ppm)	Median Lifespan (d)	Increased Lung-to-Body Weight Ratio[a] (%)	Histopathologic Findings in the Lung Mucosa (%) (as of number of observations [obs])[b]
9.9	4	68	Not specified
5.6	16	100	Not tabulated; stated 4/5 animals examined had tracheal epithelium squamous metaplasia
2.1	68	100	Tracheal [obs = 17]: hyperplasia (76), with atypia (18) Broncheal [obs = 12]: hyperplasia (58), with atypia (33)
0.7	657	100	Not tabulated; reported increased pneumonitis (67% vs. 23% in controls; incidences not given), and few animals had bronchial hyperplasia (± atypia), alveolar or bronchoalveolar metaplasia.
Control	675	0	Tracheal [obs = 23]: hyperplasia (18) Broncheal [obs = 25]: hyperplasia (4)

[a]Relative lung weight is greater than the control mean plus 3 standard deviations.
[b]Report does not state how the "number of observations" was determined, relative to the original 25 animals per dose group.
Source: Adapted from Drew et al. 1975.

Groups of 50 hamsters were exposed 1, 3, 10, or 30 times to BCME for 6 h at 1 ppm (Drew et al., 1975). The study results were reported in terms of percentage of findings per number of observations, but it was not clear how the "number of observations" was determined relative to the initial 50 animals/group. All groups receiving 3, 10, or 30 exposures had increased mortality compared with controls. Treated hamsters had generally concentration-related increases in the incidence of tracheal and bronchial hyperplasia and squamous metaplasia (with and without atypia), with minor increases evident after a single exposure (see Table 1-10). Several other findings were reported in the 1-, 3-, and 10-exposure groups. Animals given 10 exposures had bronchoalveolar metaplasia (4/26; one atypical), bronchoalveolar squamous metaplasia with atypia (1/26), and atypical alveolar epithelium (4/26). One hamster given three exposures had turbinate mucosa metaplasia, and one hamster that died 756 days after three exposures had an early nasal esthesioneuroepithelioma. Animals exposed once had bronchoalveolar metaplasia (1/24), atypical alveolar epithelium (1/24), and one animal that died after 1,000 days had an undifferentiated malignant nose tumor. Central nervous system effects and extreme irritability were seen in animals given 10 or 30 exposures; subarachnoid hemorrhage was seen microscopically in 8% of the hamsters given 30 exposures.

TABLE 1-10 Median Lifespan and Histopathologic Findings in Hamsters Exposed to bis-Chloromethyl Ether at 1 ppm for 6 Hours

Number Exposures	Median Lifespan (d)	Histopathologic Findings in the Lung Mucosa (%) (as of number of observations [obs])[a]
30	42	Tracheal [obs = 18]: hyperplasia (67), with atypia (6); squamous metaplasia (44) Broncheal [obs = 10]: hyperplasia (60), with atypia (40)
10	137	Tracheal [obs = 30]: hyperplasia (70), with atypia (33); squamous metaplasia (20) Broncheal [obs = 30]: hyperplasia (50), with atypia (20); squamous metaplasia (7)
3	471	Tracheal [obs = 39]: hyperplasia (21), with atypia (13) Broncheal [obs = 40]: hyperplasia (20), with atypia (8); squamous metaplasia (0), with atypia (0)
1	620	Tracheal [obs = 31]: hyperplasia (16), with atypia (3); squamous metaplasia (3) Broncheal [obs = 40]: hyperplasia (13), with atypia (3)
Control	675	Tracheal [obs = 23]: hyperplasia (18) Broncheal [obs = 25]: hyperplasia (4)

[a]Report does not state how the "number of observations" was determined, relative to the original 50 animals per dose group.
Source: Adapted from Drew et al. 1975.

3.2. Nonlethal Toxicity

3.2.1. Rats

Three multiple-exposure rat studies in which carcinogenicity was an end point are detailed in Section 3.5.1. (Kuschner et al. 1975; Leong et al. 1975, 1981; Dulak and Snyder 1980).

3.2.2. Mice

In an upper respiratory tract screening assessment (Alarie 1966) with strain A/Heston male mice, 60-sec exposure to BCME was nonirritating at concentrations as high as 10.6 ppm (Leong et al. 1971). No further details of the experiment were given. However, in the screening technique, mice are typically placed in body plethysmographs and a decrease in their breathing rate during the 60-sec exposure or during the ensuing 15-min observation period is considered indicative of irritation.

Two multiple-exposure carcinogenicity studies conducted by Leong et al. (1971, 1981) are summarized in Section 3.5.2.

3.2.3. Hamsters

A multiple-exposure study of BCME in hamsters (Kuschner et al. 1975) is described in Section 3.5.3.

3.3. Developmental and Reproductive Effects

No studies were found assessing developmental or reproductive effects of BCME on animals.

3.4. Genotoxicity

BCME was mutagenic in *Salmonella typhimurium* TA100, but not in TA1535, TA1538, or TA98 in a plate incorporation assay when tested at a concentration of 20 μg/plate, with activation (Anderson and Styles 1978). Another laboratory found that exposure to BCME at 0.5 μL per 2,000 cm^3 in the absence of metabolic activation was weakly mutagenic in *S. typhimurium* TA1535 (Norpoth et al. 1980). BCME was found to be mutagenic in *Escherichia coli* and *S. typhimurium* by Mukai and Hawryluk (1973), but experimental details were not provided.

A 6.6-fold increase in the frequency of transformed cells occurred in BHK-21 cells cultured with BCME at 0.008-25 mg/mL in the presence of exogenous activation (Styles 1978).

Chromosome aberrations were not induced in the bone marrow cells of Sprague-Dawley rats examined 5 days after being exposed by inhalation to BCME at 1-100 ppb for 6 h/day, 5 days/week for 6 months (Leong et al. 1981).

DNA synthesis was inhibited in the epidermis of mice for up to 24 h after dermal exposure to BCME at 9 or 18 μmols, as detected by radiolabeled thymidine, cytidine, or leucine administered after treatment. RNA synthesis was increased maximally after 12 h (Slaga et al. 1973).

Goldschmidt et al. (1975) showed that BCME binds to DNA at guanine and adenine residues in vitro. However, in other in vitro studies, BCME did not form any isolable discrete base-alkylation products (assessed by thin-layer chromatography) and had no effect on the λ max, T_m, and buoyant density of salmon sperm DNA (Van Duuren et al. 1969, 1972).

3.5. Chronic Toxicity and Carcinogenicity

3.5.1. Rats

Male Sprague-Dawley rats (70) were exposed to BCME at 0.1 ppm for 6 h/day, 5 days/week, for their lifetimes (Kuschner et al. 1975). Animals were exposed in a 1.3-m^3 chamber, and air concentrations of BCME were measured at 30-min intervals using the coupling agent 4-(*p*-nitrobenzyl) pyridine. Because mortality was high (43% after 80 exposures [16 weeks]), additional groups of rats were exposed to BCME at 0.1 ppm for a total of 10, 20, 40, 60, 80, or 100 exposures and observed until death (20-50 animals per concentration). A control group of 240 rats was included, but only the mortality results were given for this group. The lungs were examined microscopically, and the nose was also examined once the first nasal tumor was found. Twenty animals from the chronic study were removed after 80 exposures and added to the limited-exposure 80-exposure group to determine cancer incidence.

Rats given ≥80 exposures had shortened lifespan and deceased weight gain. In the limited-exposure study, mortality after 80 exposures was about half of that in the initial chronic study, for unknown reasons. Animals given 10-100 exposures had 40 nasal and lung cancers; 17 nasal esthesioneuroepitheliomas, 13 lung squamous-cell carcinomas, four poorly differentiated nasal-epithelial tumors, two nasal adenocarcinomas, and one each of lung adenocarcinoma, malignant olfactory tumor, ganglioneuroepithelioma, and nasal squamous-cell carcinoma. Only one rat (100 exposures) had both cancer types. The median induction time for all tumors was 440 days, and it was determined that there was a probability of ≤1% of developing a tumor before exposure for 210 days. When the survival cutoff of 210 days was used, a clear concentration-response relationship was seen in animals given 10-100 exposures. The shortest number of exposures that resulted in cancer was 10. In that case, a nasal adenocarcinoma was found in one rat that died after 652 days. It is possible that some early nasal tumors were missed because the nose was not dissected in animals that died

early in the study. Information on controls was not provided by Kuschner et al. (1975), but the incidence of cancer was given as 0/240 in the EPA (2002) Integrated Risk Information System (IRIS) carcinogenicity risk assessment. The limited-exposure study results, summarized in Table 1-11, were used by EPA (2002) to derive a cancer slope factor and unit risk for BCME (see Appendix B).

TABLE 1-11 Median Lifespan and Respiratory Cancers in Rats after Limited Exposures to bis-Chloromethyl Ether at 0.1 ppm

		Number of Rats			
Number of Exposures	Median Lifespan (wk)	At start	At ≥210 d	At ≥210 d with cancer (%)	Cancer Types (number of affected animals)
100	50	30	20	12 (60.0)	Nose: ENE (3), unclassified malignant tumor (1), PD epithelial tumor (1) Lung: squamous-cell carcinoma (8)
80	43	30 + 20[a]	34	15 (44.1)	Nose: ENE (9), squamous-cell carcinoma (1), ganglioneuroepithelioma (1), PD epithelial tumor (1) Lung: squamous-cell carcinoma (3)
60	61	20	18	4 (22.2)	Nose: ENE (2) Lung: squamous-cell carcinoma (2)
40	71	20	18	4 (22.2)	Nose: ENE (2), PD epithelial tumor (1) Lung: adenocarcinoma (1)
20	69	50	46	3 (6.5)	Nose: ENE (1), PD epithelial tumor (1), adenocarcinoma (1)
10	69	50	41	1 (2.4)	Nose: adenocarcinoma (1)
0	66	240	NR[b]	NR[b]	NR[b] (none)

[a]Twenty animals from the chronic-exposure study were removed after 80 exposures and added to this group to determine cancer incidence.
[b]The incidence of rats with respiratory cancers was not specified in the study, but was reported as 0/240 in EPA (2002).
Abbreviations: ENE, esthesioneuroepithelioma; NR, not reported; PD, poorly differentiated.
Source: Adapted from Kuschner et al. 1975.

Leong et al. (1975, 1981) attempted to determine whether there is a non-tumorigenic or NOEL for BCME inhalation in rodents. Groups of 120 male rats (Sprague-Dawley Specific Pathogen-free) were exposed to BCME at 0, 1, 10, or 100 ppb for 6 h/day, 5 days/week for 6 months (129 exposures), followed by lifetime observation. Some animals were sacrificed after 6 months for pulmonary exfoliative cytologic examination on day 1 of the post-exposure period, and cytogenetic evaluation of bone marrow chromosomes on day 5 postexposure. Tests were performed in a 3.7-m^3 stainless steel chamber where concentrated vapor was delivered via a dual syringe pump and the BCME concentration was measured at least once daily. Parameters assessed included periodic and terminal body weights, gross and microscopic pathology, organ weights, hematology (packed cell volume, mean hemoglobin concentration, red- and white-blood-cell count, and differential white-blood-cell count). No treatment-related non-neoplastic gross or microscopic changes, effects on hematology, organ weights, bone marrow cell chromosome integrity, or pulmonary exfoliated cells were seen in any group of rats. Neither respiratory tumors nor increased mortality occurred in rats or mice exposed to BCME at 1 or 10 ppb. Rats exposed to BCME at 100 ppb, however, had increased (tumor-related) mortality starting at the seventh experimental month (1 month postexposure) and all died or were euthanized by the nineteenth experimental month. Most of the 100-ppb rats developed esthesioneuroepitheliomas (96/111; 86.5%), of which four also had pulmonary adenoma. The tumors were frequently found 2-7 months postexposure, with the first case occurring during the sixth month of exposure. Many of the animals had a distended gastrointestinal-tract lumen secondary to the nasal obstruction and subsequent mouth breathing.

Male Sprague-Dawley rats (number not specified) were exposed by inhalation to BCME at 0.1 ppm for 30 exposures (6 h/day, 5 days/week) with lifetime follow-up (Dulak and Snyder 1980). Approximately 35% of the animals died with respiratory tract tumors, which were first observed 350 days after exposure.

3.5.2. Mice

A/Heston male mice (47) were exposed to BCME at 1 ppm for 6 h/day, 5 days/week, for 82 times over 27 weeks, after which they were sacrificed (Leong et al. 1971). Testing was performed in 100-L acrylate plastic chambers, and BCME vapor was generated by metering liquid BCME into the airstream entering the exposure chamber; the analytic concentration inside the chamber was not measured. The lungs of all the treated animals, as well as the 49 control males (exposed to filtered room air for 28 weeks) were examined histologically. Compared with untreated controls, the BCME-exposed mice had an increased incidence (55% vs. 41% for controls) and multiplicity (5.2 vs. 2.2 for controls)

of lung adenomas. These mice had body weight loss, respiratory distress, and 37/50 died during the exposure period. Gross necropsy revealed 27/47 animals with lung tumors and 11/47 with pinpoint hemorrhages or patchy consolidation in the lungs.

Leong et al. (1981) exposed groups of 144-157 male Ha/ICR mice to BCME at 0, 1, 10, or 100 ppb for 6 months (129 exposures) followed by lifetime observation to determine whether there is a non-tumorigenic or no-observable-effect level for BCME inhalation. Animals were exposed for 6 h/day, 5 days/week, in a 3.7-m^3 stainless steel chamber where concentrated vapor was delivered via a dual syringe pump and the chamber BCME concentration was measured at least once daily. Parameters assessed included periodic body weights and terminal gross and microscopic pathology. All groups had ascending urinary tract infections, which "may have been aggravated by exposure to BCME." No treatment-related toxic or neoplastic effects were seen in mice exposed at 1 or 10 ppb. However, when mice that died prematurely from urinary tract infections were excluded from analysis, the 100-ppb group had increased mortality and incidence of pulmonary adenomas (8/27 vs. 9/86 for controls). No nasal tumors were seen. Leong et al. (1981) concluded that "10 and 1 ppb appear to be the no-observable-effect-levels for a 6-month exposure period."

3.5.3. Hamsters

Male Syrian golden hamsters (100) were exposed to BCME at 0.1 ppm for 6 h/day, 5 days/week, for their lifetimes (Kuschner et al. 1975). Mortality was increased after 20 weeks and one hamster that received 334 exposures developed an undifferentiated lung carcinoma and died on day 501 (Kuschner et al. 1975).

3.5.4. Carcinogenicity by Other Exposure Routes

BCME is also shown to be a carcinogen by other routes of exposure. Application of BCME (2 mg in 0.1 mL benzene) to the skin of female ICR/Ha Swiss mice three times per week for 325 days caused papillomas in 13 of 20 mice, 12 of which became squamous-cell carcinomas (Van Duuren et al. 1968, 1972). A single dermal application of BCME (1 mg in 0.1 mL benzene) had no effect, but when followed by promotion with acetone/phorbol esters, papilloma developed in five of 20 mice, two of which progressed to squamous-cell carcinoma (Van Duuren et al. 1972). Other investigators also showed that BCME (1 mg applied dermally) was a potent tumor initiator in mice (Slaga et al. 1973; Zajdela et al. 1980). Newborn ICR-Swiss mice (50/sex) injected subcutaneously with BCME at 0.0125 mg/kg in peanut oil had a 45% incidence

and 0.64 multiplicity of pulmonary adenomas at the 6-month sacrifice, and two mice developed papilloma or fibrosarcoma at the injection sites (Gargus et al. 1969). The vehicle control had a 15% incidence and 0.14 multiplicity of lung tumors. Female Sprague-Dawley rats (20) injected with BCME subcutaneously once weekly for 300 days at 1 or 3 mg in Nujol developed local fibromas (2/20) and fibrosarcomas (5/20), but there was no increase in distal tumors or any tumors in rats injected with the solvent only (Van Duuren et al. 1969). ICR/HA Swiss mice (Van Duuren et al. 1975) and XVIInc/Z mice (Zajdela et al. 1980) injected subcutaneously with 0.3 mg of BCME in Nujol once weekly for over a year developed a high incidence (~40%) of sarcomas at the injection site. Van Duuren et al. (1975) also found one sarcoma (1/50 mice) in the Nujol-only controls, and Zajdela et al. (1980) found pulmonary adenomas in 7of 57 mice. Female ICR/HA Swiss mice that received weekly intraperitoneal injections of BCME (0.0.02 mg in 0.05 mL of Nujol) for 537 days developed local sarcomas (4/30) and had a decreased median survival time; no sarcomas were found in the Nujol-treated or untreated controls (Van Duuren et al. 1975).

3.6. Summary

Rats and mice had no apparent irritation from exposure to BCME at concentration greater than those producing carcinogenicity or toxicity. The LC_{50} of BCME for rats and hamsters, based on a 7-h exposure and 2-week observation period, was about 7 ppm for both species (Drew et al. 1975). An examination of the long-term effects of a single 7-h exposure of BCME at 0.7-9.5 ppm in rats and hamsters showed that some pathologic changes of the respiratory system occurred at even the lowest concentration, although overt treatment-related toxicity and increased mortality occurred at concentration of ≥2.1 ppm (tracheal epithelial hyperplasia in rats and pneumonitis in hamsters) (Drew et al. 1975). Rats and hamsters given 1, 3, 10, or 30 six-hour exposures to BCME at 1 ppm had generally exposure-related increases in the incidence of tracheal and bronchial hyperplasia and squamous metaplasia, and mortality was increased with ≥3 exposures (Drew et al. 1975). Rats, mice, and hamsters exposed by inhalation to BCME at 0.1 ppm for as few as 10 six-hour exposures developed respiratory tumors or had shortened lifetimes (Kuschner et al. 1975; Leong et al. 1975, 1981; Dulak and Snyder 1980). No treatment-related non-neoplastic or neoplastic effects were seen in rats or mice exposed to BCME at 1 or 10 ppb for 6 h/day for 6 months (Leong et al. 1975, 1981). No studies were located assessing developmental or reproductive effects of BCME in animals. BCME was mutagenic in several strains of *S. typhimurium*, increased the transformation frequency of BHK-21 cells, inhibited DNA synthesis, and was shown to bind DNA, but did not induce chromosome aberrations in rat bone marrow.

Summaries of BCME single-exposure and multiple-exposure animal studies are presented in Table 1-12 and Table 1-13, respectively.

TABLE 1-12 Animal Studies of Single Exposure to bis-Chloromethyl Ether

Species	Exposure Duration	Concentration (ppm)	Effects (Reference)
Rat	4 h	7.8, 15.6	14-d LC_{50} = 10.26 ppm; 1/6 died at 7.8 ppm (day 14) and 6/6 died at 15.6 ppm (day 2, 4, 7). Decedents had lung hemorrhage and blood in the intestines. Survivors had morphologic lung changes ("consolidated" or "greatly enlarged" areas) (Union Carbide 1968; Smyth et al. 1969).
Rat	3 min 8 min	Saturated (~40,000)	Irritation and prostration; 6/6 died (Union Carbide 1968).
Rat	3 min	Saturated (~40,000)	12/12 died; mucous membrane irritation, milky opacity of the cornea, narcosis, and dyspnea (Zeller and Hoffmann 1973).
Rat	7 h	0.94,4.6, 6.2, 7.3, 9, 19, 74	14-d LC_{50} = 7 ppm; 100% mortality at ≥9 ppm (most on day 2). Extensive lung congestion, edema, and hemorrhage, and increased lung-to-body weight ratio (Drew et al. 1975).
Rat	7 h	0.7, 2.1, 6.9, 9.5	At 0.7 ppm, increase in tracheal epithelial hyperplasia; at >2.1 ppm, shortened lifespan, weight loss, increased lung-to-body weight ratio, lung edema, congestion, hemorrhage, tracheal and bronchial hyperplasia (+ nuclear atypia), and squamous metaplasia (Drew et al. 1975).
Rat	15 min	14.4, 32.5, 49.8, 82.8, 125, 233	Lacrimation at all concentrations; RD_{50} = 145 ppm (calculated); red nasal discharge at ≥125 ppm; severe weight loss and increasing mortality at ≥82.8 ppm (48 h after exposure) (Gardner et al. 1985).
Mouse	6 h	2.7-10.6	14-d LC_{50} = 5.3 ppm; no respiratory-tract irritation (Leong et al. 1971).
Mouse	60 sec	≤10.6	No decrease in breathing rate during exposure or 15-min observation period (Leong et al. 1971).
Hamster	7 h	0.94, 4.6, 6.2, 7.3, 9, 19, 74	14-d LC_{50} = 7 ppm; mortality increased at ≥4.6 ppm; increased relative lung weights and damaged lungs (congestion, edema, and hemorrhage) (Drew et al. 1975).
Hamster	7 h	0.7, 2.1, 5.6, 9.9	At 0.7 ppm, increased pneumonitis and some alveolar changes; at ≥2.1 ppm, shortened lifespan, weight loss, increased lung-to-body weight ratio, lung edema, congestion, hemorrhage, and tracheal and bronchial hyperplasia (often atypical) (Drew et al. 1975).

TABLE 1-13 Animal Studies of Multiple Exposures to bis-Chloromethyl Ether

Species	Exposure Duration	Concentration (ppm)	Effects (Reference)
Rat	1 × 6 h 3 × 6 h 10 × 6 h 30 × 6 h	1	1 exposure: alveolar changes 3 or more exposures: increased mortality; tracheal and bronchial hyperplasia and squamous metaplasia; central nervous system effects; extreme irritability 10 or 30 exposures: subarachnoid hemorrhage (Drew et al. 1975)
Rat	6 h/d, 5 d/wk, 6 mo (129 exp.)	0.001, 0.01, 0.1	No effects at 1 or 10 ppb. At 100 ppb, increased death from month 7; all died or were killed by month 19; some had pulmonary adenoma; most had esthesioneuroepitheliomas (Leong et al. 1975, 1981).
Rat	6 h/d, 5 d/wk for life	0.1	High mortality (43% after 80 exposures [16 wk]); discontinued after 80 exposures (Kuschner et al. 1975).
Rat	10 × 6 h 20 × 6 h 40 × 6 h 60 × 6 h 80 × 6 h 100 × 6 h	0.1	≥80 exposures had shortened lifespan and deceased weight gain; using survival cutoff of 210 days, concentration-response in tumor incidence from 10-100 exposures, primarily nasal esthesioneuroepithelioma and lung squamous cell carcinoma (Kuschner et al. 1975).
Rat	6 h/d, 5 d/wk, 6 wk (30 exp.)	0.1	Approximately 35% mortality from respiratory-tract tumors, first observed 350 days after beginning exposure (Dulak and Snyder 1980).
Mouse	6 h/d, 5 d/wk, 6 mo (129 exp.)	0.001, 0.01, 0.1	No effects at 1 or 10 ppb. At 100 ppb, increased mortality and incidence of pulmonary adenoma when mice that died early from urinary tract infections excluded (Leong et al. 1975, 1981).
Mouse	6 h/d, 5 d/wk, 27 wk (82 exp.)	1	74% mortality; body weight loss; respiratory distress; lung hemorrhages or patchy consolidation; lung adenomas (Leong et al. 1971).
Hamster	1 × 6 h 3 × 6 h 10 × 6 h 30 × 6 h	1	1 exposures: alveolar changes; one undifferentiated nasal tumor 3 or more exposures: increased mortality; tracheal and bronchial hyperplasia; squamous metaplasia 10-30 exposures: central nervous system effects; irritability 30 exposures: subarachnoid hemorrhage (Drew et al. 1975).
Hamster	6 h/d, 5 d/wk for life	0.1	1/100 developed undifferentiated lung carcinoma after 334 exposures and died on day 501 (Kuschner et al. 1975).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No information was found in the literature regarding BCME metabolism. BCME is hydrolyzed within 10-60 sec in water to form HCl and formaldehyde, with about 20% of the original compound remaining at equilibrium (Van Duuren et al. 1972; Van Duuren 1980). Consistent with its in situ hydrolysis, the respiratory tract is the primary site of BCME toxicity and carcinogenicity after inhalation, and the skin is the target organ after dermal application and subcutaneous injection in humans and animals.

Whether BCME or its hydrolysis products are metabolized in vivo, or to what extent any such metabolites contribute to its toxicity and carcinogenicity, is unknown.

4.2. Mechanism of Toxicity

The mechanism of BCME toxicity and carcinogenicity has not been determined. The chemical structure of BCME predicts that it would be an alkylating agent, which is consistent with its ability to react in vitro with the guanine and adenine of calf thymus DNA (Goldschmidt et al. 1975), its mutagenicity in the Ames test, and its carcinogenicity in animals and humans. This is inconsistent, however, with other in vitro studies in which BCME did not form any isolable discrete base-alkylation products detected by thin-layer chromatography, or have any effect on the λ max, T_m, and buoyant density of salmon sperm DNA (Van Duuren et al. 1969, 1972).

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4.3. Structure-Activity Relationships

The chemical most related to BCME is CMME. BCME was more toxic and carcinogenic than technical grade CMME in all studies, although CMME

odor was more readily detected (Rohm and Haas, personal communication, Feb. 1998). Comparison of LC_{50} values for CMME and BCME in rats and hamsters (55-65 ppm for CMME; 7 ppm for BCME) indicates that BCME is more acutely toxic by inhalation than CMME (Drew et al. 1975). Animal carcinogenesis studies indicate that BCME is at least 10-fold more potent a carcinogen than CMME, both by inhalation (Drew et al. 1975; Kuschner et al. 1975; Laskin et al. 1975) and by dermal application and subcutaneous injection (Van Duuren et al. 1968, 1969; Gargus et al. 1969).

It has been reported that the higher carcinogenic potency of BCME compared with CMME is not due to the potential of cross-linking DNA strands by BCME (Burchfield and Storrs 1977). The reason is that the reactive groups of a bifunctional alkylating agent should be able to reach across approximately 8Å, and the distance between the reactive halogens in BCME is too short for cross-linking to be likely or possible.

When the chlorine and oxygen atoms are separated in structurally-related chloroethers by two or more carbon atoms (e.g., bis(β-chloroethyl) ether), the alkylating power and carcinogenicity are greatly reduced (Burchfield and Storrs 1977), whereas eye irritation seems to be unaffected by chain length (Kirwin and Galvin 1993).

4.4. Other Relevant Information

4.4.1. Species Variability

The study by Drew et al. (1975) indicated little variability in the acute toxicity of BCME between species. The 7-h LC_{50} for both rats and hamsters was 7 ppm. A similar 6-h LC_{50} of 5.3 ppm for mice was reported by Leong et al. (1971).

4.4.2. Concentration-Exposure Duration Relationship

No data were available from which to determine the concentration-time relationship for BCME-related toxic effects. 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 ranges from 0.8 to 3.5. To obtain protective AEGL-2 and AEGL-3 values for durations of 30-480 min (AEGL-1 values were not derived), scaling across time was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points than the exposure duration in the key study. Extrapolations were not used to determine 10-min values because the National Advisory Committee judged that extrapolation from ≥4 h to 10 min has unacceptably large inherent uncertainty. The 30-min value is adopted for 10-min value to be protective of human health.

5. RATIONALE AND PROPOSED AEGL-1

5.1. Human Data Relevant to AEGL-1

No studies were identified that could be used to develop AEGL-1 values. BCME has poor warning properties, and has caused severe eye damage in humans several hours after exposure at concentrations that were not perceived (<3 ppm) (Travenius 1982).

5.2. Animal Data Relevant to AEGL-1

No relevant studies were found because toxicity exceeding the severity of AEGL-1 occurred at concentrations that did not produce sensory irritation. A decrease in the breathing rate of A/Heston male mice, indicative of respiratory irritation, was not observed after inhalation of BCME at concentrations up to 10.6 ppm for 60 sec, although mortality was observed at that concentration after a 6-h exposure (LC_{50} of 5.3 ppm) (Leong et al. 1971).

5.3. Derivation of AEGL-1

AEGL-1 values are not recommended because no studies were available in which toxicity was limited to AEGL-1 effects. Effects exceeding the severity of AEGL-1 effects occurred at concentrations that did not produce sensory irritation in humans or animals.

6. RATIONALE AND PROPOSED AEGL-2

6.1. Human Data Relevant to AEGL-2

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

6.2. Animal Data Relevant to AEGL-2

The studies considered relevant for derivation of AEGL-2 values included the following:

- The 14-day LC_{50} study of Drew et al. (1975), in which male Sprague-Dawley rats and Syrian golden hamsters were exposed to BCME at 0.94-74 ppm for 7 h and observed for 14 days. At the lowest test concentration of 0.94 ppm, no mortality occurred, and both species had increased lung-to-body weight ratios (40% of rats and 10% of hamsters), lung congestion, edema, and

hemorrhage. An adjustment factor of 3 was used to estimate an NOAEL of 0.31 ppm for lung lesions, which could be a point-of-departure for developing AEGL-2 values.

- The Drew et al. (1975) study which examined the long-term effects of a single 7-h exposure to BCME at 0.7, 2.1, 6.9, and 9.5 ppm in rats and 0.7, 2.1, 5.6, and 9.9 ppm in hamsters. At 0.7 ppm, both species had increased lung-to-body weight ratios (96% rats; 100% hamsters), and there was an increased incidence of tracheal epithelial hyperplasia in rats (67% vs. 36% in controls) and of pneumonitis in hamsters (67% vs. 23% in controls). The respiratory lesions were considered irreversible because they were seen after lifetime observation. At ≥2.1 ppm, both species had increased mortality and lung lesions. The lowest-observed-adverse-effect level (LOAEL) of 0.7 ppm can be divided by an adjustment factor of 3 to estimate a NOAEL of 0.23 ppm for lung lesions as a point-of-departure for developing AEGL-2 values.
- The single-exposure scenario of the Drew et al. (1975) study in which rats and hamsters were subjected to 1, 3, 10, or 30 six-hour exposures of BCME at 1 ppm followed by lifetime observation. After one exposure, rats and hamsters had slightly increased incidences of alveolar, tracheal, or bronchial transformation. An adjustment factor of 3 was used to estimate a NOAEL of 0.33 ppm for lung lesions, which could be a point-of-departure for developing AEGL-2 values.
- The respiratory inhibition study in which male Crl-CD rats were exposed head-only for 15 min to BCME at 14-233 ppm (Gardner et al. 1985). Lacrimation occurred at all test concentrations and exposure to ≥82.8 ppm caused severe weight loss and mortality during the 48-h observation period. AEGL-2 values could be based on exposure for 15 min to 14.4 ppm, which caused 14% respiratory inhibition and lacrimation, which could impede the ability to escape. However, 14 ppm might cause toxicity exceeding the severity of AEGL-2, on the basis of reports that the highest tolerable BCME air concentration for humans is 5 ppm (Travenius 1982), and that BCME was distinctly irritating at 3 ppm (Flury and Zernik 1931) (no exposure durations were specified in the two references).

6.3. Derivation of AEGL-2

The AEGL-2 values are based on the lowest LOAEL (0.7 ppm) for irreversible respiratory lesions in rats and hamsters (Drew et al. 1975), which was divided by 3 to estimate a NOAEL of 0.23 ppm. This point-of-departure is supported by two other single-exposure experiments by Drew et al. (1975) that had similar LOAELs for irreversible or serious lung lesions. No data were available from which to determine the BCME concentration-time relationship in order to derive AEGL-2 values for time periods other than 7 h. ten Berge et al. (1986) showed that the concentration-time relationship for many irritant and systemically acting vapors and gases can be described by $C^n \times t = k$, where the

exponent n ranges from 0.8 to 3.5. To obtain protective AEGL-2 values, scaling across time was performed using n = 3 for exposure durations shorter than 7 h and n = 1for exposure durations longer than 7 h. However, such extrapolation was not performed for the 10-min values because of unacceptably large inherent uncertainty; instead, the 30-min AEGL values were adopted for the 10-min values to be protective of human health (see Section 4.2.2.). A total uncertainty factor of 10 was used. An uncertainty factor of 3 was applied for interspecies extrapolation because BCME caused a similar toxic response in two species at the same test concentration in the key study, and is expected to cause toxicity similarly in human lung. An uncertainty factor of 3 was applied for intraspecies variability as recommended by NRC (2001) for chemicals with a steep dose-response relationship (such as BCME), as the effects are unlikely to vary greatly among humans. Using the intraspecies default uncertainty factor of 10 would reduce the 4- and 8-h AEGL-2 values to below 0.010 ppm, which was shown to be a no-effect level after 129 exposures to BCME in rats and mice (6 h/day, 5 days/week) (Leong et al. 1981). The AEGL-2 values are shown in Table 1-14. Analytic methods are able to routinely detect concentrations of BCME below 1 ppb in the air (Collier 1972; Blease et al. 1989).

An inhalation cancer slope factor for BCME was derived by EPA (2002). It was used to calculate the concentration of BCME associated with a 1×10^{-4} cancer risk from a single exposure to BCME for 30 min to 8 h, as shown in Appendix B. For exposures of 30 min and 1 h, the BCME concentrations predicted to cause a 1×10^{-4} cancer risk are similar to the 30-min and 1-h AEGL-2 values. For exposures of 4-8 h, BCME concentrations calculated to cause a 1×10^{-4} cancer risk are up to 5-fold lower than the AEGL-2 values. The noncarcinogenic end points were considered more appropriate for AEGL derivation because the data did not show that tumor formation could result from a single exposure. Additionally, a direct comparison of BCME cancer risk and AEGL values is of unknown validity because different methods are used to calculate the two sets of numbers (cancer risk calculation uses a linear extrapolation from 25,600 days to 0.5 to 8 h whereas AEGL values were extrapolated from a single 7-h exposure using either n = 3 or n = 1, and different uncertainties are addressed by the two methods).

7. RATIONALE AND PROPOSED AEGL-3

7.1. Human Data Relevant to AEGL-3

No appropriate human studies were available.

7.2. Animal Data Relevant to AEGL-3

The following studies were considered relevant for AEGL-3 derivation:

TABLE 1-14 AEGL-2 Values for bis-Chloromethyl Ether

10 min	30 min	1 h	4 h	8 h
0.055 ppm (0.26 mg/m^3)	0.055 ppm (0.26 mg/m^3)	0.044 ppm (0.21 mg/m^3)	0.028 ppm (0.13 mg/m^3)	0.020 ppm (0.095 mg/m^3)

- The 14-day LC_{50} study by Drew et al. (1975), in which male Sprague-Dawley rats and Syrian golden hamsters were exposed to BCME at 0.94-74 ppm for 7 h and observed for 14 days. All dose groups of both species had increased lung-to-body weight ratios and extensive lung lesions, including congestion, edema, and hemorrhage. AEGL-3 values could be derived using the $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) of 3.7 ppm for hamsters and 4.2 for rats. BMC_{01} [benchmark concentration with 1% response] values were 4.1 and 4.7 ppm, respectively, which were obtained using the log/probit model from EPA's Benchmark Dose Software, Version 1.3.2 (EPA 2005).
- The study by Drew et al. (1975), which examined the long-term effects of a single 7-h exposure to BCME at 0.7, 2.1, 6.9, and 9.5 ppm in rats and 0.7, 2.1, 5.6, and 9.9 ppm in hamsters. At 0.7 ppm, rats had increased incidences of lung lesions but mortality was comparable to controls, whereas at ≥2.1 ppm, both species had increased mortality, weight loss, and lung lesions. The first deaths occurred during week 2 in rats and week 4 in hamsters. Exposure to BCME for 7 h to 0.7 ppm could be considered a NOEL for lethality.
- The single-exposure scenario of the study in which rats and hamsters were subjected to 1, 3, 10, or 30 six-hour exposures of BCME at 1 ppm followed by lifetime observation (Drew et al. 1975). Rats and hamsters had slightly increased incidences of lung lesions after one exposure, whereas increased mortality and lung lesions were observed after three exposures. Exposure for 6 h to 1 ppm could be considered a NOEL for lethality.
- The respiratory inhibition study in which male Crl-CD rats were exposed head-only for 15 min to BCME at 14.4, 32.5, 49.8, 82.8, 125, or 233 ppm (Gardner et al. 1985). Lacrimation occurred at all test concentrations, and exposure at ≥82.8 ppm caused severe weight loss and mortality during the 48-h observation period. AEGL-3 values could be based on exposure for 15 min to 49.8 ppm, which caused 37% respiratory inhibition and was the NOEL for increased mortality. This study has the drawback of an insufficient observation period, which could have missed treatment-related deaths.
- The acute lethality study in which an LC_{50} of 5.3 ppm was obtained for A/Heston male mice given BCME at 2.7-10.6 ppm for 6 h and observed for 14 days (Leong et al. 1971). Data were not provided to be able determine a $BMCL_{05}$ or BMC_{01}, although an adjustment factor of 3 could be applied to the LC_{50} to estimate 1.8 ppm as an estimated NOEL for lethality from a 6-h exposure. However, 1.8 ppm is similar to 2.1 ppm, which caused lethality from a single 7-h exposure in a lifetime observation study (Drew et al. 1975).

7.3. Derivation of AEGL-3

AEGL-3 values were derived from the single-exposure scenario of a study in which rats and hamsters were subjected to 1, 3, 10, or 30 six-hour exposures to BCME at 1 ppm followed by lifetime observation (Drew et al. 1975). Rats and hamsters had slightly increased incidences of lung lesions after one exposure, whereas increased mortality occurred after three exposures. This study was chosen because it had the highest concentration of BCME that was shown to not cause lethality after lifetime observation. The 7-h $BMCL_{05}$ of 4.2 ppm for rats and 3.7 ppm for hamsters exceeded a concentration (2.1 ppm) that caused mortality in rats and hamsters from a single 7-h exposure in a lifetime observation study (Drew et al. 1975). Because no data were available from which to determine the BCME concentration-time relationship, scaling across time was performed as for AEGL-2 values, using n = 3 and n = 1 to for durations shorter and longer, respectively, than 6 h. The 10-min AEGL values were set equal to the 30-min values to be protective of human health (see Section 4.4.2.). A total uncertainty factor of 10 was used. An uncertainty factor of 3 was applied for interspecies extrapolation because the NOEL for lethality was the same in two species in the key study, and lethality is expected to occur by a similar mode of action in human and animals. An uncertainty factor of 3 was applied for intraspecies variability as recommended by NRC (2001) for chemicals with a steep dose-response relationship (such as BCME), as the effects are unlikely to vary greatly among humans. The resulting AEGL-3 values are shown in Table 1-15.

8. SUMMARY OF PROPOSED AEGLs

8.1. AEGL Values and Toxicity End Points

AEGL-1 values were not recommended because effects exceeding the severity of AEGL-1 effects occurred at concentrations that did not produce sensory irritation in humans or animals.

The AEGL-2 values were based on a study in which rats and hamsters were exposed for 7 h to BCME at 0.7-9.5 and 0.7-9.9 ppm, respectively, followed by lifetime observation (Drew et al. 1975). The lowest concentration tested of 0.7 ppm was a LOAEL for irreversible respiratory lesions, and an adjustment factor of 3 was applied to estimate a NOAEL of 0.23 ppm. This point-of-departure is supported by two other experiments by Drew et al. (1975) in which BCME caused irreversible or serious lung lesions. No data were available to determine the BCME concentration-time relationship, and AEGL-2 values for time periods other than 7 h were calculated using the ten Berge et al. (1986) equation $C^n \times t = k$, with n = 3 and n = 1 for exposure durations shorter and longer, respectively, than 7 h. The 30-min values were adopted for the 10-

TABLE 1-15 AEGL-3 Values for bis-Chloromethyl Ether

10 min	30 min	1 h	4 h	8 h
0.23 ppm (1.1 mg/m^3)	0.23 ppm (1.1 mg/m^3)	0.18 ppm (0.86 mg/m^3)	0.11 ppm (0.52 mg/m^3)	0.075 ppm (0.36 mg/m^3)

min values to be protective of human health (see Section .2.2.). A total uncertainty factor of 10 was used. An uncertainty factor of 3 was applied for interspecies extrapolation because BCME caused a similar toxic response in two species at the same test concentration in the key study, and is expected to cause toxicity similarly in human lung. An uncertainty factor of 3 was applied for intraspecies variability as recommended by NRC (2001) for chemicals with a steep dose-response relationship, because the effects are unlikely to vary greatly among humans. Using the intraspecies default uncertainty factor of 10 would reduce the 4- and 8-h AEGL-2 values to below 0.010 ppm, which was shown to be a no-effect level in a study of rats and mice exposed to BCME 6 h/day, 5 days/week, for a total of 129 exposures (Leong et al. 1981).

AEGL-3 values were derived from the single-exposure scenario of a study in which rats and hamsters were subjected to 1, 3, 10, or 30 six-hour exposures to BCME at 1 ppm, followed by lifetime observation (Drew et al. 1975). After one exposure, rats and hamsters had slightly increased incidences of lung lesions, whereas three exposures caused lung lesions and increased mortality. This study was chosen because it had the highest concentration of BCME that was shown to not cause lethality after lifetime observation. Because no data were available from which to determine the BCME concentration-time relationship, scaling across time was performed as for AEGL-2 values. A total uncertainty factor of 10 was used. An uncertainty factor of 3 was applied for interspecies extrapolation because the NOEL for lethality was the same in two species in the key study, and lethality is expected to occur by a similar mode of action in humans and animals. An uncertainty factor of 3 was applied for intraspecies variability as recommended by NRC (2001) for chemicals with a steep dose-response relationship, because the effects are unlikely to vary greatly among humans.

An inhalation cancer slope factor for BCME was derived by EPA (2002). It was used to calculate the concentration of BCME associated with a 1×10^{-4} cancer risk from a single exposure for 30 min to 8 h, as shown in Appendix B. For exposures of 30 min and 1 h, the BCME concentrations predicted to cause a 1×10^{-4} cancer risk are similar to the 30-min and 1-h AEGL-2 values. For exposures of 4-8 h, BCME concentrations calculated to cause a 1×10^{-4} cancer risk are up to 5-fold lower than the AEGL-2 values. The noncarcinogenic end points were considered more appropriate for AEGL derivation because the data did not show that tumor formation could result from a single exposure. Additionally, the validity of comparing cancer risk and AEGL values is unknown because different methods are used to calculate the two sets of values

(the cancer-risk calculation involves a linear extrapolation from 25,600 days to 0.5 to 8 h whereas AEGL values were extrapolated from a single 7-h exposure using either n = 3 or n = 1, and different uncertainties are addressed by the two methods).

A summary of the AEGL values for BCME is shown in Table 1-16.

8.2. Comparison with Other Standards and Criteria

The existing standards and guidelines for BCME are shown in Table 1-17. OSHA, NIOSH, Germany, Austria, and Sweden have no permissible limits for BCME because it is a human carcinogen. A TLV-TWA of 0.001 ppm was adopted by the ACGIH and the Belgium based on the carcinogenic potential of BCME.

A large chemical manufacturer in Philadelphia has developed internal Emergency Response Planning Guideline (ERPG) values (1-h exposure) for BCME of 1 ppb for the ERPG-2 and 100 ppb for ERPG-3 (no ERPG-1) (Rohm and Haas, personal communication, Feb. 1998).

8.3. Data Quality and Research Needs

No studies of BCME had defined exposures and responses that fell within the scope of AEGL-1 severity. Perhaps a more sensitive, molecular-based assay could be developed to detect subclinical respiratory toxicity.

Adequate single-exposure animal studies were available for derivation of AEGL-2 and AEGL-3 values. The AEGL-2 and AEGL-3 values were each supported by several studies with rats and hamsters. However, no relevant human studies were available that adequately documented exposures to BCME (time and concentration).

TABLE 1-16 Summary of AEGLs Values for bis-Chloromethyl Ether

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR[a]	NR	NR	NR	NR
AEGL-2	0.055 ppm (0.26 mg/m^3)	0.055 ppm (0.26 mg/m^3)	0.044 ppm[b] (0.21 mg/m^3)	0.028 ppm[b] (0.13 mg/m^3)	0.020 ppm[b] (0.095 mg/m^3)
AEGL-3	0.23 ppm[b] (1.1 mg/m^3)	0.23 ppm[b] (1.1 mg/m^3)	0.18 ppm[b] (0.86 mg/m^3)	0.11 ppm[b] (0.52 mg/m^3)	0.075 ppm[b] (0.36 mg/m^3)

[a]Not recommended (effects exceeding the severity of AEGL-1 effects occurred at concentrations that did not produce sensory irritation in humans or animals).
[b]These concentrations are estimated to have a cancer risk greater than 1×10^{-4}, on the basis of an inhalation cancer slope factor derived by EPA (2002).

TABLE 1-17 Extant Standards and Guidelines for bis-Chloromethyl Ether

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR[a]	NR	NR	NR	NR
AEGL-2	0.055 ppm	0.055 ppm	0.044 ppm	0.028 ppm	0.020 ppm
AEGL-3	0.23 ppm	0.23 ppm	0.18 ppm	0.11 ppm	0.075 ppm
ERPG-1 (AIHA)[b]			Not derived		
ERPG-2 (AIHA)			0.1 ppm		
ERPG-3 (AIHA)			0.5 ppm		
PEL-TWA (OSHA)[c]					No value[c]
REL-TWA (NIOSH)[d]					No value[d]
TLV-TWA (ACGIH)[e]					0.001 ppm
MAK (Germany)[f]					No value[f]
OELV-LLV (Sweden)[g]					No value[g]
VLEP (Belgium)[h]					0.001 ppm

[a]Not recommended (effects exceeding the severity of AEGL-1 effects occurred at concentrations that did not produce sensory irritation in humans or animals).

[b]ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association) (AIHA 2000, 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 effects other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. An ERPG-1 was not derived because of insufficient data.

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-2 for BCME is based on animal data, and was intended to be below 0.21 ppm, which was calculated to have a 1×10^{-4} excess cancer risk, and 0.7 ppm, which caused serious respiratory lesions in animals.

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 BCME is based on animal lethality data.

[c]OSHA PEL-TWA (Occupational Safety and Health Administration, Permissible Exposure Limits - Time Weighted Average) (54 Fed. Reg. 2931[1989]) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week. A numeric value was not assigned, but OSHA identifies BCME as an occupational carcinogen and workplace exposure is regulated by law (29 CFR 1910.1006 [1996]).

[d]NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average) (NIOSH 2005) is defined analogous to the ACGIH TLV-TWA. A numeric value was not assigned, but NIOSH considers BCME to be an occupational carcinogen subject to Federal regulation (29 CFR 1910.1006 [1996]), and recommends that exposure to it be limited to the lowest feasible concentrations.

[e]ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average) (ACGIH 2007) 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. BCME was classified as carcinogenicity category A1 ("confirmed human carcinogen").

[f]MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration]) (Deutsche Forschungsgemeinschaft -German Research Association (DFG 2002) is defined analogous to the ACGIH TLV-TWA. A value was not developed but BCME was classified as a human carcinogen (category 1).

[g]OELV-LLV (Occupational Exposure Limit Value - Level Limit Value) (Swedish Work Environment Authority 2005) is defined analogous to the ACGIH TLV-TWA. A value was not developed but BCME is classified as Group A, a carcinogenic substance that may not be handled.

[h]VLEP [Occupational Exposure Limit (valeurs limites d'exposition professionnelle)] (Ministry of Employment and Work, Belgium 2002) is defined analogous to the ACGIH TLV-TWA. BCME was classified as a carcinogenic substance.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR bis-CHLOROMETHYL ETHER

Derivation of AEGL-1 Values

AEGL-1 values were not recommended because effects exceeding the severity of AEGL-1 occurred at concentrations that did not produce sensory irritation in humans or animals.

Derivation of AEGL-2 Values

Key study:	Drew et al. 1975
Toxicity end point:	0.23 ppm was NOAEL for irreversible respiratory lesions in rats and hamsters
Time scaling:	$C^n \times t = k$ (n = 3 for longer to shorter exposure periods; n = 1 for shorter to longer exposure periods); extrapolation not performed for 10-min $(0.23 \text{ ppm}/10)^3 \times 7 \text{ h} = 8.52 \times 10^{-5} \text{ ppm}^3\text{-h}$ $(0.23 \text{ ppm}/10)^1 \times 7 \text{ hr } 0.16 \text{ ppm-h}$
Uncertainty factors:	3 for interspecies variability 3 for intraspecies variability Combined uncertainty factor of 10
Modifying factor:	None
Calculations:	
10-min AEGL-2:	Set equal to 30-min value because of uncertainty in extrpolating a 7-h exposure to 10 min
30-min AEGL-2:	$C^3 \times 0.5 \text{ h} = 8.52 \times 10^{-5} \text{ ppm}^3\text{-h}$ $C = 0.055 \text{ ppm } [0.26 \text{ mg/m}^3]$
60-min AEGL-2:	$C^3 \times 1 \text{ h} = 8.52 \times 10^{-5} \text{ ppm}^3\text{-h}$ $C = 0.044 \text{ ppm } [0.21 \text{ mg/m}^3]$
4-h AEGL-2:	$C^3 \times 4 \text{ h} = 8.52 \times 10^{-5} \text{ ppm}^3\text{-h}$

	C = 0.028 ppm [0.13 mg/m^3]
8-h AEGL-2:	$C^1 \times 8$ hr = 0.16 ppm-h C = 0.020 ppm [0.095 mg/m^3]

Derivation AEGL-3 Values

Key study:	Drew et al. (1975)
Toxicity end point:	NOEL of 1 ppm for lethality from lung lesions.
Time scaling:	$C^n \times t = k$ (n = 3 for longer to shorter exposure periods; n = 1 for shorter to longer exposure periods); extrapolation not performed for 10-min values $(1.0 \text{ ppm}/10)^3 \times 6 \text{ h} = 6.0 \times 10^{-3}$ ppm^3-h $(1.0 \text{ ppm}/10)^1 \times 6 \text{ h} = 0.60$ ppm-h
Uncertainty factors:	3 for interspecies variability 3 for intraspecies variability Combined uncertainty factor of 10
Calculations:	
10-min AEGL-2:	Set equal to 30-min value because of uncertainty in extrapolating a 6-h exposure to 10 min
30-min AEGL-3:	$C^3 \times 0.5$ h = 6.0×10^{-3} ppm^3-h C = 0.23 ppm [1.1 mg/m^3]
60-min AEGL-3:	$C^3 \times 1$ h = 6.0×10^{-3} ppm^3-h C = 0.18 ppm [0.86 mg/m^3]
4-h AEGL-3:	$C^3 \times 4$ hr = 6.0×10^{-3} ppm^3-h C = 0.11 ppm [0.52 mg/m^3]
8-h AEGL-3:	$C^1 \times 8$ h = 0.60 ppm-h C = 0.075 ppm [0.36 mg/m^3]

APPENDIX B

CARCINOGENICITY ASSESSMENT FOR BIS-CHLOROMETHYL ETHER

Cancer Assessment

A cancer assessment of BCME was performed by EPA (2002) on the basis of data from Kuschner et al. (1975). That study is summarized in Section 3.5.1.

The inhalation unit risk for BCME was calculated to be 6.2×10^{-2} per $\mu g/m^3$, using the linearized multistage procedure, extra risk (EPA 2002). The concentration of BCME corresponding to a lifetime risk of 1×10^{-4} is calculated as follows:

$$(1 \times 10^{-4}) \div [6.2 \times 10^{-2} (\mu g/m^3)^{-1}] = 1.6 \times 10^{-3} \mu g/m^3$$

To convert a 70-year exposure to a 24-h exposure, one multiplies by the number of days in 70 years (25,600 days). The concentration of BCME corresponding to a 1×10^{-4} risk from a 24-h exposure is:

$$(1.6 \times 10^{-3} \mu g/m^3)(25{,}600 \text{ days}) = 40.96 \mu g/m^3 \ (0.041 \text{ mg/m}^3 \text{ or } 0.0086 \text{ ppm})$$

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

$$(40.96 \mu g/m^3) \div 6 = 6.83 \mu g/m^3 \ (0.0068 \text{ mg/m}^3 \text{ or } 0.0014 \text{ ppm})$$

If the exposure is reduced to a fraction of a 24-h period, the fractional exposure (f) becomes (1/f) × 24 h (NRC 1985). Extrapolation to 10 min was not calculated because of unacceptably large inherent uncertainty. Because the animal dose was converted to an air concentration that results in an equivalent human inhaled dose for the derivation of the cancer slope factor, no reduction in the exposure concentrations is made to account for interspecies variability.

A comparison of the AEGL-2 and AEGL-3 values for BCME with the estimated concentration associated with a cancer risk of 1×10^{-4} is shown below. For risks of 1×10^{-5} and 1×10^{-6}, the 1×10^{-4} values are reduced 10-fold or 100-fold, respectively. Also shown are the estimated cancer risks for the AEGL-2 and AEGL-3 values, obtained by assuming a linear relationship between exposure concentration and cancer risk.

TABLE B-1 Estimated Cancer Risks Associated with a Single Exposure to bis-Chloromethyl Ether

Exposure Duration	10 min	30 min	1 h	4 h	8 h
BCME concentration:	Not calculated	0.069 ppm	0.035 ppm	0.0086 ppm	0.0043 ppm
Estimated cancer risk:		1.0×10^{-4}	1.0×10^{-4}	1.0×10^{-4}	1.0×10^{-4}
AEGL-2 value:	0.055 ppm	0.055 ppm	0.044 ppm	0.028 ppm	0.020 ppm
Estimated cancer risk:	Not calculated	8.0×10^{-5}	1.3×10^{-4}	3.3×10^{-4}	4.7×10^{-4}
AEGL-3 value:	0.23 ppm	0.23 ppm	0.18 ppm	0.11 ppm	0.075 ppm
Estimated cancer risk:	Not calculated	3.3×10^{-4}	5.1×10^{-4}	1.3×10^{-3}	$1.7 \times x\ 10^{-3}$

APPENDIX C

ACUTE EXPOSURE GUIDELINE LEVELS FOR bis-CHLOROMETHYL ETHER

Derivation Summary

AEGL-1 VALUES

30 min	30 min	1 h	4 h	8 h
Not Recommended (effects exceeding the severity of AEGL-1 effects occurred at concentrations that did not produce sensory irritation in humans or animals)				
Reference: Not applicable				
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 support for AEGL-1 values: Values were not derived because no studies were available in which toxicity was limited to AEGL-1 effects.				

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.055 ppm (0.26 mg/m^3)	0.055 ppm (0.26 mg/m^3)	0.044 ppm (0.21 mg/m^3)	0.028 ppm (0.13 mg/m^3)	0.020 ppm (0.095 mg/m^3)
Reference: Drew, R.T., S. Laskin, M. Kuschner, and N. Nelson. 1975. Inhalation carcinogenicity of alpha halo ethers. I. The acute inhalation toxicity of chloromethyl methyl ether and bis(chloromethyl)ether. Arch. Environ. Health 30(2):61-69.				
Test species/Strain/Sex/Number: Male Sprague-Dawley rats and Syrian golden hamsters; 25/test concentration/species				
Exposure route/Concentrations/Durations: Inhaled BCME at 0.7, 2.1, 6.9, or 9.5 ppm (rats) or 0.7, 2.1, 5.6, or 9.9 ppm (hamsters) for 7 h. Lifetime observation.				
Effects: At 0.7 ppm, both species had increased lung-to-body weight ratios; rats had increased incidence of tracheal epithelial hyperplasia, and hamsters had increased incidence of pneumonitis. Respiratory lesions were considered irreversible because they were found after lifetime observation. At ≥2.1 ppm, both species had increased mortality and lung lesions.				

(Continued)

AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
0.055 ppm (0.26 mg/m^3)	0.055 ppm (0.26 mg/m^3)	0.044 ppm (0.21 mg/m^3)	0.028 ppm (0.13 mg/m^3)	0.020 ppm (0.095 mg/m^3)

End point/Concentration/Rationale: A NOAEL of 0.23 ppm for irreversible respiratory lesions in rats and hamsters was estimated by applying an adjustment factor of 3 to LOAEL of 0.7 ppm.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3 applied because BCME caused a similar toxic response in two species at the same test concentration in the key study, and is expected to cause toxicity similarly in human lungs.
Intraspecies: 3 recommended in the Standard Operating Procedures (NRC 2001) for deriving AEGLs for chemicals with a steep dose-response relationship, because effects are unlikely to vary greatly among humans. Using the intraspecies default uncertainty factor of 10 would reduce the 4- and 8-h AEGL-2 values below 0.010 ppm, the NOEL in a study of rats and mice exposed to BCME for 6 h/day, 5 days/week, for a total of 129 exposures (Leong et al. 1981).

Modifying factor: None

Animal-to-human dosimetric adjustment: Not applied

Time saling: $C^n \times t = k$. Default value of n = 3 when scaling from longer to shorter durations, and n = 1 when scaling from shorter to longer durations. The 30-min AEGL value was adopted for the 10-min value to protect human health (see Section 4.4.2.).

Data quality and support for AEGL-2 values: Adequate data were available to develop values. The estimated NOAEL of 0.23 ppm was supported by two other single-exposure experiments by Drew et al. (1975) that had similar LOAELs for irreversible or serious lung lesions.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
0.23 ppm (1.1 mg/m^3)	0.23 ppm (1.1 mg/m^3)	0.18 ppm (0.86 mg/m^3)	0.11 ppm (0.52 mg/m^3)	0.075 ppm (0.36 mg/m^3)

Reference: Drew, R.T., S. Laskin, M. Kuschner, and N. Nelson. 1975. Inhalation carcinogenicity of alpha halo ethers. I. The acute inhalation toxicity of chloromethyl methyl ether and bis(chloromethyl)ether. Arch. Environ. Health 30(2):61-69.

Test species/Strain/Sex/Number: Male Sprague-Dawley rats and Syrian golden hamsters; 50/test concentration/species

Exposure route/Concentrations/Durations: Inhalation of BCME at 1 ppm for 6 h/day for 1, 3, 10, or 30 days. Lifetime observation.

(Continued)

AEGL-3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
0.23 ppm (1.1 mg/m^3)	0.23 ppm (1.1 mg/m^3)	0.18 ppm (0.86 mg/m^3)	0.11 ppm (0.52 mg/m^3)	0.075 ppm (0.36 mg/m^3)

Effects: Slightly increased incidences of lung lesions in rats and hamsters after single exposure; lung lesions and increased mortality with ≥3 exposures.

End point/Concentration/Rationale: A single exposure of 1 ppm for 6 h was the NOEL for lethality from lung lesions.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3 applied because NOEL for lethality was the same in two species in the key study, and lethality is expected to occur by a similar mode of action in humans and animals.
Intraspecies: 3 recommended in the Standard Operating Procedures (NRC 2001) for deriving AEGLs for chemicals with a steep dose-response relationship, because effects are unlikely to vary greatly among humans.

Modifying factor: None

Animal-to-human dosimetric adjustment: Not applied

Time scaling: $C^n \times t = k$. Default value of n = 3 when scaling from longer to shorter durations, and n = 1 when scaling from shorter to longer durations. The 30-min AEGL value was adopted for the 10-min value to protect human health (see Section 4.4.2.).

Data quality and support for AEGL-3 values: The database was sufficient to develop AEGL-3 values. The key study was chosen because it had the highest concentration of BCME that did not cause lethality after lifetime observation; another study by the same authors found a lethality NOEL of 0.7 ppm (7 h) for rats and hamsters after lifetime observation. A 7-h LC_{50} study using rats and hamsters (Drew et al. 1975) was not used because it yielded a $BMCL_{05}$ of 4.2 ppm for rats and 3.7 ppm for hamsters, which exceed 2.1 ppm, the concentration that caused mortality in rats and hamsters after a single 7-h exposure to BCME in a lifetime observation study (Drew et al. 1975).

APPENDIX D

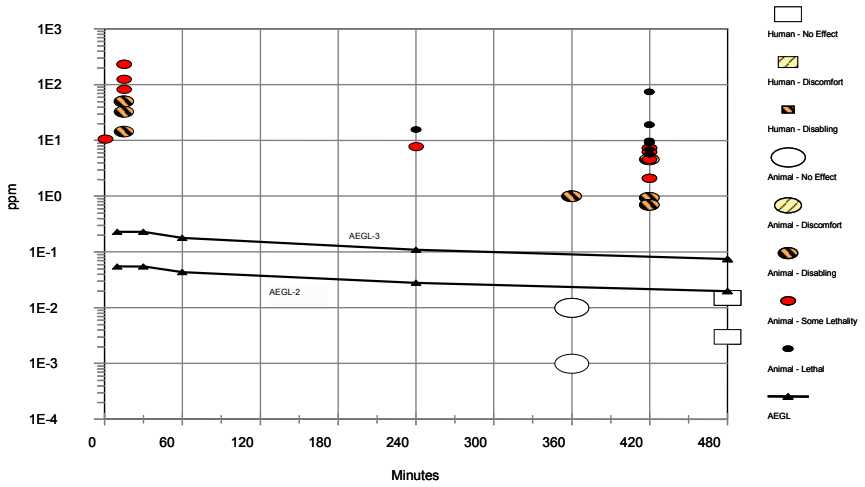

FIGURE D-1 Category plot for bis-chloromethyl ether. Multiple-exposure studies were not included in the plot except for Leong et al. (1975, 1981).

2

Chloromethyl Methyl Ether[1]

Acute Exposure Guideline Levels

PREFACE

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

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, 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 or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory

[1]This document was prepared by the AEGL Development Team composed of Sylvia Milanez (Oak Ridge National Laboratory), Mark Follansbee (Syracuse Research Corporation), and Chemical Manager Ernest V. Falke (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 guidelines reports (NRC 1993, 2001).

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

SUMMARY

Chloromethyl methyl ether (CMME) is a man-made chemical that is highly flammable, and causes severe irritation of the respiratory tract, eyes, nose, and skin. Chronic occupational exposure has caused small-cell lung carcinoma with histology distinct from that caused by cigarette smoke, and with a shorter latency period. The U.S. Environmental Protection Agency (EPA) classifies technical-grade CMME as a human carcinogen. Upon contact with water, CMME hydrolyzes completely and irreversibly to form hydrochloric acid, methanol, and formaldehyde. Technical-grade CMME contains 1-10% bis-chloromethyl ether (BCME) as a contaminant. Because humans are exposed only to technical-grade CMME (a great deal of effort is needed to remove "all" BCME from CMME), and the human and animal inhalation-exposure data all involved technical-grade CMME, the AEGL values derived in this document will address the toxicity and carcinogenicity of technical-grade CMME.

AEGL-1 values were not recommended because no studies were available in which toxicity was limited to AEGL-1 effects.

AEGL-2 values for technical-grade CMME were based on an acute toxicity study in which rats and hamsters were exposed to CMME for 7 h at 12.5-225 ppm (contamination by BCME not given) and observed for 14 days (Drew et al. 1975). Toxic effects were not attributed to specific concentrations, but it was reported that animals that died, and to a lesser degree, animals that

survived, had increased relative lung weights, pulmonary congestion, edema, hemorrhage, and acute necrotizing bronchitis. Therefore, 12.5 ppm was considered the lowest-observed-adverse-effect level (LOAEL) for serious or irreversible lung lesions in both species (also a no-observed-effect level [NOEL] for lethality in rats), and was divided by 3 to obtain an estimated no-observed-adverse-effect level (NOAEL) of 4.2 ppm. No data were available from which to determine the CMME concentration-time relationship to derive AEGL-2 values for time periods other than 7 h. ten Berge et al. (1986) showed that the concentration-time relationship for many irritant and systemically acting vapors and gases can be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. To obtain protective AEGL-2 values, scaling across time was performed using n = 3 and n = 1 for exposure durations shorter and longer, respectively, than 7 h. The 30-min values were adopted for 10-min value to be protective of human health (see Section 4.4.3.). An uncertainty factor of 10 was used. A factor of 3 was applied for interspecies extrapolation because CMME caused a similar degree of lung toxicity in two animal species and is expected to cause similar toxicity in human lungs. A factor of 3 was applied for intraspecies variability as recommended by NRC (2001) for chemicals with a steep dose-response relationship, because the effects are unlikely to vary greatly among humans. An intraspecies uncertainty factor of 3 also was used in the derivation of AEGL-2 values for BCME. A modifying factor of 1.7 was applied because the BCME content in technical-grade CMME in the key study was unknown. The modifying factor was obtained by assuming 10% contamination with BCME (the maximum reported) and accounting for the greater toxicity of BCME (the rat LC_{50} [lethal concentration, 50% lethality] was 55 ppm for CMME and 7 ppm for BCME in the key study) in the following calculation: $[0.1 \times (55/7)] + [0.9 \times 1] = 1.7$.

AEGL-3 values were based on the same study as the AEGL-2 values (Drew et al. 1975). The threshold for lethality from severe lung lesions, expressed as the $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response), was approximately 18 ppm for hamsters and 19 ppm for rats; the lower value was used in the derivation. Data were not available to determine the concentration-time relationship, and scaling across time was performed using the ten Berge et al.(1986) equation described above for AEGL-2. An uncertainty factor of 10 was used. A factor of 3 was applied for interspecies extrapolation because the NOEL for lethality was virtually the same in two species in the key study, and lethality is expected to occur by a similar mode of action in humans and animals. A factor of 3 was applied for intraspecies variability as recommended by NRC (2001) for chemicals with a steep dose-response relationship, as the effects are unlikely to vary greatly among humans. An intraspecies uncertainty factor of 3 also was used in the derivation of AEGL-3 values for BCME. A modifying factor of 1.7 was also applied because the content of BCME in technical-grade CMME in the key study was unknown. The AEGL values are summarized in Table 2-1.

TABLE 2-1 Summary of AEGL Values for Chloromethyl Methyl Ether

Level	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1[a] (nondisabling)	NR[b]	NR	NR	NR	NR	
AEGL-2 (disabling)	0.60 ppm (2.0 mg/m^3)	0.60 ppm (2.0 mg/m^3)	0.47 ppm (1.5 mg/m^3)	0.30 ppm (0.98 mg/m^3)	0.22 ppm (0.72 mg/m^3)	Estimated NOAEL for serious or irreversible lung lesions in rats and hamsters (Drew et al. 1975)
AEGL-3 (lethal)	2.6 ppm (8.6 mg/m^3)	2.6 ppm (8.6 mg/m^3)	2.0 ppm (6.6 mg/m^3)	1.3 ppm (4.3 mg/m^3)	0.93 ppm (3.1 mg/m^3)	Lethality threshold for hamsters and rats (Drew et al. 1975)

[a]Data on odor threshold not found for CMME, but industrial experience indicates that 1.5 ppm is barely detectable and 23 ppm is easily detectable.
[b]Not recommended (no studies were available in which toxicity was limited to AEGL-1 effects).

Data were unavailable to conduct a carcinogenicity risk assessment for CMME, but an assessment was conducted for the related compound BCME (see Appendix D). If the assumptions are made that technical-grade CMME contains 10% BCME, and that the carcinogenicity of "pure" BCME is 10-fold more potent than "pure" CMME (Van Duuren et al. 1968, 1969; Gargus et al. 1969; Drew et al. 1975; Kuschner et al. 1975; Laskin et al. 1975), then it follows that technical-grade CMME has, at most, 9% of the carcinogenic activity of BCME. Thus, if a linear relationship between exposure concentration and cancer risk is assumed for CMME and BCME, the cancer risk associated with the AEGL-2 values are estimated to range from 5.5×10^{-5} to 9.6×10^{-4}, and for AEGL-3 values the estimates range from 2.4×10^{-4} to 4.1×10^{-3}, as shown in Appendix D. It is unknown, however, how valid the stated assumptions are to predict the carcinogenicity of CMME. Because of this uncertainty and the large differences in methods used to derive the AEGL values as compared with extrapolating the carcinogenic potency from a lifetime study to a single exposure, the non-carcinogenic end points were considered to be more appropriate for deriving AEGLs for CMME.

1. INTRODUCTION

Technical grade CMME is a highly volatile, colorless, flammable liquid (CHRIS 1985). CMME vapor is severely irritating to the respiratory tract, eyes, nose, and skin, and exposure to high air concentrations causes sore throat, fever, chills, and difficulty breathing (Hake and Rowe 1963). The odor has been reported as barely detectable at 1.5 ppm and easily detectable at 23 ppm

(Wagoner et al. 1972), concentrations shown to cause lung lesions or mortality in animals. Technical-grade CMME contains 1-10% BCME as a contaminant, which is a more potent human carcinogen than CMME and is believed to be responsible for most or all of the carcinogenic activity of technical-grade CMME (Travenius 1982; HSDB 2010).

CMME decomposes so rapidly in aqueous solution that its half-life cannot be accurately measured. The half-life of CMME in pure water was estimated to be <1 seconds (sec) (Tou and Kallos 1974). In humid air (ambient temperature; 81% relative humidity), CMME and BCME were more stable, although the half-life depended on the surface coating of the container; the half-life was 7-25 h for BCME and 2.3 min to 6.5 h for CMME (Tou and Kallos 1974). It was reported that of the CMME decomposition products in water (methanol, formaldehyde, and hydrochloric acid [HCl]), the latter two can recombine to form BCME, and that vapors of HCl and formaldehyde, which are commonly used in industries and laboratories, can combine spontaneously in the air to form BCME (it has not been shown that CMME can be formed spontaneously in air or water). The hydrolysis of CMME is believed to be irreversible, whereas that of BCME is reversible, although the extent of conversion from CMME to BCME in water or air has not been well-characterized (Travenius 1982).

CMME does not occur naturally, and human exposure occurs in only occupational settings. CMME is usually prepared "in-house" by passing HCl through a mixture of formalin and methanol, and is used industrially in the manufacture of ion-exchange resins, bactericides, pesticides, dispersing agents, water repellants, solvents for industrial polymerization reactions, and flame-proofing agents (Van Duuren 1989; Budavari et al. 1996; Kirwin and Galvin 1993). CMME is very reactive because of the high electronegativity of the oxygen and its attachment to the same carbon atom as chlorine; nucleophilic displacement of the halogen-bearing carbon atom occurs readily and, therefore, CMME and BCME are referred to as alkylating agents. CMME and BCME react spontaneously with nucleophilic substrates, such as DNA, without enzymatic conversion (Burchfield and Storrs 1977).

CMME and BCME were recognized as potent human respiratory-tract carcinogens in the early 1970s by the U.S. industry, prompting facilities to develop hermetically isolated systems for their use (Travenius 1982; Collingwood et al. 1987). In 1973, BCME and CMME were listed by the Occupational Safety and Health Administration as part of the first 14 chemicals to be restricted by Federal regulations because of their human carcinogenicity, effective February 11, 1974 (39 Fed. Reg. 3756). Their use, storage, and handling must be in a controlled area (38 Fed. Reg. 10929). These regulations apply to all preparations containing CMME or BCME at ≥0.1% (by weight or volume). Subsequent studies examined the carcinogenicity of CMME and BCME in animals, although it has been practically impossible to assess the effect of CMME alone because, unless extraordinary measures are taken, it is contaminated with BCME.

In 1993, the U.S. International Trade Commission listed only one company producing CMME in the United States, although the amount produced or sold was not published to avoid disclosure of individual company operations (USITC 1994). The amount of CMME produced in situ during the production of other chemicals, and the companies involved, was not determined. The physical and chemical properties of CMME are listed in Table 2-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No quantitative information was located regarding acute exposure to CMME in humans. The vapors are severely irritating and painful to the eyes and nose. Vapor concentrations that are rapidly fatal are "irrespirable" (term used in reference; no further explanation given) for humans, and illness or death that results from exposure to CMME will occur several days after exposure from lung edema or secondary pneumonia (Hake and Rowe 1963).

2.2. Nonlethal Toxicity

No short-term quantitative studies were located describing nonlethal effects of CMME exposure in humans. CMME vapor was reported to be very irritating and painful to the eyes and nose at 100 ppm, but exposure duration was not specified (Hake and Rowe 1963). One U.S. manufacturer set an in-house threshold limit value (TLV) of 1 ppm for CMME in the early years of its use, presumably because its odor was not detected or was not irritating at <1 ppm (Weiss 1992). This Michigan plant did not have an elevated incidence of respiratory-tract cancer in an industry-wide study by Collingwood et al. (1987). However, a 1-h exposure to CMME at1 ppm is presently considered dangerous to human health according to an in-house exposure standard of a large chemical company (Rohm & Haas, personal communication, February 1998).

Chronic occupational exposure to CMME resulted in coughing, wheezing, blood-stained sputum, breathing difficulty (dyspnea), and weight loss (NIOSH 1988). Several long-term occupational exposure studies described nonlethal toxic end points; however, respiratory tract cancer was the principal focus of these studies. Leong et al. (1971) indicated that CMME (and BCME) are a health risk at concentrations that do not produce sensory irritation.

2.2.1 Odor Threshold and Awareness

Industrial experience indicates that the odor of CMME is undetectable at 0.5 ppm, barely detectable at 1.5 ppm, easily detectable at 23 ppm, and strong at 100 ppm (Wagoner et al. 1972; AIHA 2000). Another source indicated that the highest tolerable concentration of CMME (or BCME) in air is 5 ppm (Travenius 1982).

TABLE 2-2 Physical and Chemical Data for Chloromethyl Methyl Ether

Parameter	Value	Reference
Synonyms	Chloromethoxymethane; chloromethyl ether; monochloromethyl ether; chlorodimethyl ether; CMME	Budavari et al. 1996
CAS registry no.	107-30-2	IARC 1974
Chemical formula	CH_3OCH_2Cl	Budavari et al. 1996
Structure	C(OC)Cl	
Molecular weight	80.51	Budavari et al. 1996
Physical state	Liquid	Budavari et al. 1996
Melting point	-103.5°C	Verschueren 1996
Boiling point	59°C at 760 mm	Budavari et al. 1996
Density		
Vapor	2.8 (air = 1)	CHRIS 1985
Liquid	1.0605 at 20/4°C (water = 1); 1.074 at 20/4°C (water = 1)	IARC 1974 Kirwin and Galvin 1993
Solubility in water	Decomposes in water (half-life <0.5 sec) to methanol, formaldehyde, and HCl	Nelson 1976; Travenius 1982
Vapor pressure	122 mm Hg at 20°C; 260 mm Hg at.20°C	IPCS 1998; HHMI 1995
Flammability/ explosive limits	4.5-22.8 (estimated)	AIHA 2000
Conversion factors	1 mg/m^3 = 0.304 ppm 1 ppm = 3.29 mg/m^3	Verschueren 1996

The data were not adequate to derive the level of distinct odor awareness per the guidance given by van Doorn et al. (2002).

2.2.2. Accidents

Accidental industrial exposure to "rather high" concentrations of CMME caused sore throat, fever, and chills, and the person was not able to work for 8 days, at which time recovery appeared complete (Hake and Rowe 1963). Another subject who received "very slight exposure" had difficulty breathing for several days (Hake and Rowe 1963).

2.3. Neurotoxicity

No studies reporting neurotoxic effects of CMME in humans were located.

2.4. Developmental and Reproductive Toxicity

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

2.5. Genotoxicity

The incidence of chromosomal aberrations was greater in the peripheral lymphocytes of workers exposed to CMME or BCME during the manufacture of ion-exchange resins than in control workers (Sram et al. 1983, 1985). The frequency of aberrations was not related to the years of exposure (1-10 years), but was related to the calculated dose of BCME exposure during the last 3 months (Sram et al. 1985).

Zudova and Landa (1977) cytogenetically scored 22 peripheral lymphocytes/person in 2 workers exposed for 2 years to CMME and BCME. Exposed workers had an average of 6.7% aberrant cells compared with 2% in the controls. Blood samples taken from 10 workers after their holidays (length not defined) had only 3.1% aberrant cells.

CMME was cytotoxic (inhibited scheduled DNA synthesis) in human lymphocytes treated for 4 h with CMME at 10^{-2} M (97-99% pure), although the cytotoxicity was reversed in the presence of metabolic activation with rat liver phenobarbital-induced S-9 mix (Perocco et al. 1983). CMME (10^{-2} to 10^{-3} M or 5 microliters per milliliters [µL/mL]) also increased in vitro DNA repair in the presence of metabolic activation, seen by increased incorporation of tritiated thymidine (Perocco and Prodi 1981; Perocco et al. 1983).

2.6. Carcinogenicity

EPA has designated technical-grade CMME (and BCME) as Group A ("human carcinogen") on the basis of an increased incidence of respiratory-tract cancer in exposed workers (EPA 2005a). This was supported by evidence of respiratory-tract tumors in mice, rats, and hamsters exposed by inhalation (EPA 2005a). The American Conference of Industrial Hygienists has classified CMME as a "suspected human carcinogen" (Class A2), has assigned no values for a TWA or short-term exposure limit (STEL), and suggests that "it may be desirable to monitor exposures on the basis of BCME (TLV = 0.001 ppm)" (ACGIH 1991). International Agency for the Research on Cancer (IARC) places technical-grade CMME in Group 1 ("sufficient evidence for carcinogenicity to humans and to animals") (IARC 1987). In epidemiologic studies, there was a

clear trend of an increasing incidence of lung cancer with increasing dose (longer and/or more intense exposure).

Several studies showed that the incidence of cancer peaked about 15-20 years post-exposure (Weiss 1982; Maher and DeFonso 1987). Exposed humans had elevated rates of respiratory-tract cancer, but not of other types of cancer. The cases occurred at a younger age than lung cancer in the general population, especially among nonsmokers. The cancer histology was most frequently small-cell carcinoma, with a high fraction of them being oat-cell carcinoma, in contrast to lung cancer caused by cigarette smoking, which is predominantly squamous-cell carcinoma (Weiss and Boucot 1975). The air concentrations of CMME in the workroom were almost never measured, although Travenius (1982) has estimated that they might have been 1-10 ppm, because higher concentrations would have been intolerable.

2.6.1. Case Reports

A nonsmoking German research chemist exposed for 2 years to high concentrations of CMME and BCME died 12 years later (at age 45) of heart circulation failure as a result of pulmonary adenocarcinoma cachexia (Reznik et al. 1977). A 42-year old chemist exposed to CMME and BCME by inhalation for 7 years died from extensive pulmonary carcinoma (Bettendorf 1977). The air concentrations of CMME or BCME were not given in either report.

2.6.2. Epidemiologic Studies

Langner (1977) reported CMME air concentrations of 0-12 ppm, with a mean of 0.7 ppm, from 230 measurements taken in 1957 at a U.S. anion exchange plant. CMME concentrations became progressively lower as processing and engineering controls were implemented to reduce exposure. The CMME contained 7-10% BCME. No excess respiratory-tract cancer or oat-cell lung cancer was found in workers during the plant's 27 years of operation.

Industrial workers exposed for months to years to CMME (containing BCME) had a dose-related increase in chronic bronchitis, although the exposure concentrations were not available (Weiss and Boucot 1975; Weiss 1976, 1977). There was no effect on the worker's ventilatory function, as measured by the forced vital capacity (FVC) and the 1-sec forced expiratory volume (FEV_1), suggesting the large airways were normal. The small airways did appear to be affected, because the end-expiratory flow rate was below predicted values in a dose-related manner. Cigarette smoking acted synergistically with CMME to produce chronic bronchitis and small-airway disorders among the workers (however, there was an inverse relationship between smoking and the induction of lung cancer by CMME; see Section 2.5.1.). When chemical exposure diminished, there was a decrease in coughing and an increase in dyspnea (shortness of breath, severity not described).

In 1972, four workers at a California chemical plant (Diamond Shamrock Co., Redwood City) with 100-200 workers involved in anion-exchange resin production (exposed to CMME and BCME) died from lung cancer and two more workers developed lung cancer (Donaldson and Johnson 1972; Fishbein 1972). The concentration of CMME or BCME in the air was not specified. One of the workers that died, a 32-year old male, worked at the plant for only 2 years. Subsequent analysis of exfoliated cells of the sputum of the workers found no difference in metaplasia or atypia between in-plant workers not involved in CMME/BCME production and controls (Lemen et al. 1976). A significant association was found between abnormal cytology and exposure to CMME/BCME for more than 5 years (34% of anion-exchange workers vs. 11% of controls). In conjunction with the cytology survey, a retrospective cohort study of 136 men who worked at the plant for at least 5 years (mean was 10 years) was initiated. Five cases of bronchogenic cancer (three deaths) were found, compared with 0.54 cases expected (in white, age-matched men from Connecticut). The mean age at diagnosis was 47 years, and the predominant histology was small cell-undifferentiated carcinoma. The majority had smoked cigarettes.

Workers exposed at least 6 months to low concentrations of CMME (containing 4-5% BCME) in a workplace in France from 1959-1971 did not have increased rates of respiratory-tract cancers (Schaffer et al. 1984). The actual concentrations of CMME in the air were not specified. The authors speculated that an increased cancer incidence might not have been found because a limited number of people were included in the study (670, of which 168 were exposed to CMME), and the observation period might have been too short.

Technical-grade CMME (unspecified BCME content) was used in the production of anion exchange resins in a factory (Rohm & Haas) in Chauny, France, from 1958 to December 31, 1986 (Gowers et al. 1993). The air concentrations of CMME in the factory were not measured, but concentrations of BCME were monitored from 1979 to 1984 with personal and stationary air-sampling devices. Approximate annual concentrations of BCME were 0.6-4.4 ppb, with an overall weighted average of 1.7 ppb. After standardization for age, workers with jobs involving exposure to CMME (258 men) had a greater incidence of lung cancer than nonexposed workers (945 men) in the same plant (rate ratio [RR] = 5.0; 95% confidence interval [CI] = 2.0-12.3) and a greater incidence than an external reference population (RR = 7.6; 95% CI = 4.3-13.5). Increased cumulative exposure was associated with an increased incidence of cancer but not with the time from first exposure to diagnosis, which was about 13 years. Exposed workers developed cancer an average of 10.5 years earlier than nonexposed workers. Of the cancers in exposed cases, 10/11 were small-cell, mostly oat-cell, carcinomas whereas in the nonexposed group only 1/8 cancers were small-cell carcinomas (16-33% were reported in the external reference population). Smoking history was not known, but reportedly a large fraction of the workers smoked. The observed-to-expected lung cancer ratio

decreased as the exposure concentrations decreased over the years. The cancer cases found while exposure to BCME was monitored were probably due to previous, much higher exposures before engineering controls were put into place in 1984.

The three cases of lung cancer (men aged 33-39) among about 45 workers who worked in the production of CMME (0.5-4% BCME) in one building of a large Philadelphia chemical plant (Rohm & Haas, about 2,500 employees) in 1962 prompted studies of cancer in potentially exposed workers. Air concentrations of CMME or BCME were not measured but were estimated retrospectively on a scale of 0-6, where 0 was "essentially" no exposure. Figueroa et al. (1973) studied a group of 125 men, some of whom were exposed to CMME in this Philadelphia plant. Of the 125 workers, 96 were current cigarette smokers, 13 were nonsmokers, 10 smoked cigars or pipes only, and six were former smokers (Weiss and Boucot 1975). Fourteen of the 125 men were lost to the study because their employment was terminated. Fourteen cases of lung cancer developed in men aged 33-55 from 1962 to 1971; these men were exposed 3-14 years with one exception (uncertain duration; possibly one year). Thirteen cancers were oat-cell carcinomas, and one was of unknown histologic type. Three of the 13 cancers occurred in nonsmokers. The workers were periodically examined (chest photofluorogram and questionnaire) between 1963 and 1968, during which time four cancers developed in men aged 35-54 years (88 men were in this age group), which was a roughly an 8-fold increase in incidence of cancer over the control group. Brown and Selvin (1973) asserted that the actual increase was 44-fold, and that Figueroa et al. (1973) had used an inappropriate control group (too old) and that all 111 men (not just the 88 men between ages 35-54) should have been included.

A 10-year prospective study of this same cohort of 125 men from January 1963 to December 1972 revealed a strong dose-response relationship for bronchogenic cancer (all small-cell carcinomas) among the men exposed for at least 3 months (Weiss and Boucot 1975; Weiss 1980). The exposed workers had symptoms, such as dose-related chronic bronchitis, and the end-expiratory flow rate was below predicted values in a dose-related manner (Weiss 1977). When chemical exposure diminished, there was a decrease in coughing and an increase in dyspnea (shortness of breath, severity not recorded). Significantly increased risk occurred only among men with moderate or heavy exposure; these workers had an inverse relationship between smoking and the incidence of lung cancer (Weiss and Boucot 1975; Weiss 1976, 1977; Weiss et al. 1979). This finding is in marked contrast to other industrial carcinogens (e.g., asbestos, uranium), where cancer was rarely induced without smoking being a cofactor (Travenius 1982). It is unknown how or whether chronic cigarette smoking was inhibiting development of cancer from CMME/BCME, but Weiss (1980) postulates that the additional or altered viscosity secretions or increased thickness of the mucous covering the bronchial epithelium of the cigarette smokers might protect the workers by chemically neutralizing or separating the CMME hydrolysis products from the lung epithelium.

A retrospective study conducted from 1973-June 1974 in the same Philadelphia plant involved workers (669 men) exposed to CMME from 1948-1972 (DeFonso and Kelton 1976). They had a statistically significant (3.8-fold) increase in lung cancer compared with unexposed workers (1,616 men). Dose-response relationships were evident for the incidence of lung cancer and the duration or intensity of exposure. There was no correlation between age at first exposure and the time from the first exposure to death, the latter being from 8.3 to 25.2 years for men whose exposures began in their late twenties. An additional 9-year follow-up of essentially this same group of men, as well as summer and short-term employees (737 exposed; 2,120 unexposed) also showed a dose-related increase in the incidence of respiratory-tract cancer in exposed workers (32 observed [obs], 11.5 expected [exp]; obs/exp = 2.79, $p < 0.01$) (Maher and DeFonso 1987). At the lowest doses, there was no increase in cancer risk (obs/exp = 1.02) whereas at the highest doses the risk was >10-fold. Most of the cases of respiratory-tract cancer (20/32) had a latency period of 10-20 years. Cancer risk was not adjusted for smoking because complete information was unavailable, although exposed and nonexposed workers had similar smoking habits. The incidence of respiratory-tract cancer decreased in parallel (after an induction period) with the decreased exposure of the workers to CMME and BCME as workplace engineering controls were adopted.

These findings agree with those of Weiss (1982) who studied a cross-section of 125 men employed at this Philadelphia plant in 1963, and followed them from January 1963 to December 1979. Weiss (1982) showed that there was a small "epidemic" of respiratory-tract cancer, including 14 cases of lung cancer and two cases of laryngeal cancer compared with two cases of lung cancer among 34 unexposed men (0.51 expected). This epidemic peaked 15-19 years after the onset of exposure and began to subside thereafter (as workplace exposure decreased). The standard mortality ratio (SMR) for lung cancer was determined to be 8.45 (white Philadelphia males as reference). Almost all the cases (13/14) of lung cancer were small-cell carcinomas (one was large-cell); the two laryngeal cancers were squamous cell carcinomas. The latency period ranged from 10 to 23 years. All the cancer cases occurred in men with moderate to heavy exposure. CMME was first used at the plant in 1948; 24 years later, the SMR was no longer statistically increased.

The lung mortality patterns of 1,794 employees (all men; <10 females were excluded) exposed to CMME (2-8% BCME) from 1948 to 1972 at six U.S. companies (accounting for the vast majority of U.S. exposure) were examined by Albert et al. (1975) and Pasternack et al. (1977). The control group was nonexposed men working in the companies during the same time. No CMME/BCME exposure concentrations were available. About 98% of the workers were white; race was not considered in the analysis. The age-adjusted rates for noncancer death and for overall cancer death were comparable in control and exposed men, whereas the age-adjusted respiratory tract cancer death rate was 2.5-fold greater in the exposed workers (1.48 in the exposed group and 0.59 in the control group). Of the 22 respiratory-tract cancer cases in

the exposed workers, 20 were bronchogenic, one was laryngeal, and the other mediastinal. At one of the firms (company 2, probably Rohm & Haas in Philadelphia, PA), where at least 5 years had elapsed since the first exposure, a clear dose-response between exposure and respiratory-tract cancer rate was obtained. All 19 respiratory-tract cancer deaths were seen in workers with heavy exposure, and occurred at an early age of onset (77% occurring before age 55, as compared with 43% in U.S. white males). Smoking histories of the workers were not considered in the analysis.

Collingwood et al. (1987) conducted a 7-year (1973-1980) follow-up of workers at the six companies above, and the seventh major producer of CMME in the United States was included for follow-up from 1953 to 1980. At company 7, 26% of the workers were female. Overall, 96% of the workers were male and 97% were white. This study showed that respiratory-tract cancer mortality was increased only at company 2 (obs = 32; SMR = 430) and company 7 (obs = 9; SMR = 603), although the sex of the workers was not specified. There was a significant exposure-response relationship with cumulative time-weighed exposure. Of the 32 respiratory-tract cancer deaths with verifiable cell type, oat-cell carcinoma accounted for the highest proportion (38%) among exposed workers, whereas adenocarcinoma accounted for the highest proportion (31%) in nonexposed workers.

Workers were exposed to CMME/BCME in a chemical factory (Rohm & Haas) in Chauny, France, where CMME was used in making anion-exchange resins since 1958. Air concentrations of BCME were measured from 1979 to 1984 (Gowers et al. 1993). The annual average air concentration of BCME was 0.6-4.4 ppb. The highest BCME concentration corresponds to CMME concentrations of 0.044-0.44 ppm, if BCME represents 1-10% of the CMME in the air. Although respiratory-tract cancer rates were increased, the workers were not examined after a sufficient latency period and the cancer cases observed were probably due to earlier, substantially higher exposures.

In a group of 318 Shanghai workers (212 men, 106 women) exposed to CMME (containing unknown amounts of BCME) for at least 1 year between 1958 1981, there were 16 cancer deaths, of which 12 were lung cancer (Hsueh et al. 1984). The air concentrations of CMME were not specified and smoking histories of the workers were not reported. Taking into account the age, sex, and calendar-year specific mortality, the SMR for all cancer was 485, and for lung cancer was 2,296, whereas the proportional mortality ratio (PMR) was 219 for all cancer and 855 for lung cancer. All cancer deaths occurred in male workers; it is unclear whether this was due to different exposures. Illness occurred after 2-18 years of exposure, the average exposure was 10.5 years. Histologic examination of the cancers indicated that 70% were undifferentiated cell type carcinomas (Hsueh et al. 1984).

A study of 276 men working in CMME production (BCME content unknown) at a factory in South Wales between 1948 and 1980 showed an increased incidence of lung cancer but not other cancers compared with a local unexposed population of 295 men (McCallum et al. 1983). Measurements of

CMME were not taken, but the author indicated that exposure "may have been high." The rate of cancer deaths was related to total exposure duration and average exposure rate, and total dose, but the authors stated that "the degree of exposure appeared to be more important than the duration of exposure in determining carcinogenicity." The incidence of cancer decreased after the manufacturing process was changed to decrease CMME exposure. In another factory in the United Kingdom (northeastern England), where air CMME concentrations were "estimated to be low" an increase in cancer rate was not found (McCallum et al. 1983). The first case of lung cancer was diagnosed about 13 years after production began. Smoking histories of the men were not available.

Wu (1998) reported that air concentrations of CMME at a chemical plant in Shanghai, China, between 1977 and 1978 were 1.2-59 ppm, and might have been much higher previously (Wu 1988). These measurements are inconsistent with the report by Travenius (1982) that the highest tolerable concentration of CMME (or BCME) in air is 5 ppm; the reason for the discrepancy is unknown but might be partly due to analytic differences in air-concentration measurements. Of the Chinese workers exposed to CMME for at least 1 year (534 men and 381 women) from the 1950s through 1981, 15 died of lung cancer compared with 0.97 death expected based on Shanghai death rates (SMR = 1,546; 95% CI = 944-2,531). The mortality incidence from lung cancer was reportedly related to the amount of CMME exposure but was unrelated to cigarette smoking. Histologic analysis of the lung cancers indicated 8/11 were undifferentiated cell cancers and 3/11 were squamous cell cancers. The average age of death was 50 years (range: 32-64 years), which was 10 years younger than the age of death from cancer in the general Shanghai population. No details of any adverse human health effects besides cancer, the method used to analyze air concentrations, or the degree of contamination by BCME were provided.

2.7. Summary

No quantitative information was located regarding acute exposure to CMME in humans, although anecdotal reports indicate that the vapors are severely irritating and painful to the eyes and nose. No short-term studies were located describing nonlethal effects of CMME exposure in humans. Chronic exposure to CMME has resulted in coughing, wheezing, blood-stained sputum, breathing difficulty (dyspnea), weight loss, and death from lung cancer.

A number of studies in the United States and abroad (Japan, China, United Kingdom, and France) have described occupational exposure to CMME and BCME that was associated with an increased incidence of lung cancer. The lung cancer occurred approximately 10 years earlier than in the general population (who would most likely get it from cigarette smoking), was of a histologic type distinct from that induced by cigarette smoking, and showed a dose-response when exposures were estimated semi-quantitatively. In the few rare reports in

which air concentrations of CMME were determined, exposure durations were insufficient or inadequate follow-up was conducted to allow the relationship between exposure and cancer development to be quantified.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Groups of 6 rats (strain not specified) exposed for 2-4 h to CMME at 100-10,000 ppm experienced marked irritation to the mucous membranes at concentrations (Hake and Rowe 1963). A 30-min exposure to 2,000 ppm or a 4-h exposure to 100 ppm was "dangerous to life." Death was usually from chemical pneumonia several days or weeks after exposure. Details of the specific concentrations, exposure durations, and accompanying animal responses were not given.

Drew et al. (1975) examined the acute inhalation toxicity of CMME (commercially obtained; BCME content specified) using approximately 8-week old male Sprague-Dawley rats. CMME vapor was generated by bubbling air through or passing it over liquid CMME before introduction into 128-L or 1.3-m^3 exposure chambers; concentration was measured every half hour. Rats were exposed to CMME for 7 h at 12.5-225 ppm (see Table 2-3) and the observation period was 14 days. The number of animals was not specified but appeared to be more than 10 per concentration. Lungs were removed from each animal and weighed. Damage was measured as an increase of 3 standard deviations (SD) in the lung-to-body weight ratio; the ratio for controls was approximately 0.6. A value of 0.9 was considered to be elevated, because previous studies in the same laboratory showed it provides an objective criterion for the evaluation of lung damage for irritants. Animals given CMME had concentration-related increases in their relative lung weights. Congestion, edema, hemorrhage, and acute necrotizing bronchitis were evident in lungs of animals that died and to a lesser degree in surviving animals. No statements were made about the incidence of lung lesions in the 12.5-ppm group, so this possibility cannot be ruled out even though no significant changes in lung-to-body weight ratio were found. The LC_{50} was graphically estimated by the authors to be 55 ppm.

Drew et al. (1975) exposed 25 male Sprague-Dawley rats daily for 30 days to technical grade CMME at 1.0 or 10.0 ppm (BCME content specified). The exposure duration was not stated but was likely 6 h/day. (Several studies were described in the same report, including other single-exposure studies that used exposure durations of 7 h/day and a multiple-exposure study in which exposure was for 6 h/day; therefore, 6 h/day was assumed for the 30-day exposure study). In the 10 ppm group, rats began to die on the third exposure day and 22/25 died by day 30. All animals that died had greatly increased lung-to-body weight

TABLE 2-3 Mortality, Lung-to-Body Weight Ratio, and Estimated LC_{50} in Rats after Single 7-Hour Exposure to Chloromethyl Methyl Ether

Concentration (ppm)	Mortality at 14 d (%)	Rats with Increased Lung-to-Body Weight Ratio (%)[a]	Estimated LC_{50}[b]
225	100[c]	80	55 ppm
141	100	80	
70	100	90	
54	43	67	
42	225 (25)[d]	55	
26	110 (10)[d]	20	
12.5	0	0	

[a]Relative lung weight is greater than the control mean plus 3 standard deviations.
[b]LC_{50} value were estimated graphically by the study authors.
[c]All rats died after 4 h of exposure.
[d]The mortality percentage in the paper appeared to be typographic errors; suggested values are in parentheses.
Source: Adapted from Drew et al. 1975.

ratios (up to 2.2 vs. 0.6 for controls), 10/25 had bronchial epithelial hyperplasia, and one rat had squamous metaplasia. Of the rats exposed to CMME at 1.0 ppm, one died on exposure day 16 and one on day 22. The cause of death was not specified. Of the survivors, five were killed at the end of the last exposure; four had normal lungs and one had slight bilateral hemorrhage. Five more rats were killed 2 weeks later, and the remaining 13 rats were observed for their lifetime. No effects on weight gain occurred in the treated rats. The rats that were observed for their lifetimes had minimal mucosal effects; two had regenerative hyperplasia, one had squamous metaplasia of the bronchial epithelium, and one had squamous metaplasia of the trachea. No tumors or effects on lung-to-body weight ratios were reported.

3.1.2. Hamsters

Drew et al. (1975) examined the acute inhalation toxicity of CMME (commercially obtained; BCME content specified) in male Syrian golden hamsters (~6 weeks old). CMME vapor was generated by bubbling air through or passing it over liquid CMME before introduction into 28-L or 1.3-m^3 exposure chambers; concentrations were measured every half hour. Hamsters were exposed to CMME for 7 h at 12.5-225 ppm (see Table 2-4) and observed for 14 days. The number of animals was not specified but appeared to be more than 10 per concentration. Lungs were removed from each animal and weighed. Damage was measured as an increase of 3 standard deviations in the lung-to-body weight ratio. Animals given CMME had concentration-related increases in their relative lung weights. Congestion, edema, hemorrhage, and acute necro-

tizing bronchitis were evident in lungs of animals that died and to a lesser degree in surviving animals. The LC_{50} was graphically estimated by the authors to be 65 ppm.

3.2. Nonlethal Toxicity

3.2.1. Mice

Using an upper-respiratory-tract screening technique (Alarie 1966) with A/Heston male mice, Leong et al. (1971) reported slight irritation in mice exposed to CMME at 40 ppm (0.3-2.6% BCME) for 60 sec. No further details of the experiment were provided; however, in this technique mice are typically placed in body plethysmographs and a decrease in their breathing rate during the 60-sec exposure or during the ensuing 15-min observation period is considered indicative of irritation.

No deaths occurred in A/Heston male mice exposed for 6 h to CMME 14.6-100 ppm (0.3-2.6% BCME) within 14 days of exposure (Leong et al. 1971). No further details of the study were provided.

3.3. Neurotoxicity

No studies were found that assessed the neurotoxicity of CMME in animals.

3.4. Developmental and Reproductive Toxicity

No studies were found that assessed the developmental or reproductive effects of CMME in animals.

TABLE 2-4 Mortality, Lung-to-Body Weight Ratio, and Estimated LC_{50} in Hamsters after Single 7-Hour Exposure to Chloromethyl Methyl Ether

Concentration (ppm)	Mortality at 14 d (%)	Hamsters with Increased Lung-to-Body Weight Ratio[a]	Estimated LC_{50}[b]
225	100[c]	90	65 ppm
141	70	80	
70	60	100	
54	33	63	
42	0	60	
26	0	10	
12.5	0	0	

[a]Relative lung weight is greater than the control mean plus 3 standard deviations.
[b]LC_{50} values were estimated graphically by the study authors.
[c]Two hamsters died during the exposure period.
Source: Adapted from Drew et al. 1975.

3.5. Genotoxicity

F344 rats given the maximum tolerated concentration of CMME (concentration not stated) had a slight but not statistically definitive increase in micronuclei of the bone marrow, but had negative results in the hypoxanthine phosphoribosyl-transferase (HPRT) specific locus assay of lung fibroblasts (Heddle et al. 1991).

CMME (5-10 mg) was weakly mutagenic in *Drosophila melanogaster* larvae (Filippova et al. 1967). Viral transformation of SA7/SHE cells was enhanced by CMME at 10 μg/mL in the absence of metabolic activation (Casto 1981).

CMME (purity unknown) was mutagenic (approximately 2-fold increase in revertants) in *Salmonella typhimurium* TA98 when tested at a concentration of 1.0 μL/2,000 cm^3 in the absence of metabolic activation (Norpoth et al. 1980). CMME was found to be mutagenic in *Escherichia coli* and *S. typhimurium* by Mukai and Hawryluk (1973), although experimental details were not provided.

Technical grade CMME (12.5 or 25 μmols) did not induce DNA, RNA, or protein synthesis in the epidermis of mice treated dermally with CMME, as measured by radiolabeled thymidine, cytidine, and leucine (Slaga et al. 1973). However, when higher amounts of CMME were applied (50 or 125 μmols) followed by the promoter croton oil, a "marginal" initiating effect was seen (Slaga et al. 1973).

3.6. Carcinogenicity

Fifty A/Heston male mice were exposed to CMME at 2 ppm (0.3-2.6% BCME) for 6 h/day, 5 days/week, for 21 weeks (total of 101 exposures), after which they were sacrificed (Leong et al. 1971). Exposure was in 100-L acrylate plastic chambers, and the CMME vapor was generated by metering liquid CMME into the airstream entering the exposure chamber; the analytic concentration of the CMME inside the chamber was not measured. There was no effect on mortality, body weight, or the appearance of the mice throughout the study. The lungs of all the treated animals, as well as the 49 control males (exposed to filtered room air for 28 weeks) were examined histologically. The incidence and frequency of lung adenomas was increased slightly in the CMME-exposed mice; 50% of the CMME-treated mice had tumors compared with 41% of the controls, and the mean number of adenomas per tumor-bearing animal was 3.1 for the treated mice and 2.2 for the controls. It was not stated whether other parts of the respiratory system were examined for tumors. Microscopically, the tumor cells from control animals were uniform in size and shape whereas tumor cells from the treated animals were less well-defined and frequently formed papillary structures in the surrounding lung tissues. The carcinogenic affect of CMME could not be definitively established from this study because of the small amount of contaminating BCME (Leong et al. 1971).

In a lifetime inhalation study conducted by Laskin et al. (1975), 74 male Sprague-Dawley rats and 90 Syrian golden hamsters were given CMME at 1 ppm for 6 h/day, 5 days/week. There was no effect on mortality or body weight gain in either species. Histologic examination of the respiratory-tract mucosa of the rats showed a marked increase in the incidence of tracheal squamous metaplasia and bronchial hyperplasia compared with controls (74 sham exposed), as well as one squamous-cell carcinoma of the lung (with metastasis to the kidneys) and one esthesioneuroepithelioma of the olfactory epithelium. Additionally, one animal had an undifferentiated pituitary tumor that was probably not related to treatment. The treated hamsters had few mucosal differences from the 80 sham exposed controls, although they had more peripheral bronchoalveolar changes, including metaplasia and alveolar cell atypia (nuclear abnormality). One exposed hamster had a lung adenocarcinoma and one had a tracheal squamous papilloma (0 in controls).

3.7. Summary

There was one major study of the acute toxicity of CMME in rats and hamsters, where the LC_{50} based on a 7-h exposure and 2-week observation period was about 55 ppm for rats and 65 ppm for hamsters (Drew et al. 1975). Death was not immediate, and usually resulted from pneumonia. Rats given 30 exposures to CMME at 1.0 or 10.0 ppm (probably for 6 h/day) had premature mortality and lung hyperplasia or metaplasia (Drew et al. 1975). Mice exposed to CMME at 2 ppm for 6 h/day for 21 weeks had a slight increase in lung tumors (Leong et al. 1971). Rats and hamsters exposed to CMME at 1 ppm for 6 h/day, 5 days/week for a lifetime had increased incidences of respiratory-tract tumors (Leong et al. 1971; Laskin et al. 1975).

Rats and mice appeared to be able to tolerate (no apparent irritation or effects on demeanor) concentrations of CMME or BCME greater than those producing carcinogenicity or toxicity (>1 ppm).

No studies were found that assessed developmental or reproductive effects of CMME on animals. CMME was genotoxic in *S. typhimurium* in the absence of metabolic activation, and caused a slight increase in bone marrow micronuclei in F344 rats and mutations in *D. melanogaster* larvae (Filippova et al. 1967; Mukai and Hawryluk 1973; Norpoth et al. 1980; Sram et al. 1983; Heddle et al. 1991).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No information was found in the literature regarding CMME metabolism. CMME hydrolyzes completely and irreversibly in water to form HCl, methanol, and formaldehyde. HCl and formaldehyde can form BCME, although the kinetics of the conversion from CMME to BCME have not been defined

(Travenius 1982). It is unknown if CMME or its hydrolysis products are further metabolized in vivo. Consistent with its in situ hydrolysis, the respiratory tract is the primary site of technical grade CMME toxicity and carcinogenicity in humans and animals. It is unknown to what extent the CMME hydrolysis products, metabolites, or any potentially-formed BCME are responsible for the toxicity and carcinogenicity of CMME.

4.2. Mechanism of Toxicity

The mechanism of CMME toxicity has not been elucidated. Several investigators have suggested that CMME is a direct-acting carcinogen that causes radiomimetic injury (Drew et al. 1975; Travenius 1982). CMME is very reactive because of the high electronegativity of the oxygen and its attachment to the same carbon atom as chlorine (Burchfield and Storrs 1977). Nucleophilic displacement of the halogen-bearing carbon atom should occur readily and, therefore, CMME is an alkylating agent. It has been shown to react with DNA (Burchfield and Storrs 1977). However, in other in vitro studies, CMME did not form any isolable discrete base-alkylation products detected by thin-layer chromatography, and had no effect on the λ max, T_m, and buoyant density of salmon sperm DNA (Van Duuren et al. 1969, 1972).

4.3. Structure Activity Relationships

The chemical most related to technical grade CMME in its behavior is BCME. Comparison of LC_{50} values for CMME and BCME in rats and hamsters (55-65 ppm for CMME; 7 ppm for BCME) indicates that BCME is more acutely toxic by inhalation than CMME (Drew et al. 1975). Animal carcinogenesis studies indicate that BCME is at least 10-fold more potent a carcinogen than CMME by inhalation (Drew et al. 1975; Kuschner et al. 1975; Laskin et al. 1975) and dermal application and subcutaneous injection (Gargus et al. 1969; Van Duuren et al. 1968, 1969). CMME odor, however, is more readily detected than BCME odor (Rohm & Haas, personal communication, February 1998).

Burchfield and Storrs (1977) reported that when chlorine and oxygen atoms are separated in structurally-related chloroethers by two or more carbon atoms (e.g., bis(β-chloroethyl) ether), the alkylating power and carcinogenicity are greatly reduced. Ocular irritation, however, seems to be unaffected by chain length (Kirwin and Galvin 1993).

4.4. Other Relevant Information

4.4.1. Species Variability

The study by Drew et al. (1975) indicated that there is not a great deal of variability in CMME acute toxicity between species; the 7-h LC_{50} for rats and hamsters was 55 and 65 ppm, respectively.

4.4.2. Susceptible Populations

No studies were found that identified populations susceptible to CMME toxicity.

4.4.3. Concentration-Exposure Duration Relationship

No data were available from which to determine the concentration-time relationship for CMME. 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 ranges from 0.8 to 3.5. To obtain protective AEGL-2 and AEGL-3 values for 30-480 minutes, n = 3 and n = 1 were used to extrapolate to shorter and longer durations, respectively, than the exposure duration in the key study. The 10-min values were not extrapolated because the National Advisory Committee determined that extrapolating from ≥4 h to 10 min has unacceptably large inherent uncertainty, so the 30-min value was adopted for 10-min value to be protective of human health. AEGL-1 values were not derived.

4.4.4. Concurrent Exposure Issues

Because commercially available CMME is contaminated with 1-10% BCME, exposure to CMME inevitably involves simultaneous exposure to BCME. No studies were found to determine the effect of varying the BCME contamination on CMME toxicity or carcinogenicity. However, since BCME is a more potent toxicant and carcinogen than CMME, its degree of contamination is expected to have an effect on CMME toxicity and carcinogenicity.

4.4.5. Neoplastic Potential by Other Routes of Exposure

CMME also has been shown to have carcinogenic potential by routes other than inhalation. Purified CMME (99.5%) was not a complete carcinogen or a promoter when applied topically (0.1 or 1 mg; 2% solution in benzene) to the skin of female ICR/Ha Swiss mice three times per week for 325 days, but did act like a tumor initiator (papillomas or squamous carcinomas) when a single application was given 2 weeks before the promoter croton resin (Van Duuren et al. 1968, 1969). When purified CMME (99.5%) was injected subcutaneously in female Sprague-Dawley rats (1-3 mg/wk for 301 days), 14/20 animals developed nodules at the injection site and 1/20 developed fibrosarcoma; no lesions developed in the controls (Van Duuren et al. 1968, 1969). Female ICR/Ha Swiss mice given weekly subcutaneous injections of CMME (99.5% pure) at 300 μg in Nujol (0.1 mL) over their lifetime developed sarcomas at the injection site (10/30 compared with 0/30 controls) (Van Duuren at al. 1972). A single

subcutaneous injection of CMME (0.3-2.6% BCME) at 125 µL/kg (0.17 mg/kg) in peanut oil was given to newborn ICR Swiss mice (1-3 days old; 48 females, 51 males). Treated mice were killed after 6 months, and necropsy showed a slightly increased incidence and multiplicity of pulmonary adenomas (incidence of 17% for treated and 14% for controls; multiplicity of 0.21 for treated and 0.14 for controls), which the study author stated might have been from the contaminating BCME (Gargus et al. 1969).

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No appropriate human studies were found.

5.2. Summary of Animal Data Relevant to AEGL-1

No appropriate animal studies were found. The mouse respiratory-inhibition study of Leong et al. (1971) had an exposure duration that was too short (60 sec), and the resulting decrease in the breathing rate was not quantified.

5.3. Derivation of AEGL-1

AEGL-1 values were not recommended because no studies were available in which toxicity was limited to AEGL-1 effects. Concentrations that caused AEGL-1 effects also caused toxicity within or exceeding the severity of AEGL-2 effects.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No appropriate human data were found.

6.2. Summary of Animal Data Relevant to AEGL-2

The following studies were considered for derivation of AEGL-2 values:

- The study in which male A/Heston mice exposed for 6 h to CMME at 14.6-100 ppm (0.3-2.6% BCME) had no deaths within 14 days of exposure (Leong et al. 1971). The presence of toxic effects in the animals was not investigated.

- The rat and hamster 7-h LC_{50} studies (Drew et al. 1975). Rats were exposed to CMME at 12.5-225 ppm (content of BCME not given) for 7 h and observed for 14 days; the number of animals tested was not stated but appeared to be 10 or more per concentration. Increased relative lung weights, congestion, edema, hemorrhage, and acute necrotizing bronchitis were evident in the lungs of animals that died and to a lesser degree in animals surviving to 14 days. It was assumed that some of these effects occurred at the lowest test concentration of 12.5 ppm. An adjustment factor of 3 could be applied to the LOAEL of 12.5 ppm to estimate a NOAEL of 4.2 ppm for lung lesions in both species.
- The 30-day exposure study in which male rats were exposed to CMME at 1 ppm (content of BCME not specified; see Section 3.1.1.) for 6 h/day, 5 days/week (Drew et al. 1975). Two rats died (on exposure days 16 and 22), although it is unknown if the deaths were treatment related. One of five rats sacrificed immediately after exposure had slight hemorrhage and several rats retained for lifetime study had lung hyperplasia or squamous metaplasia but no tumors.
- Lifetime exposure study of male rats and hamsters to CMME at 1 ppm for 6 h/day, 5 days/week (Laskin et al. 1975). Mortality and body weight gain were unaffected. Rats had an increased incidence of tracheal squamous metaplasia and bronchial hyperplasia, and two had respiratory-tract tumors. Hamsters had an increased incidence of bronchoalveolar metaplasia and alveolar cell atypia, and one had lung adenocarcinoma and another had tracheal squamous papilloma.
- The study in which male mice were exposed to CMME at 2 ppm (0.3-2.6% BCME) for 6 h/day, 5 days/week, for 101 exposures over 21 weeks, after which they were killed (Leong et al. 1971). CMME had no effect on mortality, body weight, or demeanor but had a slightly increased incidence and frequency of lung adenomas.

6.3. Derivation of AEGL-2

AEGL-2 values were based on an acute toxicity study in which rats and hamsters were exposed to CMME at 12.5-225 ppm (content of BCME not given) for 7 h and observed for 14 days (Drew et al. 1975). Toxic effects were not attributed to specific concentrations, but it was stated that animals that died had increased relative lung weights, pulmonary congestion, edema, hemorrhage, and acute necrotizing bronchitis. These effects were found to a lesser degree in surviving animals. Therefore, 12.5 ppm was considered the LOAEL for serious or irreversible lung lesions in both species, and was also a NOEL for lethality in rats. An estimated NOAEL of 4.2 ppm for serious or irreversible lung lesions in both species was obtained by dividing the LOAEL by an adjustment factor of 3. No data were available from which to determine the CMME concentration-time relationship to derive AEGL-2 values for time periods other than 7 h. ten Berge et al. (1986) showed that the concentration-time relationship for many irritant

and systemically acting vapors and gases can be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. To obtain protective AEGL-2 values, scaling across time was performed using n = 3 and n = 1 for exposure durations shorter and longer, respectively, than 7 h. The 30-min values were adopted for the 10-min values to be protective of human health (see Section 4.4.3.). A total uncertainty factor of 10 was used. A factor of 3 was applied for interspecies extrapolation because CMME caused a similar degree of lung toxicity in two animal species, and is expected to cause similar toxicity in human lungs. A factor of 3 was applied for intraspecies variability as recommended by NRC (2001) for chemicals with a steep dose-response relationship, as the effects are unlikely to vary greatly among humans. An intraspecies uncertainty factor of 3 was also used in the derivation of AEGL-2 values for BCME. A modifying factor of 1.7 was also applied because the BCME content in technical grade CMME in the key study was unknown. The modifying factor was obtained by assuming contamination with 10% BCME (the maximum reported) and accounting for its greater toxicity (LC_{50} for rats was 55 ppm for CMME and 7 ppm for BCME in the key study), as follows: [0.1 × (55 ppm ÷ 7 ppm)] + [0.9 × 1] = 1.7. The resulting AEGL-2 values are shown in Table 2-5; calculations are detailed in Appendix A. The analytic detection limit of CMME in the air is <1 ppb; the AEGL-2 values are well above the detection limit.

Data were unavailable to conduct a carcinogenicity risk assessment for CMME, but an assessment was conducted for the related compound BCME (see Appendix D). If the assumptions are made that technical CMME contains 10% BCME, and that "pure" BCME is 10-fold more potent a carcinogen than "pure" CMME (Gargus et al. 1969; Van Duuren et al. 1968, 1969; Drew et al. 1975; Kuschner et al. 1975; Laskin et al. 1975), then it follows that technical CMME at most has 19% of the carcinogenic activity of BCME. Thus, if a linear relationship between exposure concentration and cancer risk is assumed for CMME and BCME, the cancer risk associated with the AEGL-2 values are estimated to range from 5.5×10^{-5} to 9.6×10^{-4}, and for AEGL-3 values are estimated range from 2.4×10^{-4} to 4.1×10^{-3}, as shown in Appendix D. It is unknown, however, how well the stated assumptions hold true and predict the carcinogenicity of CMME. Because of this uncertainty and the large differences in the methods used for deriving AEGL values and for extrapolating carcinogenic potency from a lifetime study to a single exposure, the noncarcinogenic end points were considered to be more appropriate for deriving AEGLS for CMME.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No appropriate human studies were available.

TABLE 2-5 AEGL-2 Values for Chloromethyl Methyl Ether

10 min	30 min	1 h	4 h	8 h
0.60 ppm (2.0 mg/m^3)	0.60 ppm (2.0 mg/m^3)	0.47 ppm (1.5 mg/m^3)	0.30 ppm (0.98 mg/m^3)	0.22 ppm (0.72 mg/m^3)

7.2. Summary of Animal Data Relevant to AEGL-3

The following studies were considered relevant for the development of AEGL-3 values:

- Study by Hake and Row (1963) in which rats exposed for 30-min to CMME at 2,000 ppm (purity unknown) or for 4-h to 100 ppm died from chemical pneumonia several days or weeks after exposure. Further study details were not provided.
- Study by Drew et al. (1975) that reported 7-h LC_{50} values of 55 ppm for rats and 65 pm for hamsters. Concentration-related increases in relative lung weights, congestion, edema, hemorrhage, and acute necrotizing bronchitis were found in all groups of treated animals that died and were found to a lesser degree in surviving animals.
- Study of male Sprague-Dawley rats exposed for 30 consecutive days to technical grade CMME at 10.0 ppm for 6 h/day (Drew et al. 1975). Rats began to die on the third exposure day and 22/25 died by day 30. All animals that died had greatly increased lung-to-body weight ratios, 10/25 had bronchial epithelial hyperplasia, and one rat had squamous metaplasia.
- Study by Leong et al. (1971) of male mice exposed to technical grade CMME at 2 ppm (0.3-2.6% BCME) for 6 h/day, 5 days/week, for 101 exposures over 21 weeks. No effect on mortality rates, body weight, or demeanor were observed, but there was a slightly increased incidence (50% vs. 41% in controls) and multiplicity (3.1 vs. 2.2 for the controls) of lung adenomas. The morphology of the tumor cells in control and treated animals differed.
- Lifetime study in which male rats and hamsters exposed to technical grade CMME at 1 ppm (6 h/day, 5 days/week) had no differences in mortality or body weight gain compared with controls, but had an increased incidence of pulmonary squamous metaplasia and hyperplasia (Laskin et al. 1975). Two rats (of 74) and two hamsters (of 90) developed respiratory tract tumors (0 in controls).

7.3. Derivation of AEGL-3

AEGL-3 values were based on the LC_{50} study in which rats and hamsters exposed for 7 h to CMME at 12.5-225 ppm (content of BCME not given) had increased relative lung weights, congestion, edema, hemorrhage, and acute necrotizing bronchitis (Drew et al. 1975). The effects occurred in animals that

died and, to a lesser degree, in animals that survived. Assuming n = 20 for all dose groups, a $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) was calculated using the long/probit model from EPA's Benchmark Dose Software, Version 1.3.2 (EPA 2005b). The $BMCL_{05}$ was approximately 18 ppm for hamsters and 19 ppm for rats; the lower value of 18 ppm was used for derivation of AEGL-3 values. (Alternatively, if it is assumed that n = 10 for all test concentrations, the $BMCL_{05}$ is 15 ppm for rats and 16 ppm for hamsters, and if n = 30 for all test concentrations the $BMCL_{05}$ is 20 ppm for rats and 19 ppm for hamsters.) Increased relative lung weights, congestion, edema, hemorrhage, and acute necrotizing bronchitis were found in animals that died and, to a lesser degree, in animals that died. Data were not available to determine the concentration-time relationship, and scaling across time was performed using the ten Berge et al. (1986) equation $C^n \times t = k$ and n = 1 or n = 3, as described above for AEGL-2 values. An uncertainty factor of 10 was used. A factor of 3 was applied for interspecies extrapolation because the NOEL for lethality was virtually the same in two species in the key study, and lethality is expected to occur by a similar mode of action in humans and animals. A factor of 3 was applied for intraspecies variability as recommended by NRC (2001) for chemicals with a steep dose-response relationship, because the effects are unlikely to vary greatly among humans. An intraspecies uncertainty factor of 3 was also used in the derivation of AEGL-3 values for BCME. As for AEGL-2, a modifying factor of 1.7 was also applied because the content of BCME in technical grade CMME in the key study was unknown. The resulting AEGL-3 values are shown in Table 2-6; 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 technical grade CMME and their relationship to one another are shown in Table 2-7. No data were available to determine the concentration-time relationship for CMME toxic effects. Scaling across time for 30-480 min was performed using the equation $C^n \times t = k$, with n = 3 and n = 1 to extrapolate to durations shorter and longer, respectively, than the exposure duration in the key study. The 10-min values were not extrapolated because the National Advisory Committee determined that extrapolating from ≥4 h to 10 min has unacceptably large inherent uncertainty. The 30-min values were adopted for 10-min values to be protective of human health.

TABLE 2-6 AEGL-3 Values for Chloromethyl Methyl Ether

10 min	30 min	1 h	4 h	8 h
2.6 ppm (8.6 mg/m^3)	2.6 ppm (8.6 mg/m^3)	2.0 ppm (6.6 mg/m^3)	1.3 ppm (4.3 mg/m^3)	0.93 ppm (3.1 mg/m^3)

AEGL-1 values were not derived because no studies were available in which toxicity was limited to AEGL-1 effects. AEGL-2 and AEGL-3 values were based on an acute toxicity study in which rats and hamsters were exposed to CMME at 12.5-225 ppm (content of BCME not given) for 7 h. A concentration of 12.5 ppm was considered the LOAEL for serious or irreversible lung lesions in both species, and was a NOEL for lethality in rats. An estimated NOAEL of 4.2 ppm for serious or irreversible lung lesions in both species was obtained by dividing the LOAEL by an adjustment factor of 3. For both the AEGL-2 and AEGL-3, an uncertainty factor of 10 was used (3 for interspecies and 3 for intraspecies variability), a modifying factor of 1.7 was applied because the BCME content in technical grade CMME in the key study was unknown, and scaling across time was performed using the ten Berge et al (1986) equation $C^n \times t = k$, with n = 1 or n = 3.

Data were unavailable to conduct a carcinogenicity risk assessment for CMME, but an assessment was conducted for the related compound BCME (see Appendix D). If the assumptions are made that technical CMME contains 10% BCME, and that "pure" BCME is 10-fold more potent as a carcinogen than "pure" CMME (which is suggested by experimental data), then technical CMME has 19% of the carcinogenic activity of BCME at most. Thus, if a linear relationship between exposure concentration and cancer risk is assumed for CMME and BCME, the cancer risk associated with the AEGL-2 values are estimated to range from 5.5×10^{-5} to 9.6×10^{-4}, and for AEGL-3 values range from 2.4×10^{-4} to 4.1×10^{-3}, as shown in Appendix D. It is unknown, however, how well the stated assumptions hold true and predict the carcinogenicity of CMME. Because of this uncertainty and the large differences in methods used to derive the AEGL values compared with extrapolating carcinogenic potency from a lifetime study to a single exposure, the noncarcinogenic end points were considered to be more appropriate for deriving AEGL values.

8.2. Comparison with Other Standards and Guidelines

Numeric standards for exposure to technical grade CMME were not established by the Occupational Health and Safety Administration (OSHA), National Institute for Occupational Safety and Health (NIOSH), or the American Conference of Governmental Industrial Hygienists (ACGIH) because of its known human carcinogenicity. The ACGIH has developed a Threshold Limit Value - Time Weighted Average (TLV-TWA) of 0.001 ppm for the related chemical BCME, and suggests that exposure to CMME could be monitored on the basis of the BCME TLV-TWA. Because studies have shown that BCME is more toxic and a more potent carcinogen than CMME, limiting CMME exposures to 0.001 ppm might be protective of CMME toxicity and carcinogenicity as well.

OSHA regulates occupational exposure to CMME under 29 CFR 1910.1006, which discusses control of exposures through the required use of engineering controls, work practices, and personal protective equipment, including respirators. NIOSH and ACGIH recommend that worker exposure be carefully controlled and reduced to the lowest achievable levels. Germany and Sweden also consider CMME a human carcinogen in their workplace exposure guidelines. The American Industrial Hygiene Association (AIHA 2000) has developed Emergency Response Planning Guidelines (ERPGs) for CMME. An ERPG-1 was not considered appropriate because CMME odor is easily noticed at 23 ppm and is strong at 100 ppm (Wagoner et al. 1972), which is above the LC_{50} values of 55 ppm for rats and 65 ppm for hamsters (Drew et al. 1975). The ERPG-2 of 1.0 ppm was selected because it was 10-fold lower than a concentration that did not produce a significant increase in the lung-to-body ratio of rats from a single 7-h exposure (Drew et al. 1975). The ERPG-3 of 10 ppm was chosen because it was below the maximum no-effect level of 12.5 ppm for pulmonary edema from a single 7-h exposure to CMME in rats and hamsters (Drew et al. 1975). The EPRG-3 value of 10 ppm was greater than the 1-h AEGL-3 value of 2 ppm. The values were based on the same study and no-effect level, but the AEGL-3 value was divided by an uncertainty factor of 10, adjusted for BCME content, and scaled across time.

A large chemical manufacturer in Philadelphia developed internal 1-h ERPG values for technical grade CMME of 0.01 ppm for ERPG-2 and 1 ppm for ERPG-3 (no ERPG-1); the respective ERPG values for BCME are 10-fold lower (Rohm & Haas, personal communication, February 1998). A TLV of 0.001 ppm was listed under "Health Hazards" by the Chemical Hazard Response Information System (CHRIS 1985).

The existing standards and guidelines for CMME are shown in Table 2-8.

8.3. Data Adequacy and Research Needs

No human or animal studies were found with defined exposures and responses that fell within the scope of AEGL-1 effects. CMME was toxic to animals and humans at concentrations below those leading to irritation and below the odor-detection level.

Appropriate single-exposure animal studies with AEGL-2 and AEGL-3 end points were few, and no useful (quantitative) human studies were available. However, two species were tested in the key study and had a similar response, and the lung is the target organ in animals and humans.

The BCME content of the CMME used in the key study should have been specified. Data quantifying the effect of BCME contamination on CMME toxicity are needed, and could be used to refine the modifying factor to account for the variability in BCME content of CMME in the AEGL derivations.

TABLE 2-8 Extant Standards and Guidelines for Chloromethyl Methyl Ether

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.60 ppm	0.60 ppm	0.47 ppm	0.30 ppm	0.22 ppm
AEGL-3	2.6 ppm	2.6 ppm	2.0 ppm	1.3 ppm	0.93 ppm
ERPG-1 (AIHA)[a]			Not appropriate		
ERPG-2 (AIHA)			1.0 ppm		
ERPG-3 (AIHA)			10 ppm		
PEL-TWA (OSHA)[b]					No value[b]
REL-TWA (NIOSH)[c]					No value[c]
TLV-TWA (ACGIH)[d]					No value[d]
MAK (Germany)[e]					No value[e]
OELV-LLV (Sweden)[f]					No value[f]

[a]ERPG (emergency response planning guidelines, American Industrial Hygiene Association (AIHA 2000).
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.
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.
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]PEL-TWA (permissible exposure limit–time-weighted average, Occupational Safety and Health Administration [54 Fed, Reg. 2931[1989]) is analogous to the ACGIH TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week. A numeric value was not assigned, but OSHA identifies CMME as an occupational carcinogen and workplace exposure is regulated by 29 CFR 1910.1006.
[c]REL-TWA (recommended exposure limit–time-weighted average, National Institute for Occupational Safety and Health (NIOSH 2005) is analogous to the ACGIH TLV-TWA. A numeric value was not assigned, but NIOSH considers CMME to be an occupational carcinogen subject to OSHA regulation (29 CFR 1910.1006), and recommends that exposure to it be reduced to the lowest feasible concentrations.
[d]TLV-TWA (threshold limit value–time-weighted average, American Conference of Governmental Industrial Hygienists (ACGIH 2004) 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. CMME was classified as carcinogenicity category A2 ("suspected human carcinogen"). No numeric value was assigned, but ACGIH (1991) recommends that worker exposure by all routes be controlled and kept as low as achievable, and suggests the exposures be monitored on the basis of the BCME TLV of 0.001 ppm.

[e]MAK (maximale Arbeitsplatzkonzentration [maximum workplace concentration], German Research Association). (DFG 2002) is analogous to the ACGIH TLV-TWA. A value was not developed but CMME was classified as a human carcinogen (Category 1), which applies to technical CMME that can be contaminated with ≤7% BCME.
[f]OELV-LLV (occupational exposure limit value-level limit value), Swedish Work Environmental Authority 2005). A value was not developed; CMME is classified as Group A, a substance that may not be handled.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR CHLOROMETHLYL METHYL ETHER

Derivation of AEGL-1 Values

AEGL-1 values were not derived because no studies were available in which toxicity was limited to AEGL-1 effects.

Derivation of AEGL-2 Values

Key study:	Drew et al. 1975
Toxicity end points:	4.2 ppm was NOAEL for serious or irreversible respiratory lesions in rats and hamsters. NOAEL obtained by dividing the LOAEL of 12.5 ppm by an adjustment factor of 3.
Time scaling:	$C^n \times t = k$ (n = 3 for longer to shorter exposure periods; n = 1 for shorter to longer exposure periods); extrapolation not performed for 10-min $(4.2 \text{ ppm}/17)^3 \times 7 \text{ h} = 0.106 \text{ ppm}^3\text{-h}$ $(4.2 \text{ ppm}/17)^1 \times 7 \text{ h} = 1.73 \text{ ppm}^3\text{-h}$
Uncertainty factors:	3 for interspecies variability 3 for intraspecies variability Combined uncertainty factor of 10
Modifying factor:	1.7 because BCME content in technical grade CMME in the key study was unknown. Calculated by assuming 10% BCME (the maximum contamination reported) and accounting for the greater toxicity of BCME (LC_{50} for rats was 55 ppm for CMME and 7 ppm for BCME in the key study): $[0.1 \times (55 \text{ ppm} \div 7 \text{ ppm})] + [0.9 \times 1] = 1.7$.

Calculations:

10-min AEGL-2	Set equal to 30-min value because of uncertainty in extrapolating a 7-h exposure to 10 min.
30-min AEGL-2:	$C^3 \times 0.5$ h = 0.106 ppm^3-h C = 0.60 ppm [2.0 mg/m^3]
60-min AEGL-2:	$C^3 \times 1$ h = 0.106 ppm^3-h C = 0.47 ppm [1.5 mg/m^3]
4-h AEGL-2:	$C^3 \times 4$ h = 0.106 ppm^3-h C = 0.30 ppm [0.98 mg/m^3]
8-h AEGL-2:	$C^1 \times 8$ h = 1.73 ppm-h C = 0.22 ppm [0.72 mg/m^3]

Derivative of AEGL-3 Values

Key study:	Drew et al. 1975
Toxicity end point:	NOEL of 18 ppm for lethality from extreme lung irritation in hamsters ($BMCL_{05}$)
Time scaling:	$C^n \times t = k$ (n = 3 for longer to shorter exposure periods; n = 1 for shorter to longer exposure periods); extrapolation not performed for 10-min $(18 \text{ ppm}/17)^3 \times 7$ h = 8.31 ppm^3-h $(18 \text{ ppm}/17)^1 \times 7$ h = 7.41 ppm-h
Uncertainty factors:	3 for interspecies variability 3 for intraspecies variability Combined uncertainty factor of 10
Modifying factor:	1.7 because BCME content in technical grade CMME in the key study was unknown. Calculated by assuming 10% BCME (the maximum contamination reported) and accounting for the greater toxicity of BCME (LC_{50} for rats was 55 ppm for CMME and 7 ppm for BCME in the key study): [0.1 × (55 ppm ÷ 7 ppm)] + [0.9 × 1] = 1.7.

Calculations:

10-min AEGL-3:	Set equal to 30-min value because of uncertainty in extrapolating a 7-h exposure to 10 min.
30-min AEGL-3:	$C^3 \times 0.5$ h = 8.31 ppm^3-hr C = 2.6 ppm [8.6 mg/m^3]
60-min AEGL-3:	$C^3 \times 1$ h = 8.31 ppm^3-h C = 2.0 ppm [6.6 mg/m^3]
4-h AEGL-3:	$C^3 \times 4$ h = 8.31 ppm^3-h C = 1.3 ppm [4.3 mg/m^3]
8-h AEGL-3:	$C^1 \times 8$ h = 4.2 ppm-h C = 0.93 ppm [3.1 mg/m^3]

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR CHRLOMETHYL METHYL ETHER

Derivation Summary

AEGL-1 VALUES

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

Reference: Not applicable

Test species/Strain/Number: Not applicable

Exposure route/Concentrations/Durations: Not applicable

Effects: Not applicable

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 adequacy: AEGL-1 values for technical grade CMME were not derived because there were no studies in which toxicity was limited to AEGL-1 effects.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.60 ppm	0.60 ppm	0.47 ppm	0.30 ppm	0.22 ppm

Reference: Drew, R.T., S. Laskin, M. Kuschner, and N. Nelson. 1975. Inhalation carcinogenicity of alpha halo ethers. I. The acute inhalation toxicity of chloromethyl methyl ether and bis(chloromethyl)ether. Arch. Environ. Health 30(2):61-69.

Test Species/Strain/Sex/Number: Male Sprague-Dawley rats and Syrian golden hamsters; number not specified but appeared to be 10 or more per concentration.

Exposure route/Concentrations/Durations: Inhalation of 12.5-225 ppm for 7 h; observed for 14 d

Effects: Concentration-related increases in relative lung weights. Congestion, edema, hemorrhage, and acute necrotizing bronchitis were evident in lungs of animals that died and, to a lesser degree, in animals surviving to 14 d (also assumed at 12.5 ppm). Mortality rates were:

(Continued)

AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
0.60 ppm	0.60 ppm	0.47 ppm	0.30 ppm	0.22 ppm

CMME (ppm)	Rats (%)	Hamsters (%)
225	100[a]	100[a]
141	100	70
70	100	60
54	43	33
42	225 (25)[b]	0
26	110 (10)[b]	0
12.5	0	0
	LC_{50} = 55 ppm (from reference) $BMCL_{05}$ = 19 ppm (probit analysis, if *n* = 20)	LC_{50} = 65 ppm (from reference) $BMCL_{05}$ = 18 ppm (probit analysis, if n = 20)

[a]The lung-to-body weight ratio was greater than the control mean plus 3 standard deviations.
[b]Appear to be typographic errors in the reference; suggested values are in parentheses.

End point/Concentration/Rationale: NOAEL of 4.2 ppm for serious or irreversible lung lesions in rats and hamsters, estimated by applying an adjustment factor of 3 to the LOAEL of 12.5 ppm.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3 applied because CMME caused a similar degree of lung toxicity in two animal species, and is expected to cause similar toxicity in human lungs.
Intraspecies: 3 recommended in the Standard Operating Procedures (NRC 2001) for chemicals with a steep dose-response relationship, because effects are unlikely to vary greatly among humans.

Modifying factor: 1.7 used because the BCME content in technical grade CMME in the key study was unknown; obtained by assuming 10% BCME (the maximum reported) and accounting for the greater toxicity of BCME (LC_{50} for rats was 55 ppm for CMME and 7 ppm for BCME in the key study): $[0.1 \times (55/7)] + [0.9 \times 1] = 1.7$.

Animal-to-human dosimetric adjustment: Not applied

Time scaling: $C^n \times t = k$. Default value of n = 3 when scaling from longer to shorter durations, and n = 1 when scaling from shorter-to-longer durations. The 30-min AEGL value was adopted for the 10-min value to protect human health (see Section 4.4.3.).

Data adequacy: The key study was adequate and the two test species had similar results. The key study did not state the number of animals per concentration, which did not affect the AEGL-2 derivation.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
2.6 ppm	2.6 ppm	2.0 ppm	1.3 ppm	0.93 ppm

Reference: Drew, R.T., S. Laskin, M. Kuschner, and N. Nelson. 1975. Inhalation carcinogenicity of alpha halo ethers. I. The acute inhalation toxicity of chloromethyl methyl ether and bis(chloromethyl)ether. Arch. Environ. Health 30(2):61-69.

Test species/Strain/Sex/Number: Male Sprague-Dawley rats and Syrian golden hamsters; number not given but appeared to be 10 or more per concentration.

Exposure route/Concentrations/Durations: Inhalation of 12.5-225 ppm for 7 h; observed for 14 d.

Effects: Concentration-related increases in relative lung weights. Congestion, edema, hemorrhage, and acute necrotizing bronchitis were evident in lungs of animals that died and, to a lesser degree, in animals surviving to 14 d (also assumed at 12.5 ppm). Mortality rates were:

CMME (ppm)	Rats (%)	Hamsters (%)
225	100[a]	100[a]
141	100	70
70	100	60
54	43	33
42	225 (25)[b]	0
26	110 (10)[b]	0
12.5	0	0
	LC_{50} = 55 ppm (from reference) $BMCL_{05}$ = 19 ppm (probit analysis, if n = 20)	LC_{50} = 65 ppm (from reference) $BMCL_{05}$ = 18 ppm (probit analysis, if n = 20)

[a]The lung-to-body weight ratio was greater than the control mean plus 3 standard deviations.
[b]Appear to be typographic errors in the reference; suggested values are in parentheses.

End point/Concentration/Rationale: NOEL of 18 ppm for lethality from extreme lung irritation in hamsters ($BMCL_{05}$).

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3 applied because the NOEL for lethality was virtually the same in two species in the key study, and lethality is expected to occur by a similar mode of action in humans and animals.
Intraspecies: 3 recommended in the Standard Operating Procedures (NRC 2001) for chemicals with a steep dose-response relationship, because effects are unlikely to vary greatly among humans.

(Continued)

AEGL-3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
2.6 ppm	2.6 ppm	2.0 ppm	1.3 ppm	0.93 ppm

Modifying factor: 1.7 used because the BCME content in technical grade CMME in the key study was unknown; obtained by assuming 10% BCME (the maximum reported) and accounting for the greater toxicity of BCME (LC_{50} for rats was 55 ppm for CMME and 7 ppm for BCME in the key study): $[0.1 \times (55/7)] + [0.9 \times 1] = 1.7$.

Animal-to-human dosimetric adjustment: Not applied

Time scaling: $C^n \times t = k$. Default value of n = 3 when scaling from longer to shorter durations, and n = 1 when scaling from shorter-to-longer durations. The 30-min AEGL value was adopted for the 10-min value to protect human health (see Section 4.4.3.).

Data adequacy: The key study was adequate and the two test species had similar results. The key study did not state the number of animals per concentration. This could have slightly affected the calculated $BMCL_{05}$ and AEGL-3 values. If it is assumed that n = 10 for all test concentrations, the $BMCL_{05}$ is 15 ppm for rats and 16 ppm for hamsters, and if n = 30, the $BMCL_{05}$ is 20 ppm for rats and 19 ppm for hamsters.

APPENDIX C

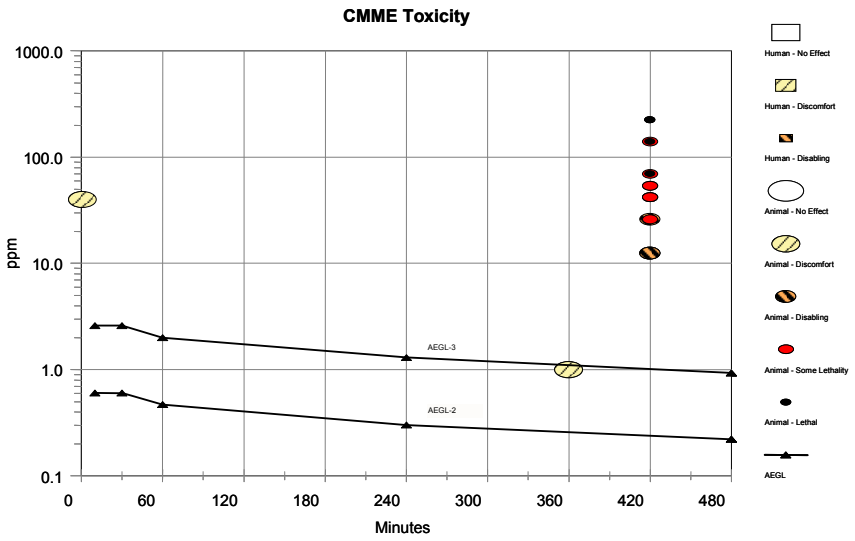

FIGURE C-1 Category plot of animal toxicity data compared with AEGL values. Multiple-exposure studies are not included in the plot.

APPENDIX D

CANCER ASSESSMENT OF CHLOROMETHYL METHYL ETHER AND bis-CHLOROMETHYL ETHER (BCME)

Data were unavailable to conduct a carcinogenicity risk assessment for CMME, but an assessment was conducted for the related compound BCME. EPA (2002) performed a cancer assessment of the related compound BCME using data from Kuschner et al. (1975). The calculated inhalation unit risk for BCME was 6.2×10^{-2} per $\mu g/m^3$, using the linearized multistage procedure, extra risk (EPA 2005b). The concentration of BCME corresponding to a lifetime risk of 1×10^{-4} is calculated as follows:

$$(1 \times 10^{-4}) \div [6.2 \times 10^{-2} (\mu g/m^3)^{-1}] = 1.6 \times 10^{-3} \mu g/m^3$$

To convert a 70-year exposure to a 24-h exposure, one multiplies by the number of days in 70 years (25,600). The concentration of BCME corresponding to a 1×10^{-4} risk from a 24-h exposure is:

$$(1.6 \times 10^{-3} \mu g/m^3)(25{,}600 \text{ days}) = 40.96 \mu g/m^3 \ (0.041 \text{ mg/m}^3 \text{ or } 0.0086 \text{ ppm})$$

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

$$(40.96 \mu g/m^3) \div 6 = 6.83 \mu g/m^3 \ (0.0068 \text{ mg/m}^3 \text{ or } 0.0014 \text{ ppm})$$

If the exposure is reduced to a fraction of a 24-h period, the fractional exposure (f) becomes (1/f) × 24 h (NRC 1985). Extrapolation to 10 min was not calculated because of unacceptably large inherent uncertainty. Because the animal dose was 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 concentrations is made to account for interspecies variability. The calculated concentration of BCME associated with a 1×10^{-4} cancer risk is shown in Table D-1 for a single exposure of 10 min to 8 h. For a 1×10^{-5} and 1×10^{-6} risk, the 1×10^{-4} values are reduced 10-fold or 100-fold, respectively.

If the assumptions are made that technical CMME contains 10% BCME, and that "pure" BCME is 10-fold more potent a carcinogen than "pure" CMME (which is suggested by experimental data), then technical-grade CMME has 19% of the carcinogenic activity of BCME at most ([90% of technical-grade CMME with 10% BCME activity] + [10% of technical grade CMME with 100% BCME activity]). Thus, if a linear relationship between exposure concentration and cancer risk is assumed for CMME and BCME, the CMME concentration associated with a 1×10^{-4} cancer risk for a given exposure duration can be

calculated by dividing the respective BCME concentration by 0.19, as shown in Table D-1. Also presented in the table is the cancer risk for the AEGL-2 and AEGL-3 concentrations from a single exposure for 30 min to 8 h. The risk for the AEGL-2 values ranges from 1.7×10^{-4} for a 30-min exposure to 9.6×10^{-4} for an 8-h exposure. The predicted carcinogenic risk for the AEGL-3 values is greater, ranging from 7.4×10^{-4} for a 30-min exposure to 4.1×10^{-3} for an 8-h exposure. It is unknown, however, how well the stated assumptions hold true and predict the carcinogenicity of CMME. Because of this uncertainty and the large differences in methods used to derive the AEGL values compared with extrapolating carcinogenic potency from a lifetime study to a single exposure, the noncarcinogenic end points were considered to be more appropriate for driving the AEGL values for CMME.

TABLE D-1 Estimated Cancer Risks Associated with a Single Exposure Chloromethyl Methyl Ether or bis-Chloromethyl Ether

Exposure	10 min	30 min	1 h	4 h	8 h
BCME					
Concentration	Not calculated	0.069 ppm	0.035 ppm	0.0086 ppm	0.0043 ppm
Estimated cancer risk		1×10^{-4}	1×10^{-4}	1×10^{-4}	1×10^{-4}
CMME, containing 10% BCME[a]					
Concentration	Not calculated	0.36 ppm	0.18 ppm	0.045 ppm	0.023 ppm
Estimated cancer risk		1×10^{-4}	1×10^{-4}	1×10^{-4}	1×10^{-4}
AEGL-2 value	0.60 ppm	0.60 ppm	0.47 ppm	0.30 ppm	0.22 ppm
Estimated cancer risk	Not calculated	1.7×10^{-4}	2.6×10^{-4}	6.7×10^{-4}	9.6×10^{-4}
AEGL-3 value	2.6 ppm	2.6 ppm	2.0 ppm	1.3 ppm	0.93 ppm
Estimated cancer risk	Not calculated	7.4×10^{-4}	1.1×10^{-3}	2.9×10^{-3}	4.1×10^{-3}

[a]Assumes BCME is a 10-fold more potent carcinogen than CMME.

3

Selected Chlorosilanes[1]

Acute Exposure Guideline Levels

PREFACE

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

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, 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 or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain 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 Chery Bast (Oak Ridge National Laboratory), Julie M. Klotzbach (Syracuse Research Corporation), and Chemical Manager Ernest V. Falke (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 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 concentrations 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 idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Chlorosilanes contain one or more chlorine atoms covalently bonded to a silicon atom; the maximum chlorine-to-silicon ratio is four. Chlorosilanes are chemical intermediates used in the production of silicone and silicone-containing materials, and are often produced in bulk and transported to manufacturing sites for use. Chlorosilanes are corrosive, and inhalation exposure might cause nasal, throat, or lung irritation, coughing, wheezing, and shortness of breath. Chlorosilanes react rapidly with water, steam, or moisture; hydrolysis yields hydrogen chloride (HCl) gas along with silanols and other condensation products.

The 26 chlorosilanes considered in this chapter are:

Allyl trichlorosilane
Amyl trichlorosilane
Butyl trichlorosilane
Chloromethyl trichlorosilane
Dichlorosilane
Diethyl dichlorosilane
Dimethyl chlorosilane
Dimethyl dichlorosilane
Diphenyl dichlorosilane
Dodecyl trichlorosilane
Ethyl trichlorosilane
Hexyl trichlorosilane
Methyl chlorosilane
Methyl dichlorosilane
Methyl trichlorosilane
Methylvinyl dichlorosilane
Nonyl trichlorosilane
Octadecyl trichlorosilane
Octyl trichlorosilane
Propyl trichlorosilane
Tetrachlorosilane
Trichloro(dichlorophenyl)silane
Trichlorophenylsilane
Trichlorosilane
Trimethyl chlorosilane
Vinyl trichlorosilane

Although chemical-specific toxicity data are not available for many of these chlorosilanes, acute inhalation data from rat studies are available for structurally-similar chlorosilanes (propyl trichlorosilane, methyl trichlorosilane, vinyl trichlorosilane, ethyl trichlorosilane, methylvinyl dichlorosilane, methyl dichlorosilane, dimethyl dichlorosilane, dimethyl chlorosilane, trimethylchlorosilane, and tetrachlorosilane). These data suggest that the acute toxicity of chlorosilanes is largely explained by the HCl hydrolysis product; acute toxicity of these chlorosilanes is qualitatively (based on clinical signs) and quantitatively (based on molar equivalents of HCl) similar to that of HCl (Jean et al. 2006).

On the basis of these data, and in the absence of appropriate chemical-specific data for the chlorosilanes considered in this document, the AEGLs for HCl were used to derive AEGLs for the chlorosilanes. For each class of chlorosilanes (mono-, di-, tri-, and tetra-chlorosilanes), the molar ratio (moles of HCl released per mole of chlorosilane, assuming complete hydrolysis) was used to adjust the AEGL values for HCl to the equivalent concentration of chlorosilane. Detailed information on the derivation of AEGLs for HCl is available in NRC (2004). The calculated values are listed in the Table 3-1.

1. INTRODUCTION

Chlorosilanes contain one or more chlorine atoms covalently bonded to a silicon atom; the maximum chlorine-to-silicon ratio is four. Chlorosilanes are chemical intermediates used in the production of silicone and silicone-containing materials, and are often produced in bulk and transported to manufacturing sites for use.

Chlorosilanes react very rapidly with water, steam, or moisture, releasing HCl gas (AIHA 1998, 1999, 2001a,b,c, 2006). The primary vapor detected in air when chlorosilanes are released is HCl; much less of the parent chlorosilane is detectable (Nakashima et al. 1996; Jean et al. 2006). In an experiment using 11 different chlorosilanes, Jean et al. (2006) reported that the percentage of parent chlorosilane in the test atmosphere ranged from <10% to 58%; other constituents of the atmosphere (in addition to HCl) included silanols and other condensation products. When x-ray microanalysis was performed on air filtered from a dichlorosilane exposure chamber, small (<1 μM in diameter), unidentified particles containing silicon and chloride were detected (Nakashima et al. 1996).

Numerous reports of chlorosilane spills and releases have been received by the U.S. Coast Guard National Response Center. For example, between January 1990 and July 2007, there were 23 reports of dichlorosilane releases ranging from 6 to 2,596 pounds; 32 reports of trichlorosilane releases ranging from 2.6 to 343 pounds; and 14 reports of tetrachlorosilane releases ranging from 2 to 330 pounds (USCG 2007). Releases were from both fixed and mobile sources and were the result of equipment failure and operator error.

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

Compound	Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
MONOCHLOROSILANES							
Dimethyl chlorosilane	AEGL-1	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	AEGLs for HCl (NRC 2004)
Methyl chlorosilane	AEGL-2	100 ppm	43 ppm	22 ppm	11 ppm	11 ppm	
Trimethylchlorosilane	AEGL-3	620 ppm	210 ppm	100 ppm	26 ppm	26 ppm	
DICHLOROSILANES							
Dichlorosilane	AEGL-1	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm	AEGLs for HCl divided by a molar adjustment factor of 2 (NRC 2004)
Diethyl dichlorosilane	AEGL-2	50 ppm	22 ppm	11 ppm	5.5 ppm	5.5 ppm	
Dimethyl dichlorosilane	AEGL-3	310 ppm	110 ppm	50 ppm	13 ppm	13 ppm	
Diphenyl dichlorosilane							
Methyl dichlorosilane							
Methylvinyl dichlorosilane							
TRICHLOROSILANES							
Allyl trichlorosilane	AEGL-1	0.60 ppm	0.60 ppm	0.60 ppm	0.60 ppm	0.60 ppm	AEGL values for HCl divided by a molar adjustment factor of 3 (NRC 2004)
Amyl trichlorosilane	AEGL-2	33 ppm	14 ppm	7.3 ppm	3.7 ppm	3.7 ppm	
Butyl trichlorosilane	AEGL-3	210 ppm	70 ppm	33 ppm	8.7 ppm	8.7 ppm	
Chloromethyl trichlorosilane							
Dodecyl trichlorosilane							
Ethyl trichlorosilane							
Hexyl trichlorosilane							
Methyl trichlorosilane							
Nonyl trichlorosilane							
Octadecyl trichlorosilane							
Octyl trichlorosilane							
Propyl trichlorosilane							

(Continued)

TABLE 3-1 Continued

Compound	Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
TRICHLOROSILANES (*continued*)							
Trichloro(dichlorophenyl)silane							
Trichlorophenylsilane							
Trichlorosilane							
Vinyl trichlorosilane							
TETRACHLOROSILANE							
	AEGL-1	0.45 ppm	0.45 ppm	0.45 ppm	0.45 ppm	0.45 ppm	AEGL values for HCl divided by a molar adjustment factor of 4 (NRC 2004)
	AEGL-2	25 ppm	11 ppm	5.5 ppm	2.8 ppm	2.8 ppm	
	AEGL-3	160 ppm	53 ppm	25 ppm	6.5 ppm	6.5 ppm	

[a]Values given in ppm. To convert ppm to mg/m^3: (ppm × molecular weight) ÷ 24.5. See Appendix A for the appropriate molecular weight. For mono-, di-, and tri-chlorosilanes not listed, use of HCl equivalents may be considered for AEGL-value derivation.

The chlorosilanes have pungent irritating odors, are corrosive, and inhalation exposure might cause nasal, throat, or lung irritation, coughing, wheezing, and shortness of breath. Although chemical-specific toxicity data are not available for many of the chlorosilanes, acute inhalation data from rat studies are available for structurally-similar chlorosilanes (propyl trichlorosilane, methyl trichlorosilane, vinyl trichlorosilane, ethyl trichlorosilane, methylvinyl dichlorosilane, methyl dichlorosilane, dimethyl dichlorosilane, dimethyl chlorosilane, trimethylchlorosilane, and tetrachlorosilane). These data suggest that the acute toxicity of chlorosilanes is from the HCl hydrolysis product; acute toxicity of the chlorosilanes is qualitatively (based on clinical signs) and quantitatively (based on molar equivalents of HCl) similar to that of HCl (Jean et al. 2006) (see Section 4.3).

On the basis, and in the absence of adequate chemical-specific data for the chlorosilanes considered in this document, the AEGL values for HCl (NRC 2004) were used to obtain AEGL values for the chlorosilanes. The molar ratio (moles HCl released per mole of chlorosilane, assuming complete hydrolysis) was used to adjust the AEGL values for HCl to the equivalent concentration of chlorosilane. Available physicochemical data for the 26 chlorosilanes covered in this chapter are presented in Appendix A.

2. HUMAN TOXICITY DATA

An accidental release of tetrachlorosilane at a chemical plant in a south San Francisco industrial park provided some human exposure data (Kizer et al. 1984). A delivery truck taking a short-cut through a chemical plant hit the tank-coupling unit of a tetrachlorosilane storage tank. The pipeline ruptured and the tetrachlorosilane liquid spilled onto the moist ground; it hydrolyzed rapidly and formed a large gray-white cloud that quickly spread. Workers were unable to stop the leak because the valve was behind a wire enclosure, and approximately 1,200 gallons of tetrachlorosilane was released before the leak was stopped several hours later. By that time, the cloud had risen 500 feet and had spread more than a mile over the industrial park. Five- to ten-thousand employees from 600 businesses over 3 square miles were evacuated. Twenty-eight people reported to local hospitals for treatment of eye or airway irritation. Seven of the patients were employees at the chemical plant, and six of them were smokers. The remaining 21 patients were firemen, policemen, passersby, and employees of other companies in the area. There were no deaths, and no one was hospitalized. Six of the chemical plant employees were referred for further evaluation; these employees were all male, ranged in age from 25 to 56, and were all smokers. Their exposures ranged from 10 to 20 min in duration. Symptoms generally resolved within 24 h, and included lacrimation, rhinorrhea, burning of the mouth and throat, headache, coughing, and wheezing. Pulmonary function tests were normal except that mild obstructive airway disease was noted in four patients. However, it was unclear if the disease was from exposure to tetrachlorosilane or

related to smoking status. Two patients also complained of pedal dysesthesias after the accident. No air concentrations of tetrachlorosilane or HCl were reported.

Reactive airways dysfunction syndrome is an asthma-like condition that develops after a single exposure to high concentrations of a chemical irritant, and has been described after exposure to HCl. Symptoms occur within minutes to hours after the initial exposure and can persist as nonspecific bronchial hyperresponsiveness for months to years (Bernstein 1993). Promisloff et al. (1990) reported reactive airways dysfunction syndrome in three male police officers (36-45 years of age) who responded to a roadside chemical spill. The subjects were exposed to unquantified amounts of sodium hydroxide, tetrachlorosilane, and HCl as a byproduct of trichlorosilane hydrolysis. Because of the mixture of irritants involved in the release, it is probable that all of the compounds contributed to the syndrome observed after this accident.

3. ANIMAL TOXICITY DATA

3.1. Acute Toxicity

One-hour LC_{50} (lethal concentration, 50% lethality) studies were conducted for 10 chlorosilanes: tetrachlorosilane, propyl trichlorosilane, vinyl trichlorosilane, methyl trichlorosilane, ethyl trichlorosilane, methylvinyl dichlorosilane, dimethyl dichlorosilane, methyl dichlorosilane, trimethyl chlorosilane, and dimethyl chlorosilane (Jean et al. 2006). In each study, groups of five male and five female Fischer 344 rats were exposed to varying concentrations of a chlorosilane for 1 h and observed for up to 14 days. The studies appeared to conform to Good Laboratory Practices and were well-described. The authors used nominal concentrations to calculate LC_{50} values because chlorosilanes react rapidly with moisture to produce HCl and other hydrolysis products. Using actual chamber concentrations of chlorosilanes would only reflect toxicity of the parent compound, not the toxicity of the parent compound and hydrolysis products. There was agreement between the electrolytic conductivity detector and the nominal concentrations, indicating efficient vaporization of the test material.

Clinical signs were consistent with HCl exposure and included lacrimation, salivation, dried material around the eyes or nose, green staining around the nose and mouth, and perineal urine staining. Labored breathing, rales, hypoactivity, closed or partially closed eyes, prostration, corneal opacity or opaqueness, and swollen or necrotic paws also were observed. Hemorrhage, congestion, and consolidation of the lungs; ectasia of the lungs; gaseous distension of the gastrointestinal tract; absence of body fat; obstruction of nostrils; dried or firm nares; alopecia around the eyes; and discoloration of hair were observed at necropsy. Mortality data and LC_{50} values from 1-h exposure studies with rats are summarized in Table 3-2.

TABLE 3-2 Mortality Data and LC_{50} Values from 1-Hour Exposure Studies with Rats

Compound	Exposure Concentration (ppm)	Mortality			LC_{50}, ppm (95% confidence limits)
		Male	Female	Total	
Tetrachlorosilane	1,209	1/5	2/5	3/10	1,312 (1,006-1,529) [a]
	1,497	5/5	3/5	8/10	
	3,051	5/5	5/5	10/10	
Propyl trichlorosilane	1,123	0/5	0/5	0/10	1,352 (1,254-1,455) [a]
	1,317	2/5	2/5	4/10	
	1,414	3/5	4/5	7/10	
Vinyl trichlorosilane	1,186	0/5	0/5	0/10	1,611 (1,505-1,724) [b]
	1,605	4/5	2/5	6/10	
	1,681	2/5	1/5	3/10	
	1,989	5/5	5/5	10/10	
Methyl trichlorosilane	622	0/5	0/5	0/10	1,365 (1,174-2,104) [a]
	1,047	0/5	1/5	1/10	
	1,439	4/5	2/5	6/10	
	3,075	5/5	5/5	10/10	
Ethyl trichlorosilane	1,156	1/5	1/5	2/10	1,257 (1,175-1,320) [a]
	1,326	4/5	2/5	6/10	
	1,415	5/5	5/5	10/10	
Methylvinyl dichlorosilane	1,597	1/5	0/5	1/10	2,021 (1,806-2,257) [a]
	2,005	3/5	2/5	5/10	
	2,119	3/5	3/5	6/10	
	2,242	4/5	3/5	7/10	
Dimethyl dichlorosilane	1,309	0/5	0/5	0/10	2,092 (1,492-2,240) [a]
	2,077	4/5	1/5	5/10	
	2,353	5/5	3/5	8/10	
	2,762	5/5	5/5	10/10	
Methyl dichlorosilane	1,431	0/5	0/5	0/10	1,785 (1,671-1,963) [a]
	1,678	1/5	2/5	3/10	
	1,889	4/5	3/5	7/10	
Trimethyl chlorosilane	3,171	0/5	0/5	0/10	4,257 (4,039-4,488) [b]
	4,139	2/5	0/5	2/10	
	4,268	3/5	3/5	6/10	
	5,121	5/5	5/5	10/10	
Dimethyl chlorosilane	4,108	1/5	1/5	2/10	4,478 (4,281-6,327) [a]
	4,179	1/5	1/5	2/10	
	4,409	3/5	3/5	6/10	
	4,589	3/5	2/5	5/10	

[a]Probit analysis.
[b]Spearman-Karber analysis.
Source: Jean et al. 2006. Reprinted with permission; copyright 2006, *Inhalation Toxicology*.

In another study, groups of 10 male ICR mice were exposed for 4 h to nominal concentrations of dichlorosilane at 49-259 ppm, followed by a 14-day observation period (Nakashima et al. 1996). Mortality was 0/10, 0/10, 1/10, 6/10, 4/10, 10/10, 10/10, 9/10, and 10/10 for groups exposed at 0, 49, 100, 131, 141, 199, 216, 218, and 259 ppm, respectively. An LC_{50} of 144 ppm was calculated.

3.2. Developmental and Reproductive Toxicity

No data on developmental or reproductive toxicity were found.

3.3. Genotoxicity

The only genotoxicity data found were for tetrachlorosilane. Tetrachlorosilane was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA 1535, TA1537, or TA1538; *Saccharomyces cerevisiae* strain D-4; or *Escherischia coli* strains W3110/polA$^+$ and P3478/polA$^-$ either with or without metabolic activation. It was also negative in a L5178Y mouse lymphoma assay (AIHA 1999).

3.4. Chronic Toxicity and Carcinogenicity

No data on chronic toxicity or carcinogenicity were found.

3.5. Summary

Although toxicity data are sparse for individual chlorosilanes, well-conducted 1-h inhalation toxicity studies in rats are available for a series of chlorosilanes (Jean et al. 2006). In general, LC_{50} values for monochlorosilanes were approximately twice the LC_{50} values for dichlorosilanes and three times the LC_{50} values for trichlorosilanes. Tetrachlorosilane had an LC_{50} value similar to the trichlorosilanes; however, there were experimental difficulties at the lowest concentration tested. Clinical signs were indicative of severe irritation or corrosion. The evidence suggests that the acute toxicity of chlorosilanes is largely attributable to the release of HCl; however, no information on the identity or potential toxicity of other decomposition products was found. No data concerning developmental or reproductive toxicity, genotoxicity, or carcinogenicity for exposure to the chlorosilanes were found in the literature.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No information was found concerning the metabolism and disposition of chlorosilanes.

4.2. Mechanism of Toxicity

Chlorosilanes react violently with water to produce HCl gas (AIHA 1998, 1999, 2001a,b,c, 2006). In an experiment using 11 different chlorosilanes, Jean et al. (2006) reported that the percentage of parent chlorosilane in the test atmosphere range from <10 to 58%; other constituents of the atmosphere (in addition to HCl) included silanols and other condensation products. Nakashima et al. (1996) reported that small particles containing silicon and chlorine were detected in an inhalation exposure chamber into which dichlorosilane was introduced; the identity and quantity of particles were not reported. IPCS (2002a) reported that, when heated, trimethylchlorosilane decomposition could release HCl and phosgene. No other information on potential decomposition products of chlorosilanes was found. Available data suggest that the acute toxicity of chlorosilanes is largely from the HCl hydrolysis product; acute toxicity of the chlorosilanes is qualitatively (based on clinical signs) and quantitatively (based on molar equivalents of HCl) similar to that of HCl.

4.3. Structure Activity Relationships

A 1-h LC_{50} study with HCl was performed in rats and used for comparison with the chlorosilane 1-h LC_{50} values (Jean et al. 2006). According to the authors, the study with HCl was unpublished, but was performed in the same laboratory and was conducted using the same protocol as that used in the chlorosilane study (1-h whole-body exposure with a 14-day recovery period). Five rats per sex were exposed to HCl at 0, 2,456, 3,236, or 4,210 ppm for 1 h and observed for up to 14 days. Chamber concentrations were determined by a Fourier transform infrared spectrophotometer analyzer. Clinical signs included labored breathing; gasping; emaciation; rough coat; lethargy; corneal opacity; crusting, necrotic, discolored, and blocked nares or nasal opening; paws with missing, necrotic, or swollen digits; and weight loss. Gross pathology of animals dying during the study included irritation and necrosis of most extremities, severe respiratory-tract injuries, and corneal opacity. A 1-h LC_{50} of 3,627 ppm was calculated for HCl.

The LC_{50} data obtained for the chlorosilanes showed a strong association with chlorine content for the mono-, di-, and tri-chlorosilanes. In general, LC_{50} values for monochlorosilanes were approximately twice the LC_{50} values for dichlorosilanes and three times the LC_{50} values for trichlorosilanes. Tetrachlorosilane exhibited an LC_{50} value similar to the trichlorosilanes.

The predicted 1-h LC_{50} values for the chlorosilanes, based on HCl equivalents, are presented in Table 3-3. The predicted values for the chlorosilanes are comparable to the experimentally-derived 1-h LC_{50} values (log * log regression analysis of chlorosilane LC_{50} values vs. the number of chlorine groups yielded an r^2 value of 0.97). The data suggest that the acute toxicity of the chlorosilanes is similar to or slightly less than what would be expected based on HCl molar

equivalents. The within-class LC_{50} values were not significantly influenced by the number or type of hydrocarbon R-group(s) present (methyl, ethyl, propyl, or vinyl). Cases where the predicted value is less might be attributed to incomplete hydrolysis in the test atmosphere; however, continued hydrolysis and generation of HCl would be expected for any remaining chlorosilane when in contact with moist tissues (mucous membranes, lung) (Jean et al. 2006). This information taken in conjunction with the observed clinical signs suggests that the acute toxicity of the chlorosilanes is quantitatively and qualitatively similar to HCl and that the HCl hydrolysis product is responsible for the acute toxicity of the chlorosilanes.

TABLE 3-3 Measured and Predicted 1-Hour LC_{50} Values for Selected Chlorosilanes

Compound	Measured LC_{50} (ppm) (95% confidence limits)	Predicted LC_{50} (ppm)	Predicted Ratio of LC_{50} Values	Measured Ratio of LC_{50} Values
Hydrogen chloride	3,627			
Tetrachlorosilane	1,312 (1,006-1,529)	3,627 ÷ 4 = 907	4:1	2.8:1
Propyl trichlorosilane	1,352 (1,254-1,455)	3,627 ÷ 3 = 1,209	3:1	2.7:1
Vinyl trichlorosilane	1,611 (1,505-1,724)	3,627 ÷ 3 = 1,209	3:1	2.3:1
Methyl trichlorosilane	1,365 (1,174-2,104)	3,627 ÷ 3 = 1,209	3:1	2.7:1
Ethyl trichlorosilane	1,257 (1,175-1,320)	3,627 ÷ 3 = 1,209	3:1	2.9:1
Methylvinyl dichlorosilane	2,021 (1,806-2,257)	3,627 ÷ 2 = 1,814	2:1	1.8:1
Dimethyl dichlorosilane	2,092 (1,492-2,240)	3,627 ÷ 2 = 1,814	2:1	1.7:1
Methyl dichlorosilane	1,785 (1,671-1,963)	3,627 ÷ 2 = 1,814	2:1	2:1
Trimethyl chlorosilane	4,257 (4,039-4,488)	3,627 ÷ 1 = 3,627	1:1	0.9:1
Dimethyl chlorosilane	4,478 (4,281-6,327)	3,627 ÷ 1 = 3,627	1:1	0.8:1

Source: Adapted from Jean et al. 2006.

The 4-h mouse LC_{50} of 144 ppm for dichlorosilane (Nakashima et al. 1996) also supports the conclusion that the acute inhalation toxicity of chlorosilanes is from the HCl hydrolysis product. The reported 1-h mouse LC_{50} for HCl is 1,108 ppm (NRC 2004). Scaling across time for HCl may be accomplished using the equation $C^n \times t = k$, where n = 1 based on regression analysis of combined rat and mouse LC_{50} data (1-100 min) (NRC 2004). Scaling the 1-h LC_{50} value for HCl of 1,108 ppm to a 4-h period yields an approximate 4-h LC_{50} value of 277 ppm. Dividing this 4-h LC_{50} by a molar adjustment factor of 2, yields a predicted LC_{50} of 139 ppm for dichlorosilane, which is similar to the experimentally-derived value of 144 ppm.

The 26 chlorosilanes addressed in this chapter include those with alkane, alkene, aromatic, and chlorinated substituents. Although the evidence from Jean et al. (2006) suggests that the acute toxicity is from HCl formed as a hydrolysis product, the data were generated using 11 of the 26 chlorosilanes, including primarily alkane-subsituted compounds and two of the three compounds with alkene substituent groups. Of the 26, two have aromatic substituents and two (including one of the aromatics) have chlorinated substituents; none of those was among the tested compounds.

4.4. Other Relevant Information

4.4.1. Species Variability

Data were not available regarding species variability in lethal and nonlethal toxicity from chlorosilane exposure. Differences in response to HCl have been observed between primates and rodents. Rodents exhibit sensory and respiratory irritation after exposure to high concentrations of HCl. Concentration-dependent decreases in respiratory frequency indicative of a protective mechanism are observed in rodents, whereas baboons exposed at 500, 5,000, or 10,000 ppm exhibited concentration-dependent increases in respiratory frequency indicative of a compensatory response to hypoxia and a possible increase in the total dose delivered to the lung (NRC 1991). Kaplan et al. (1988) found that five of six mice died when exposed to HCl at 2,550 ppm for 15 min, but no baboons died when exposed at 10,000 ppm for 15 min. The LC_{50} values reported by Darmer et al. (1974), Wohlslagel et al. (1976), and Higgins et al. (1972) indicate that mice are approximately three times more sensitive than rats to HCl. Guinea pigs also appear to be more sensitive than rats to HCl; however, the guinea pig studies have provided conflicting results. For respiratory irritants such as HCl, the mouse "may not be a good model for extrapolation to humans," because "mice appear to be much more susceptible to the lethal effects of HCl than other rodents or baboons. To some extent, this increased susceptibility may be due to less effective scrubbing of HCl in the upper respiratory tract" (NRC 1991).

Because most rodents are obligatory nose breathers whereas humans may be mouth breathers, especially during exercise, Stavert et al. (1991) studied the effects of inhaling HCl through the nose and mouth in rats. HCl was delivered directly to the trachea by cannulation. Higher mortality rates occurred with orally-cannulated rats compared with rats exposed by nose. Tracheal necrosis and inflammatory-cell accumulation were found in cannulated rats, whereas effects in nose-breathing rats were confined to the nasal passages. These results indicate that the site of injury and resultant toxicologic effects differ with oral or nasal breathing, with the former mode resulting in more severe responses under similar exposure situations.

4.4.2. Susceptible Populations

No information was available on populations that might be especially sensitive to chlorosilane or HCl. However, clinical signs of chlorosilane and HCl exposure are consistent with contact irritation. In general, contact-irritant effects are not expected to vary widely among individuals. However, as noted by NRC (2004), asthmatic persons and others with sensitive airways might be more susceptible to the effects of HCl inhalation.

On the basis of the study by Stavert et al. (1991), which showed more severe respiratory responses to HCl in orally-cannulated rats compared with nose-breathing rats, it is possible that persons who habitually breathe orally might experience more pronounced or different health effects than those who primarily breathe nasally. Likewise, physical exertion might intensify the respiratory effects of HCl or chlorosilane exposure as individuals shift from nasal to oral breathing during exertion.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No human data relevant to development of AEGL-1 values were found.

5.2. Summary of Animal Data Relevant to AEGL-1

No animal data relevant to development of AEGL-1 values were found.

5.3. Derivation of AEGL-1

AEGL-1 values for the chlorosilanes were determined by modifying the AEGL-1 values that were established for HCl. The use of HCl as a surrogate for chlorosilanes was deemed appropriate because adverse effects from exposure to chlorosilanes have been attributed to their hydrolysis product, HCl. The AEGL-1 values for HCl were based on a no-observed-adverse-effect level in exercising adult with asthma (NRC 2004). The same AEGL-1 value was applied across all

specified exposure periods, because mild irritation generally does not vary greatly over time and because prolonged exposure is not expected to result in an enhanced effect (NRC 2004). The key study and calculations used to determine the AEGL-1 values for HCl are summarized in Appendixes C and E (more detail is available in the technical support document for HCl published in NRC [2004]). The molar ratio (moles of HCl released per mole of chlorosilane, assuming complete hydrolysis) was used to adjust the AEGLs for HCl to the equivalent concentration of chlorosilane. Although the 1-h rat LC_{50} value for tetrachlorosilane suggests that only 3 moles of HCl were produced, the use of a molar adjustment factor of 4 is considered appropriate because of experimental difficulties that occurred at lower exposure concentrations in this study. The use of the molar adjustment factor of 4 will yield protective AEGL values and is consistent with the approach taken for the overall chlorosilane database. The AEGL-1 values for the chlorosilanes are presented in Table 3-4, and their calculations are presented in Appendix B.

TABLE 3-4 AEGL-1 Values for Selected Chlorosilanes[a]

Compound	10 min	30 min	1 h	4 h	8 h
MONOCHLOROSILANES					
Dimethyl chlorosilane	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm
Methyl chlorosilane					
Trimethyl chlorosilane					
DICHLOROSILANES					
Dichlorosilane	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm
Diethyl dichlorosilane					
Dimethyl dichlorosilane					
Diphenyl dichlorosilane					
Methyl dichlorosilane					
Methylvinyl dichlorosilane					
TRICHLOROSILANES					
Allyl trichlorosilane	0.60 ppm	0.60 ppm	0.60 ppm	0.60 ppm	0.60 ppm
Amyl trichlorosilane					
Butyl trichlorosilane					
Chloromethyl trichlorosilane					
Dodecyl trichlorosilane					
Ethyl trichlorosilane					
Hexyl trichlorosilane					
Methyl trichlorosilane					
Nonyl trichlorosilane					
Octadecyl trichlorosilane					
Octyl trichlorosilane					
Propyl trichlorosilane					
Trichloro(dichlorophenyl)silane					
Trichlorophenylsilane					
Trichlorosilane					
Vinyl trichlorosilane					
TETRACHLOROSILANE	0.45 ppm	0.45 ppm	0.45 ppm	0.45 ppm	0.45 ppm

[a]Values given in ppm. To convert ppm to mg/m^3: (ppm × molecular weight) ÷ 24.5. See Appendix A for the appropriate molecular weight.

6.3. Derivation of AEGL-2

AEGL-2 values for the chlorosilanes were determined by modifying the AEGL-2 values that were established for HCl. The use of HCl as a surrogate for chlorosilanes was deemed appropriate because adverse effects from exposure to chlorosilanes have been attributed to their hydrolysis product, HCl. AEGL-2 values for HCl were based on severe nasal or pulmonary histopathologic changes in rats (exposed for 30 min to 8 h) or a modification of the mouse 50% respiratory rate decrease (RD_{50}) (exposed for 10 min) (NRC 2004). The key study and calculations used to determine the AEGL-2 values for HCl are summarized in Appendixes C and E (more detail is available in the technical support document for HCl published in NRC [2004]). The molar ratio (moles of HCl released per mole of chlorosilane, assuming complete hydrolysis) was used to adjust the AEGLs for HCl to the equivalent concentration of chlorosilane. The AEGL-2 values for the chlorosilanes are presented in Table 3-5, and their calculations are presented in Appendix B.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human data relevant to development of AEGL-3 values were found.

7.2. Summary of Animal Data Relevant to AEGL-3

One-hour rat LC_{50} values were reported by Jean et al. (2006) to be 4,478 ppm for dimethyl dichlorosilane and 2,021 ppm for methylvinyl dichlorosilane. One-hour rat LC_{50} values for trichlorsilanes were 1,257, 1,352, and 1,611 ppm for ethyl trichlorosilane, propyl trichlorosilane, and vinyl trichlorosilane, respectively (Jean et al. 2006). A 1-h rat LC_{50} value of 1,312 ppm was reported for tetrachlorosilane (Jean et al. 2006). A 4-h mouse LC_{50} value of 144 ppm was reported for dichlorosilane (Nakashima et al. 1996), but the mouse is considered to be an unreliable model for the acute toxicity of HCl in humans (NRC 1991, 2004). No animal data relevant to development of AEGL-3 values were found for the other chlorosilanes.

7.3. Derivation of AEGL-3

AEGL-3 values for the chlorosilanes were determined by modifying the AEGL-3 values that were established for HCl. The use of HCl as a surrogate for chlorosilanes was deemed appropriate because adverse effects from exposure to chlorosilanes have been attributed to their hydrolysis product, HCl. The AEGL-3 values for HCl were based on a 1-h rat LC_{50} value divided by 3 to estimate a lethality threshold (NRC 2004). The key study and calculations used to determine the AEGL-3 values for HCl are summarized in Appendixes C and E (more detail

is available in the technical support document for HCl published in NRC [2004]). The molar ratio (moles of HCl released per mole of chlorosilane, assuming complete hydrolysis) was used to adjust the AEGLs for HCl to the equivalent concentration of chlorosilane. The AEGL-2 values for the chlorosilanes are presented in Table 3-6, and their calculations are presented in Appendix B.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

AEGL values for selected chlorosilanes are summarized in Table 3-7. Derivation summary tables appear in Appendix E, and category plots for the selected chlorosilanes are in Appendix F. AEGL values were based on molar adjustments of the AEGL values for HCl. For mono-, di-, and tri- chlorosilanes not listed, use of HCl equivalents may be considered for AEGL-value derivation.

TABLE 3-5 AEGL-2 Values for Selected Chlorosilanes[a]

Compound	10 min	30 min	1 h	4 h	8 h
MONOCHLOROSILANES					
Dimethyl chlorosilane	100 ppm	43 ppm	22 ppm	11 ppm	11 ppm
Methyl chlorosilane					
Trimethyl chlorosilane					
DICHLOROSILANES					
Dichlorosilane	50 ppm	22 ppm	11 ppm	5.5 pm	5.5 ppm
Diethyl dichlorosilane					
Dimethyl dichlorosilane					
Diphenyl dichlorosilane					
Methyl dichlorosilane					
Methylvinyl dichlorosilane					
TRICHLOROSILANES					
Allyl trichlorosilane	33 ppm	14 ppm	7.3 ppm	3.7 pm	3.7 ppm
Amyl trichlorosilane					
Butyl trichlorosilane					
Chloromethyl trichlorosilane					
Dodecyl trichlorosilane					
Ethyl trichlorosilane					
Hexyl trichlorosilane					
Methyl trichlorosilane					
Nonyl trichlorosilane					
Octadecyl trichlorosilane					
Octyl trichlorosilane					
Propyl trichlorosilane					
Trichloro(dichlorophenyl)silane					
Trichlorophenylsilane					
Trichlorosilane					
Vinyl trichlorosilane					
TETRACHLOROSILANE	25 ppm	11 ppm	5.5 ppm	2.8 ppm	2.8 ppm

[a]Values given in ppm. To convert ppm to mg/m^3: (ppm × molecular weight) ÷ 24.5. See Appendix A for the appropriate molecular weight.

TABLE 3-6 AEGL-3 Values for Selected Chlorosilanes

Compound	10 min	30 min	1 h	4 h	8 h
MONOCHLOROSILANES					
Dimethyl chlorosilane	620 ppm	210 ppm	100 ppm	26 ppm	26 ppm
Methyl chlorosilane					
Trimethyl chlorosilane					
DICHLOROSILANES					
Dichlorosilane	310 ppm	110 ppm	50 ppm	13 ppm	13 ppm
Diethyl dichlorosilane					
Dimethyl dichlorosilane					
Diphenyl dichlorosilane					
Methyl dichlorosilane					
Methylvinyl dichlorosilane					
TRICHLOROSILANES					
Allyl trichlorosilane	210 ppm	70 ppm	33 ppm	8.7 ppm	8.7 ppm
Amyl trichlorosilane					
Butyl trichlorosilane					
Chloromethyl trichlorosilane					
Dodecyl trichlorosilane					
Ethyl trichlorosilane					
Hexyl trichlorosilane					
Methyl trichlorosilane					
Nonyl trichlorosilane					
Octadecyl trichlorosilane					
Octyl trichlorosilane					
Propyl trichlorosilane					
Trichloro(dichlorophenyl)silane					
Trichlorophenylsilane					
Trichlorosilane					
Vinyl trichlorosilane					
TETRACHLOROSILANE	160 ppm	53 ppm	25 ppm	6.5 ppm	6.5 ppm

[a]Values given in ppm. To convert ppm to mg/m^3: (ppm × molecular weight) ÷ 24.5. See Appendix A for the appropriate molecular weight.

8.2. Comparison with Other Standards and Guidelines

There are no standards or guidelines for most of the chlorosilanes considered in this chapter. The few guidelines available are Emergency Response Planning Guidelines (ERPGs) and Workplace Environmental Exposure Level (WEEL) ceiling levels for trimethylchlorosilane, dimethyl dichlorosilane, trichlorosilane, methyl trichlorosilane, vinyl trichlorosilane, and tetrachlorosilane. Available standards and guidelines are presented in Tables 3-8. The available ERPG values are comparable to the AEGLs derived herein.

TABLE 3-7 Summary of AEGL Values for Selected Chlorosilanes[a]

Compound	Classification	10 min	30 min	1 h	4 h	8 h
MONOCHLOROSILANES						
Dimethyl chlorosilane	AEGL-1	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm
Methyl chlorosilane	AEGL-2	100 ppm	43 ppm	22 ppm	11 ppm	11 ppm
Trimethyl chlorosilane	AEGL-3	620 ppm	210 ppm	100 ppm	26 ppm	26 ppm
DICHLOROSILANES						
Dichlorosilane	AEGL-1	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm
Diethyl dichlorosilane	AEGL-2	50 ppm	22 ppm	11 ppm	5.5 pm	5.5 ppm
Dimethyl dichlorosilane	AEGL-3	310 ppm	110 ppm	50 ppm	13 ppm	13 ppm
Diphenyl dichlorosilane						
Methyl dichlorosilane						
Methylvinyl dichlorosilane						
TRICHLOROSILANES						
Allyl trichlorosilane	AEGL-1	0.60 ppm	0.60 ppm	0.60 ppm	0.60 ppm	0.60 ppm
Amyl trichlorosilane	AEGL-2	33 ppm	14 ppm	7.3 ppm	3.7 pm	3.7 ppm
Butyl trichlorosilane	AEGL-3	210 ppm	70 ppm	33 ppm	8.7 ppm	8.7 ppm
Chloromethyl trichlorosilane						
Dodecyl trichlorosilane						
Ethyl trichlorosilane						
Hexyl trichlorosilane						
Methyl trichlorosilane						
Nonyl trichlor osilane						
Octadecyl trichlorosilane						
Octyl trichlorosilane						
Propyl trichlorosilane						
Trichloro(dichlorophenyl)silane						
Trichlorophenylsilane						
Trichlorosilane						
Vinyl trichlorosilane						

(Continued)

TABLE 3-7 Continued

Compound	Classification	10 min	30 min	1 h	4 h	8 h
TETRACHLOROSILANE						
	AEGL-1	0.45 ppm	0.45 ppm	0.45 ppm	0.45 ppm	0.45 ppm
	AEGL-2	25 ppm	11 ppm	5.5 ppm	2.8 ppm	2.8 ppm
	AEGL-3	160 ppm	53 ppm	25 ppm	6.5 ppm	6.5 ppm

[a]Values given in ppm. To convert ppm to mg/m^3: (ppm × molecular weight) ÷ 24.5. See Appendix A for the appropriate molecular weight.

TABLE 3-8 Extant Standards and Guidelines for Selected Chlorosilanes

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
MONOCHLOROSILANES					
AEGL-1	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm
AEGL-2	100 ppm	43 ppm	22 ppm	11 ppm	11 ppm
AEGL-3	620 ppm	210 ppm	100 ppm	26 ppm	26 ppm
Trimethylchlorosilane					
ERPG-1 (AIHA)[a]			3 ppm		
ERPG-2 (AIHA)[a]			20 ppm		
ERPG-3 (AIHA)[a]			150 ppm		
WEEL (AIHA)[b]			5 ppm (ceiling)		
DICHLOROSILANES					
AEGL-1	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm
AEGL-2	50 ppm	22 ppm	11 ppm	5.5 ppm	5.5 ppm
AEGL-3	310 ppm	110 ppm	50 ppm	13 ppm	13 ppm
Dimethyl dichlorosilane					
ERPG-1 (AIHA)[a]			2 ppm		
ERPG-2 (AIHA)[a]			10 ppm		
ERPG-3 (AIHA)[a]			75 ppm		
WEEL (AIHA)[b]			2 ppm (ceiling)		
TRICHLOROSILANES					
AEGL-1	0.60 ppm	0.60 ppm	0.60 ppm	0.60 ppm	0.60 ppm
AEGL-2	33 ppm	14 ppm	7.3 ppm	3.7 ppm	3.7 ppm
AEGL-3	210 ppm	70 ppm	33 ppm	8.7 ppm	8.7 ppm
Trichlorosilane					
ERPG-1 (AIHA)[a]			1 ppm		
ERPG-2 (AIHA)[a]			3 ppm		
ERPG-3 (AIHA)[a]			25 ppm		
WEEL (AIHA)[b]			0.5 ppm (ceiling)		
Methyl trichlorosilane					
ERPG-1 (AIHA)[a]			0.5 ppm		
ERPG-2 (AIHA)[a]			3 ppm		
ERPG-3 (AIHA)[a]			15 ppm		
WEEL (AIHA)[b]			1 ppm (ceiling)		
Methyl trichlorosilane					
ERPG-1 (AIHA)[a]			0.5 ppm		
ERPG-2 (AIHA)[a]			5 ppm		

(Continued)

TABLE 3-8 Continued

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
ERPG-3 (AIHA)[a]			50 ppm		
WEEL (AIHA)[b]			1 ppm (ceiling)		
TETRACHLOROSILANE					
AEGL-1	0.45 ppm	0.45 ppm	0.45 ppm	0.45 ppm	0.45 ppm
AEGL-2	25 ppm	11 ppm	5.5 ppm	2.8 ppm	2.8 ppm
AEGL-3	160 ppm	53 ppm	25 ppm	6.5 ppm	6.5 ppm
ERPG-1 (AIHA)[a]			0.75 ppm		
ERPG-2 (AIHA)[a]			5 ppm		
ERPG-3 (AIHA)[a]			37 ppm		
WEEL (AIHA)[b]			1 ppm (ceiling)		

[a]ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association) (AIHA 2010).
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 effects other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. An ERPG-1 was not derived because of insufficient data.
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-2 for BCME is based on animal data, and was intended to be below 0.21 ppm, which was calculated to have a 1×10^{-4} excess carcinogenicity risk, and 0.7 ppm, which caused serious respiratory lesions in animals.
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 BCME is based on animal lethality data.
[b]WEEL (Workplace Environmental Exposure Level, American Industrial Hygiene Association) (AIHA 2010).
WEELs are health-based values, expressed as either time-weighted average (TWA) concentrations or ceiling values believed to provide guidance for protection of most workers exposed as a result of their occupations. A WEEL ceiling value is the instantaneous concentration that should not be exceeded at any time during the workday to prevent acute adverse health effects or discomfort.

8.3. Data Adequacy and Research Needs

There are no human or animal data on chlorosilanes relevant to AEGL-1 health end points. Likewise, there are no appropriate human data and few animal data relevant to AEGL-2 end points. A single study (Jean et al. 2006) that estimated LC_{50} values for 11 of the 26 chlorosilanes considered in this chapter provided data on lethality (an AEGL-3 end point). This study also supports the inference that the hydrolysis product, HCl, is largely responsible for the acute

inhalation toxicity of the chlorosilanes. There is anecdotal information on other hydrolysis and decomposition products (Nakashima et al. 1996). However, no information on the chemical form, physiological disposition, or potential toxicity of these decomposition products was found. Additional research on the identity and potential toxicity of decomposition products would enhance confidence in the database.

The available data on chlorosilane toxicity is limited to 11 of the 26 compounds addressed herein, and there were no data on chlorosilanes with aromatic or chlorinated substituents. The lack of data on the contribution of aromatic or chlorinated substituents to the toxicity of the chlorosilanes introduces uncertainty with respect to the protection afforded by using the molar equivalent of AEGL values for HCl as a surrogate for the AEGLs estimated for diphenyl dichlorosilane, trichloro(dichlorophenyl)silane, and trichlorophenylsilane. Additional research would enhance confidence in the AEGLs for these compounds.

The database on HCl was described by NRC (2004, pp. 107-109) as follows:

> Human data are limited to one study showing no significant effects in asthmatic subjects and to dated anecdotal information. Furthermore, the involvement of [reactive airway dysfunction syndrome] in HCl toxicity is unclear. Many more data are available for animal exposures; however, many of those studies used compromised animals or very small experimental groups, resulting in limited data for many species but no in-depth database for a given species. Also, some studies involve very short exposures to high concentrations of HCl. Thus, confidence in the AEGL values is at best moderate.

One important area of uncertainty is the role of ambient humidity on the release of HCl and the toxicity of chlorosilanes. The LC_{50} values reported by Jean et al. (2006), and used as the basis for concluding that the toxicity of chlorosilanes is well-predicted by HCl content, were obtained at a relative humidity of 35%. Higher humidity would probably have increased the degree of hydrolysis, resulting in higher HCl concentrations and lower concentrations of parent compound; whether this would affect the lethal concentrations is unknown and merits additional research.

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APPENDIX A

PHYSICAL AND CHEMICAL PROPERTIES OF SELECTED CHLOROSILANES

TABLE A-1 Chemical and Physical Properties for Allyl Trichlorosilane

Parameter	Value	References
Synonyms	Propen-3-yltrichlorosilane; trichloroallylsilane; trichloro-2-propenyl-silane	HSDB 2007a
CAS registry no.	107-37-9	HSDB 2007a
Chemical formula	$C_3H_5Cl_3Si$	HSDB 2007a
Molecular weight	175.52	HSDB 2007a
Physical state	Colorless liquid	HSDB 2007a
Melting point	35°C	HSDB 2007a
Boiling point	117.5°C	HSDB 2007a
Vapor density (air = 1)	6.05	HSDB 2007a
Liquid density/specific gravity	1.20 g/cm^3 at 20°C	HSDB 2007a
Solubility in water	Hydrolyzes to form HCl	HSDB 2007a
Vapor pressure	53 mm Hg at 47.5°C	HSDB 2007a
Conversion factors	1 ppm = 7.2 mg/m^3 1 mg/m^3 = 0.14 ppm	

TABLE A-2 Chemical and Physical Properties for Amyl Trichlorosilane

Parameter	Value	References
Synonyms	Pentylsilicon trichloride; pentyltrichlorosilane; trichloropentylsilane; trichloroamylsilane; trichloropentylsilane	HSDB 2007b
CAS registry no.	107-72-2	HSDB 2007b
Chemical formula	$C_5H_{11}Cl_3Si$	HSDB 2007b
Molecular weight	205.59	HSDB 2007b
Physical state	Colorless to yellow liquid	HSDB 2007b
Boiling point	172°C	HSDB 2007b
Liquid density/specific gravity	1.1330 g/cm^3 at 20°C	HSDB 2007b
Solubility in water	Hydrolyzes to form HCl	HSDB 2007b
Conversion factors	1 ppm = 8.4 mg/m^3 1 mg/m^3 = 0.12 ppm	

TABLE A-3 Chemical and Physical Properties for Butyl Trichlorosilane

Parameter	Value	References
Synonyms	Trichlorobutyl silane; butylsilicon trichloride	HSDB 2007c
CAS registry no.	7521-80-4	HSDB 2007c
Chemical formula	$C_4H_9Cl_3Si$	HSDB 2007c
Molecular weight	191.56	HSDB 2007c
Physical state	Colorless liquid	HSDB 2007c
Boiling point	148.5°C	HSDB 2007c
Vapor density (air = 1)	6.4	HSDB 2007c
Liquid density/specific gravity	1.160 g/cm^3 at 20°C	HSDB 2007c
Solubility in water	Hydrolyzes to form HCl	HSDB 2007c
Conversion factors	1 ppm = 7.8 mg/m^3 1 mg/m^3 = 0.13 ppm	

TABLE A-4 Chemical and Physical Properties for Chloromethyl Trichlorosilane

Parameter	Value	References
Synonyms	Silane, trichloro(chloromethyl)-; Chloromethyl(trichloro)-silane	HSDB 2002a
CAS registry no.	1558-25-4	HSDB 2002a
Chemical formula	CH_2Cl_4Si	HSDB 2002a
Molecular weight	183.93	HSDB 2002a
Physical state	Liquid	HSDB 2002a
Boiling point	118°C	EPA 1987
Liquid density/specific gravity	1.476 g/cm^3	HSDB 2002a
Vapor pressure	30 mm Hg at 25°C	EPA 1987
Conversion factors	1 ppm = 7.5 mg/m^3 1 mg/m^3 = 0.13 ppm	

TABLE A-5 Chemical and Physical Properties for Dichlorosilane

Parameter	Value	References
Synonyms	Chlorosilane; silicon chloride hydride	IPCS 1997
CAS registry no.	4109-96-0	IPCS 1997
Chemical formula	H_2Cl_2Si	IPCS 1997
Molecular weight	101.01	IPCS 1997

(Continued)

TABLE A-5 Continued

Parameter	Value	References
Physical state	Colorless gas	IPCS 1997
Melting point	-122°C	IPCS 1997
Boiling point	8°C	IPCS 1997
Vapor density (air = 1)	3.48	IPCS 1997
Solubility in water	Hydrolyzes to form HCl	IPCS 1997
Vapor pressure	163.6 kPa at 20°C	IPCS 1997
Conversion factors	1 ppm = 4.1 mg/m^3 1 mg/m^3 = 0.24 ppm	

TABLE A-6 Chemical and Physical Properties for Diethyl Dichlorosilane

Parameter	Value	References
Synonyms	Dichloroethylsilane	HSDB 2007d
CAS registry no.	1719-53-5	HSDB 2007d
Chemical formula	$C_4H_{10}Cl_2Si$	HSDB 2007d
Molecular weight	157.11	HSDB 2007d
Physical state	Colorless liquid	HSDB 2007d
Melting point	-96.5°C	HSDB 2007d
Boiling point	129°C	HSDB 2007d
Vapor density (air = 1)	5.14	HSDB 2007d
Liquid density/specific gravity	1.0504 at 20°C	HSDB 2007d
Solubility in water	Hydrolyzes to form HCl	HSDB 2007d
Vapor pressure	11.9 mm Hg at 25°C	HSDB 2007d
Conversion factors	1 ppm = 6.4 mg/m^3 1 mg/m^3 = 0.16 ppm	

TABLE A-7 Chemical and Physical Properties for Dimethyl Chlorosilane

Parameter	Value	References
Synonyms	Chlorodimethylsilane	ChemFinder 2007a
CAS registry no.	1066-35-9	ChemFinder 2007a
Chemical formula	C_2H_7ClSi	ChemFinder 2007a
Molecular weight	94.62	ChemFinder 2007a
Melting point	-111°C	ChemFinder 2007a
Boiling point	36.4°C	ChemFinder 2007a
Conversion factors	1 ppm = 3.9 mg/m^3 1 mg/m^3 = 0.26 ppm	

TABLE A-8 Chemical and Physical Properties for Dimethyl Dichlorosilane

Parameter	Values	Reference
Synonyms	Dichlorodimethylsilane	AIHA 2001a
CAS registry no.	75-78-5	HSDB 2010a
Chemical formula	$C_2H_6Cl_2Si$	HSDB 2010a
Molecular weight	129.06	HSDB 2010a
Physical state	Colorless liquid	HSDB 2010a
Melting point	<-70°C	AIHA 2001a
Boiling point	70.3°C	HSDB 2010a
Flash point	-9°C	AIHA 2001a
Density	1.07 g/cm^3 at 25°C	HSDB 2010a
Solubility in water	Reacts and decomposes	AIHA 2001a
Vapor pressure	115 mm Hg at 20°C	AIHA 2001a
Conversion factors	1 mg/m^3 = 0.19 ppm 1 ppm = 5.3 mg/m^3	

TABLE A-9 Chemical and Physical Properties for Diphenyl Dichlorosilane

Parameter	Value	References
Synonyms	Dichlorodiphenyl silane; diphenylsilicon dichloride; diphenylsilyl dichloride	HSDB 2007e
CAS registry no.	80-10-4	HSDB 2007e
Chemical formula	$C_{12}H_{10}Cl_2Si$	HSDB 2007e
Molecular weight	253.2	HSDB 2007e
Physical state	Colorless liquid	HSDB 2007e
Melting point	-22°C	HSDB 2007e
Boiling point	305°C	HSDB 2007e
Vapor density (air = 1)	8.45	HSDB 2007e
Liquid density/specific gravity	1.204 at 25°C	HSDB 2007e
Solubility in water	Hydrolyzes to form HCl	HSDB 2007e
Vapor pressure	4.986 kPa at 192°C	HSDB 2007e
Conversion factors	1 ppm = 10.3 mg/m^3 1 mg/m^3 = 0.097 ppm	

TABLE A-10 Chemical and Physical Properties for Dodecyl Trichlorosilane

Parameter	Value	References
Synonyms	Trichlorododecyl silane	HSDB 2007f
CAS registry no.	4484-72-4	HSDB 2007f
Chemical formula	$C_{12}H_{25}Cl_3Si$	HSDB 2007f
Molecular weight	303.77	HSDB 2007f
Physical state	Colorless to yellow liquid	HSDB 2007f
Boiling point	288°C	HSDB 2007f
Liquid density/specific gravity	1.026 at 25°C	HSDB 2007f
Solubility in water	Hydrolyzes to form HCl	HSDB 2007f
Conversion factors	1 ppm = 12 mg/m^3 1 mg/m^3 = 0.081 ppm	

TABLE A-11 Chemical and Physical Properties for Ethyl Trichlorosilane

Parameter	Value	References
Synonyms	Ethyl silicon trichloride; trichloro ethylsilane; trichloroethylsilicane; trichloroethyl silicon	HSDB 2007g
CAS registry no.	115-21-9	HSDB 2007g
Chemical formula	$C_2H_5Cl_3Si$	HSDB 2007g
Molecular weight	163.51	HSDB 2007g
Physical state	Colorless liquid	HSDB 2007g
Melting point	-105.6°C	HSDB 2007g
Boiling point	100.5°C	HSDB 2007g
Vapor density (air = 1)	5.6	HSDB 2007g
Liquid density/specific gravity	1.238 at 20°C	HSDB 2007g
Solubility in water	Hydrolyzes to form HCl	HSDB 2007g
Vapor pressure	47.18 mm Hg at 25°C	HSDB 2007g
Conversion factors	1 ppm = 6.7 mg/m^3 1 mg/m^3 = 0.15 ppm	

TABLE A-12 Chemical and Physical Properties for Hexyl Trichlorosilane

Parameter	Value	References
Synonyms	Trichlorohexylsilane	HSDB 2007h
CAS registry no.	928-65-4	HSDB 2007h
Chemical formula	$C_6H_{13}Cl_3Si$	HSDB 2007h
Molecular weight	219.61	HSDB 2007h
Physical state	Colorless liquid	HSDB 2007h
Boiling point	190°C	HSDB 2007h
Liquid density/specific gravity	1.1100 g/cm^3 at 20°C	HSDB 2007h
Solubility in water	Hydrolyzes to form HCl	HSDB 2007h
Conversion factors	1 ppm = 8.9 mg/m^3 1 mg/m^3 = 0.11 ppm	

TABLE A-13 Chemical and Physical Properties for Methyl Chlorosilane

Parameter	Values	Reference
Synonyms	Chloromethylsilane	ESIS 2011
CAS registry no.	993-00-0	SRC 2011
Chemical formula	CH_5ClSi	ESIS 2011
Molecular weight	77.57	SRC 2011
Physical state	Liquid	SRC 2011
Melting point	-135°C	SRC 2011
Boiling point	7° C	SRC 20114
Solubility in water	Reacts and decomposes in water	NJ DHSS 2009
Log P (octanol-water partition coefficient)	1.33	SRC 2011
Conversion factors	1 mg/m^3 = 0.32 ppm 1 ppm = 3.2 mg/m^3	

TABLE A-14 Chemical and Physical Properties for Methyl Dichlorosilane

Parameter	Values	Reference
Synonyms	Dichloromethylsilane; monomethyl dichlorosilane	IPCS 2002b
CAS registry no.	75-54-7	IPCS 2002b
Chemical formula	CH_4Cl_2Si	IPCS 2002b
Molecular weight	115.0	IPCS 2002b
Physical state	Colorless liquid	IPCS 2002b
Melting point	-92°C	IPCS 2002b
Boiling point	41°C	IPCS 2002b
Vapor Density (air = 1)	3.97	IPCS 2002b
Solubility in water	Reacts and decomposes in water; soluble in benzene, ether, and heptane	IPCS 2002b
Vapor pressure	47.1 kPa at 20°C	IPCS 2002b
Flash point	-22°C	IPCS 2002b
Auto-ignition temperature	290°C	IPCS 2002b
Conversion factors	1 mg/m^3 = 0.21 ppm 1 ppm = 4.7 mg/m^3	

TABLE A-15 Chemical and Physical Properties for Methyl Trichlorosilane

Parameter	Value	Reference
Synonyms	Trichloromethylsilane	AIHA 2001b
CAS registry no.	75-79-6	HSDB 2007i
Chemical formula	CH_3Cl_3Si	HSDB 2007i
Molecular weight	149.48	HSDB 2007i
Physical state	Liquid	AIHA 2001b
Melting point	-90°C	HSDB 2007i
Boiling point	65.6°C	HSDB 2007i
Density	5.17 g/cm^3	Bisesi 1994
Solubility in water	Reacts and decomposes	AIHA 2001b
Vapor pressure	134 mm Hg at 20°C	AIHA 2001b
Flash point	3°C	Bisesi 1994
Conversion factors	1 mg/m^3 = 0.16 ppm 1 ppm = 6.1 mg/m^3	

TABLE A-16 Chemical and Physical Properties for Methylvinyl Dichlorosilane

Parameter	Value	References
Synonyms	Dicloro methylvinylsilane; Vinyl methyl dichlorosilane	ChemFinder 2007b
CAS registry no.	124-70-9	ChemFinder 2007b
Chemical formula	$C_3H_6Cl_2Si$	ChemFinder 2007b
Molecular weight	141.1	ChemFinder 2007b
Boiling point	92°C	ChemFinder 2007b
Liquid density/specific gravity	1.08 at 20°C	ChemFinder 2007b
Conversion factors	1 ppm = 5.8 mg/m^3 1 mg/m^3 = 0.17 ppm	

TABLE A-17 Chemical and Physical Properties for Nonyl Trichlorosilane

Parameter	Value	References
Synonyms	Trichlorononylsilane	HSDB 2007j
CAS registry no.	5283-67-0	HSDB 2007j
Chemical formula	$C_9H_{19}Cl_3Si$	HSDB 2007j
Molecular weight	261.72	HSDB 2007j
Physical state	Water-white liquid	HSDB 2007j
Liquid density/specific gravity	1.072 g/cm^3 at 25°C	HSDB 2007j
Solubility in water	Hydrolyzes to form HCl	HSDB 2007j
Conversion factors	1 ppm = 10.7 mg/m^3 1 mg/m^3 = 0.094 ppm	

TABLE A-18 Chemical and Physical Properties for Octadecyl Trichlorosilane

Parameter	Value	References
Synonyms	Silane, trichlorooctadecyl, trichlorooctadecylsilane	HSDB 2010b
CAS registry no.	112-04-9	HSDB 2010b
Chemical formula	$C_{18}H_{37}Cl_3Si$	HSDB 2010b
Molecular weight	387.93	HSDB 2010b
Physical state	Water-white liquid	HSDB 2010b
Melting point	About 20°C	HSDB 2010b
Boiling point	380°C	HSDB 2010b
Liquid density/specific gravity	0.984 g/cm^3 at 25°C	HSDB 2010b
Conversion factors	1 ppm = 16 mg/m^3 1 mg/m^3 = 0.063 ppm	

TABLE A-19 Chemical and Physical Properties for Octyl Trichlorosilane

Parameter	Value	References
Synonyms	Trichlorooctylsilane	HSDB 2007k
CAS registry no.	5283-66-9	HSDB 2007k
Chemical formula	$C_8H_{17}Cl_3Si$	HSDB 2007k
Molecular weight	247.67	HSDB 2007k
Physical state	Fuming liquid	HSDB 2007k
Boiling point	232°C	HSDB 2007k
Liquid density/specific gravity	1.073 g/mL	HSDB 2007k
Solubility in water	Hydrolyzes to form HCl	HSDB 2007k
Conversion factors	1 ppm = 10 mg/m^3 1 mg/m^3 = 0.099 ppm	

TABLE A-20 Chemical and Physical Properties for Propyl Trichlorosilane

Parameter	Value	References
Synonyms	Trichloropropylsilane; *n*-propyl trichlorosilane	HSDB 2007l
CAS registry no.	141-57-1	HSDB 2007l
Chemical formula	$C_3H_7Cl_3Si$	HSDB 2007l
Molecular weight	177.53	HSDB 2007l
Physical state	Colorless liquid	HSDB 2007l
Boiling point	123.5°C	HSDB 2007l
Vapor density (air = 1)	6.1215	HSDB 2007l
Liquid density/specific gravity	1.195 g/cm^3 at 20°C	HSDB 2007l
Solubility in water	Hydrolyzes to form HCl	HSDB 2007l
Vapor pressure	28.8 mm Hg at 20°C	HSDB 2007l
Conversion factors	1 ppm = 7.2 mg/m^3 1 mg/m^3 = 0.14 ppm	

TABLE A-21 Chemical and Physical Properties for Tetrachlorosilane

Parameter	Value	References
Synonyms	Silicon tetrachloride; silicon chloride	HSDB 2002b
CAS registry no.	10026-04-7	HSDB 2002b
Chemical formula	$SiCl_4$	HSDB 2002b
Molecular weight	169.9	HSDB 2002b
Physical state	Colorless, clear, mobile, fuming liquid	HSDB 2002b
Melting point	-70°C	HSDB 2002b
Boiling point	59°C	HSDB 2002b
Vapor density (air = 1)	7.59 g/L	HSDB 2002b
Liquid density/specific gravity	1.52 g/cm^3 at 0°/4°C	HSDB 2002b
Solubility in water	Decomposes to HCl and silicic acid	HSDB 2002b
Vapor pressure	236 mm Hg at 25°C	HSDB 2002b
Flammability limits	Nonflammable	HSDB 2002b
Conversion factors	1 ppm = 6.9 mg/m^3 1 mg/m^3 = 0.14 ppm	

TABLE A-22 Chemical and Physical Properties for Trichloro(dichlorophenyl)silane

Parameter	Value	References
Synonyms	Dichlorophenyltrichlorosilane	HSDB 2007m
CAS registry no.	27137-85-5	HSDB 2007m
Chemical formula	$C_6H_3Cl_5Si$	HSDB 2007m
Molecular weight	280.43	HSDB 2007m
Physical state	Straw-colored liquid	HSDB 2007m
Boiling point	260°C	HSDB 2007m
Liquid density/specific gravity	1.562 g/cm^3	HSDB 2007m
Conversion factors	1 ppm = 11.4 mg/m^3 1 mg/m^3 = 0.087 ppm	

TABLE A-23 Chemical and Physical Properties for Trichlorophenylsilane

Parameter	Value	References
Synonyms	Phenyltrichlorosilane; phenylsilicon trichloride	HSDB 2007n
CAS registry no.	98-13-5	HSDB 2007n
Chemical formula	$C_6H_5Cl_3Si$	HSDB 2007n
Molecular weight	211.55	HSDB 2007n
Physical state	Colorless liquid	HSDB 2007n
Boiling point	201°C	HSDB 2007n
Vapor density (air = 1)	7.36	HSDB 2007n
Liquid density/specific gravity	1.321 g/cm^3 at 20°C	HSDB 2007n
Solubility in water	Hydrolyzes to form HCl	HSDB 2007n
Vapor pressure	0.426 mm Hg at 25°C	HSDB 2007n
Conversion factors	1 ppm = 8.6 mg/m^3 1 mg/m^3 = 0.12 ppm	

TABLE A-24 Chemical and Physical Properties for Trichlorosilane

Parameter	Value	References
Synonyms	Silicochloroform	HSDB 2007o
CAS registry no.	10025-78-2	HSDB 2007o
Chemical formula	Cl_3HSi	HSDB 2007o
Molecular weight	135.47	HSDB 2007o
Physical state	Colorless liquid	HSDB 2007o
Melting point	-126.5°C	HSDB 2007o
Boiling point	31.8°C	HSDB 2007o
Vapor density (air = 1)	4.67	HSDB 2007o
Liquid density/specific gravity	1.3417 g/cm^3 at 20°C	HSDB 2007o
Solubility in water	Hydrolyzes to form HCl	HSDB 2007o
Vapor pressure	594 mm Hg at 25°C	HSDB 2007o
Conversion factors	1 ppm = 5.3 mg/m^3 1 mg/m^3 = 0.18 ppm	

TABLE A-25 Chemical and Physical Properties for Trimethyl Chlorosilane

Parameter	Value	References
Synonyms	Chlorotrimethylsilane; monochlorotrimethylsilicon	HSDB 2007p
CAS registry no.	75-77-4	HSDB 2007p
Chemical formula	C_3H_9ClSi	HSDB 2007p
Molecular weight	108.642	HSDB 2007p
Physical state	Colorless liquid	HSDB 2007p
Melting point	-40°C	HSDB 2007p
Boiling point	57°C	HSDB 2007p
Vapor density (air = 1)	3.75	HSDB 2007p
Liquid density/specific gravity	0.854 g/cm^3 at 25°C	HSDB 2007p
Solubility in water	Hydrolyzes rapidly	HSDB 2007p
Flash point	0°F (open cup)	HSDB 2007p
Conversion factors in air	1 mg/m^3 = 0.23 ppm 1 ppm = 4.4 mg/m^3	

TABLE A-26 Chemical and Physical Properties for Vinyl Trichlorosilane

Parameter	Value	References
Synonyms	Trichlorovinylsilane; vinylsilicon tetrachloride; trichlorovinyl silicon	HSDB 2007q
CAS registry no.	75-94-5	HSDB 2007q
Chemical formula	$C_2H_3Cl_3Si$	HSDB 2007q
Molecular weight	161.49	HSDB 2007q
Physical state	Fuming liquid	HSDB 2007q
Melting point	-95°C	HSDB 2007q
Boiling point	91.5°C	HSDB 2007q
Vapor density (air = 1)	5.61	HSDB 2007q
Liquid density/specific gravity	1.2426 g/cm^3 at 20°C	HSDB 2007q
Solubility in water	Hydrolyzes to form HCl	HSDB 2007q
Vapor pressure	65.9 mm Hg at 25°C	HSDB 2007q
Conversion factors	1 ppm = 6.6 mg/m^3 1 mg/m^3 = 0.15 ppm	

APPENDIX B

DERIVATION OF AEGL VALUES FOR SELECTED CHLOROSILANES

Derivation of AEGL-1

Monochlorosilanes

Key study:	AEGL-1 values for HCl (Stevens et al. 1992; NRC 2004)
10-min AEGL-1:	1.8 ppm
30-min AEGL-1:	1.8 ppm
1-h AEGL-1:	1.8 ppm
4-h AEGL-1:	1.8 ppm
8-h AEGL-1:	1.8 ppm

Dichlorosilanes

Key study:	AEGL-1 values for HCl (Stevens et al. 1992; NRC 2004) divided by a molar adjustment factor of 2
10-min AEGL-1:	1.8 ppm ÷ 2 = 0.90 ppm
30-min AEGL-1:	1.8 ppm ÷ 2 = 0.90 ppm
1-h AEGL-1:	1.8 ppm ÷ 2 = 0.90 ppm
4-h AEGL-1:	1.8 ppm ÷ 2 = 0.90 ppm
8-h AEGL-1:	1.8 ppm ÷ 2 = 0.90 ppm

Trichlorosilanes

Key study:	AEGL-1 values for HCl (Stevens et al. 1992; NRC 2004) divided by a molar adjustment factor of 3
10-min AEGL-1:	1.8 ppm ÷ 3 = 0.60 ppm
30-min AEGL-1:	1.8 ppm ÷ 3 = 0.60 ppm
1-h AEGL-1:	1.8 ppm ÷ 3 = 0.60 ppm
4-h AEGL-1:	1.8 ppm ÷ 3 = 0.60 ppm
8-h AEGL-1:	1.8 ppm ÷ 3 = 0.60 ppm

Tetrachlorosilane

Key study: AEGL-1 values for HCl (Stevens et al. 1992; NRC 2004) divided by a molar adjustment factor of 4

10-min AEGL-1: 1.8 ppm ÷ 4 = 0.45 ppm
30-min AEGL-1: 1.8 ppm ÷ 4 = 0.45 ppm
1-h AEGL-1: 1.8 ppm ÷ 4 = 0.45 ppm
4-h AEGL-1: 1.8 ppm ÷ 4 = 0.45 ppm
8-h AEGL-1: 1.8 ppm ÷ 4 = 0.45 ppm

Derivation of AEGL-2

Monochlorosilanes

Key study: AEGL-2 values for HCl (Barrow et al. 1977; Stavert et al. 1991; NRC 2004).

10-min AEGL-1: 100 ppm
30-min AEGL-1: 43 ppm
1-h AEGL-1: 22 ppm
4-h AEGL-1: 11 ppm
8-h AEGL-1: 11 ppm

Dichlorosilanes

Key study: AEGL-2 values for HCl (Barrow et al. 1977; Stavert et al. 1991; NRC 2004) divided by a molar adjustment factor of 2

10-min AEGL-2: 100 ppm ÷ 2 = 50 ppm
30-min AEGL-2: 43 ppm ÷ 2 = 22 ppm
1-h AEGL-2: 22 ppm ÷ 2 = 11 ppm
4-h AEGL-2: 11 ppm ÷ 2 = 5.5 ppm
8-h AEGL-2: 11 ppm ÷ 2 = 5.5 ppm

Trichlorosilanes

Key study: AEGL-2 values for HCl (Barrow et al. 1977; Stavert et al. 1991; NRC 2004) divided by a molar adjustment factor of 3

10-min AEGL-2:	100 ppm ÷ 3 = 33 ppm
30-min AEGL-2:	43 ppm ÷ 3 = 14 ppm
1-h AEGL-2:	22 ppm ÷ 3 = 7.3 ppm
4-h AEGL-2:	11 ppm ÷ 3 = 3.7 ppm
8-h AEGL-2:	11 ppm ÷ 3 = 3.7 ppm

Tetrachlorosilane

Key study:	AEGL-2 values for HCl (Barrow et al. 1977; Stavert et al. 1991; NRC 2004) divided by a molar adjustment factor of 4
10-min AEGL-2:	100 ppm ÷ 4 = 25 ppm
30-min AEGL-2:	43 ppm ÷ 4 = 11 ppm
1-h AEGL-2:	22 ppm ÷ 4 = 5.5 ppm
4-h AEGL-2:	11 ppm ÷ 4 = 2.8 ppm
8-h AEGL-2:	11 ppm ÷ 4 = 2.8 ppm

Derivation of AEGL-3

Monochlorosilanes

Key study:	AEGL-3 values for HCl (Wohlslagel et al. 1976; Vernot et al. 1977; NRC 2004)
10-min AEGL-1:	620 ppm
30-min AEGL-1:	210 ppm
1-h AEGL-1:	100 ppm
4-h AEGL-1:	26 ppm
8-h AEGL-1:	26 ppm

Dichlorosilanes

Key study:	AEGL-3 values for HCl (Wohlslagel et al. 1976; Vernot et al. 1977; NRC 2004) divided by a molar adjustment factor of 2
10-min AEGL-3:	620 ppm ÷ 2 = 310 ppm
30-min AEGL-3:	210 ppm ÷ 2 = 105 ppm (rounded to 110)
1-h AEGL-3:	100 ppm ÷ 2 = 50 ppm
4-h AEGL-3:	26 ppm ÷ 2 = 13 ppm
8-h AEGL-3:	26 ppm ÷ 2 = 13 ppm

Trichlorosilanes

Key study:	AEGL-3 values for HCl (Wohlslagel et al. 1976; Vernot et al. 1977; NRC 2004) divided by a molar adjustment factor of 3
10-min AEGL-3:	620 ppm ÷ 3 = 210 ppm
30-min AEGL-3:	210 ppm ÷ 3 = 70 ppm
1-h AEGL-3:	100 ppm ÷ 3 = 33 ppm
4-h AEGL-3:	26 ppm ÷ 3 = 8.7 ppm
8-h AEGL-3:	26 ppm ÷ 3 = 8.7 ppm

Tetrachlorosilane

Key study:	AEGL-3 values for HCl (Wohlslagel et al. 1976; Vernot et al. 1977; NRC 2004) divided by a molar adjustment factor of 4
10-min AEGL-3:	620 ppm ÷ 4 = 160 ppm
30-min AEGL-3:	210 ppm ÷ 4 = 53 ppm
1-h AEGL-3:	100 ppm ÷ 4 = 25 ppm
4-h AEGL-3:	26 ppm ÷ 4 = 6.5 ppm
8-h AEGL-3:	26 ppm ÷ 4 = 6.5 ppm

APPENDIX C

DERIVATION OF AEGL VALUES FOR HYDROGEN CHLORIDE (NRC 2004)

Derivation of AEGL-1 Values

Key study:	Stevens et al. 1992
Toxicity end point:	No-observed-adverse-effect level in exercising asthmatic subjects
Time-scaling:	$C^n \times t = k$ (default of n = 1 for shorter to longer exposure period) $(1.8 \text{ ppm})^1 \times 0.75 \text{ h} = 1.35 \text{ ppm-h}$
Uncertainty factors:	None
10-min AEGL-1:	1.8 ppm
30-min AEGL-1:	1.8 ppm
1-h AEGL-1:	1.8 ppm
4-h AEGL-1:	1.8 ppm
8-h AEGL-1:	1.8 ppm

Derivation of AEGL-2 Values

10-min AEGL-2

Key study:	Barrow et al. (1977)
Toxicity end point:	Mouse RD_{50} of 309 ppm
10-min AEGL-2:	309 ppm ÷ 3 = 100 ppm One-third of the RD_{50} corresponds to an approximate decrease in respiratory rate of 30%, and decreases in the range of 20-50% correspond to moderate irritation (ASTM 1991).

30-min, 1-, 4-, and 8-h AEGL-2

Key study:	Stavert et al. 1991
Toxicity end point:	Severe nasal (nose breathers) or pulmonary (mouth breathers) effects in rats exposed at 1,300 ppm for 30 min
Time-scaling:	$C^1 \times t = k$ (n = 1 for shorter to longer exposure periods) $(1{,}300 \text{ ppm})^1 \times 0.5 \text{ h} = 650 \text{ ppm-h}$
Uncertainty factors:	3 for intraspecies variability 3 for interspecies variability Combined uncertainty factor of 10
Modifying factor:	3 for sparse database
30-min AEGL-2:	$C^1 \times 0.5 \text{ h} = 650 \text{ ppm-h}$ C = 1,300 ppm 1,300 ppm ÷ 30 = 43 ppm
1-h AEGL-2:	$C^1 \times 1 \text{ h} = 650 \text{ ppm-h}$ C = 650 ppm 650 ppm ÷ 30 = 22 ppm
4-h AEGL-2:	1-h AEGL-2 ÷ 2 = 11 ppm
8-h AEGL-2:	1-h AEGL-2 ÷ 2 = 11 ppm

Derivation of AEGL-3 Values

Key studies:	Wohlslagel et al. (1976); Vernot et al. (1977)
Toxicity end point:	One-third of the rat 1-h LC_{50} (an estimated no-effect level for death) LC_{50} = 3,124 ppm ÷ 3 = 1,041 ppm
Time-scaling:	$C^1 \times t = k$ (n = 1 for shorter to longer exposure periods) $(1{,}041 \text{ ppm})^1 \times 1 \text{ h} = 1{,}041 \text{ ppm-h}$
Uncertainty factors:	3 for intraspecies variability 3 for interspecies variability Combined uncertainty factor of 10

10-min AEGL-3:	$C^1 \times 0.167$ h = 1,041 ppm-h C = 6,234 ppm 6,234 ppm ÷ 10 = 623.4 ppm
30-min AEGL-3:	$C^1 \times 0.5$ h = 1,041 ppm-h C = 2,082 ppm 2,082 ppm ÷ 10 = 208 ppm
1-h AEGL-3:	$C^1 \times 1$ h = 1,041 ppm-h C = 1,041 ppm 1,041 ppm ÷ 10 = 104.1 ppm
4-h AEGL-3:	$C^1 \times 4$ h = 1,041 ppm-h C = 260.25 ppm 260.25 ppm ÷ 10 = 26 ppm
8-h AEGL-3:	Set equal to 4-h AEGL-3 = 26 ppm

SUMMARY OF KEY STUDY AND RATIONALE USED TO DERIVE AEGL VALUES FOR HYDROGEN CHLORIDE (Excerpted from NRC 2004)

AEGL-1 Values

Because appropriate human data exist for exposure to HCl, they were used to identify AEGL-1 values. Exposure to HCl at 1.8 ppm for 45 min resulted in a no-observed-adverse-effect level in 10 exercising young adult asthmatic subjects (Stevens et al. 1992). Because exercise will increase HCl uptake and exacerbate irritation, those asthmatic subjects are considered a sensitive subpopulation. Therefore, because the test subjects were a sensitive subpopulation and the end point was essentially a no-effect level, no uncertainty factor was applied to account for sensitive human subpopulations. Adequate human data were available, so no uncertainty factor was applied for animal to human extrapolation. The no-effect level was held constant across the 10- and 30-min and 1-, 4-, and 8-h exposure time periods. That approach was considered appropriate because mild irritant effects generally do not vary greatly over time, and the end point of a no-effect level in a sensitive population is inherently conservative.

AEGL-2 Values

The AEGL-2 for the 30-min and 1-, 4-, and 8-h time points was based on severe nasal or pulmonary histopathology in rats exposed to HCl at 1,300 ppm for 30 min (Stavert et al. 1991). A modifying factor of 3 was applied to account for the relatively sparse database describing effects defined by AEGL-2. The AEGL-2 values were further adjusted by a total uncertainty factor of 10—3 for intraspecies variability, supported by the steep concentration-response curve, which implies little individual variability; and 3 for interspecies variability. Using the default value of 10 for interspecies variability would bring the total adjustment to 100 instead of 30. That would generate AEGL-2 values that are not supported by data on exercising asthmatic subjects, an especially sensitive subpopulation. Exercise increases HCl uptake and exacerbates irritation; no effects were noted in exercising young adult asthmatic subjects exposed to HCl at 1.8 ppm for 45 min (Stevens et al. 1992). Using a total uncertainty factor of 30 would yield 4- and 8-h values of 3.6 ppm (instead of 11 ppm). The prediction that humans would be disabled by exposure for 4 or 8 h to 3.6 ppm cannot be supported when exercising asthmatic subjects exposed to one-half that concentration for 45 min exhibited no effects. The shorter time points would yield values 4 to 7 times the 1.8-ppm value; however, confidence in the time-scaling for HCl is good for times up to 100 min, because the value of n was derived from a regression analysis of rat and mouse mortality data with exposure durations ranging from 1 min to 100 min. The 30-min value of 43 ppm derived with a total uncertainty factor of 10 is reasonable in light of the fact that baboons exposed at

500 ppm for 15 min experienced only a slightly increased respiratory rate. Therefore, a total uncertainty factor of 10, accompanied by the modifying factor of 3, is most consistent with the database. Thus, the total factor is 30. Time-scaling for the 1-h AEGL exposure period used the $C^n \times t = k$ relationship, where n = 1 based on regression analysis of combined rat and mouse LC_{50} data (1 to 100 min) as reported by ten Berge et al. (1986). The 4- and 8-h AEGL-2 values were derived by applying a modifying factor of 2 to the 1-h AEGL-2 value, because time-scaling would yield a 4-h AEGL-2 of 5.4 ppm and an 8-h AEGL-2 of 2.7 ppm, close to the 1.8 ppm tolerated by exercising asthmatic subjects without observed adverse health effects. Repeated-exposure rat data suggest that the 4- and 8-h values of 11 ppm are protective. Rats exposed to HCl at 10 ppm for 6 h/day, 5 days/week for life exhibited only tracheal and laryngeal hyperplasia, and rats exposed to HCl at 50 ppm for 6 h/day, 5 days/week for 90 days exhibited only mild rhinitis.

The 10-min AEGL-2 was derived by dividing the mouse RD_{50} of 309 ppm by a factor of 3 to obtain a concentration causing irritation (Barrow et al. 1977). It has been determined that human response to sensory irritants can be predicted on the basis of the mouse RD_{50}. For example, Schaper (1993) has validated the correlation of $0.03 \times RD_{50}$ = TLV (threshold limit value) as a value that will prevent sensory irritation in humans. The 0.03 represents the half-way point between 0.1 and 0.01 on a logarithmic scale, and Alarie (1981) has shown that the RD_{50} multiplied by 0.1 corresponds to "some sensory irritation," whereas the RD_{50} value itself is considered "intolerable to humans." Thus, it is reasonable that one-third of the RD_{50}, a value half-way between 0.1 and 1 on a logarithmic scale, might cause significant irritation to humans. Furthermore, one-third of the mouse RD_{50} for HCl corresponds to an approximate decrease in respiratory rate of 30%, and decreases in the range of 20-50% correspond to moderate irritation (ASTM 1991).

AEGL-3 Values

The AEGL-3 was based on a 1-h rat LC_{50} study (Wohlslagel et al. 1976; Vernot et al. 1977). One-third of the 1-h LC_{50} value of 3,124 ppm was used as an estimated concentration causing no deaths. That estimate is inherently conservative (no deaths observed in the same study at 1,813 ppm). A total uncertainty factor of 10 will be applied—3 for intraspecies variation, because the steep concentration-response curve implies limited individual variability; and 3 to protect susceptible individuals. Using a full value of 10 for interspecies variability (total uncertainty factor of 30) would yield AEGL-3 values that are inconsistent with the overall data set.

A number of factors argue for the use of an uncertainty factor of 10 instead of 30, they are: (1) the steep concentration-response curve for lethality observed in the Wohlslagel et al. (1976) study in which the estimated LC_0 (one-third of the LC_{50} of 3,124 ppm) is lower than the experimental LC_0 of 1,813

ppm. The LC_0 selection is conservative, and the steep concentration-response curve argues for little interindividual variability; (2) AEGL-3 values generated from a total uncertainty factor of 30 would be close (within a factor of 2) to the AEGL-2 values generated from data on exercising asthmatic subjects; (3) Sellakumar et al. (1985) exposed rats to HCl at 10 ppm for 6 h/day, 5 days/week for life and only observed increased trachael and laryngeal hyperplasia. The estimated 6-h AEGL-3 using an intraspecies uncertainty factor of 3 is 17 ppm, close to the concentration inhaled in the lifetime study in which only mild effects were induced; and (4) rats exposed to HCl at 50 ppm for 6 h/day, 5 days/week for 90 days exhibited mild rhinitis (Toxigenics Inc. 1984). This level is already twice the AEGL-3 value, which is intended to protect against death.

Thus, the total uncertainty factor was set at 10. It was then time-scaled to the specified 10- and 30-min and 4-h AEGL exposure periods using the $C^n \times t = k$ relationship, where n = 1 based on regression analysis of combined rat and mouse LC_{50} data (1 min to 100 min) as reported by ten Berge et al. (1986). The 4-h AEGL-3 also was adopted as the 8-h AEGL-3 because of the uncertainty of time-scaling to 8 h with an n value derived from exposure durations of up to 100 min.

The 5-min rat LC_0 of 30,000 ppm (Higgins et al. 1972) supports the 10-min AEGL-3 value. Extrapolating that value across time (n = 1) to 10 min and applying an uncertainty factor of 10 yields a value of 1,500 ppm, suggesting that the proposed AEGL-3 value is protective. Also, if the 5-min rat LC_{50} of 41,000 ppm for HCl vapor (Darmer et al. 1974) is divided by 3 to estimate a no-effect level for death, extrapolated to 10 min, and an uncertainty factor of 10 is applied, a supporting value of 683 ppm is obtained.

APPENDIX D

ACUTE EXPOSURE GUIDELINE LEVELS FOR SELECTED CHLOROSILANES

Derivation Summary

AEGL-1 VALUES FOR MONOCHLOROSILANES

10 min	30 min	1 h	4 h	8 r
1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm

Key reference: NRC (National Research Council). 2004. Hydrogen chloride. Pp. 22-122 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 4. Washington, DC: National Academies Press.

End point/Concentration/Rationale: AEGL-1 values for HCl were adopted as AEGL-1 values for monochlorosilanes. This approach is considered reasonable because qualitative and quantitative data on chlorosilanes suggest that the HCl hydrolysis product is largely responsible for the acute toxicity of the chlorosilanes.

Data adequacy: Mechanism-of-action data were considered adequate for the derivation of AEGL-1 values for chlorosilanes based on analogy to HCl. Confidence in the AEGL-1 values for chlorosilanes is low, reflecting the lack of data on AEGL-1 end points after chlorosilane exposure and reliance on HCl data. Additional research on AEGL-1 effects of chlorosilanes would reduce uncertainty.

AEGL-1 VALUES FOR DICHLOROSILANES

10 min	30 min	1 h	4 h	8 h
0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm

Key reference: NRC (National Research Council). 2004. Hydrogen chloride. Pp. 77-122 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 4. Washington, DC: National Academies Press.

End point/Concentration/Rationale: AEGL-1 values for dichlorosilanes were derived by adjusting the AEGL-1 values for HCl by the molar ratio of HCl to trichlorosilanes. This approach is considered reasonable because qualitative and quantitative data on chlorosilanes suggest that the HCl hydrolysis product is largely responsible for the acute toxicity of the chlorosilanes.

Molar Adjustment Factor: 2

Data adequacy: Mechanism-of-action data were considered adequate for the derivation of AEGL-1 values for chlorosilanes based on analogy to HCl. Confidence in the AEGL-1 values for chlorosilanes is low, reflecting the lack of data on AEGL-1 end points after chlorosilane exposure and reliance on HCl data. Additional research on AEGL-1 effects of chlorosilanes would reduce uncertainty.

AEGL-1 VALUES FOR TRICHLOROSILANES

10 min	30 min	1 h	4 h	8 h
0.60 ppm	0.60 ppm	0.60 ppm	0.60 ppm	0.60 ppm

Key reference: NRC (National Research Council). 2004. Hydrogen chloride. Pp. 77-122 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 4. Washington, DC: National Academies Press.

End point/Concentration/Rationale: AEGL-1 values for trichlorosilanes were derived by adjusting the AEGL-1 values for HCl by the molar ratio of HCl to trichlorosilanes. This approach is considered reasonable because qualitative and quantitative data on chlorosilanes suggest that the HCl hydrolysis product is largely responsible for the acute toxicity of the chlorosilanes.

Molar Adjustment Factor: 3

Data adequacy: Mechanism-of-action data were considered adequate for the derivation of AEGL-1 values for chlorosilanes based on analogy to HCl. Confidence in the AEGL-1 values for chlorosilanes is low, reflecting the lack of data on AEGL-1 end points after chlorosilane exposure and reliance on HCl data. Additional research on AEGL-1 effects of chlorosilanes would reduce uncertainty.

AEGL-1 VALUES FOR TETRACHLOROSILANE

10 min	30 min	1 h	4 h	8 h
0.45 ppm	0.45 ppm	0.45 ppm	0.45 ppm	0.45 ppm

Key reference: NRC (National Research Council). 2004. Hydrogen chloride. Pp. 77-122 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 4. Washington, DC: National Academies Press.

End point/Concentration/Rationale: AEGL-1 values for tetrachlorosilane were derived by adjusting the AEGL-1 values for HCl by the molar ratio of HCl to tetrachlorosilane. This approach is considered reasonable because qualitative and quantitative data on chlorosilanes suggest that the HCl hydrolysis product is largely responsible for the acute toxicity of the chlorosilanes.

Molar adjustment factor: 4

Data adequacy: Mechanism-of-action data were considered adequate for the derivation of AEGL-1 values for chlorosilanes based on analogy to HCl. Confidence in the AEGL-1 values for chlorosilanes is low, reflecting the lack of data on AEGL-1 end points after chlorosilane exposure and reliance on HCl data. Additional research on AEGL-1 effects of chlorosilanes would reduce uncertainty.

AEGL-2 VALUES FOR MONOCHLOROSILANES

10 min	30 min	1 h	4 h	8 h
100 ppm	43 ppm	22 ppm	11 ppm	11 ppm

Key reference: NRC (National Research Council). 2004. Hydrogen chloride. Pp. 77-122 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 4. Washington, DC: National Academies Press.

End point/Concentration/Rationale: AEGL-2 values for HCl were adopted as AEGL-2 values for monochlorosilanes. This approach is considered reasonable because qualitative and quantitative data on chlorosilanes suggest that the HCl hydrolysis product is largely responsible for the acute toxicity of the chlorosilanes.

Data adequacy: Mechanism-of-action data were considered adequate for the derivation of AEGL-2 values for chlorosilanes based on analogy to HCl. Confidence in the AEGL-2 values for chlorosilanes is moderate, reflecting the limited data on AEGL-2 end points after chlorosilane exposure and reliance on HCl data. Additional research on AEGL-2 effects of chlorosilanes would reduce uncertainty.

AEGL-2 VALUES FOR DICHLOROSILANES

10 min	30 min	1 h	4 h	8 h
50 ppm	22 ppm	11 ppm	5.5 ppm	5.5 ppm

Key reference: NRC (National Research Council). 2004. Hydrogen chloride. Pp. 77-122 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 4. Washington, DC: National Academies Press.

End point/Concentration/Rationale: AEGL-2 values for dichlorosilanes were derived by adjusting the AEGL-2 values for HCl by the molar ratio of HCl to dichlorosilane. This approach is considered reasonable because qualitative and quantitative data on chlorosilanes suggest that the HCl hydrolysis product is largely responsible for the acute toxicity of the chlorosilanes.

Molar adjustment factor: 2

Data adequacy: Mechanism-of-action data were considered adequate for the derivation of AEGL-2 values for chlorosilanes based on analogy to HCl. Confidence in the AEGL-2 values for chlorosilanes is moderate, reflecting the limited data on AEGL-2 end points after chlorosilane exposure and reliance on HCl data. Additional research on AEGL-2 effects of chlorosilanes would reduce uncertainty.

AEGL-2 VALUES FOR TRICHLOROSILANES

10 min	30 min	1 h	4 h	8 h
33 ppm	14 ppm	7.3 ppm	3.7 ppm	3.7 ppm

Key reference: NRC (National Research Council). 2004. Hydrogen chloride. Pp. 77-122 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 4. Washington, DC: National Academies Press.

End point/Concentration/Rationale: AEGL-2 values for trichlorosilanes were derived by adjusting the AEGL-2 values for HCl by the molar ratio of HCl to trichlorosilane. This approach is considered reasonable because qualitative and quantitative data on chlorosilanes suggest that the HCl hydrolysis product is largely responsible for the acute toxicity of the chlorosilanes.

Molar adjustment factor: 3

Data adequacy: Mechanism-of-action data were considered adequate for the derivation of AEGL-2 values for chlorosilanes based on analogy to HCl. Confidence in the AEGL-2 values for chlorosilanes is moderate, reflecting the limited data on AEGL-2 end points after chlorosilane exposure and reliance on HCl data. Additional research on AEGL-2 effects of chlorosilanes would reduce uncertainty.

AEGL-2 VALUES FOR TETRACHLOROSILANE

10 min	30 min	1 h	4 h	8 h
25 ppm	11 ppm	5.5 ppm	2.8 ppm	2.8 ppm

Key reference: NRC (National Research Council). 2004. Hydrogen chloride. Pp. 77-122 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 4. Washington, DC: National Academies Press.

End point/Concentration/Rationale: AEGL-2 values for tetrachlorosilane were derived by adjusting the AEGL-2 values for HCl by the molar ratio of HCl to tetrachlorosilane. This approach is considered reasonable because qualitative and quantitative data on chlorosilanes suggest that the HCl hydrolysis product is largely responsible for the acute toxicity of the chlorosilanes.

Molar adjustment factor: 4

Data adequacy: Mechanism-of-action data were considered adequate for the derivation of AEGL-2 values for chlorosilanes based on analogy to HCl. Confidence in the AEGL-2 values for chlorosilanes is moderate, reflecting the limited data on AEGL-2 end points after chlorosilane exposure and reliance on HCl data. Additional research on AEGL-2 effects of chlorosilanes would reduce uncertainty.

AEGL-3 VALUES FOR MONOCHLOROSILANES

10 min	30 min	1 h	4 h	8 h
620 ppm	210 ppm	100 ppm	26 ppm	26 ppm

Key reference: NRC (National Research Council). 2004. Hydrogen chloride. Pp. 77-122 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 4. Washington, DC: National Academies Press..

End point/Concentration/Rationale: AEGL-3 values for HCl were adopted as AEGL-3 values for monochlorosilanes. This approach is considered reasonable because qualitative and quantitative data on chlorosilanes suggest that the HCl hydrolysis product is largely responsible for the acute toxicity of the chlorosilanes.

Data adequacy: Data were considered adequate for the derivation of AEGL-3 values for chlorosilanes based on analogy to HCl. Confidence in the AEGL-3 values for chlorosilanes is high, reflecting the availability of lethality data on 11 of the 26 chlorosilanes considered and evidence for the role of HCl as the proximate toxicant. No additional research is needed on AEGL-3 end points.

AEGL-3 VALUES FOR DICHLOROSILANES

10 min	30 min	1 h	4 h	8 h
310 ppm	110 ppm	50 ppm	13 ppm	13 ppm

Key reference: NRC (National Research Council). 2004. Hydrogen chloride. Pp. 77-122 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 4. Washington, DC: National Academies Press.

End point/Concentration/Rationale: AEGL-3 values for dichlorosilanes were derived by adjusting the AEGL-3 values for HCl by the molar ratio of HCl to dichlorosilane. This approach is considered reasonable because qualitative and quantitative data on chlorosilanes suggest that the HCl hydrolysis product is largely responsible for the acute toxicity of the chlorosilanes.

Molar adjustment factor: 2

Data adequacy: Data were considered adequate for the derivation of AEGL-3 values for chlorosilanes based on analogy to HCl. Confidence in the AEGL-3 values for chlorosilanes is high, reflecting the availability of lethality data on 11 of the 26 chlorosilanes considered and evidence for the role of HCl as the proximate toxicant. No additional research is needed on AEGL-3 end points.

AEGL-3 VALUES FOR TRICHLOROSILANES

10 min	30 min	1 h	4 h	8 h
210 ppm	70 ppm	33 ppm	8.7 ppm	8.7 ppm

Key reference: NRC (National Research Council). 2004. Hydrogen chloride. Pp. 77-122 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 4. Washington, DC: National Academies Press.

End point/Concentration/Rationale: AEGL-3 values for trichlorosilanes were derived by adjusting the AEGL-3 values for HCl by the molar ratio of HCl to trichlorosilane. This approach is considered reasonable because qualitative and quantitative data on chlorosilanes suggest that the HCl hydrolysis product is largely responsible for the acute toxicity of the chlorosilanes.

Molar adjustment factor: 3

Data adequacy: Data were considered adequate for the derivation of AEGL-3 values for chlorosilanes based on analogy to HCl. Confidence in the AEGL-3 values for chlorosilanes is high, reflecting the availability of lethality data on 11 of the 26 chlorosilanes considered and evidence for the role of HCl as the proximate toxicant. No additional research is needed on AEGL-3 end points.

AEGL-3 VALUES FOR TETRACHLOROSILANE

10 min	30 min	1 h	4 h	8 h
160 ppm	53 ppm	25 ppm	6.5 ppm	6.5 ppm

Key reference: NRC (National Research Council). 2004. Hydrogen chloride. Pp. 77-122 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 4. Washington, DC: National Academies Press.

End point/Concentration/Rationale: AEGL-3 values for tetrachlorosilane were derived by adjusting the AEGL-3 values for HCl by the molar ratio of HCl to tetrachlorosilane. This approach is considered reasonable because qualitative and quantitative data on chlorosilanes suggest that the HCl hydrolysis product is largely responsible for the acute toxicity of the chlorosilanes.

Molar adjustment factor: 4

Data adequacy: Data were considered adequate for the derivation of AEGL-3 values for chlorosilanes based on analogy to HCl. Confidence in the AEGL-3 values for chlorosilanes is high, reflecting the availability of lethality data on 11 of the 26 chlorosilanes considered and evidence for the role of HCl as the proximate toxicant. No additional research is needed on AEGL-3 end points.

APPENDIX E

DERIVATION SUMMARY TABLES FOR HYDROGEN CHLORIDE (Excerpted from NRC 2004)

Derivation Summary

AEGL-1 VALUES FOR HYDROGEN CHLORIDE

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

Key reference: Stevens, B., J.Q. Koenig, V. Rebolledo, Q.S. Hanley, and D.S. Covert, D.S. 1992. Respiratory effects from the inhalation of hydrogen chloride in young adults with asthma. J. Occup. Med. 34(9): 923-929.

Test species/Strain/Number: Human adults with asthma, 10

Exposure route/Concentrations/Durations: Inhalation at 0, 0.8, or 1.8 ppm for 45 min while exercising (1.8 ppm was determinant for AEGL-1)

Effects: No treatment-related effects were observed in any of the individuals tested

End point/Concentration/Rationale: The highest concentration tested was a no-effect level for irritation in a sensitive human population (10 asthmatic individuals tested) and was selected as the basis of AEGL-1. Effects assessed included sore throat, nasal discharge, cough, chest pain or burning, dyspnea, wheezing, fatigue, headache, unusual taste or smell, total respiratory resistance, thoracic gas volume at functional residual capacity, forced expiratory volume, and forced vital capacity. All subjects continued the requisite exercise routine for the duration of the test period.

Uncertainty factors/Rationale:
Total uncertainty factor:
Interspecies: 1, test subjects were human
Intraspecies: 1, test subjects were sensitive population (exercising asthmatic subjects)

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Insufficient data

Time-scaling: The AEGL-1 values for a sensory irritant were held constant across time because it is a threshold effect and prolonged exposure will not result in an enhanced effect. In fact one might become desensitized to the respiratory-tract irritant over time. Also, this approach was considered valid since the end point (no treatment-related effects at the highest concentration tested in exercising asthmatic subjects) is inherently conservative.

Data quality and research needs: The key study was well-conducted in a sensitive human population and is based on no treatment-related effects. Additionally, the direct-acting irritation response is not expected to vary greatly among individuals. Therefore, confidence in the AEGL values is high.

AEGL-2 VALUES FOR HYDROGEN CHLORIDE

10 min	30 min	1 h	4 h	8 h
100 ppm	43 ppm	22 ppm	11 ppm	11 ppm

Key references: Stavert, D.M., D.C. Archuleta, M.F. Behr, and B.E. Lehnert. 1991. Relative acute toxicities of hydrogen chloride, hydrogen fluoride, and hydrogen bromide in nose- and pseudo-mouth-breathing rats. Fundam. Appl. Toxicol. 16(4):636-655. (30-, 1-, 4-min and 8-h AEGLs)
Barrow, C.S., Y. Alarie, M. Warrick, and M.F. Stock. 1977. Comparison of the sensory irritation response in mice to chlorine and hydrogen chloride. Arch. Environ. Health 32(2):68-76. (10-min AEGL)

Test species/Strain/Number: F344 rats, 8 males/concentration (30-min, 1-, 4-, and 8-h); Male Swiss Webster mice (10-min)

Exposure route/Concentrations/Durations: inhalation at 0 or 1,300 ppm for 30 min (1,300 ppm was determinant for 30-min, 1-, 4-, and 8-h AEGL-2)

Effects (30-min, 1-, 4-, and 8-h): 0 ppm, no effects; 1,300 ppm, severe necrotizing rhinitis, turbinate necrosis, thrombosis of nasal submucosa vessels in nose-breathers; 1,300 ppm, severe ulcerative tracheitis accompanied by necrosis and luminal ulceration in mouth-breathers (determinant for AEGL-2); RD_{50} = 309 ppm (determinant for 10-min AEGL-2)

End point/Concentration/Rationale: 1,300 ppm for 30 min; severe lung effects (ulcerative tracheitis accompanied by necrosis and luminal ulceration) or nasal effects (necrotizing rhinitis, turbinate necrosis, thrombosis of nasal submucosa vessels histopathology) in pseudo-mouth breathing male F344 rats (30-min, 1-, 4-, and 8-h); RD_{50} of 309 ppm ÷ 3 to estimate irritation (10-min)

Uncertainty Factors/Rationale (30-min, 1-, 4-, and 8-h):
Total uncertainty factor: 10
Intraspecies: 3, steep concentration-response curve implies limited individual variability.
Interspecies: 3, use of an intraspecies uncertainty factor of 10 would bring the total uncertainty/modifying factor to 100 instead of 30. That would generate AEGL-2 values that are not supported by data on exercising asthmatic subjects, an especially sensitive subpopulation because exercise increases HCl uptake and exacerbates irritation. No effects were noted in exercising young adult with asthma exposed to HCl at 1.8 ppm for 45 min (Stevens et al. 1992). Using a total uncertainty factor of 30 would yield 4- and 8-h values of 3.6 ppm (instead of 11 ppm). It is not supportable to predict that humans would be disabled by exposure at 3.6 ppm for 4- or 8-h when exercising asthmatic subjects exposed to one-half this level for 45 min had no effects. The shorter time points would yield values 4- to 7 times above 1.8 ppm; however, the confidence in the time scaling for HCl is good for times up to 100 min because the value of n value was derived from a regression analysis of rat and mouse mortality data with exposure durations ranging from 1 min to 100 min. The 30-min value of 43 ppm derived with the total uncertainty factor of 10 is reasonable in light of the fact that baboons exposed to 500 ppm for 15 min experienced only a slightly increased respiratory rate.

(Continued)

AEGL-2 VALUES FOR HYDROGEN CHLORIDE Continued

10 min	30 min	1 h	4 h	8 h
100 ppm	43 ppm	22 ppm	11 ppm	11 ppm

Modifying factor:
30-min, 1-, 4-, and 8-h AEGLs: 3 based on sparse database for AEGL-2 effects and that the effects observed at the concentration used as the basis for AEGL-2 values were somewhat severe.
10-min AEGL-2: the 10-min AEGL-2 value was derived by dividing the mouse RD_{50} of 309 ppm by a factor of 3 to obtain a concentration causing irritation (Barrow et al. 1977). One-third of the mouse RD_{50} for HCl corresponds to an approximate decrease in respiratory rate of 30%, and decreases in the range of 20% to 50% correspond to moderate irritation (ASTM 1991).

Animal-to-human dosimetric adjustment: Insufficient data

Time-scaling: $C^n \times t = k$, where n=1, based on regression analysis of combined rat and mouse LC_{50} data (1 min to 100 min) reported by ten Berge et al. (1986). Data point used to derive AEGL-2 was 30 min. AEGL-2 values for 1-h exposure period was based on extrapolation from the 30-min value. The 4- and 8-h AEGL-2 values were derived by applying a modifying factor of 2 to the 1-h AEGL-2 value because time scaling would yield a 4-h AEGL-2 value of 5.4 ppm and an 8-h AEGL-2 of 2.7 ppm, close to the 1.8 ppm tolerated by exercising asthmatic subjects without adverse health effects.

Data quality and research needs: Confidence is moderate since the species used is more sensitive than primates to the effects of HCl, the chemical is a direct-acting irritant, and a modifying factor was included to account for the relative severity of effects and sparse data base.

AEGL-3 VALUES FOR HYDROGEN CHLORIDE

10 min	30 min	1 h	4 h	8 h
620 ppm	210 ppm	100 ppm	26 ppm	26 ppm

Key reference: Vernot, E.H., J.D. MacEwen, C.C. Haun, and E.R. Kinkead. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol. Appl. Pharmacol. 42(2):417-423. Wohlslagel, J., L.C. DiPasquale, and E.H. Vernot. 1976. Toxicity of solid rocket motor exhaust: Effects of HCl, HF, and alumina on rodents. J. Combust. Toxicol. 3:61-69.

Test species/Strain/Sex/Number: Sprague-Dawley rats, 10 males per concentration

Exposure route/Concentrations/Durations: inhalation at 0, 1,813, 2,585, 3,274, 3,941, or 4,455 ppm for 1 h

(Continued)

AEGL-3 VALUES FOR HYDROGEN CHLORIDE Continued

10 min	30 min	1 h	4 h	8 h
620 ppm	210 ppm	100 ppm	26 ppm	26 ppm

Effects:

Concentration	Mortality
0 ppm	0/10
1,813 ppm	0/10
2,585 ppm	2/10
3,274 ppm	6/10
3,941 ppm	8/10
4,455 ppm	10/10

LC_{50}: reported as 3,124 ppm (determinant for AEGL-3)

End point/Concentration/Rationale: One-third of the 1-h LC_{50} (3,124 × 1/3 = 1,041 ppm) to estimate a concentration causing no deaths.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Intraspecies: 3, a steep concentration-response curve implies limited individual variability.
Interspecies: 3, (1) the steep concentration-response curve for lethality observed in the Wohlslagel et al. (1976) study in which 1,041 ppm (one-third of the LC_{50} of 3,124 ppm) was lower than the LC_0 of 1,813 ppm. This is a conservative selection of the LC_0 and the steep concentration-response curve argues for little interindividual variability; (2)AEGL-3 values generated from a total uncertainty factor of 30 would be close to the AEGL-2 values (within a factor of 2) generated above which are reasonable when compared with data on exercising asthmatic subjects; (3) Sellakumar et al. (1985) exposed rats to 10 ppm of HCl for 6 h/day, 5 days/week for life and only observed increased trachael and laryngeal hyperplasia. The estimated 6-h AEGL-3 using an intraspecies uncertainty factor of 3 is 17 ppm, close to the level used in the lifetime study in which only mild effects were induced; and (4) rats exposed at 50 ppm for 6 h/day, 5 days/week for 90 days exhibited mild rhinitis (Toxigenics Inc. 1984). This level is already 2 times that of the AEGL-3 value for death. Thus, the total uncertainty factor is 10.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Insufficient data

Time-scaling: $C^n \times t = k$, where n = 1, based on regression analysis of rat and mouse mortality data (1 min to 100 min) reported by ten Berge et al. (1986). Reported 1-h data point was used to derive AEGL-3 values. AEGL-3 values for 10-min, 30-min, and 4-h were based on extrapolation from the 1-h value. The 4-h value was adopted as the 8-h value.

Data quality and research needs: Study is considered appropriate for AEGL-3 derivation because exposures are over a wide range of HCl concentrations and utilize a sufficient number of animals. Data were insufficient to derive a no-effect level for death. One-third of the LC_{50} has been utilized previously for chemicals with steep concentration-response curves. Also, in the key study, no deaths were observed in rats exposed at 1,813 ppm.

APPENDIX F

CATEGORY PLOTS FOR SELECTED CHLOROSILANES

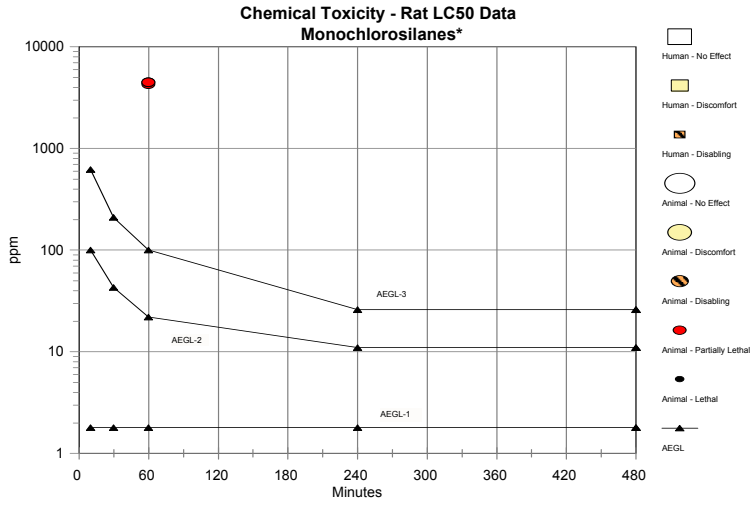

FIGURE F-1 Category plot for monochlorosilanes. *Data plotted are for trimethyl chlorosilane and dimethyl chlorosilane.

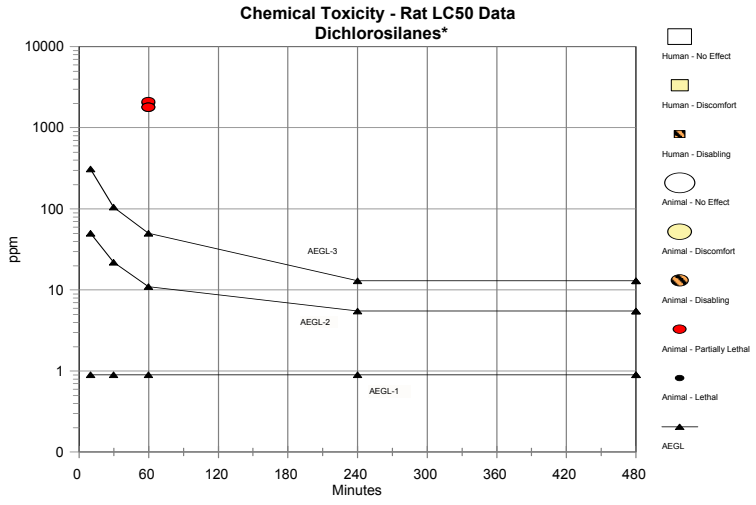

FIGURE F-2 Category plat of dichlorosilanes. *Data plotted are for methylvinyl dichlorosilane, dimethyl dichlorosilane, and methyl dichlorosilane.

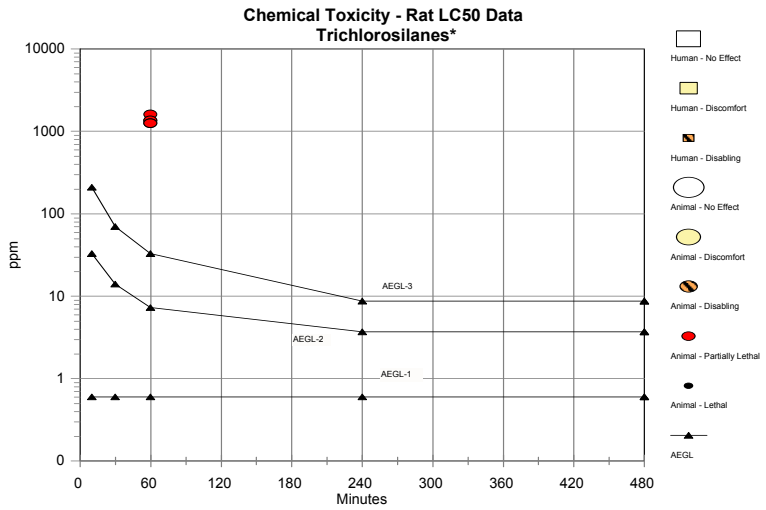

FIGURE F-3 Category plot for trichlorosilanes. *Data plotted are for propyl trichlorosilane, vinyl trichlorosilane, methyl trichlorosilane, and ethyl trichlorosilane.

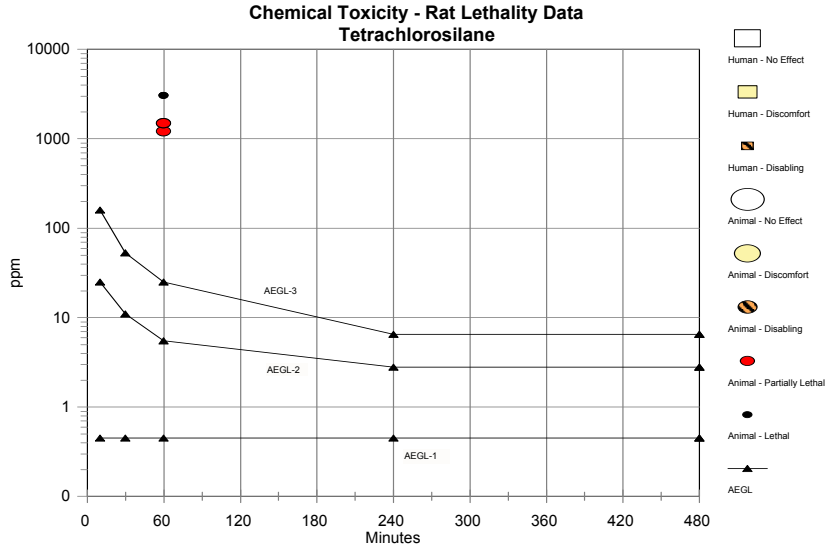

FIGURE F-4 Category plot for tetrachlorosilane.

4

Nitrogen Oxides[1]

Acute Exposure Guideline Levels

PREFACE

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

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, 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 or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory

[1]This document was prepared by the AEGL Development Team composed of Carol Wood (Oak Ridge National Laboratory), Gary Diamond (Syracuse Research Corporation), Chemical Managers George Woodall and Loren Koller (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (U.S. Environmental Protection Agency). 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 guidelines reports (NRC 1993, 2001).

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

SUMMARY

Nitrogen oxide compounds occur from both natural and anthropogenic sources. Nitrogen dioxide (NO_2) is the most ubiquitous of the oxides of nitrogen and has the greatest impact on human health. Nitrogen tetroxide (N_2O_4) is a component of rocket fuels. Very few inhalation toxicity data are available on N_2O_4. Nitric oxide (NO) is an endogenous molecule that mediates the biologic action of endothelium-derived relaxing factor. The toxicity of NO is associated with methemoglobin formation and oxidation to NO_2. NO is also a component of air pollution and is generally measured as part of the total oxides of nitrogen ($NO + NO_2$).

The reactions of the oxides of nitrogen consist of a family of reaction paths that is temperature dependent and generally favors NO_2 production. A significant fraction of N_2O_4 and NO will be converted to NO_2. Since NO_2 is the most ubiquitous and the most toxic of the oxides of nitrogen, AEGL values derived from NO_2 toxicity data are considered applicable to all oxides of nitrogen. NO_2 exists as an equilibrium mixture of NO_2 and N_2O_4, but the dimer is not important at ambient concentrations (EPA 1993). When N_2O_4 is released, it vaporizes and dissociates into NO_2, making it nearly impossible to generate a significant concentration of N_2O_4 at atmospheric pressure and ambient temperatures without generating a vastly higher concentration of NO_2. Almost no inhalation toxicity data are available on N_2O_4 because of this effect, and no information was found on the interactions of nitrogen trioxide (N_2O_3).

NO is unstable in air and undergoes spontaneous oxidation to NO_2 making experimental effects difficult to separate and studies difficult to perform (EPA 1993). Studies on the conversion of NO to NO_2 in medicinal applications have found the conversion to be significant at an atmospheric concentration of oxygen (20.9%) at room temperature. NO reacts with oxygen in air to form NO_2, which then reacts with water to form nitric acid (NIOSH 1976). For this reason, careful monitoring of NO_2 concentrations has been suggested when NO is used therapeutically at concentrations ≥80 ppm, especially when coadministered with oxygen (Foubert et al. 1992; Miller et al. 1994). Although closed-system experiments on a laboratory scale clearly indicate the potential for the production of NO_2, the chemical kinetics of NO conversion during a large-scale atmospheric release and dispersion are not well-documented. The estimation of the concentration isopleths following an accidental release would require the use of a finite-element model along with several assumptions about the chemical-rate constants. As a result, the conversion of NO to NO_2 during the atmospheric release is of concern to emergency planners. In photochemical smog, NO_2 absorbs sunlight at wavelengths between 290 and 430 nanometers (nm) and decomposes to NO and oxygen (EPA 1993).

AEGL values were based on studies of NO_2, the predominant form of the nitrogen oxides, and values are considered applicable to all nitrogen oxides. Values for N_2O_4 in units of ppm have been calculated on a molar basis. Because conversion to NO_2 is expected to occur in the atmosphere, and because NO_2 is more toxic than NO, the AEGL values for NO_2 are recommended for use with emergency planning for NO. The National Advisory Committee recognizes, however, that short-term exposures to NO below 80 ppm should not constitute a health hazard.

NO_2 is an irritant to the mucous membranes and might cause coughing and dyspnea during exposure. After less severe exposure, symptoms might persist for several hours before subsiding (NIOSH 1976). With more severe exposure, pulmonary edema ensues with signs of chest pain, cough, dyspnea, cyanosis, and moist rales heard on auscultation (NIOSH 1976; Douglas et al. 1989). Death from NO_2 inhalation is caused by bronchospasm and pulmonary edema in association with hypoxemia and respiratory acidosis, metabolic acidosis, shift of the oxyhemoglobin dissociation curve to the left, and arterial hypotension (Douglas et al. 1989). A characteristic of NO_2 intoxication after the acute phase is a period of apparent recovery followed by late-onset bronchiolar injury that manifests as bronchiolitis fibrosa obliterans (NIOSH 1976; NRC 1977; Hamilton 1983; Douglas et al. 1989). In addition, experiments with laboratory animals indicate that exposure to NO_2 increases susceptibility to infection (Henry et al. 1969; EPA 1993) due, in part, to alterations in host pulmonary defense mechanisms (Gardner et al. 1969).

For AEGL-1, a concentration of 0.5 ppm was adopted for all time points. Although the response of asthmatics to NO_2 is variable, asthmatics were identified as a potentially susceptible population. The evidence indicates that some asthmatics exposed to NO_2 at 0.3-0.5 ppm might respond with either

subjective symptoms or slight changes in pulmonary function that are not clinically significant. In contrast, some asthmatics did not respond to NO_2 at concentrations of 0.5-4 ppm. Because of the weight of evidence, the study by Kerr et al. (1978, 1979) was considered the most appropriate for derivation of AEGL-1 values. They reported that 7/13 asthmatics experienced slight burning of the eyes, slight headache, and chest tightness or labored breathing with exercise when exposed at 0.5 ppm for 2 h; at this concentration, the odor of NO_2 was perceptible but the subjects became unaware of it after about 15 min. No changes in any pulmonary function tests were found immediately following the chamber exposure (Kerr et al. 1978, 1979). Therefore, 0.50 ppm was considered a no-adverse-effect level for the asthmatic population. Since asthmatics are potentially the most susceptible population, no uncertainty factor was applied. Time scaling was not performed because adaptation to mild sensory irritation occurs. In addition, animal responses to NO_2 exposure have demonstrated a much greater dependence on concentration than on time; therefore, extending the 2-h concentration to 8 h should not exacerbate the human response.

Supporting studies for AEGL-1 effects report findings similar to the key studies. Significant group mean reductions in forced expiratory volume (FEV_1) (-17.3% with NO_2 vs. -10.0% with air) and specific airway conductance (-13.5% with NO_2 vs. -8.5% with air) occurred in asthmatics after exercise when exposed at 0.3 ppm for 4 h and 1/6 individuals experienced chest tightness and wheezing (Bauer et al. 1985). The onset of effects was delayed when exposures were by oral-nasal inhalation as compared with oral inhalation, and might have resulted from scrubbing within the upper airway. In a similar study, asthmatics exposed at 0.3 ppm for 30 min at rest followed by 10 min of exercise had significantly greater reductions in FEV_1 (10% with NO_2 vs. 4% with air) and partial expiratory flow rates at 60% of total lung capacity, but no symptoms were reported (Bauer et al. 1986). In a preliminary study with 13 asthmatic subjects exposed at 0.3 ppm for 110 min, slight cough and dry mouth and throat and significantly greater reduction in FEV_1 occurred after exercise (11% vs. 7%); however, in a larger study, no changes in pulmonary function were measured and no symptoms were reported in 21 asthmatic subjects exposed to concentrations up to 0.6 ppm for 75 min (Roger et al. 1990).

Human data also were used as the basis for AEGL-2 values. Three healthy male volunteers experienced discomfort from exposure to NO_2 at 30 ppm for 2 h (Henschler et al. 1960). Three individuals exposed at 30 ppm for 2 h perceived an intense odor on entering the chamber, but odor perception quickly diminished and was completely absent after 25-40 min. One individual experienced a slight tickling of the nose and throat mucous membranes after 30 min, the two others after 40 min. From 70 min and longer, all subjects experienced a burning sensation and an increasingly severe cough for the next 10-20 min, but coughing decreased from 100 min. However, the burning sensation continued and moved into the lower sections of the airways and was finally felt deep in the chest. At that time, marked sputum secretion and dyspnea were noted. Toward the end of the exposure, the subjects reported the exposure conditions to be bothersome

and barely tolerable. A sensation of pressure and increased sputum secretion continued for several hours after exposure ceased (Henschler et al. 1960). The point-of-departure is considered a threshold for AEGL-2 effects because the effects experienced by the subjects would not impair ability to escape and the effects were reversible after cessation of exposure.

AEGL-3 values were based on animal data and supported by a human case report. A study of monkeys exposed to NO_2 at 10-50 ppm for 2 h (Henry et al. 1969) was used to derive the AEGL-3 values. Monkeys exposed at 50 and 35 ppm had markedly increased respiratory rates and decreased tidal volumes, but only slight effects were observed at 15 and 10 ppm. Mild histopathologic changes in the lungs were observed at 10 and 15 ppm, whereas marked changes in lung structure were found at 35 and 50 ppm. The alveoli were expanded with septal wall thinning, bronchi were inflamed with proliferation or erosion of the surface epithelium, and lymphocyte infiltration was seen with edema. In addition to the effects on the lungs, interstitial fibrosis (35 ppm) and edema (50 ppm) of cardiac tissue, glomerular tuft swelling in the kidney (35 and 50 ppm), lymphocyte infiltration in the kidney and liver (50 ppm), and congestion and centrilobular necrosis in the liver (50 ppm) were observed.

The AEGL-3 values are supported by a case study of a welder. Pulmonary edema, confirmed on x-ray and requiring medical intervention, resulted from exposure to NO_2 at approximately 90 ppm for up to 40 min (Norwood et al. 1966). If this exposure scenario is used for derivation of AEGL-3 values with an uncertainty factor of 3, the values are nearly identical to those derived using the data on monkeys. The AEGL-3 values also are below the concentrations at which lethality first occurred in five animal species: 75 ppm for 4 h in the dog and 1 h in the rabbit, 50 ppm for 1 h in the guinea pig, and 50 ppm for 24 h in the rat and mouse (Hine et al. 1970).

For AEGL-2 and AEGL-3, the 10- and 30-min, and 1-, 4-, and 8-h AEGL end points were calculated using the equation $C^n \times t = k$, with $n = 3.5$ (ten Berge et al. 1986). The value of n was calculated by ten Berge et al. (1986) using the data of Hine et al. (1970) in five species of laboratory animals. A total uncertainty factor of 3 was applied, which includes 3 for intraspecies variability and 1 for interspecies variability. Use of a greater intraspecies uncertainty factor was considered unnecessary because the mechanism of action for a direct-acting respiratory irritant is not expected to differ greatly among individuals (see Section 4.2 for detailed information regarding the mechanism of respiratory toxicity). An interspecies uncertainty factors was considered unnecessary because human data were used as the point-of-departure for AEGL-2 values, the end point in the monkey study was below the definition of AEGL-3, human data support the AEGL-3 point-of-departure and derived values, the mechanism of action does not vary between species with the target at the alveoli, and the respiratory tract of humans and monkeys is similar.

The AEGLs values for NO_2, NO, and N_2O_4 are presented in Tables 4-1 and 4-2.

TABLE 4-1 Summary of AEGL Values for Nitrogen Dioxide and Nitric Oxide

Classification	10 min	30 min	1 h	4 h	8 h	End Point[a] (Reference)
AEGL-1[b] (ondisabling)	0.50 ppm (0.94 mg/m^3)	0.50 ppm (0.94 mg/m^3)	0.50 ppm (0.94 mg/m^3)	0.50 ppm (0.94 mg/m^3)	0.50 ppm (0.94 mg/m^3)	Slight burning of the eyes, slight headache, chest tightness or labored breathing with exercise in 7/13 asthmatics (Kerr et al. 1978, 1979)
AEGL-2 (disabling)	20 ppm (38 mg/m^3)	15 ppm (28 mg/m^3)	12 ppm (23 mg/m^3)	8.2 ppm (15 mg/m^3)	6.7 ppm (13 mg/m^3)	Burning sensation in nose and chest, cough, dyspnea, sputum production in normal volunteers (Henschler et al. 1960)
AEGL-3 (lethal)	34 ppm (64 mg/m^3)	25 ppm (47 mg/m^3)	20 ppm (38 mg/m^3)	14 ppm (26 mg/m^3)	11 ppm (21 mg/m^3)	Marked irritation, histopathologic changes in lungs, fibrosis and edema of cardiac tissue, necrosis in liver, no deaths in monkeys (Henry et al. 1969)

[a]Some effects might be delayed.
[b]The sweet odor of NO_2 may be perceptible to most individuals at this concentration; however, adaptation occurs rapidly.

TABLE 4-2 Summary of AEGL Values for Nitrogen Tetroxide

Classification	10 min	30 min	1 h	4 h	8 h	End Point[a] (Reference)
AEGL-1[b] (nondisabling)	0.25 ppm (0.94 mg/m^3)	0.25 ppm (0.94 mg/m^3)	0.25 ppm (0.94 mg/m^3)	0.25 ppm (0.94 mg/m^3)	0.25 ppm (0.94 mg/m^3)	Slight burning of the eyes, slight headache, chest tightness or labored breathing with exercise in 7/13 asthmatics (Kerr et al. 1978, 1979)
AEGL-2 (disabling)	10 ppm (38 mg/m^3)	7.6 ppm (28 mg/m^3)	6.2 ppm (23 mg/m^3)	4.1 ppm (15 mg/m^3)	3.5 ppm (13 mg/m^3)	Burning sensation in nose and chest, cough, dyspnea, sputum production in normal volunteers (Henschler et al. 1960)
AEGL-3 (lethal)	17 ppm (64 mg/m^3)	13 ppm (47 mg/m^3)	10 ppm (38 mg/m^3)	7.0 ppm (26 mg/m^3)	5.7 ppm (21 mg/m^3)	Marked irritation, histopathologic changes in lungs, fibrosis and edema of cardiac tissue, necrosis in liver, no deaths in monkeys (Henry et al. 1969)

[a]Some effects might be delayed.
[b]The sweet odor of NO_2 may be perceptible to most individuals at this concentration; however, adaptation occurs rapidly.

1. INTRODUCTION

NO_2 is the most ubiquitous of the oxides of nitrogen and has the greatest impact on human health. NO_2, which exists as an equilibrium mixture of NO_2 and N_2O_4, is a reddish-brown gas with a sweet odor, is heavier than air, and reacts with water (EPA 1993; Mohsenin 1994). NO_2 is shipped under pressure and the equilibrium between NO_2 and N_2O_4 is altered with changes in pressure, with N_2O_4 becoming predominant at very high pressures. NO_2 is a free radical with sufficient stability to exist in relatively high concentrations in ambient air (Mohsenin 1994). NO is also a component of air pollution and is generally measured as part of the total oxides of nitrogen ($NO + NO_2$) present. NO reacts with oxygen in air to form NO_2: $2NO + O_2 \rightarrow 2NO_2$ (NIOSH 1976).

The major source of atmospheric nitrogen oxides is from the combustion of fossil fuels for heating, household appliances, power generation, and in motor vehicles. Consequently, the chemicals are a major contributor to smog and a concern for indoor air quality. Ambient concentrations in urban air pollution episodes in the United States have been measured between 0.1 and 0.8 ppm as a maximum hourly average with short-term peaks as high as 1.27 ppm. Indoor NO_2 concentrations might reach a maximum 1-h concentration of 0.25-1.0 ppm, with peak concentrations as high as 2-4 ppm where gas appliances or kerosene heaters are used (Mohsenin 1994).

N_2O_4 is a commonly used as a rocket propellant (Yue et al. 2004). Toxicity data on N_2O_4 show effects similar to those of NO_2.

NO is an endogenous molecule that mediates the biologic action of endothelium-derived relaxing factor. Because of this action, inhaled NO has been used to treat adult respiratory-distress syndrome, persistent pulmonary hypertension of the newborn, pulmonary hypertension in congenital heart disease and diaphragmatic hernia, pulmonary hypertension following thoracic organ transplantation, idiopathic pulmonary hypertension, and chronic obstructive pulmonary disease (Troncy et al. 1997a). The major mechanism of toxicity of NO is binding of hemoglobin (EPA 1993). NO reacts with oxygen in air to form NO_2, possibly potentiating toxicity, and causing pulmonary edema. For this reason, careful monitoring of NO_2 concentrations has been suggested when NO is used therapeutically at concentrations $\geq$80 ppm, especially when administered with oxygen (Foubert et al. 1992; Miller et al. 1994).

No toxicity data or information on the uses or sources of N_2O_3 were found. Information on the chemical interactions of N_2O_3 with the other oxides of nitrogen was not available. Therefore, N_2O_3 was not considered further.

NO_2 is an irritant of the mucous membranes and might cause coughing and dyspnea during exposure. After less severe exposure, symptoms might persist for several hours before subsiding (NIOSH 1976). With more severe exposure, pulmonary edema ensues with chest pain, cough, dyspnea, cyanosis, and moist rales heard on auscultation (NIOSH 1976; Douglas et al. 1989). Death from NO_2 inhalation is caused by bronchospasm and pulmonary edema in association with hypoxemia and respiratory acidosis, metabolic acidosis, shift of

the oxyhemoglobin dissociation curve to the left, and arterial hypotension (Douglas et al. 1989). A characteristic of NO_2 intoxication after the acute phase is a period of apparent recovery followed by late-onset bronchiolar injury that manifests as bronchiolitis fibrosa obliterans (NIOSH 1976; NRC 1977; Hamilton 1983; Douglas et al. 1989).

Selected physical and chemical properties of NO_2, N_2O_4, and NO are presented in Tables 4-3, 4-4, and 4-5, respectively.

TABLE 4-3 Physical and Chemical Properties for Nitrogen Dioxide

Parameter	Value	Reference
Common name	Nitrogen dioxide	
CAS registry no.	10102-44-0	
Chemical formula	NO_2	Budavari et al. 1996
Molecular weight	46.01	Budavari et al. 1996
Physical state	Reddish-brown gas	Budavari et al. 1996
Melting point	-9.3°C	Budavari et al. 1996
Boiling point	21.15°C	Budavari et al. 1996
Vapor density (air = 1)	1.58	Budavari et al. 1996
Solubility in water	0.037 mL at 35°C	Mohsenin 1994
Vapor pressure	720 mm Hg at 20°C; 800 mm Hg at 25°C	EPA 1990; ACGIH 1991
Flammability	Does not burn	Budavari et al. 1996
Conversion factors in air	1 ppm = 1.88 mg/m^3 1 mg/m^3 = 0.53 ppm	EPA 1993
Reactivity	Decomposes in water forming nitric oxide and nitric acid	Budavari et al. 1996

TABLE 4-4 Physical and Chemical Properties for Nitrogen Tetroxide

Parameter	Value	Reference
Common name	Dinitrogen dioxide	
CAS registry no.	10544-72-6	
Chemical formula	N_2O_4	Lide 1988
Molecular weight	92.01	Lide 1988
Physical state	Colored liquid	Lide 1988
Melting point	-9.3°C	Lide 1988; Kushneva and Gorshkova 1999
Boiling point	21.5°C	Lide 1988; Kushneva and Gorshkova 1999
Vapor density (air = 1)	1.45 at 20°C	Lide 1988
Solubility in water	No data	
Vapor pressure	760 mm Hg at 21°C	Lide 1988
Conversion factors in air	1 ppm = 3.70 mg/m^3 1 mg/m^3 = 0.27 ppm	Calculated
Reactivity	Reacts violently with organic compounds; reacts with water	Lide 1988; Kushneva and Gorshkova 1999

TABLE 4-5 Physical and Chemical Properties for Nitric Oxide

Parameter	Value	Reference
Common name	Nitric oxide	
Synonyms	Nitrogen monoxide	Budavari et al. 1996
CAS Reg. No.	10102-43-9	
Chemical formula	NO	Budavari et al. 1996
Molecular weight	30.01	Budavari et al. 1996
Physical state	Colorless gas	Budavari et al. 1996
Melting point	-163.6°C	Budavari et al. 1996
Boiling point	-151.7°C	Budavari et al. 1996
Vapor density (air = 1)	1.04	Budavari et al., 1996
Solubility in water	4.6 mL/100 mL (20°C)	Budavari et al. 1996
Vapor pressure	26,000 mm Hg at 20°C	ACGIH 1991
Conversion factors in air	1 ppm = 1.25 mg/m^3 1 mg/m^3 = 0.8 ppm	NIOSH 1976
Reactivity	Combines with oxygen to form NO_2	Budavari et al. 1996

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Book (1982) used allometric scaling based on minute volume and LC_{50} (lethal concentration, 50% lethality) values for NO_2 for five animal species to calculate a human 1-h LC_{50} of 174 ppm. Concentrations >200 ppm were reported to induce immediate symptoms of bronchospasm and pulmonary edema and might cause syncope, unconsciousness, and quick death (Douglas et al. 1989).

Clinical responses to "acute" inhalation of high concentrations of NO_2 based on occupational exposures are presented in Table 4-6 (NRC 1977). Durations of exposure were not specified except for the statement that workers in a nitric acid manufacturing plant in Italy were exposed to average concentrations of 30-35 ppm for an unspecified number of years with no adverse signs or symptoms.

Following induction of anesthesia with nitrous oxide and oxygen, a woman became cyanotic within 2 min. Treatment with methylene blue reversed the methemoglobinemia, but she developed severe pulmonary edema several hours later and died of cardiac arrest. A second patient also became cyanotic after initiation of anesthesia and the nitrous oxide was discontinued immediately. Several hours later, the second patient developed some respiratory distress but recovered completely after oxygen and steroid therapy. It was determined that the nitrous oxide cylinder had been contaminated with NO (Clutton-Brock 1967). The possible exposure concentration was not determined nor was the contribution of the formation of NO_2 addressed in the study. Greenbaum et al. (1967) made several assumptions about retention volume, time-to-cyanosis, and ventilation rate and estimated that the contamination by NO must have been 1% (10,000 ppm) or greater.

TABLE 4-6 Effects of Acute Exposure to High Concentrations Nitrogen Dioxide

Concentration (ppm)	Effect
0.4	Approximate odor threshold
15-25	Respiratory and nasal irritation
25-75	Reversible pneumonia and bronchiolitis
150-300+	Fatal bronchiolitis and bronchopneumonia

Source: NRC 1977.

2.2. Nonlethal Toxicity

2.2.1. Case Reports

2.2.1.1. Nitrogen Dioxide

Probably the most well-known occupational manifestation of NO_2 toxicity is that of silo filler's disease. In a silo, the gas that accumulates above the silage is depleted of oxygen, is rich in carbon dioxide, and contains a mixture of nitrogen oxides, mainly NO_2, which can reach concentrations of 200-4,000 ppm within 2 days (Lowry and Schuman 1956; Douglas et al. 1989). The term silo filler's disease was first used by Lowry and Schuman in 1956 in an article that described the clinical progression of the disease: inhalation of irritant gas from a silo; immediate cough and dyspnea with a sensation of choking; apparent remission 2-3 weeks after exposure; second phase of illness accompanied by fever and progressively more severe dyspnea, cyanosis, and cough; inspiratory and expiratory rales; discrete nodular densities on the lung; and neutrophilic leukocytosis (Lowry and Schuman 1956). Douglas et al. (1989) reported on 17 patients examined at the Mayo Clinic between 1955 and 1987 after exposure to silo gas. Ocular irritation was described during exposure, acute lung injury occurred in 11 individuals, and 16 had persistent or delayed symptoms of dyspnea, cough, chest pain, and rapid breathing. One patient died and autopsy revealed diffuse alveolar damage with hyaline membranes and hemorrhagic pulmonary edema and acute edema of the airways. Bronchiolitis fibrosa obliterans developed in one patient many years later; however, prophylactic administration of corticosteroids might have prevented chronic obstructive pulmonary disease in the other patients. Similar case reports and outcomes of silo filler's disease and industrial exposure were described in earlier literature (Grayson 1956; Lowry and Schuman 1956; Milne 1969).

A welder developed shortness of breath and chest discomfort during the use of an acetylene torch for metal-cutting in a poorly ventilated water main; the worker had spent approximately 30 min welding in the confined space before being forced to vacate. Several hours later, the worker became so short of breath that he could not sleep. Chest x-ray 18 h after exposure revealed pulmonary edema, and a pulmonary function test showed 42% of the predicted value for

forced vital capacity (FVC). The individual was admitted to the hospital and treated with antibiotics and oxygen. The patient fully recovered 21 days after exposure. Simulation of the accident produced an NO_2 concentration of 90 ppm within 40 min and total oxides of nitrogen in excess of 300 ppm (Norwood et al. 1966). It was assumed that the individual was exposed to at least 90 ppm of NO_2 during the welding operation and that the outcome could have been more severe, or even fatal, without medical intervention.

An outbreak of NO_2-induced respiratory illness was reported among players and spectators at two high school hockey games (Hedberg et al. 1989). Patients presented with acute onset of cough, hemoptysis, or dyspnea during or within 48 h of attending the hockey game. No changes in lung function were measured 10 days and 2 months after exposure. NO_2 concentrations were not measured in the arena during the outbreak, but the source was traced to a malfunctioning motor in the ice resurfacer. Other cases of respiratory illness in hockey players, referees, and spectators have been associated with elevated NO_2 concentrations in the arena because of malfunctioning resurfacers or ventilation systems, combined with elevated carbon monoxide concentrations (Smith et al. 1992; Soparkar et al. 1993; Karlson-Stiber et al. 1996; Morgan 1995). Attempts to measure NO_2 concentrations in the arenas or to reconstruct the situations were described by the authors as not indicative of the actual exposure scenario that resulted in adverse effects.

Morley and Silk (1970) described a number of cases in which welders involved in ship repair and shipbuilding were exposed to nitrous fumes. Symptoms included dyspnea, cough, headache, tightness or pain in chest, nausea, and cyanosis. Most patients recovered after treatment with oxygen and antibiotics; however, one man died 43 days later from viral pneumonia. Two individuals admitted to the hospital with cyanosis, dyspnea, and pulmonary edema, were exposed to NO_2 at 30 ppm during a 40-min welding operation. However, the authors noted that seven other individuals present at the time were unaffected.

A railroad tank car ruptured at a chemical plant, releasing a cloud of NO_2 in a small community (Bauer et al. 1998). In the first 30 h after the release, the most common symptoms reported in emergency room visits were headache, burning eyes, and sore throat. Most air samples collected 3-7 h after the release showed concentrations of 0 ppm with one sample of 1.4 ppm. No attempt was made to correlate symptoms with estimated exposure.

Acute toxic reactions were described in four firemen exposed to NO_2 that originated from a leak in a chemical plant (Tse and Bockman 1970). Concentrations were not reported and exposure durations were defined as “barely a few minutes” to “about ten minutes.” Initial responses included headache, a dry hacking cough, pulmonary edema, sinusitis, and upper respiratory tract irritation; effects cleared within several days. Four to six weeks after exposure, three of the patients developed fever, chest tightness, shortness of breath, and a productive cough; these effects subsided and the patients remained asymptomatic. The fourth

patient developed chronic pulmonary insufficiency, consisting of dyspnea on exertion, despite normal chest x-ray.

Four cases of exposure to unknown concentrations of nitrous fumes were reported for individuals involved in the use of an oxyacetylene burner during a leak at a chemical plant or in shotfiring (Jones et al. 1973). Three patients presented with pulmonary edema, one of which progressed to bronchiolitis obliterans; the fourth patient presented with clinical features of bronchiolitis obliterans. All recovered completely following corticosteroid treatment.

2.2.1.2. Nitrogen Tetroxide

A large number of patients were treated for respiratory complaints following release of a cloud of N_2O_4 from a railroad tank car. The most common symptoms were headache, burning eyes, and sore throat; an abnormal lung exam and an abnormal chest x-ray were also reported for some individuals, but these findings were not further defined (Bauer et al. 1996). No pulmonary edema or deaths were attributed to the accident. However, six individuals were diagnosed with reactive airways dysfunction syndrome (RADS) 3 months after exposure (Conrad et al. 1998). Concentrations of oxides of nitrogen in the cloud were not reported.

2.2.1.3. Nitric Oxide

Methemoglobin concentrations rose to 9.4% in one lung transplantation patient after treatment with NO at 80 ppm for 8 h. A reduction in NO concentration to 40 ppm over 4 h reduced methemoglobin concentrations to 6.6%, and a further reduction of NO to 20 ppm for 12 h decreased the methemoglobin concentration to 0.9% (Adatia et al. 1994). A Japanese newborn developed a methemoglobin concentration of 40% after being exposed to NO at 80 ppm for 26 h; the concentration decreased to 3.9% within 20 min of infusion with methylene blue and gradual reduction of the NO concentration over 1 h then discontinuation. No methemoglobin concentrations were reported before the 26-h time point. The infant survived with no indications of hypoxic brain damage at 4 months of age (Nakajima et al. 1997).

The therapeutic use of NO has been studied extensively in patients with acute respiratory distress syndrome. Manktelow et al. (1997) reviewed data collected over 5 years from patients treated with NO inhalation therapy. In general, patients received NO at 20 ppm for 48 h, with a reduction to 10 ppm for the next 8 days. No patient had an adverse response to NO and 58% of all patients had clinically significant responses to NO, measured as increases in the inspiratory fraction of oxygen and decreases in pulmonary vascular resistance. Another review (Troncy et al. 1997b) found that the optimal concentration of NO for producing the greatest improvement in hypoxia score among patients with acute respiratory distress syndrome ranged from 0.5 to 40 ppm. This range

was confirmed in a more recent study in which patients were treated with NO at 1-40 ppm for 30 min. Concentration-dependent decreases in pulmonary capillary pressure and post-capillary resistance were observed with a maximum effect at 20 ppm (Benzing et al. 1998). Other studies confirm improvements in oxygenation and pulmonary artery pressure in patients with acute respiratory distress syndrome treated with NO at 40 ppm for 20 min (Doering et al. 1997), 0.1-2 ppm for 15-20 min (Puybasset et al. 1994), 100 ppm for 20 min (Wenz et al. 1997), and 0.1-100 ppm for 15 min (Gerlach et al. 1993). Mortality was not affected by NO inhalation in any of these studies. A large increase in cardiac output was reported for one patient with acute respiratory distress syndrome and acute right heart failure treated with NO at 20 ppm for 3 days; methemoglobin concentrations were ≤1.7% (Benzing et al. 1997).

Newborns and children diagnosed with hypoxemic respiratory failure (Abman et al. 1994; Day et al. 1997; Goldman et al. 1997) or persistent pulmonary hypertension (Goldman et al. 1995; Ichida et al. 1997; Kinsella et al. 1997; Nakagawa et al. 1997; Wessel et al. 1997) showed decreased pulmonary artery pressure and improved oxygen saturation when treated with NO at 10 ppm for up to 24 h, 20 ppm for up to 4 h, 60 ppm for 10 min, or 80 ppm for up to 12 h. Two studies reported longer-term therapies in which hypoxemic newborns were treated with NO at 10 ppm for 6-331 h (Biban et al. 1998) and newborns with persistent pulmonary hypertension were treated with 80 ppm for a mean duration of 65.1 h (Davidson et al. 1998). The large variation in exposure duration is explained by the fact that in most of these trials, treatment was continued until success or failure criteria were met as defined by the study protocol.

NO inhalation has also been used to treat patients with lung or heart disease and following surgery. Decreased pulmonary artery pressure occurred in adult patients with chronic obstructive pulmonary disease treated with NO at 40 ppm for 20 min (Roger et al. 1997) and with pulmonary fibrosis treated with 2 ppm for 10 min (Yoshida et al. 1997). Pulmonary vascular resistance also was significantly reduced in preterm infants treated with NO at 20 ppm for 2 h, followed by 5 ppm for 70 h (Subhedar and Shaw 1997), in patients with heart failure treated with up to 80 ppm for 5 min (Semigran et al. 1994), in patients implanted with a left ventricular assist device treated at 25-40 ppm for up to 48 h (Wagner et al. 1997), and in lung-transplant patients treated at 80 ppm for 15 min, with a decrease to 10 ppm for up to 69 h (Adatia et al. 1994). Patients with congestive heart failure had increased oxygen uptake and decreased pulmonary hypertension when administered NO at 20 ppm during light exercise (duration not specified) (Matsumoto et al. 1997) and attenuation of excessive increases in tidal volume, which contribute to exercise-induced hyperventilation, when exposed to NO at 30 ppm for about 20 min (Bocchi et al. 1997). Decreased pulmonary artery pressure, increased cardiac output, and increased oxygen arterial saturation occurred in infants treated with NO at 20 ppm for 4-250 h (Journois et al. 1994) or at 50 ppm for a mean of 41 h (methemoglobin, 1.4%) (Schulze-Neick et al. 1997) after surgery for congenital heart defects.

Inhalation of NO at 20 ppm had no effect on PaO_2 (arterial partial pressure of oxygen) during one-lung ventilation in patients undergoing thoracoscopic procedures. However, when combined with intravenous almitrine, it limited the decrease of PaO_2 (Moutafis et al. 1997).

2.2.2. Epidemiologic Studies

Several epidemiologic studies associating ambient NO_2 exposure with an increase in the prevalence of respiratory illness have been inconclusive. Increased odds ratios (1.2-1.7) were found for bronchitis, chronic cough, and chest illness but not for wheeze or asthma in children from six U.S. cities with annual average NO_2 concentration of 0.0065-0.0226 ppm (Dockery et al. 1989). No association was found between long-term differences in NO_2 concentrations (change of 0.0106 ppm/6-week average) and mean annual rates of respiratory episodes in children from urban and rural regions in Switzerland; however, the duration of symptoms was increased (Braun-Fahrlaender et al. 1992). An increase in the cases of croup in children was associated with total suspended particulate matter and NO_2 (Schwartz et al. 1991), and decreased lung function in children was linked to sulfur dioxide (SO_2) in combination with NO_2 (Mostardi et al. 1981). Symptoms of chronic obstructive pulmonary disease have been linked to exposure to total oxidants (>0.1 ppm), NO_2, and sulfates, but not to NO_2 alone (Detels et al. 1981; Euler et al. 1988). Combined effects of NO_2, SO_2, particulate matter, hydrogen sulfide (H_2S), and other pollutants were considered as contributing factors to a positive association between the occurrence of upper respiratory infections in children (<2 and 6 years of age) and living in polluted areas of Finland (Jaakkola et al. 1991).

In a more recent study, children from 12 communities in California were assessed for respiratory disease prevalence and pulmonary function (Peters et al. 1999a,b). Wheeze prevalence was correlated with concentrations of nitric acid and NO_2 in boys, whereas regression analysis showed that NO_2 was significantly associated with lower FVC, FEV_1, and maximal midexpiratory flow in girls. When these data were analyzed by month (Millstein et al. 2004), wheezing during the spring and summer months was not associated with either nitric acid or NO_2. However, among asthmatics, the monthly prevalence of asthma medication use was associated with monthly concentrations of ozone, nitric acid, and acetic acid (Millstein et al. 2004). Similar results were reported for eight areas of Switzerland in which an average increase in NO_2 of 10 $\mu g/m^3$ was associated with decreases in FVC (Schindler et al. 1998).

Several recent studies have attempted to describe the correlation between NO_2 concentrations and mortality or respiratory symptoms by pooling large datasets from multiple cities or countries. One of these studies used information collected from up to 12 cities in Canada. These authors found that an approximate 20 ppb increase in NO_2 was positively associated with a 2.25% increase in mortality (Burnett et al. 2004), intrauterine growth retardation (odds

ratio of 1.14-1.16) (Liu et al. 2007), a 17.72% increase in the incidence of sudden infant death syndrome (Dales et al. 2004), increased numbers of hospitalizations from cardiac disease (Cakmak et al. 2006), and greater asthma hospitalizations in children of 6-12 years of age (Lin et al. 2003). However, many of the positive findings in Canada were also positively correlated with other pollutants, such as particulate matter, ozone, and SO_2. Similarly, a significant association of NO_2 with cardiovascular and respiratory mortality was found in 30 European cities (Samoli et al. 2006) and in nine French cities (Le Tertre et al. 2002), but evidence of confounding effects of black smoke, SO_2, and ozone were also found in both studies.

Asthma and allergy prevalence in conjunction with NO_2 concentrations also have been assessed in multiple city or country studies. Positive correlations were found for asthma attacks, tightness in the chest, wheeze, and allergic rhinitis in children from eight Japanese communities (Shima et al. 2002) and in 13 areas of Italy, with the most pronounced effects in the warmer Mediterranean areas (de Marco et al. 2002). An increased incidence of morning symptoms was associated with a 6-day average increase in NO_2 (odds ratio of 1.48) in asthmatic children from eight U.S. cities (Mortimer et al. 2002). In a cross-sectional study of five countries, long-term NO_2 concentrations were correlated with sensitivity to inhaled allergens, but not to prevalence of bronchitis or asthma (Pattenden et al. 2006). No association was found between NO_2 concentrations and asthma, allergic rhinitis, or atopic dermatitis in children from six French cities (Pénard-Morand et al. 2005).

As a component of air pollution, NO concentrations have been studied in association with various diseases; however, other pollutants such as NO_2 and ozone were also involved. In Helsinki, Finland, emergency room admissions from ischemic cardiac diseases were significantly correlated with NO and ozone concentrations. NO concentrations were 7-467 $\mu g/m^3$ (5.6-373.6 ppb) during the 3-year study (Pönkä and Virtanen 1996). In Copenhagen, Denmark, NO and NO_x ($NO + NO_2$) were significantly associated with the number of emergency medical contacts for children who had respiratory illnesses.

The yearly mean concentration of NO was 229 $\mu g/m^3$(183.2 ppb) and higher NO concentrations correlated with higher NO_x concentrations, which were linked to traffic pollution (Keiding et al. 1995). In contrast, no relationship was found between exposure to oxides of nitrogen and respiratory symptoms or decline in FEV_1 among British coal miners exposed to NO at peak concentrations of 4-100 ppm (Robertson et al. 1984).

Epidemiologic studies of indoor NO_2 also have been inconclusive. One study found no evidence of any short-term association between prevalence of respiratory symptoms in infants and median indoor and outdoor concentrations of NO_2 at 6.8 and 12.6 ppb, respectively (Farrow et al. 1997). Similarly, no

associations were found between indoor NO_2 and wheeze or asthma in children from seven Japanese communities (Shima and Adachi 2000). Other studies found a significant increase in the occurrence of sore throat, colds, and absences from school among children exposed to hourly peak concentrations of

NO_2 at ≥80 ppb from unvented gas heating in the classrooms (Pilotto et al. 1997), increased respiratory illness in children from homes using gas cooking where NO_2 concentrations in the children's bedroom were 4-169 ppb (Florey et al. 1979), and slight decreases in FVC and peak expiratory flow among adult asthmatics exposed at >0.3 ppm while cooking on a gas range (Goldstein et al. 1988). Similarly, Neas et al. (1991) found that a 15 ppb increase the mean annual concentration of NO_2 in the household was associated with an increased cumulative incidence of attacks of shortness of breath, with wheeze, chronic wheeze, chronic cough, chronic phlegm, or bronchitis in children.

As part of a review of the National Ambient Air Quality Standards (NAAQS) for NO_2, EPA (1995) conducted a meta-analysis of studies that examined the respiratory effects in children living in homes with gas stoves. Conclusions drawn from that analysis were that children (5-12 years of age) had an increased risk of about 20% for developing respiratory symptoms and disease with each increase of 0.015 ppm in estimated 2-week average NO_2 exposure (mean weekly concentrations in bedrooms 0.008-0.065 ppm) and that no evidence for increased risk was found for infants <2 years old. Several limitations of this meta-analysis have been noted, including the following: uncertainty between monitored vs. actual exposure concentration; peak and average exposures could not be distinguished by the method used; and confounding effects of other gas combustion byproducts. In context of the NAAQS review, it was noted that indoor exposures do not mimic outdoor exposures (EPA 1995). EPA (2008) performed an Integrated Health Assessment for Oxides of Nitrogen in support of the 2010 revision of the NAAQS for NO_2. The assessment concluded that recent epidemiology studies confirm previous findings that short-term NO_2 exposure is associated with respiratory symptoms and increased airway responsiveness, especially in children and asthmatics. In considering the uncertainties associated with the epidemiologic evidence, the EPA (2008) assessment noted that it is difficult to determine ''the extent to which NO_2 is independently associated with respiratory effects or if NO_2 is a marker for the effects of another traffic-related pollutant or mix of pollutants."

Several occupations result in exposure to NO_2 concentrations higher than ambient concentrations. In diesel bus garage workers, NO_2 concentrations of ≥0.3 ppm, along with respirable particulates, were associated with work-related symptoms of cough; itching, burning, or watering eyes; difficult breathing; chest tightness; and wheeze, but there were no reductions in pulmonary function (Gamble et al. 1987). In contrast, no relationship was found between respiratory symptoms or decline in FEV_1 among British coalminers and exposure to peak NO_2 concentrations of up to 14 ppm; controls were matched for age, dust exposure, smoking habits, coal rank, and type of work (Robertson et al. 1984). No differences in pulmonary function were noted among shipyard welders exposed to average concentrations of oxides of nitrogen of 0.04 ppm (Peters et al. 1973). Slight increases in prevalence of bronchitis (17.2 vs. 12.6%) and colds (37.5 vs. 30.7%) were noted in traffic officers exposed to automobile exhaust containing mean concentrations of NO_2 of 0.045-0.06 ppm (Speizer and Ferris 1973).

In conclusion, indoor air quality might be more significant than outdoor air quality in the prevalence of respiratory illness from NO_2. An early review of epidemiology studies that assessed ambient air quality (EPA 1993) yielded insufficient evidence to reach any conclusion about the long- or short-term health effects of NO_2. EPA (2008) concluded that recent epidemiology studies confirmed an association between ambient NO_2 concentrations with respiratory symptoms and airway reactivity in children and asthmatics, but cautioned that it was unclear whether NO_2 was the proximate toxicant or a marker for other air contaminants. Review of epidemiology studies that assessed indoor air quality in homes with gas stoves, found that meta-analysis yielded insufficient evidence that NO_2 had an effect on infants 2 years and younger while several considerations limited the interpretation of the positive results for children aged 5-12 years.

2.2.3. Experimental Studies

2.2.3.1. Nitrogen Dioxide

Healthy Subjects

The odor threshold for NO_2 in air has been reported as 0.4 ppm for recognition and 4.0 ppm for less than 100% identification (NIOSH 1976). In an experimental study, the odor of NO_2 was perceived by 3/9 volunteers exposed at 0.12 ppm and by 8/13 subjects at 0.22 ppm. At concentrations of ≤4 ppm, the volunteers perceived the odor for 1-10 min, but the duration of perception was not directly related to concentration. The olfactory response to NO_2 returned 1-1.5 min after cessation of exposure (Henschler et al. 1960). There appears to be a difference between perception and recognition concentrations and the volunteers perceiving the odor at the lowest concentrations were described as "olfactory sensitive."

Studies of healthy individuals exposed to NO_2 at <2 ppm have shown no effects on pulmonary function or symptoms. In several studies, healthy men and women were exposed to NO_2 at 0.6 ppm for 1-3 h with intermittent or continuous exercise. No significant effects were observed in any study on pulmonary function, cardiovascular function, metabolism, or symptoms of exposure (Folinsbee et al. 1978; Adams et al. 1987; Frampton et al. 1991; Hazucha et al. 1994). No changes in pulmonary function occurred following exposure to NO_2 at 1.5 ppm for 3 h or to a baseline of 0.05 ppm with intermittent peaks of 2 ppm; however, continuous exposure to 1.5 ppm for 3 h resulted in a slight but significantly greater decrease in FEV_1 and FVC in response to carbachol (Frampton et al. 1991). Pulmonary function was not affected in competitive athletes exposed to NO_2 at 0.18 and 0.30 ppm for 30 min during heavy exercise (Kim et al. 1991) or in healthy adults exposed at 0.3 ppm for 4 h with intermittent exercise (Smeglin et al. 1985).

Studies at higher concentrations of NO_2 indicate an apparent threshold before pulmonary function is affected. No changes in pulmonary function, airway reactivity, or indications of irritation were measured in healthy adults exposed to NO_2 at 1 ppm for 2 h, 2 ppm for 3 h (Hackney et al. 1978), 2 ppm for 4 h (Devlin et al. 1992), 3 ppm for 2 h (Goings et al. 1989), or 2.3 ppm for 5 h (Rasmussen et al. 1992). Normal subjects exposed to 2 ppm for 1 h developed an increase in airway reactivity to methacholine challenge without changes in lung volume or pulmonary function (Mohsenin 1988). No statistically significant effects on airway resistance, symptoms, heart rate, skin conductance, or self-reported emotional state were found in healthy volunteers exposed to NO_2 at 4 ppm for 1 h and 15 min with intermittent light and heavy exercise (Linn and Hackney 1983). However, a significant decrease in mean (n = 11) alveolar oxygen partial pressure by 8 mm Hg and a significant increase in mean (n = 11) airway resistance from 1.51 to 2.41 cm H_2O/(L/s) occurred in healthy volunteers exposed at 5 ppm for 2 h with 6/11 individuals responding (von Nieding et al. 1979). Similarly, a 10-min exposure to NO_2 at 4-5 ppm resulted in increased expiratory and inspiratory flow resistance in five healthy males; the effect was greatest 30 min after exposure (Abe 1967).

Henschler et al. (1960) performed several experiments on healthy, male volunteers. They reported that a 2-h exposure to NO_2 at 20 ppm did not cause any irritation when preceded by several exposures to lower concentrations during the preceding days; however, exposure at 30 ppm for 2 h caused definite discomfort. Three individuals exposed to NO_2 at 30 ppm for 2 h perceived an intense odor on entering the chamber; odor detection quickly diminished and was completely absent after 25-40 min. One individual experienced a slight tickling of the nose and throat mucous membranes after 30 min, and the others after 40 min. All subjects experienced a burning sensation after 70 min and an increasingly severe cough for the next 10-20 min, but coughing decreased after 100 min. However, the burning sensation continued and moved into the lower sections of the airways and was finally felt deep in the chest. At that time, marked sputum secretion and dyspnea were noted. Toward the end of the exposure, the subjects reported the exposure conditions to be bothersome and barely tolerable. A sensation of pressure and increased sputum secretion continued for several hours after cessation of exposure (Henschler et al. 1960).

In a similar experiment (Henschler and Lütge 1963), groups of four or eight healthy, male volunteers were exposed to NO_2 at 10 ppm for 6 h or to 20 ppm for 2 h. All subjects noted the odor on entering the chamber, but it diminished rapidly. At 20 ppm, minor scratchiness of the throat was reported after about 50 min, and 3/8 experienced slight headaches toward the end of the exposure period. Methemoglobin concentrations remained within the normal range in all subjects after exposure.

Biochemical changes in bronchoalveolar lavage fluid and blood also have been studied in healthy adults exposed to NO_2. Exposures at 2 ppm for 4 h (Devlin et al. 1992) or 6 h (Frampton et al. 1992) caused an influx of polymorphonuclear leukocytes in bronchoalveolar lavage fluid, 2.3 ppm for 5 h resulted in a decrease

in serum-glutathione-peroxidase activity (Rasmusen et al. 1992), 1 and 2 ppm for 3 h caused a decrease in red-blood-cell membrane acetylcholinesterase activity, 2 ppm for 3 h resulted in an increase in peroxidized red-blood-cell lipids and glucose-6-phosphate dehydrogenase activity (Posin et al. 1978), and 3 or 4 ppm for 3 h resulted in a decrease in α-1-protease inhibitor activity but not in enzyme concentration in bronchoalveolar lavage fluid (Mohsenin and Gee 1987). After exposure to NO_2 at 2 ppm for 4 h, neutrophilic inflammation was detected in bronchial washings but no changes in inflammatory cells were observed in endobronchial biopsy samples (Blomberg et al. 1997). Mucociliary activity was completely stopped in healthy individuals 45 min after a 20-min exposure to NO_2 at 1.5 and 3.5 ppm (Helleday et al. 1995).

Asthmatic Subjects

Studies of the effects of NO_2 on pulmonary function in asthmatics are inconclusive and conflicting. No consistent changes in pulmonary function or reported symptoms were found in exercising asthmatic adults and adolescents exposed to NO_2 at 0.12 or 0.18 ppm for 40 min (Koenig et al. 1987); 0.12 ppm for 1 h at rest (Koenig et al. 1985); 0.2 ppm for 2 h with intermittent exercise (Kleinman et al. 1983), 0.3 ppm for 30 min (Rubinstein et al. 1990), 1 h (Vagaggini et al. 1996), or 4 h with exercise (Morrow and Utell 1989); 0.5 ppm for 1 h at rest (Mohsenin 1987); up to 0.6 ppm for 75 min with intermittent exercise (Roger et al. 1990); and up to 1 ppm for 4 h (Sackner et al. 1981). No statistically significant differences between control and NO_2 exposure were found for airway resistance, symptoms, heart rate, skin conductance, or self-reported emotional state of asthmatic subjects exposed to NO_2 at 4 ppm for 75 min with intermittent exercise (Linn and Hackney 1984).

Kerr et al. (1978, 1979) studied the effects of NO_2 on pulmonary function and reported other symptoms that were not reported in many other studies. The subjects were asked note symptoms they experienced during exposure to NO_2 at 0.5 ppm for 2 h, specifically cough, sputum, irritation of mucus membranes, and chest discomfort. The odor of NO_2 was perceptible but the subjects became unaware of it after about 15 min. Seven of 13 asthmatic subjects reported symptoms with exposure, compared with only 1/10 normal subjects and 1/7 subjects with chronic bronchitis. In the group of asthmatics, two had slight burning of the eyes, one had a slight headache, three reported chest tightness, and one had labored breathing with exercise, compared with slight nasal discharge in the normal and chronic bronchitis individuals. No changes in any pulmonary function tests were found immediately after the exposure.

Significant group mean reductions in FEV_1 (-17.3% with NO_2 vs. -10.0% with air) and specific airway conductance (-13.5% with NO_2 vs. -8.5% with air) occurred in asthmatic subjects after exposure during exercise to NO_2 at 0.3 ppm for 4 h, and 1/6 individuals experienced chest tightness and wheezing (Bauer et al. 1985). The onset of effects was delayed when exposures were by oral-nasal

inhalation compared with oral inhalation; the delay might have resulted from scrubbing within the upper airway. In a similar study, 15 asthmatic subjects exposed at rest to NO_2 at 0.3 ppm for 20 min followed by 10 min of exercise had significantly greater reductions in FEV_1 (-10 vs. -4% with air) and partial expiratory flow rates at 60% of total lung capacity, but no symptoms were reported (Bauer et al. 1986). In a preliminary study with 13 asthmatic subjects exposed to NO_2 at 0.3 ppm for 110 min, slight cough, dry mouth and throat, and significantly greater reduction in FEV_1 (-11 vs. -7%) occurred after exercise; however, in a larger study, no changes in pulmonary function were measured and no symptoms were reported when 21 asthmatic subjects were exposed to NO_2 at concentrations up to 0.6 ppm for 75 min (Roger et al. 1990). The mean drop in FEV_1 for asthmatics during a 3-h to NO_2 at 1 ppm with intermittent exercise (-2.5%) was significantly greater than the drop during air exposure (-1.3%); concentrations of 6-keto-prostaglandin$_{1\alpha}$ were decreased and concentrations of thromboxane B_2 and prostaglandin D_2 were increased bronchoalveolar lavage fluid after NO_2 exposure (Jörres et al. 1995).

Studies on the effects of NO_2 on airway hyper-reactivity in asthmatic subjects also have been inconclusive. Methacholine responsiveness in asthmatics was not increased following exposure to NO_2 at 0.25 ppm for 20 min at rest, plus 10 min of exercise (Jörres and Magnussen 1991), or by exposure to 0.1 ppm for 1 h at rest (Hazucha et al. 1983). Exposure at 0.1 ppm for 1 h caused an increase in specific airway resistance in 3/20 asthmatic subjects (the other 17 individuals had little or no response) and enhanced the bronchoconstrictor effect of carbachol in 13/20 asthmatic subjects, but the remaining seven subjects were unaffected. When the study was repeated in four individuals (two responders and two nonresponders) exposed to NO_2 at 0.2 ppm, the results were variable; the two nonresponders were still unaffected, while one responder had an equal response and the other had a greater response to carbachol challenge compared with the response at 0.1 ppm (Orehek et al. 1976). Slight but significant potentiation of airway reactivity in asthmatic subjects occurred from exposure to NO_2 at 0.5 ppm for 1 h followed by methacholine challenge (Mohsenin 1987), 0.3 ppm for 40 min followed by isocapnic cold air hyperventilation (Bauer et al. 1986), 0.2 ppm for 2 h followed by methacholine challenge (Kleinman et al. 1983), and 0.25 ppm for 30 min followed by isocapnic hyperventilation (Jörres and Magnussen 1990). A significantly greater decrease in FEV_1 from challenge with house-dust-mite antigen was reported for asthmatic subjects compared with controls (-7.76 vs. -2.85%) following exposure to NO_2 at 0.4 ppm for 1 h (Tunnicliffe et al. 1994), but no significant changes were found in a similar study using a 6-h exposure (Devalia et al. 1994). Exposure of asthmatic subjects to NO_2 at 0.4 ppm for 3 h significantly decreased the amount of inhaled allergen required to decrease FEV_1 by 20%, but no changes in airway responsiveness occurred following exposure to 0.2 ppm for 6 h; these results suggest a concentration threshold rather than a duration effect (Jenkins et al. 1999).

Folinsbee (1992) conducted a meta-analysis of 20 studies that measured airway responsiveness in asthmatic subjects following exposure to NO_2. Eight

different agents were used to induce nonspecific airway responsiveness and the analysis was restricted to exposures of 0.2-0.3 ppm. The fraction of asthmatic subjects with an increase in airway responsiveness was significant ($p \leq 0.01$) following exposures at rest, but not with exercise. When only those studies that used a cholinergic agonist were analyzed, similar results were found in that a greater proportion of subjects showed an increased response when exposed during rest than during exercise.

Subjects with Chronic Lung Disease

Studies of NO_2 on pulmonary function in patients with chronic lung disease or bronchitis are conflicting. No significant differences in pulmonary function or symptom were observed in patients with chronic respiratory illness exposed at rest to NO_2 at 0.3 ppm for 4 h (Hackney et al. 1992), in patients with chronic obstructive pulmonary disease exposed at up to 2 ppm for 1 h with intermittent exercise (Linn et al. 1985), and in patients with chronic bronchitis exposed at 0.5 ppm for 2 h with exercise (Kerr et al. 1978, 1979). In contrast to these reports, forced expiratory volume of patients with chronic obstructive pulmonary disease significantly decreased from 18.8 L after exposure to air to 13.6 L after exposure to NO_2 at 0.3 ppm for 1 h (Vagaggini et al. 1996). A significant reduction in FVC that progressed during exercise (from -1.2 to -8.2%) occurred in elderly patients with chronic obstructive pulmonary disease exposed to NO_2 at 0.3 ppm for 4 h, while no effects were seen in an age- and gender-matched healthy control group (Morrow and Utell 1989; Morrow et al. 1992).

The effects of NO_2 on respiratory gas exchange were investigated in patients with chronic bronchitis. Inhalation of NO_2 at 4 and 5 ppm for 15-60 min significantly decreased the carbon-monoxide diffusing capacity and arterial pO_2 (partial pressure of oxygen), with no progressive changes over time. Exposure at 5 ppm for 15 min resulted in an average decrease in carbon monoxide diffusion capacity of 3.8 mL/min/Torr and a decrease in arterial pO_2 from an average of 76.5-71.3 Torr. A slight, but statistically significant, increase in airway resistance (approximately 20-30% above the initial value) was measured at concentrations of 1.6-5 ppm for 5 min; no effects occurred at ≤ 1.5 ppm (von Nieding et al. 1973a; von Nieding and Wagner 1979).

2.2.3.2. Nitric Oxide

Seven male and five female healthy volunteers were exposed to NO at 40 ppm through a tight facial mask for 2 h (Luhr et al. 1998). Concentrations of NO_2 were closely monitored and did not exceed 2.3 ppm. No changes in blood pressure, heart rate, or peripheral oxygen saturation were noted during exposure. Mean methemoglobin concentration increased from 0.63% to 1.13% during inhalation of NO.

NO was administered by inhalation at 80 ppm for 10 min to four groups of volunteers: healthy adults, adults with hyper-reactive airways during provocation with methacholine, patients with bronchial asthma, and patients with chronic obstructive pulmonary disease. Bronchodilatory effects were measured as changes in specific airway conductance. No unusual smell, taste, or discomfort was noted and no individual reacted with bronchoconstriction when exposed to NO. NO did not affect airway conductance in healthy adults or in patients with pulmonary disease. However, inhalation of NO attenuated the methacholine-induced bronchoconstriction in individuals with hyper-reactive airways and increased airway conductance in patients with asthma (Högman et al. 1993a).

Ten healthy volunteers, eight patients with pulmonary hypertension, and 10 cardiac patients were exposed to NO at 40 ppm for 5 min (Pepke-Zaba et al. 1991). No clinical signs of toxicity were reported by any individual. Pulmonary vascular resistance was significantly reduced in patients with pulmonary hypertension and in cardiac patients, but not in healthy volunteers. No effect on systemic vascular resistance was observed in any patient or volunteer. Methemoglobin concentrations in the volunteer group increased from 0.33% with air to 0.42% with NO.

Eight healthy adult male volunteers were exposed to NO at 1 ppm for 2 h while performing intermittent light exercise consisting of pedaling a stationary bicycle for 15 min of every half hour (Kagawa 1982). Pulmonary-function tests were performed after 1 and 2 h of exposure, and 1 h after exposure ceased. No clinical symptoms in any volunteer were associated with exposure. A small but significant ($p \leq 0.05$) decrease in airway conductance was observed in 4/8 individuals during NO exposure and resolved in all but two subjects 1 h post-exposure; no significant difference in the group mean was found. As a group, a significant reduction in the percentage increase of maximal expiratory flow at 50% of FVC while breathing a helium-oxygen mixture was noted at the end of the exposure period. However, since this reduction was not accompanied by a reduction in FVC or an increase in the alveolar plateau slope, the author questioned its biologic relevance. In a similar study, respiratory resistance was significantly increased (10-12%) in healthy adults and smokers exposed to ≥20 ppm for 15 min (von Nieding et al. 1973b).

In another report, specific airway conductance was significantly ($p \leq 0.05$) increased in healthy men exposed to NO at 80 ppm for 4 min following methacholine-induced bronchoconstriction (Sanna et al. 1994). The bronchodilator action of NO described in the report is consistent with experiments in rabbits and guinea pigs summarized below.

Pulmonary vasoconstriction was induced in one healthy male volunteer by inhalation of a hypoxic gas mixture (Dupuy et al. 1995). NO was then administered at 10, 20, and 80 ppm for 15-min intervals. NO induced a dose-dependent, rapid, consistent, and reversible decrease in pulmonary artery pressure, but no distress, discomfort, or pain were noted from exposure. In a similar experiment, healthy volunteers breathed a 12% oxygen atmosphere to induce hypoxic pulmonary vasoconstriction. Addition of NO at 40 ppm to the

inspired gas decreased pulmonary artery pressure to baseline levels within 10 min (Frostell et al. 1993).

In several inhalation studies, NO was shown to affect bleeding times or platelet aggregation, although adverse clinical effects were not demonstrated. The bleeding-time ratio increased to 1.33 in six healthy volunteers exposed at 30 ppm for 15 min, but returned to near normal 60 min after exposure (Högman et al. 1993b). Platelet aggregation was inhibited after 4 h in mechanically ventilated neonates treated with NO at 2-80 ppm for hypoxic respiratory failure (Cheung et al. 1998). Cardiopulmonary bypass surgery in children with congenital heart defects resulted in a decrease in platelet numbers by 50%; with the therapeutic use of NO at 20 ppm after surgery (duration not specified), platelet numbers decreased by 70%. However, no prolonged bleeding after withdrawal of indwelling catheters or drainage tubes was detected in those patients treated with NO (Breuer et al. 1998).

NO had no effect on left ventricular function in normal healthy adults exposed at 20 ppm for 10 min and no increase in methemoglobin concentrations was found (Hayward et al. 1997).

2.3. Developmental and Reproductive Toxicity

No information was found regarding the developmental or reproductive toxicity of nitrogen oxides in humans.

2.4. Genotoxicity

No information was found regarding the genotoxicity toxicity of NO_2 in humans.

No increase in chromosome aberrations was found in human peripheral blood lymphocytes after exposure to NO at 40 ppm for 2 h (Luhr et al. 1998). No other information was found regarding the genotoxicity of NO in humans.

2.5. Carcinogenicity

No information was found regarding the carcinogenicity of nitrogen oxides in humans.

2.6. Summary

In humans, exposure to NO_2 at $\geq$15 ppm causes immediate irritation with pulmonary edema followed by a latent period of apparent recovery in healthy individuals. A second phase of symptoms can occur after several hours or days, which include fever with progressively more severe dyspnea, cyanosis, and cough, and inspiratory and expiratory rales. The concentration causing death in humans is approximately $\geq$150 ppm, but no duration of exposure was given. Most case reports do not contain information on concentrations or durations of

exposure; however, welders exposed at 30 and 90 ppm for 40 min experienced varying degrees of dyspnea, cough, headache, chest tightness, nausea, and cyanosis, and hospitalization was required for pulmonary edema at the higher concentration (Norwood et al. 1966; Morley and Silk 1970). Similar symptoms and respiratory complaints were reported following release of a cloud of N_2O_4 from a railroad tank car (Bauer et al. 1996).

Epidemiologic studies on the long-term effects of elevated concentrations of NO_2 are conflicting. It is likely that increases in respiratory illnesses are from NO_2 in combination with other pollutants and that short-term peak concentrations are more detrimental than chronic, low-level exposures. Evidence suggests that children (5-12 years old) have a greater risk for developing respiratory disease from long-term exposure to higher concentrations, but infants do not.

Experimental studies with both healthy and asthmatic individuals exposed to NO_2 are inconclusive. Negative results were obtained in many studies with exposures up to 4 ppm for 1 h; however, other studies report positive effects on pulmonary function at lower concentrations. In the studies that found statistically significant differences with NO_2 exposure, the changes were within 10% of the measured value after air-only exposure and of questionable biologic significance even for asthmatic subjects. However, the available evidence also suggests that asthmatic subjects may experience an increase in airway responsiveness at 0.2-0.3 ppm.

NO has been used extensively in adults and children to lower pulmonary vascular resistance caused by acute respiratory distress syndrome, hypoxemic respiratory failure, persistent pulmonary hypertension, other heart or lung disease, and organ transplantation. The toxicity of NO is associated with methemoglobin formation and oxidation to NO_2. Contamination of anesthesia gases has resulted in one fatality, but exposure concentrations were not measured. Therapeutic concentrations of 20-80 ppm for 24 h or 100 ppm for 20 min have not resulted in adverse effects among treated patients. However, an infant exposed at 80 ppm for 26 h developed clinically significant concentrations of methemoglobin, which were rapidly lowered with infusion of methylene blue and reduction of the NO concentration. Effects of NO on the airways are somewhat variable. It appears that NO might have either no effect or cause bronchoconstriction in normal subjects, but might result in bronchodilation in individuals with chemically-induced bronchoconstriction or asthma.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Acute lethality data from NO_2 were found for several species. One group of investigators (Hine et al. 1970) studied the effects of varying concentration and duration of exposure in five different species of laboratory animal; these

results are described separately by species below and are summarized in Table 4-7. In this study, deaths generally occurred within 2-8 h of exposure and the majority within 24 h. Additional data from rabbit, rat, and mouse studies were available and agree with the results of the Hine et al. (1970) study. LC_{50} values for N_2O_4 were listed for four species, but duration of exposure was not specified; effects were similar to those described following NO_2 exposure. With NO, most of the experimental animal studies available focused on the therapeutic use of NO in an animal model of human disease. Lethality studies in dogs, rats, and mice lacked complete concentration-response information, were confounded by possible NO_2 contamination, or were secondary citations in which the original source could not be obtained.

TABLE 4-7 Summary of Nitrogen Dioxide Mortality in Five Species[a]

Concentration (ppm)	Time (h)	Rat	Mouse	Guinea Pig	Rabbit	Dog
50	1	0/17	0/5	1/6	0/4	0/1
	8	0/12	0/5	4/6	0/4	0/2
	24	3/10	5/10	—	0/4	—
75	1	3/31	1/6	1/4	1/8	0/2
	2	1/12	2/6	3/4	0/6	0/2
	4	7/12	5/6	2/4	2/8	1/3
	8	12/12	6/6	4/4	6/8	1/4
100	0.5	0/5	2/10	1/2	1/3	0/2
	2	8/8	13/14	3/4	2/4	1/3
	4	29/29	10/10	—	3/4	2/2
	8	—	10/10	—	—	—
150	0.5	2/10	—	3/4	—	—
	1	10/13	—	—	1/6	2/3
	2	10/12	—	3/3	—	—
	4	4/4	—	—	3/4	—
200	0.08	6/12	4/6	2/2	0/2	—
	0.17	8/12	6/6	—	1/2	—
	0.33	5/5	6/6	—	2/4	2/2
	0.50	4/4	—	—	—	—

[a]Deaths generally occurred within 2-8 h after exposure and the majority within 24 h.
Source: Adapted from Hine et al. 1970.

3.1.1. Dogs

Greenbaum et al. (1967) exposed mongrel dogs (n = 1/concentration) to NO_2 at 0.1% (1,000 ppm) for 136 min, 0.5% (5,000 ppm) for 5-45 min, or 2% (20,000 ppm) for 15 min. All dogs that were exposed at 0.5% for 35-45 min or 2% for 15 min died. They exhibited shallow respiration and gasping, and death was from pulmonary edema. Fluid was visible in the tracheobronchial tree at necropsy. Cyanosis from methemoglobin formation (78%) was noted in one animal exposed at 2% for 15 min. At concentrations of 0.5% and 2%, arterial pO_2 and systemic arterial pressure were reduced. The authors stated that pulmonary edema was caused by the action of NO_2 on the alveolar lining fluid, which formed nitric and nitrous acids that denatured proteins, ruptured lysosomes, and caused chemical pneumonitis.

Hine et al. (1970) studied the effects of varying concentration and duration of NO_2 exposure on mongrel dogs. Animals (n = 1-4) were exposed to NO_2 at 5-250 ppm for 30 min to 24 h. At concentrations of ≥40 ppm, signs of toxicity included lacrimation, reddening of the conjunctivae, and increased respiration, which became labored and difficult as the concentration increased. Mortality was first observed at 75 ppm for 4 h (see Table 4-7). Gasping and spasmodic respiration were observed, and pulmonary edema was found at necropsy. Histologic findings in the lungs included bronchiolitis, desquamated bronchial epithelium, infiltration by polymorphonuclear cells, and edema.

Kushneva and Gorshkova (1999) reported an LC_{50} of 260 mg/m^3 (70 ppm) for N_2O_4. The cause of death was pulmonary edema; duration of exposure was not specified and no experimental details were provided.

Greenbaum et al. (1967) exposed dogs to NO at 0.5% (5,000 ppm) for 25 min or at 2% (20,000 ppm) for 7-50 min. All dogs died either within 16 min of exposure or at the end of exposure. Death was associated with a reduction in arterial oxygen caused by methemoglobinemia, low arterial pO_2 from pulmonary edema, and acidemia. Concurrent studies described above were conducted in which dogs were exposed to NO_2. No difference in the effects of either gas was observed, and it is probable that the pulmonary effects observed for NO were from the formation of NO_2 within the test system prior to inhalation by the dogs. This assumption is supported by the authors' observation that considerable oxidation to NO_2 occurred, as indicated by the brown contents of the reservoir bag of the inhalation system. Further, methemoglobin concentrations increased as a function of time and NO concentration. Administration of methylene blue did not return arterial oxygen to safe levels in all dogs and the dogs died with methemoglobin concentrations of 3-5%. The authors stated that the cause of pulmonary edema was the action of NO_2 on the alveolar lining fluid forming nitric and nitrous acids that denatured proteins, ruptured lysosomes, and caused chemical pneumonitis.

3.1.2. Rabbits

The 15-min LC_{50} for NO_2 was 315 ppm in the rabbit (strain not specified; n = 5). Clinical signs of toxicity included severe respiratory distress, ocular irritation, 10-15% body-weight suppression for 2 days, and death; time-to-death varied from 30 min to 3 days. Gross pathology revealed darkened areas on the surface of the lungs. Histopathologic changes in the lungs of survivors 7 and 21 days after exposure included focal accumulation of intra-alveolar macrophages, some proliferation of the alveolar lining epithelium, and varying amounts of inflammatory cells (Carson et al. 1962).

Hine et al. (1970) studied the effects of varying concentration and duration of NO_2 exposure rabbits (strain not specified). Animals (n = 2-8) were exposed to NO_2 at 5-200 ppm for 30 min to 24 h. At concentrations of ≥40 ppm, signs of toxicity included lacrimation, reddening of the conjunctivae, and increased respiration, which became labored and difficult as the intoxication increased. One death was observed at 75 ppm for 1 h but none occurred after 2 h, which makes attributing the death after 1 h to NO_2 questionable (see Table 4-7). The rabbits were gasping and had spasmodic respiration at the end of the study, and pulmonary edema was observed at necropsy. Histologic findings in the lungs included bronchiolitis, desquamated bronchial epithelium, infiltration by polymorphonuclear cells, and edema.

In a similar study, rabbits (strain not specified; n = 3) were exposed to NO_2 at 125, 175, 250, 400, 600, or 800 ppm for 10 min (Meulenbelt et al. 1994). Two of three animals exposed at 800 ppm died 7-21 h after exposure. Lung weights were significantly greater and lung homogenates contained greater amounts of protein and higher concentrations of lactate dehydrogenase, glutathione peroxidase, and glutathione-dehydrogenase activity in animals exposed at ≥250 ppm. Bronchoalveolar lavage fluid from animals exposed to ≥175 ppm contained greater amounts of protein and albumin, and higher concentrations of lactate dehydrogenase and angiotensin converting enzyme activity than unexposed controls and all treated groups had increased numbers of neutrophilic leucocytes. Dose-related increases in severity of centriacinar catarrhal pneumonitis, macrophage influx, and neutrophilic leucocytes were observed on histopathologic examination of the lungs. Edema occurred at ≥250 ppm, subpleural hemorrhaging at ≥400 ppm, and desquamation of the bronchiolar epithelium was seen at ≥600 ppm.

Kushneva and Gorshkova (1999) list an LC_{50} of 320 mg/m^3 (86 ppm) for N_2O_4, with the cause of death pulmonary edema; duration of exposure was not given and no experimental details were included.

3.1.3. Guinea Pigs

Hine et al. (1970) also studied the effects of varying concentration of NO_2 and duration of exposure in the guinea pig (strain not specified). Animals (n = 2-

6) were exposed to NO_2 at 5-200 ppm for 30 min to 8 h. At concentrations of ≥40 ppm, signs of toxicity included lacrimation, reddening of the conjunctivae, and increased respiration, which became labored and difficult as the intoxication increased. Deaths first occurred at 50 ppm for 1 h (see Table 4-7). Guinea pigs exhibited gasping and spasmodic respiration, and lung edema was observed at necropsy. Histologic findings in the lungs included bronchiolitis, desquamated bronchial epithelium, infiltration by polymorphonuclear cells, and edema.

To determine the sensitivity of adult and neonate animals to NO_2, Duncan-Hartley guinea pigs (ages 5, 10, 21, 45, 55, and 60 days) were exposed continuously for 3 days to NO_2 at 2 or 10 ppm (Azoulay-Dupuis et al. 1983). A total of 17-27 animals were studied in each age group. Exposure of neonates before weaning included the dam. At 10 ppm, clinical signs of toxicity in adults over 45 days of age included difficulty in moving, reduced food and water consumption, and hyperventilation. Body weight gain was decreased until 21 days, and body weight was reduced after 45 days in all exposed animals. These effects were most pronounced in the dams. Mortality in the high-concentration group increased with age; deaths occurred in 4% of 5-day-old animals, up to 60% in 55-day-old animals died, and 67% in dams. Most of the older animals died after the first 24 h, whereas the younger animals died later in the 3-day period. At 2 ppm, lung histopathology was normal until animals were 45 days of age, when thickening of the alveolar walls, infiltration by polymorphonuclear neutrophils, and alveolar edema were observed. In dams, bronchioles were devoid of cilia in some areas. At 10 ppm, guinea pigs of all ages were affected by these changes, and were more pronounced in older animals.

3.1.4. Rats

The 5-, 15-, 30-, and 60-min LC_{50} values for NO_2 in the male rat (100-120 g; strain not specified; n = 10) are 416, 201, 162, and 115 ppm, respectively. Clinical signs of toxicity included severe respiratory distress, ocular irritation, 10-15% body weight suppression, and death; time-to-death varied from 30 min to 3 days. Gross pathology revealed darkened areas on the surface of the lungs, and purulent nodules involving the entire lungs was found in some of the survivors (Carson et al. 1962).

An older study reported LC_{50} values for NO_2 in male rats (200-300 g; strain not specified; n = 10) of 1,445 ppm for 2 min, 833 ppm for 5 min, 420 ppm for 15 min, 174 ppm for 30 min, 168 ppm for 60 min, and 88 ppm for 240 min (Gray et al. 1954). Deaths were attributed to pulmonary edema. The differences in LC_{50} values between this study and Carson et al. (1962) might be from differences in the size and age of the rats used the studies.

Meulenbelt et al. (1992a,b) investigated the effects of NO_2 concentration and duration of exposure in Wistar rats. The effect of concentration was studied by exposing 6-9 rats/group to NO_2 at 25, 75, 125, 175, or 200 ppm for 10 min. No signs of toxicity were observed at 25 ppm. Stertorous respiration was heard in

animals exposed at 175 and 200 ppm. Rats exposed at ≥75 ppm had significantly increased lung weight, and subpleural hemorrhages and pale discolorations of the lung were observed during gross examination. Histologic changes in the lungs included atypical pneumonia, edema, focal desquamation of the terminal bronchiolar epithelium, increased numbers of macrophages and neutrophilic leucocytes, and interstitial thickening of the centriacinar septa (175 and 200 ppm only), with the severity increasing at the higher concentrations. One rat died in both the 175- and 200-ppm groups after 14-20 h of exposure. Biochemical changes in bronchoalveolar lavage fluid included concentration-dependent increases in protein and albumin concentrations, angiotensin converting enzyme activity, β-glucuronidase activity, and neutrophilic leukocytes.

Duration of exposure was investigated by exposing 6 rats/group to NO_2 at 175 ppm for 10, 20, or 30 min or at 400 ppm for 5, 10, or 20 min (Meulenbelt et al. 1992a,b). Stertorous respiration was heard in animals at both concentrations for all exposure durations, and lung weight was significantly higher than that of the controls. At 175 ppm, 5/6 rats died in the 20- and 30-min groups exposed at 400 ppm, 6/6 rats died in the 10- and 20-min groups. Necropsy revealed foamy, seroanguinous fluid in the trachea, subpleural bleeding, and pale discoloration. Histologic alterations were similar to those described above. Methemoglobin concentrationss, measured after exposure at 175 ppm for 10 min, were not elevated, but plasma nitrate concentrations were significantly greater than controls.

Hine et al. (1970) also studied the effects of varying NO_2 concentration and duration of exposure in Long-Evans rats. Animals (n = 4-31) were exposed to NO_2 at 5-250 ppm at duration of 30 min to 24 h. At concentrations of ≥40 ppm, signs of toxicity included lacrimation, reddening of the conjunctivae, and increased respiration, which became labored and difficult as the intoxication increased. Mortalities were first observed at 50 ppm for 24 h (see Table 4-7). Animals exhibited gasping and spasmodic respiration, and pulmonary edema was observed at necropsy. Histologic findings in the lungs included bronchiolitis, desquamated bronchial epithelium, infiltration by polymorphonuclear cells, and edema.

Kushneva and Gorshkova (1999) reported an LC_{50} of 105 mg/m^3 (28 ppm) for N_2O_4, with the cause of death pulmonary edema; duration of exposure was not specified and no experimental details were provided.

To assess acute lung injury caused by inhalation of NO, rats were exposed at 500-1,500 ppm for 5-30 min (Stavert and Lehnert 1990). At 1,000 ppm for 30 min, the animals were cyanotic and 11/20 died within 30 min after exposure ended. Deaths were attributed to methemoglobin formation, although concentrations of methemoglobin were not measured in this study. At concentrations up to 1,500 ppm for 15 min or at 1,000 ppm for 30 min, NO produced no increases in lung weight and did not result in any histopathologic changes in the lungs.

Groups of five male and five female rats were exposed for 6 h to NO at 0, 80, 200, 300, 400, or 500 ppm by nose-only inhalation (Waters et al. 1998). Concentrations of ≥300 ppm were lethal, and methemoglobin concentrations were significantly elevated at ≥200 ppm. No histopathologic changes in animals

exposed at 200 ppm were observed with light microscopy, but interstitial edema attributed to NO_2 contamination (2.6 ppm) was seen by electron microscopy. Further details of the results and experimental procedures were not available in the abstract.

3.1.5. Mice

BALB/c mice (n = 5-7) were exposed to NO_2 at 5, 20, or 40 ppm for 12 h (Hidekazu and Fujio 1981). Body weight was markedly decreased 1 and 2 days after exposure at 20 and 40 ppm, and 3/38 (7.8%) animals exposed at 40 ppm died within 2 days of exposure.

Hine et al. (1970) studied the effects of varying concentration and duration of exposure in Swiss-Webster mice. Animals (n = 5-14) were exposed to NO_2 at 5-250 ppm for durations of 30 min to 24 h. At concentrations of ≥40 ppm, signs of toxicity included lacrimation, reddening of the conjunctivae, and increased respiration, which became labored and difficult as the intoxication increased. Mortality was first observed at 50 ppm for 24 h (see Table 4-7). Animals exhibited gasping and spasmodic respiration, and lung edema was observed at necropsy. Histologic findings in the lungs included bronchiolitis, desquamated bronchial epithelium, infiltration by polymorphonuclear cells, and edema.

Kushneva and Gorshkova (1999) reported an LC_{50} of 190 mg/m^3 (51 ppm) for N_2O_4, with the cause of death pulmonary edema. Duration of exposure was not specified and no experimental details were provided.

In a series of experiments, mice were exposed to "predominantly" NO (Pflesser 1935). All of the animals exposed at 350 and 3,500 ppm died, and all animals exposed at 310 ppm for up to 8 h survived. The 8-h LC_{50} was reported as 320 ppm. Death appeared to be from methemoglobin formation; at necropsy, no evidence of lung injury or pulmonary edema was observed.

3.2. Nonlethal Toxicity

3.2.1. Monkeys

Squirrel monkeys (n = 2-6/group) were exposed to NO_2 at 10-50 ppm for 2 h and respiratory function monitored during exposure (Henry et al. 1969). Exposure at 35 or 50 ppm resulted in a markedly increased respiratory rate and decreased tidal volume, which returned to normal 7 days post-exposure. Only slight effects on respiratory function were noted at 15 and 10 ppm. Mild histopathologic changes in the lungs were noted after exposure at 10 and 15 ppm; however, marked changes in lung structure were observed after exposure at 35 and 50 ppm. At 35 ppm, areas of the lung were collapsed and had basophilic alveolar septa, alveoli were expanded with septal wall thinning, the bronchi were moderately inflamed and had some proliferation of the surface epithelium. At 50 ppm, extreme vesicular dilatation of alveoli or total collapse

was observed, lymphocyte infiltration was seen with extensive edema, and surface erosion of the epithelium of the bronchi was found. In addition to the effects on the lungs, interstitial fibrosis (35 ppm) and edema (50 ppm) of cardiac tissue, glomerular tuft swelling in the kidney (35 and 50 ppm), lymphocyte infiltration in the kidney and liver (50 ppm), and congestion and centrilobular necrosis in the liver (50 ppm) were observed. Although no animals died following the single exposure to NO_2 at 50 ppm, one animal died after a second exposure 2 months after the first exposure, suggesting that some of the lesions were irreversible.

3.2.2. Dogs

Carson et al. (1962) conducted a series of experiments on dogs (breed not specified; n = 2) at target concentrations of NO_2 at 50% and 25% of the LC_{50} for the rat (see Section 3.1.4). The actual concentrations varied slightly, but were within 10% of the target. Dogs exposed to NO_2 at 164 ppm for 5 min, 85 ppm for 15 min, or 53 ppm for 60 min (approximately 50% of the rat LC_{50}) had some respiratory distress, a mild cough, and ocular irritation, all of which cleared within 2 days of exposure. Dogs exposed at 125 ppm for 5 min, 52 ppm for 15 min, or 39 ppm for 60 min (approximately 25% of the rat LC_{50}) showed only mild sensory effects. No gross or microscopic lesions were found in any dog.

Greenbaum et al. (1967) exposed mongrel dogs (n = 1) to NO_2 at 0.1% (1,000 ppm) for 136 min or at 0.5% (5,000 ppm) for 5-45 min. The dog exposed at 0.1% remained in good condition throughout the exposure. Exposures at 0.5% for 15 and 22 min were not lethal, but resulted in respiratory distress and gave rise to anxiety for about 2 h and then resolved without therapy. Histopathologic examination of the lungs was not performed.

No treatment-related changes in behavior or clinical signs were observed in mongrel dogs (n = 1) exposed to NO_2 at 10-40 ppm for 6 h (Henschler and Lütge 1963).

Mongrel dogs (number not specified) exposed to NO_2 at 20 ppm for up to 24 h showed minimal signs of irritation and changes in behavior. Microscopic lesions were described as questionable evidence of lung congestion and interstitial inflammation for up to 48 h post-exposure (Hine et al. 1970).

Pulmonary ultrastructural changes were examined in beagle dogs (n = 1) exposed to NO_2 at 3-16 ppm for 1 h (Dowell et al. 1971). Intra-alveolar edema occurred in most dogs exposed at $\geq$7 ppm and was associated with impaired surfactant activity and lung compliance. Ultrastructural alterations included wide-spread bleb formation, loss of pinocytic vesicles, and mitochondrial swelling of endothelial cells. Exposure at 3 ppm resulted in bleb formation in the alveolar endothelium (observed by electron microscopy) without biochemical or physiologic changes.

Anesthetized beagle dogs (3-4 per group) were exposed to NO at 0, 80, 160, 320, or 640 ppm for 6 h (Mihalko et al. 1998; Wilhelm et al. 1998). One

animal in the 640-ppm group died. Decreased arterial oxygen concentrations were measured following exposure at 320 and 640 ppm, and increased minute volumes and decreased systemic arterial pressures were observed at 640 ppm. Methemoglobin concentrations were 3, 6.6, 24, and 78%, respectively. Further details of the results and experimental procedures were not available in the abstracts.

The pulmonary vasodilating effects of NO have been demonstrated in several canine models of lung injury, including hypoxia (Channick et al. 1994; Romand et al. 1994), oleic acid-induced injury (Putensen et al. 1994a,b; Romand et al. 1994; Zwissler et al. 1995), pulmonary microembolism (Zwissler et al. 1995), cardiac transplant (Chen et al. 1997), and pulmonary shunt (Hopkins et al. 1997). Following lung injury, dogs were given NO at concentrations ranging from 40 to 80 ppm for up to 40 min. In all studies, NO significantly decreased pulmonary vascular resistance, decreased pulmonary artery pressure, and improved ventilation-perfusion mismatch. Methemoglobin concentrations did not exceed 1.1% (Channick et al. 1994; Putensen et al. 1994a; Romand et al. 1994).

3.2.3. Rabbits

Rabbits (strain not specified; number not specified) exposed to NO_2 at 20 ppm for up to 24 h showed minimal signs of irritation and changes in behavior. Microscopic lesions were described as questionable evidence of lung congestion and interstitial inflammation for up to 48 h post-exposure (Hine et al. 1970).

Rabbits exposed to NO_2 at 10 ppm for 2 h showed accelerated alveolar particle clearance (Vollmuth et al. 1986) and altered pulmonary arachidonic acid metabolism (Schlesinger et al. 1990). Continuous exposure of rabbits to NO_2 at 3.6 ppm for 6 days did not cause morphologic changes in the lungs (Hugod 1979).

Rabbits (strain, sex, and number not specified) exposed continuously for up to 20 h to NO_2 at 7, 14, or 28 ppm had an increase in polymorphonuclear neutrophils in the lavage fluid throughout the exposure (Gardner et al. 1977).

NO has been shown to attenuate the effects of experimentally-induced lung injury in the rabbit. Rabbits were given NO at 20 ppm for 6 h with or without prior endotoxin-induced lung injury. In control animals, NO had no effect on pulmonary artery pressure, mean arterial pressure, heart rate, central venous pressure, or oxygenation. Pulmonary hypertension and deterioration of oxygenation by endotoxin were less pronounced in rabbits exposed to NO, but the inflammatory response was not reduced. Methemoglobin concentrations did not exceed 1.5% after 6 h (Nishina et al. 1997). In another study of endotoxin-induced lung injury, increased survival occurred in rabbits treated with 10 ppm for 90 min (7/7 vs. 5/9 controls), but improvement in pulmonary gas exchange was not demonstrated (Uchida et al. 1996).

The influence of NO on airway responsiveness to acetylcholine in normal and hyper-responsive rabbits was investigated (Mensing et al. 1997). Following provocation with acetylcholine, animals were treated with NO at 150 or 300 ppm for 5-10 min. No effects were seen with acetylcholine at concentrations of ≤2%; however, NO significantly reduced airway resistance caused by acetylcholine at 4 and 8%. Animals were then made hyper-responsive to acetylcholine by exposing them to ammonium persulfate. NO at 300 ppm significantly decreased the response to acetylcholine to almost the same level before ammonium persulfate was administered. Similar results were obtained with methacholine-induced bronchoconstriction (Högman et al. 1993c). Rabbits were exposed to increasing concentrations of nebulized methacholine with or without exposure to NO at 80 ppm, and airway resistance was measured after 5 min. There was no significant increase in methacholine-induced airway resistance.

In rabbits exposed to NO at 30 or 300 ppm for 15 min, bleeding times increased 46% and 72%, respectively, but there were no changes in hematocrit, whole blood or plasma viscosity, erythrocyte aggregation tendency, or erythrocyte deformation (Högman et al. 1993b, 1994).

3.2.4. Pigs

Inhalation of NO at 20, 40, or 80 ppm for 5 min by healthy pigs resulted in slight, but significant ($p = 0.04$), reductions in pulmonary artery pressure (Goldstein et al. 1997). The effects of NO also have been studied in porcine models of adult and neonatal pulmonary hypertension. Dose-related decreases in pulmonary artery pressure and input resistance, and increases in vascular efficiency have been observed in adult pigs administered NO at 10-80 ppm for up to 20 min after vasoconstriction induced by hypoxia (Hillman et al. 1997), thromboxane administration (Goldstein et al. 1997), or oleic acid administration (Shah et al. 1994). No effects on cardiac output, systemic arterial pressure, or left ventricular contractility were observed in any study. Exposure to NO at 40 ppm for 30 min by pigs with with oleic-acid-induced lung injury, resulted in sustained improvements in pulmonary artery pressure, oxygen partial pressure, and intrapulmonary shunt fraction, which deteriorated to control levels following termination of NO exposure (Shah et al. 1994). NO inhalation did not cause histopathologic changes in the lungs, and methemoglobin concentrations were 1.7% after exposure at 80 ppm (Shah et al. 1994).

The effects of NO were studied in a porcine model of neonatal pulmonary hypertension (Nelin et al. 1994). Pigs (approximately 13 days old) were administered room air, NO at 25 ppm, nitrogen in 14% oxygen (hypoxia), or NO at 25 ppm in 14% oxygen for 15 min. NO significantly reduced pulmonary artery pressure both alone and after hypoxia, with no changes in dynamic lung compliance, pulmonary resistance, hemoglobin, hematocrit, or methemoglobin.

At the end of the experiment, NO at 1,000 ppm was administered to one animal for 15 min, which resulted in a methemoglobin concentration of 20%.

3.2.5. Sheep

Lung mechanics, hemodynamics, and blood chemistry were assessed in crossbred sheep (n = 5-6) exposed by nose- or lung-only (to mimic mouth breathing) to NO_2 at 500 ppm for 15 min; in another group exposed by lung-only, bronchoalveolar lavage fluid was examined after a 20-min exposure to NO_2 at 500 ppm (Januszkiewicz and Mayorga 1994). No changes in hemodynamics or blood chemistry occurred in either group. Mean inspired minute ventilation was significantly increased, resulting in increased breathing rate and decreased mean tidal volume, in the lung-only exposure group, but not the nose-only group. Both nose- and lung-only exposure groups had significantly increased lung resistance and decreased dynamic lung compliance. Histopathologic examination of tissue from the lung-only exposed group revealed exudative fluid distributed in a patchy, lobular pattern, with mild neutrophil infiltration; little evidence of exudation was seen in the nose-only exposed group. Epithelial cell number and total protein in bronchoalveolar lavage fluid were significantly increased in the animals exposed to NO_2, while macrophage number was decreased.

Airway reactivity to aerosolized carbachol was evaluated in crossbred sheep (n = 4-10) exposed to NO_2 at 7.5 or 15 ppm for 2 h (Abraham et al. 1980). Group means for pulmonary resistance, bronchial reactivity to carbachol, and static lung compliance were similar to those from controls at both concentrations. However, after exposure to NO_2 at 7.5 ppm, 5/9 animals showed at 57% increase in pulmonary resistance after carbachol exposure. At 15 ppm, 9/10 animals responded with either bronchoconstriction or hyper-reactivity. In a concurrent experiment, sheep were exposed to NO_2 at 15 ppm for 4 h (Abraham et al. 1980). Mean pulmonary resistance was significantly increased from the pre-exposure value, but there were no changes in pulmonary hemodynamics or clinical signs of distress.

Frostell et al. (1991) examined the effects of inhalation of NO at 5-80 ppm on the normal and acutely constricted pulmonary circulation in awake lambs. Dose-response data were collected for a 6-min exposure, and toxicity data were collected after 1 and 3 h. Pulmonary constriction was induced by either infusion of the endoperoxide analog of thromboxane, U46619, or by hypoxia. In normal lambs, exposure to NO at 80 ppm for 6 min did not affect pulmonary artery pressure or vascular resistance. However, in lambs with constricted pulmonary circulation, a dose-related increase in vasodilation occurred with significantly reduced pulmonary artery pressure at 5 ppm and an almost complete vasodilator response at 40 and 80 ppm. Systemic vasodilation did not occur. Inhalation of NO at 80 ppm for 1 and 3 h did not increase extravascular lung water or

methemoglobin concentrations, or modify lung histology compared with control lambs.

Decreased pulmonary artery pressure also has been demonstrated in several other ovine models of experimental pulmonary hypertension. The therapeutic effects of NO described by Frostell et al. (1991) were confirmed in another study (DeMarco et al. 1996) in which exposures to NO at 80 ppm for 3 h completely reversed U46619-induced pulmonary hypertension without affecting systemic circulation. In this study, maximum methemoglobin concentrations of 4.7% were reached in the last half hour. A similar dose-dependent reduction in pulmonary artery pressure was shown at concentrations of 4-512 ppm, with maximum effect at 64 ppm within 5-10 min. Inhalation of NO at 512 ppm for 20 min resulted in methemoglobin concentrations of 11% (Dyar et al. 1993). In newborn lambs with persistent pulmonary hypertension, significantly increased survival occurred in lambs treated with 80 ppm for 23 h; no evidence of lung injury from NO inhalation was observed. Arterial oxygen tension in the NO treated lambs was significantly greater (63 vs. 14 mm Hg) within 15 min and continued to increase over time. At the end of the study, methemoglobin concentrations were 3% (Zayek et al. 1993).

Decreased pulmonary artery pressure and increased arterial oxygenation occurred in sheep treated with NO at 20 ppm for 48 h following lung injury from smoke inhalation, but airway inflammation was not reduced (Ogura et al. 1994). In premature lambs with hyaline membrane disease, exposure to NO at 20 ppm for 5 h did not significantly change oxidative stress parameters or induce lung inflammation (Storme et al. 1998).

3.2.6. Guinea Pigs

Guinea pigs (strain not specified; number not given) exposed to NO_2 at 20 ppm for up to 24 h showed minimal signs of irritation and changes in behavior. Microscopic lesions were described as questionable evidence of lung congestion and interstitial inflammation for up to 48 h post-exposure (Hine et al. 1970). Guinea pigs exposed at 9 and 13 ppm for 2 h or at 5.2 and 6.5 ppm for 4 h had significantly increased respiratory rate and decreased tidal volume with complete recovery after cessation of exposure (Murphy et al. 1964).

Hartley guinea pigs (n = 5-16) on an ascorbic-acid-deficient diet had increased lung lavage fluid protein following exposure to NO_2 at 4.8 ppm for 3 h and increased wet lung weight, increased nonprotein-sulfhydryl and ascorbic-acid content of the lungs, and decreased α-tocopherol content of the lungs following exposure to NO_2 at 4.5 ppm for 16 h. These changes were not seen in animals on normal guinea pig diets (Hatch et al. 1986). Similarly, vitamin-C-deficient male Hartley guinea pigs (n = 3-12) exposed to NO_2 at 1, 3, or 5 ppm for 72 h had significantly increased protein and lipid content in lavage fluid (Selegrade et al. 1981). No effects were seen at 0.4 ppm. At 5 ppm, 50% of the animals died and histopathology revealed multifocal interstitial pneumonia.

When the exposure to 5 ppm was shortened to 3 h, lavage protein was increased with a peak effect 15 h post-exposure.

Guinea pigs (strain not specified; n = 12-18) were exposed to NO_2 at 20, 40, or 70 ppm for 30 min followed by a 30-min exposure to aerosolized albumin; this regimen was repeated 5-7 times at intervals of several days (Matsumura 1970). During the first exposure at 70 ppm, labored breathing, though not severe, was observed in "some" animals, but was not seen with subsequent exposures. Immediately after the fifth exposure to antigen, one-half of the animals in the 70-ppm group showed enhanced airway sensitization (anaphylactic attacks). No effects were seen at 20 or 40 ppm.

Changes in airway responsiveness to histamine were investigated in Hartley guinea pigs (number not specified) exposed to NO_2 at 7-146 ppm for 1 h (Silbaugh et al. 1981). Pulmonary-function measurements and histamine challenge tests were performed 2 h before and at about 10 min and 2 and 19 h after exposure to NO_2. Increased sensitivity to histamine occurred at concentrations ≥40 ppm for 10-min exposures, but returned to baseline thereafter. Significant concentration-related increases in breathing frequency and decreased tidal volume were measured at 10 min (exact concentrations not specified) and remained correlated with concentration at 2 and 19 h.

Pulmonary resistance was significantly decreased in guinea pigs exposed to NO at 300 ppm for 6 min. In the same study, exposure at 5-300 ppm for 10 min resulted in a dose-related, rapid, consistent, and reversible reduction of pulmonary resistance and an increase in lung compliance following methacholine-induced bronchoconstriction (Dupuy et al. 1992).

3.2.7. Hamsters

Syrian golden hamsters (n = 5) were administered NO_2 at 28 ppm for 6, 24, or 48 h and histopathologic changes in the lungs were examined by light and electron microscopy (Case et al. 1982; Gordon et al. 1983). The bronchiolar epithelium showed ciliary loss and surface-membrane damage, loss of ciliated cells, and epithelial flattening at 24 and 48 h and epithelial hyperplasia, nonciliated cell hypertrophy, and loss of tight junctions between type I pneumocytes at 48 h.

3.2.8. Ferrets

Weanling domestic ferrets (n = 4-6; 6 weeks of age) were exposed to NO_2 at5, 10, 15, or 20 ppm for 4 h (Rasmussen 1992). A transient inflammatory response was evident as a significantly increased number of neutrophils in the lavage fluid for up to 48 h post-exposure at all concentrations. Morphometrically, dose-related decreased alveolar size and thickened alveolar walls indicative of exposure were observed in the lungs.

3.2.9. Rats

Only one study was found in which rats were exposed to N_2O_4; pulmonary lesions were similar to those described following NO_2 exposure. Male Wistar rats exposed to N_2O_4 at 43 ppm for 15 min had increased lung weight, lung edema, and hemorrhaging (Yue et al. 2004). The chamber atmosphere was generated by injecting liquid N_2O_4 and heating to evaporate it. Thus, it is likely that much of the dimer was converted to NO_2.

Pulmonary injury from NO_2 indicated by increases in lung weight was assessed in male Fischer 344 rats (n = 6-12) after exposure to NO_2 at 10, 25, or 50 ppm for 5, 15, or 30 min or at 100 ppm for 5 or 15 min (Stavert and Lehnert 1990). No significant changes in lung weight occurred in rats exposed at 10 ppm for 30 min or at 25-50 ppm for up to 15 min. Significant increases in lung wet weight and right cranial-lobe dry weight were found after exposure at 50 ppm for 30 min or at 100 ppm for 5 and 15 min. However, histologic evidence of lung injury was seen in animals exposed at 25 ppm for 30 min, 50 ppm for ≥5 min, and 100 ppm for 5 and 15 min. Findings included accumulation of fibrin, increased numbers of polymorphonuclear neutrophils and macrophages, extravasated erythrocytes, and type II pneumocyte hyperplasia, the severity of which increased with concentration and duration of exposure.

In an expanded study, Lehnert et al. (1994) determined that NO_2 concentration was more important than exposure duration in the severity of lung injury. Male Fischer 344 rats (n = 8-12) were exposed to NO_2 at 25, 50, 75, 100, 150, 200, or 250 ppm for 5-30 min. Lung wet weight was significantly increased after exposure at ≥150 ppm for 5 min, 100 ppm for 15 min, or 75 ppm for 30 min and further increases were observed as exposure duration increased. The pulmonary edematous response to a given concentration was not proportional to duration; however, increasing concentrations produced proportional increases in lung wet weight when similar exposure durations were compared. Histologically, fibrin and type II cell hyperplasia were observed after 5-min exposures at ≥50 ppm, and the severity increased proportionally to concentration. As further confirmation of concentration-dependent lung injury, rats were exposed to 1-min bursts of NO_2 at 500-2,000 ppm. The severity of pulmonary edema (measured by lung wet weight) was directly proportional to exposure concentration. The authors concluded that brief exposures to high concentrations of NO_2 are more injurious than longer-duration exposures to lower concentrations. Dietary taurine (an antioxidant) was not protective against the increase in lung wet weight, and exercise potentiated the severity of the pulmonary edema.

The concentration-dependent response of the lung to NO_2 was confirmed in another study in which Sprague-Dawley rats (n = 5-6) were exposed at 3.6-14.4 ppm for 6-24 h/day for 3 days (Gelzleichter et al. 1992). Increases in protein content and cell types in lavage fluid demonstrated that the magnitude of lung injury was a function of exposure concentration.

Carson et al. (1962) conducted a series of experiments of NO_2 at concentrations approximating 50, 25, and 15% of the rat LC_{50}. At the 50% LC_{50}, rats (strain not specified; n = 30) exposed to 190 ppm for 5 min, 90 ppm for 15 min, or 72 ppm for 60 min showed signs of severe respiratory distress and ocular irritation lasting about 2 days; lung-to-body weight ratios were significantly increased during the first 48 h after exposure. Pathologic examination showed darkened areas of the lungs, pulmonary edema, and an increased incidence of chronic murine pneumonia. Rats exposed at 104 ppm for 5 min, 65 ppm for 15 min, or 28 ppm for 60 min (about 25% of the LC_{50} values) showed some respiratory distress or mild signs of nasal irritation but lung-to-body-weight ratios were increased only at 104 and 65 ppm. No gross lesions were observed, but pulmonary edema was seen microscopically. No adverse clinical signs of toxicity or pathologic changes were seen in rats exposed at 15% of the LC_{50} (74 and 33 ppm for 5 and 15 min, respectively).

Histologic changes were examined in the lungs of male rats (strain and number of animals not specified) exposed to NO_2 at 17 ppm continuously (Stephens et al. 1972). After 2 h, there was some pre- and post-capillary engorgement in the alveoli. Loss of cilia and occasional alveolar type-I cell swelling were detectable by 4 h, the terminal bronchiolar epithelium had become uniform by 16 h, maximal macrophage numbers were reached by 24 h, cellular hypertrophy had begun by 48 h, and mitotic figures became more prevalent in the epithelium of the terminal bronchiole between 16 and 48 h. Type-I alveolar cells appeared to be the most sensitive to NO_2 insult.

Results similar to those described above were obtained in a morphologic study of the Wistar-rat lung (number of animals not specified) after exposure to NO_2 at 20 ppm for 20 h (Hayashi et al. 1987). Cytoplasmic blebbing occurred in a small number of type-I cells immediately after exposure. Swelling and hyperplasia of type-II cells and pinocytotic vesicles of endothelial cells in capillaries followed by interstitial edema in the alveolar walls were observed between days 5 and 15 postexposure. Twenty days after exposure, the lesions lessened and the lungs appeared normal after 35 days. Other studies have confirmed alveolar and interstitial edema, bronchiolitis, bronchiolar epithelial-cell hyperplasia, loss of cilia, necrosis of type-I cells, and type-II cell hyperplasia 1-3 days after exposure at 26 ppm for 24 h (Schnizlein et al. 1980; Hillam et al. 1983) or at 20 ppm for 24 h (Rombout et al. 1986).

Long-Evans rats (number of animals not specified) exposed to NO_2 at 20 ppm for up to 24 h showed minimal signs of irritation and changes in behavior. Microscopic lesions were described as questionable evidence of lung congestion and interstitial inflammation for up to 48 h post-exposure (Hine et al. 1970).

The effects of NO_2 on the lung neonatal and adult Sprague-Dawley rats (number of animals not specified). Animals (1-40 days old) were exposed to NO_2 at 14 ppm for 24, 48, or 72 h continuously. Before weaning (20 days old), exposure resulted in only minor injury and loss of cilia from epithelial cells lining the terminal airways. Subsequent to weaning, there was a progressive

increase in lung injury; maximum response was reached at about 35 days of age (Stephens et al. 1978).

In a similar study to determine the sensitivity of adult and neonate animals to NO_2, Wistar rats (number of animals not specified; 5-60 days of age) were continually exposed at 2 or 10 ppm for 3 days (Azoulay-Dupuis et al. 1983). Exposure of the litters before weaning included the dam. No clinical signs of toxicity or deaths were observed in animals of any age except for body weight loss in dams of the 10 ppm-group. At 2 ppm, lung histopathology was normal in all animals. At 10 ppm, fibrinous deposits were observed in the alveoli and the tracheal and bronchiolar epithelia were occasionally devoid of cilia in animals of ≥45 days of age.

Alterations in lavage fluid have been assessed in male Long Evans rats (n = 6) after exposure to NO_2 at 10, 20, 30, or 40 ppm for 4 h. Cell-free lavage fluid contained elevated lactate dehydrogenase, malate dehydrogenase, isocitrate dehydrogenase, glutathione dehydrogenase, acid phosphatase, and aryl sulfatase activity levels after exposure at ≥30 ppm. Total protein and sialic acid were increased after exposure at ≥20 ppm. Protein and sialic-acid concentrations and acid-phosphatase activity were similar to those in plasma, indicating transudation into the airways (Guth and Mavis 1985). Increases in lactate dehydrogenase, malate dehydrogenase, and glutathione-dehydrogenase activity were significantly attenuated in animals on diets providing 1,000 mg/kg of α-tocopherol, suggesting that lipid peroxidation is involved in NO_2-induced lung injury (Guth and Mavis 1986). Antioxidants in the lung were depleted, lipid-peroxidation products were elevated, and total cell count in bronchoalveolar lavage fluid and alveolar macrophage count were decreased, while epithelial cell count was increased after exposure of male Sprague-Dawley rats (n = 5) at 200 ppm for 15 min (Elsayed et al. 2002). Another study found changes in fatty-acid composition of alveolar lavage phospholipids after Wistar rats (n = 6) were exposed to NO_2 at 20 ppm for 12 h (Kobayashi et al. 1984). Increases in lavageable protein, polymorphonuclear lymphocytes, and alveolar macrophages also were observed aftermale Fischer 344 rats (number not secified) were exposed to NO_2 at 100 ppm for 15 min (Lehnert et al. 1994).

Changes in minute ventilation, V_E, were measured in male Fischer 344 rats (n = 12) after exposure to NO_2 at 100, 300, or 1,000 ppm for 1-20 min (Lehnert et al. 1994). In general, reductions in V_E were greater with the higher concentrations. For example, reductions of about 7 and 15% were measured during 15- and 20-min exposures at 100 ppm, while a reduction of about 20% and 28% were measured during 1- and 2-min exposures to 1,000 ppm. Similarly, male Sprague-Dawley rats (n = 5) exposed at 200 ppm for 15 min showed a decrease in minute ventilation that was from a decline in tidal volume but not in frequency of breathing (Elsayed et al. 2002).

Changes in lung immunity after exposure to NO_2 have been described as increased specific IgE, IgA, and IgG titers after exposure at 87 ppm for 1 h (Siegel et al. 1997) or 5 ppm for 3 h (Gilmour 1995), increased number of IgG anti-sheep red blood cell antibody-forming cells in the lung-associated lymph

nodes (Schnizlein et al. 1980), and cell proliferation in the spleen and thoracic lymph nodes (Hillam et al. 1983) after exposure at 26 ppm for 24 h.

Male Porton rats (n = 4) were exposed to an atmosphere of oxides of nitrogen that was produced by mixing NO_2 and NO (Brown et al. 1983). The ratio of each chemical was not specified or measured in the exposure chambers. Exposures were at 518 ppm for 5 min or to 1,435 ppm for 1 min. No clinical signs of toxicity were observed but "stertorous respirations" appeared within 24 h. Histologically, initial lung damage showed thickening and blebbing of the alveolar epithelium, followed by a latent period of about 6 h, after which development of edema of the interstitium and alveolar septum was observed. The early changes were attributed to a direct oxidant effect. Clinical signs and histologic findings were more severe following exposure at 518 ppm for 5 min.

The effects of NO on discrimination learning and brain activity were studied in rats (Groll-Knapp et al. 1988). Rats were exposed to NO at 10 or 50 ppm for 180 min, and the test atmospheres were maintained during behavioral testing and EEG examination. The high concentration significantly reduced the number of correct trials and the total number of lever presses in the operant conditioning chamber. Both concentrations resulted in increased amplitudes and prolonged peak latencies of the auditory evoked potentials assessed by electroencephalography. Maximum methemoglobin concentrations were 3.98%. The authors suggested that the effects could be, in part, from diminished oxygen-carrying capacity related to methemoglobin formation.

The effects of NO on hyperoxic lung injury in rats were investigated (Garat et al. 1997). Animals were exposed to NO at 10 or 100 ppm while breathing 21% or 100% oxygen for 40 h. No toxic effects on any lung parameter were observed at either concentration under normoxic conditions. Under hyperoxic conditions, NO at 10 ppm prevented increases in thiobarbituric acid reactive substances and wet-to-dry lung weight ratios, had no effect on the alveolar barrier impermeability to protein, and improved alveolar liquid clearance. These effects did not occur at 100 ppm with hyperoxia, and the lack of protection might have been from the formation of NO_2 in the exposure chambers.

3.2.10. Mice

Swiss-Webster mice (number not specified) exposed to NO_2 at 20 ppm for up to 24 h showed minimal signs of irritation and changes in behavior. Histologically, there was questionable evidence of lung congestion and interstitial inflammation for up to 48 h post-exposure (Hine et al. 1970). The voluntary running activity of mice on an activity-wheel was 80% and 17% of pre-exposure levels at 7.7 and 20.9 ppm, respectively, during 6-h exposures (Murphy et al. 1964).

Female CD-1 mice (n = 29-60) were examined for phenobarbital-induced sleeping time after a 3-h, whole-body exposure to NO_2 at 0.125-5.0 ppm (Miller

et al. 1980). Sleeping time was significantly increased in animals exposed at ≥0.25 ppm compared with air-exposed controls. The authors stated that no effects in males were observed until after 3 days of exposure (data not included). In contrast, the effect in females decreased after the third day of exposure suggesting some tolerance might have developed.

The alveolar septum from two female NMRI mice was examined microscopically 36 h after exposure to NO_2 at 35 ppm for 6 h (Dillmann et al. 1967). Morphometric measurements found that the arithmetic mean thickness of the alveoli was approximately 1.5 times that of unexposed controls. No changes in the numbers or types of cells present were observed and no interstitial edema was found with ultrastructure examination by electron microscopy.

Male CD-1 mice (n = 5-9) were exposed to NO_2 at 50-140 ppm for 1 h and biochemical and histologic responses were assessed immediately and 48 h after exposure (Siegel et al. 1989). Immediately after exposure at 140 ppm, cell death was visible in the terminal bronchioles and there were significant increases in protease-inhibitor activity, pulmonary protein, and lung wet weight. Two days after exposure at 140 ppm, the histologic damage was exacerbated with complete obliteration of the alveolar structure, progressive edema and congestion of the lungs, hypertrophy and hyperplasia of the epithelial cells, and increased numbers of intra-alveolar macrophages and neutrophils. In addition, there were dose-related increases in β-glucuronidase, lactate-dehydrogenase, and choline-kinase activity, as well as increased protease-inhibitor activity, pulmonary protein, and lung wet weight.

To examine the effects of NO_2 on gaseous exchange in the lung, JCL:ICR mice (n = 6) were exposed at 5, 10, or 20 ppm for 24 h (Suzuki et al. 1982). Significantly increased lung wet weight and lung water content occurred at 10 and 20 ppm. The gaseous exchange and metabolic rate of oxygen and carbon dioxide were accelerated in animals exposed at 5 ppm, while gaseous exchange in the lung was inhibited in animals exposed at 10 and 20 ppm.

Continuous exposure of C56Bl/6 mice (n = 60) to NO_2 at 20 ppm for 4 days resulted in significantly decreased food consumption and body weight, but no deaths (Bouley et al. 1986).

3.3. Developmental and Reproductive Toxicity

The postnatal effects of prenatal exposure to NO_2 were investigated (Tabacova et al. 1985). Pregnant Wistar rats (n = 20) were exposed to NO_2 at 0.265, 0.053, 0.53, or 5.3 ppm for 6 h/day throughout pregnancy. Maternal effects were not reported or discussed. Pup viability and body weight of the 5.3-ppm group were significantly less ($p \leq 0.05$) than those of controls on lactation day 21. Exposure at ≥0.53 ppm resulted in developmental delays and exposure at ≥0.053 ppm caused disturbances in neuromotor development. Also at the two highest concentrations, hexobarbital sleeping time was increased in the offspring and correlated with altered biochemical parameters in the liver.

No information was found regarding the developmental or reproductive toxicity of exogenously administered NO in animals. Growth retardation and hind-limb reduction were found in the offspring of rats given N^G-nitro-L-arginine methyl ester, a NO-synthase inhibitor, at 0.3 and 1.0 mg/mL in drinking water on gestation days 13-19 (Shepard 1995).

3.4. Genotoxicity

Three-week-old male Sprague-Dawley rats were exposed by inhalation to NO_2 at 8, 15, 21, or 27 ppm for 3 h or to NO at 9, 19, or 27 ppm for 3 h. Animals were maintained overnight before sacrifice, and lung cells were isolated. At NO_2 concentrations of ≥15 ppm and NO concentrations of 27 ppm, mutations to ouabain resistance in lung cells was increased. Concentration-dependent increases in chromosome aberrations were observed with NO_2 at 8 and 27 ppm, the only concentrations analyzed for aberrations. Chromosome aberrations were not observed following exposure to NO (Isomura et al. 1984).

A dose-related increase in the number of revertants of *Salmonella typhimurium* (TA1535) occurred when culture dishes were exposed to atmospheres containing NO at 0-20 ppm for 30 min. Oxygen was required and mutation was inhibited by antioxidants. Cytotoxicity was seen with NO at 50 ppm (Arroyo et al. 1992).

3.5. Carcinogenicity

The effect of NO_2 on promotion of lung tumorigenesis induced by *N*-bis(2-hydroxypropyl)-nitrosamine (BHPN) was investigated in male Wistar rats (Ichinose et al. 1991). Animals were given a single intraperitoneal injection of BHPN at 0.5 g/kg body weight at 6 weeks of age and exposed to NO_2 at 0.04, 0.4, or 4.0 ppm for 17 months. The incidence of pulmonary tumors in rats exposed to BHPN and NO_2 at 4 ppm was 12.5% (n.s.), with adenomas found in 4/40 rats (10%) and adenocarcinomas found in 1/40 rats (2.5%). One adenoma was found in the control group (2.5%) and one in the 0.04-ppm group, but none in the 0.4-ppm group. In addition, marked bronchiolar mucosal hyperplasia was found in 17/40 rats (42.5%, $p \leq 0.001$) in the group exposed to BHPN and NO_2 at 4.0 ppm.

No information was found regarding the carcinogenicity of NO or N_2O_4 in animals.

3.6. Summary

Five- to 60-min LC_{50} values for NO_2 in the rat ranged from 416 to 115 ppm, respectively, in one study (Carson et al. 1962) and from 833 to 168 ppm in another study (Gray et al. 1954). The 15-min LC_{50} for rabbits was 315 ppm (Carson et al. 1962). In a study using varying concentration and duration of exposure, the first mortalities were observed in dogs exposed at 75 ppm for 4 h,

in rabbits at 75 ppm for 1 h, in guinea pigs at 50 ppm for 1 h, and in rats and mice at 50 ppm for 24 h (Hine et al. 1970). Histologic alterations of the lungs following death included bronchiolitis, desquamated bronchial epithelium, infiltration by polymorphonuclear cells, and edema. Enhanced susceptibility to infection was shown in monkeys after exposure to NO_2 at 50 ppm for 2 h (Henry et al. 1969) and in mice exposed at 2 or 3.5 ppm for 3 h (Ehrlich 1978).

Pulmonary edema and histologic alterations induced by exposure to NO_2 have been characterized in dogs, sheep, guinea pigs, hamsters, rats, and mice. Numerous studies in rats have confirmed alveolar and interstitial edema, bronchiolitis, bronchiolar epithelial-cell hyperplasia, loss of cilia, necrosis of type-I cells, and type-II cell hyperplasia 1-3 day after exposure to NO_2 at 26 ppm for 24 h (Schnizlein et al. 1980; Hillam et al. 1983) or at 20 ppm for 20 h (Hayashi et al. 1987) or 24 h (Rombout et al. 1986).

Neonates appeared less sensitive to NO_2 than adult animals; progressive increases in lung injury and deaths were seen in older rats and guinea pigs (Stephens et al. 1978; Azoulay-Dupuis et al. 1983).

Only one study was found in which rats were exposed to N_2O_4, and pulmonary lesions were similar to those described after NO_2 exposure. No studies of exposure to N_2O_3 were found.

For NO, most of the experimental animal studies focused on the therapeutic use of NO in animal models of human disease. Lethality studies in dogs, rats, and mice lacked complete concentration-response information, some of the studies were confounded by possible NO_2 contamination, or the study was a secondary citation in which the original source could not be obtained. From these studies, however, it appears that in the absence of lung injury, the mechanism of toxicity of NO is methemoglobin formation.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Total respiratory-tract absorption by humans exposed to NO_2 at 0.29-7.2 ppm for ≤30 min during quiet respiration and during exercise was 81-90% and 91-92%, respectively, in healthy adults, and 72% and 87%, respectively, in asthmatic subjects (EPA 1993). In monkeys exposed to NO_2 at 0.30-0.91 ppm for <10 min, 50-60% of the inspired gas was retained during quiet respiration and was distributed throughout the lungs (Goldstein et al. 1977). While the isolated rat lung, ventilated with NO_2 at 5 ppm for 90 min, retained 36% of the NO_2 (Postlethwait and Mustafa 1981), the majority of labeled NO_2 (exposure parameters not specified) was retained by the upper-respiratory tract of the rat (Russell et al. 1991).

Pulmonary absorption of NO_2 has been studied using in-vivo and in-vitro models. Uptake appears to be governed by the reaction between inhaled NO_2 and constituents of the pulmonary surface lining layer, which forms nitrite (Postlethwait and Bidani 1990, 1994). NO_2 uptake is saturable, with absorption

proportional to inspired dose (Saul and Archer 1983; Postlethwait and Bidani 1994) and increased as temperature increases to a maximum of NO_2 at 10.6 μg/min in an isolated lung model (Postlethwait and Bidani 1990). The predominant reaction in the lungs involves hydrogen abstraction by readily oxidizable tissue components, such as proteins and lipids, to form nitrous acid and the nitrite radical (Postlethwait and Bidani 1994), and reaction with water to form nitrous and nitric acids (Goldstein et al. 1977).

Distribution of inhaled NO_2 or its metabolites is via the blood stream (Goldstein et al. 1977). Nitrite formed in the lungs is oxidized to nitrate by interactions with red blood cells after diffusion into the vascular space (Postlethwait and Mustafa 1981). Mice exposed to NO_2 at 40 ppm had slight (0.2%) nitrosylhemoglobin but no methemoglobin (Oda et al. 1980), and an increase in both nitrite and nitrate that reached equilibrium in 10 and 30 min, respectively (Oda et al. 1981). After cessation of exposure, the half-life of nitrite was several minutes and that of nitrate about 1 h (Oda et al. 1981). Urinary excretion of nitrate has been shown to be have a linear relationship to the inhaled concentration of NO_2 (Saul and Archer 1983).

Approximately 85-92% of NO is absorbed into the body by humans breathing normally when exposed to NO at 0.33-5.0 ppm (0.4-6.1 mg/m^3) (Yoshida and Kasama 1987). In contrast, about 35% of the total amount of NO delivered is taken up by the lungs in patients with acute lung injury given NO at 5-40 ppm as ongoing therapy (Westfelt et al. 1997). Once absorbed, inhaled NO reacts with hemoglobin to form nitrosylhemoglobin from which nitrite and nitrate are generated. Most of the nitrates are excreted in the urine with a small portion secreted into the oral cavity through the salivary glands and transformed to nitrite. Nitrate in the intestine is reduced to ammonia through nitrite, reabsorbed into the body, and converted to urea (Yoshida and Kasama 1987). Pigs given sequentially exposed to NO at 10-80 ppm for 10-min periods, followed by 40 ppm for 30 min, showed a concentration-related increase in plasma nitrites and nitrates with a combined concentration of 67 μmol/L at the end of exposure compared with a baseline of 30 μmol/L (Shah et al. 1994). A high ^{15}N content was found in serum and urine of rats after inhalation of ^{15}NO at 138-880 ppm, and within 24 h, about 40% of the inhaled ^{15}N was excreted into the urine. Small amounts of ^{15}N were found in lung, trachea, liver, kidney, and muscle (Yoshida et al. 1980).

Nitrate (10.4 μmol/L) has been detected in the bronchoalveolar lavage fluid of healthy children from the metabolism of endogenous NO in the lower respiratory tract (Grasemann et al. 1997).

4.2. Mechanism of Toxicity

4.2.1. Nitrogen Dioxide

NO_2 is an irritant to the mucous membranes and might cause coughing and dyspnea during exposure. After less severe exposure, symptoms might persist

for several hours before subsiding (NIOSH 1976). With more severe exposure, pulmonary edema ensues with signs of chest pain, cough, dyspnea, cyanosis, and moist rales heard on auscultation (NIOSH 1976; Douglas et al. 1989). Death from NO_2 inhalation is caused by bronchospasm and pulmonary edema in association with hypoxemia and respiratory acidosis, metabolic acidosis, shift of the oxyhemoglobin dissociation curve to the left, and arterial hypotension (Douglas et al. 1989). A characteristic of NO_2 intoxication after the acute phase is a period of apparent recovery followed by late-onset bronchiolar injury that manifests as bronchiolitis fibrosa obliterans (NIOSH 1976; NRC 1977; Hamilton 1983; Douglas et al. 1989).

Toxicity from acute exposure can be described in one of three categories: (1) immediate death after very heavy exposure, (2) delayed symptoms with development of edema within 48 h, and (3) apparent recovery from immediate effects but later chronic chest disease of varying severity (NRC 1977; Hamilton 1983). Morphologic and biochemical changes in the lungs during these phases were studied in mice exposed at 140 ppm for 1 h (Siegel et al. 1989). Immediately after exposure, cell death was noted in areas adjacent to the distal terminal bronchioles, and protease inhibitor activity, lung protein content, and lung wet weight were significantly elevated. Two days after exposure, the histologic damage was exacerbated with complete obliteration of the alveolar structure, progressive edema and congestion of the lungs, hypertrophy and hyperplasia of the epithelial cells, and increased numbers of intra-alveolar macrophages and neutrophils. In addition, there were dose-related increases in β-glucuronidase, lactate-dehydrogenase, and choline-kinase activity as well as increased protease-inhibitor activity, pulmonary protein, and lung wet weight. Pulmonary injury is characterized by loss of ciliated cells, disruption of tight capillary junctions, degeneration of type-I cells, and proliferation of type-II cells (Siegel et al. 1989; Elsayed 1994).

The predominant reaction in the lungs involves hydrogen abstraction by readily oxidizable tissue components, such as proteins and lipids, to form nitrous acid and the nitrite radical (Postlethwait and Bidani 1994; EPA 1995) and reaction with water to form nitrous and nitric acids (Greenbaum et al. 1967; Goldstein et al. 1977). This reaction can lead to one mechanism by which NO_2 causes pulmonary injury, lipid peroxidation. NO_2 is a free radical that can attack unsaturated fatty acids in the cell membrane forming carbon and oxygen centered radicals in a chain reaction (Ainslie 1993; Elsayed 1994; EPA 1995). This hypothesis is supported by studies on the effects of antioxidants on NO_2 exposure in humans and animals. Four-week supplementation with vitamins C and E before exposure at 4 ppm for 3 h resulted in a marked decrease in the amount of conjugated dienes and attenuated the decrease in elastase activity inhibitory capacity in the alveolar lining fluid of healthy volunteers (Mohsenin 1991). Guinea pigs maintained on an ascorbic-acid-deficient diet had increased lung lavage fluid protein following exposure to NO_2 at 4.8 ppm for 3 h and increased wet lung weight, increased nonprotein sulfhydryl and ascorbic acid content of the lungs, and decreased α-tocopherol content of the lungs following

exposure at 4.5 ppm for 16 h. These changes were not seen in animals maintained on normal guinea pig diets (Hatch et al. 1986). Rats exposed at 30 and 40 ppm for 4 h had elevations of lactate-dehydrogenase, MDH, and glutathione-dehydrogenase activity in lavage fluid, which were significantly attenuated in animals maintained on diets with α-tocopherol at 1,000 mg/kg (Guth and Mavis 1986). Another study found changes in fatty-acid composition of alveolar lavage phospholipids in rats exposed to NO_2 at 10 ppm for 12 h (Kobayashi et al. 1984).

4.2.2. Nitric Oxide

From the available studies, it appears that the major mechanism of toxic action of NO is the binding of hemoglobin (EPA 1993). Inhaled NO is absorbed into the bloodstream and binds to hemoglobin forming nitrosylhemoglobin, which is rapidly oxidized to methemoglobin (Sharrock et al. 1984; Maeda et al. 1987; EPA 1993). The affinity of NO for hemoglobin is about 1,500 times greater than that of carbon monoxide (Gibson and Roughton 1957) and the binding and formation of methemoglobin is dependent on NO concentration and time (Sharrock et al. 1984; Maeda et al. 1987; Ripple et al. 1989). Experiments with rats (Maeda et al. 1987) and rabbits (Sharrock et al. 1984) show that binding of NO to hemoglobin is rapidly reversible, with a half-life of 15-20 min when animals are placed in clean air.

The signs and symptoms of methemoglobinemia in humans are summarized in Table 4-8. Clinical signs do not appear until methemoglobin concentrations are 15-20% and toxicity is not evident until about 30%.

TABLE 4-8 Signs and Symptoms Associated with Methemoglobin Concentrations

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

Sources: Kiese 1974; Seger 1992.

In most of the human and animal experimental studies and the human case reports described earlier in this chapter, methemoglobin concentrations were <5% even after exposure to NO at as much as 50 ppm for 41 h (human infant) or at 80 ppm for 23 h (lamb). Methemoglobin concentrations rose to 9.4% in one lung transplantation patient after treatment with NO at 80 ppm for 8 h. A reduction in concentration to 40 ppm over 4 h resulted in a decrease to 6.6%, and a further reduction to 20 ppm for the 12 h reduced methemoglobin concentrations to 0.9% (Adatia et al. 1994). In one patient with pulmonary hypertension, methemoglobin concentration rose to 9.6% after 108 h of treatment with NO at 80 ppm; in another patient, the concentration was 14% after 18 h (Wessel et al. 1994). An American Indian patient with pulmonary hypertension treated with NO at 80 ppm for 6 h developed methemoglobin concentrations of 9.4%, which decreased rapidly with a reduction in NO to 40 ppm (Wessel et al. 1994). Methemoglobinemia >7% occurred in 13/37 newborns treated for persistent pulmonary hypertension with NO at 80 ppm. The average time to peak concentration in all patients was 19.6 h and the highest concentration was 11.9% at 8 h in one patient (Davidson et al. 1998).

Despite the relatively low concentrations of methemoglobin measured in most studies, clinically significant concentrations have been reported. A newborn (Japanese) developed a methemoglobin concentration of 40% after 26 h of exposure at 80 ppm; the concentration was reduced to 3.9% within 20 min of infusion with methylene blue and reduction in the NO concentration (Nakajima et al. 1997). Sheep administered NO at 512 ppm for 20 min (Dyar et al. 1993) and pigs exposed at 1,000 ppm for 15 min (Nelin et al. 1994) developed methemoglobin concentrations of 11% and 20%, respectively. Cyanosis appeared in dogs within 3-8 min of exposure to NO at 0.5 or 2% (5,000 or 20,000 ppm) and methemoglobin concentrations were 5-25%. However, concentrations reached 100% in one dog that died after exposure at 2% (20,000 ppm) for 50 min (Greenbaum et al. 1967). A single 6-h exposure of dogs to NO at 80, 160, 320, or 640 ppm resulted in methemoglobin concentrations of 3, 6.6, 24, and 78%, respectively (Wilhelm et al. 1998). Rats exposed to NO at 1,000 ppm for 30 min appeared cyanotic and 11/20 died from methemoglobin formation but concentrations were not measured (Stavert and Lehnert 1990).

The main toxicologic effect of inhaled NO is the induction of methemoglobin, whereas that of NO_2 is pulmonary edema. Methemoglobin concentrations did not increase in rats exposed to NO_2 at 40 ppm despite a slight elevation (0.2%) in nitrosylhemoglobin concentrations (Oda et al. 1980). Rats exposed to NO at 1,000 ppm for 30 min appeared cyanotic and 11/20 died from methemoglobin formation, but no changes in lung weight or histopathology were observed. In the same study, increased lung weight occurred following exposure to NO_2 at 50 ppm for 30 min and histopathologic changes were observed after exposure at 25 ppm for 30 min (Stavert and Lehnert 1990). Other studies have failed to show any effect of NO on the respiratory tract of humans (Kagawa 1982; Pepke-Zaba et al. 1991; Högman et al. 1993a; Manktelow et al. 1997), mice (Pflesser 1935), pigs (Nelin et al. 1994), or lambs (Frostell et al.

1991). An NO concentration of 10 ppm, but not 100 ppm, offered protection against hyperoxic lung injury in rats, and it is probable that the higher concentration of NO resulted in significant NO_2 formation (Garat et al. 1997). NIOSH (1976) summarized the effects of NO_2 in humans as initial irritation with mild dyspnea during exposure, followed by delayed onset of pulmonary edema after several hours of apparent recovery. A similar toxic response, including interstitial fibrosis, has been shown in five species of animals following acute inhalation exposure to NO_2 (Hine et al. 1970) and in rats exposed to mixed oxides of nitrogen (Brown et al. 1983). These results indicate that NO_2 has a direct toxic action on the respiratory tract, but that NO does not.

The relative toxicities of NO and NO_2 are complex. NIOSH (1976) summarized experiments by Paribok and Grokholskaya (1962) in mice and guinea pigs. At concentrations >833 ppm for 1 h, NO was more toxic than NO_2; however, at lower concentrations, NO_2 was more toxic. It appears that for NO, if the concentration is not high enough to be lethal from methemoglobin formation, the animal recovers completely. On the other hand, concentrations of NO_2 that are not rapidly lethal may cause more persistent effects and in some cases cause death from pulmonary edema after a delay of several days (NIOSH 1976).

4.3. Chemical Transformation of Nitrogen Oxides

Figure 4-1 summarizes the reactions of the oxides of nitrogen. This family of reaction pathways is temperature dependent, but in general favors NO_2 production. The National Advisory Committee was unable to provide any significant guidance, other than to indicate that a significant fraction of the N_2O_4 and NO will be converted to NO_2. Because NO_2 is the most ubiquitous and the most toxic of the oxides of nitrogen, AEGL values derived from NO_2 toxicity data were considered applicable to all oxides of nitrogen.

$$2NO + O_2 \rightarrow 2NO_2$$

$$NO + O_3 \rightarrow NO_2 + O_2$$

$$NO + HO_2\cdot \rightarrow NO_2 + HO\cdot$$

$$NO + RO_2 \rightarrow NO_2 + RO\cdot$$

$$NO_2 + HO\cdot \rightarrow HNO_3$$

$$N_2O_4 \rightarrow 2NO_2$$

FIGURE 4-1 Environmental reactions of the oxides of nitrogen.

NO_2 exists as an equilibrium mixture of NO_2 and N_2O_4 but the dimer is not important at ambient concentrations (EPA 1993). The two compounds are phase-related forms with N_2O_4 favored in the liquid phase and NO_2 favored in the gaseous phase. An equilibrium distribution is reached, which favors the lowest energy state in the phase. As a result, when N_2O_4 is released, it vaporizes and dissociates into NO_2, making it nearly impossible to generate a significant concentration of N_2O_4 at atmospheric pressure and ambient temperature without generating a vastly higher concentration of NO_2. Because of this effect, almost no inhalation toxicity data are available on N_2O_4, and a rate for the reaction was not found. No information was found on the interactions of N_2O_3.

NO is unstable in air and undergoes spontaneous oxidation to NO_2 making experimental effects difficult to separate and studies difficult to perform (EPA 1993). Studies on the conversion of NO to NO_2 in medicinal applications have found the conversion to be significant in an atmospheric concentration of oxygen (20.9%) at room temperature. The delivery of NO 100 ppm in 21% oxygen through a pediatric tube (d = 0.009 m, l = 0.9 m) at a flow rate of 2 L/min is calculated to produce NO_2 at 1.13 ppm (Lindberg and Rydgren 1998). For NO at 80 ppm, a concentration commonly used therapeutically, about 5 ppm of NO_2 is calculated to form after 3 min in air (Foubert et al. 1992). NO reacts with oxygen in air to form NO_2, which then reacts with water to form nitric acid (NIOSH 1976). For this reason, careful monitoring of NO_2 concentrations has been suggested when NO is used therapeutically at concentrations $\geq$80 ppm, especially when coadministered with oxygen (Foubert et al. 1992; Miller et al. 1994).

While closed-system experiments clearly indicate the potential for the production of NO_2, the chemical kinetics of NO conversion during a large-scale atmospheric release and dispersion are not well documented. The estimation of the concentration isopleths following an accidental release would require the use of a finite element model along with several assumptions as to the chemical-rate constants. As a result, the conversion of NO to NO_2 during the atmospheric release is of concern to emergency planners. In photochemical smog, NO_2 absorbs sunlight of wavelengths between 290 and 430 nm and decomposes to NO and O (EPA 1993).

4.4. Other Relevant Information

4.4.1. Species Variability

Several studies indicate that there is a size-dependent species sensitivity to NO_2; larger animals are apparently less sensitive than smaller animals. Dogs showed only mild signs of irritation at concentrations that caused pulmonary edema in rats (Carson et al. 1962). Dogs also survived exposures to NO_2 at 1,000 ppm for 136 min and at 5,000 ppm for up to 22 min (Greenbaum et al. 1967) and sheep survived exposure at 500 ppm for 15-20 min (Januszkiewicz and Mayorga 1994). In contrast, 15-min and 1-h LC_{50} values in the rat were 201-

420 and 115-168 ppm, respectively (Gray et al. 1954; Carson et al. 1962). On the basis of the available data, humans are not more sensitive than larger laboratory animals. For example, irritation was reported for humans exposed to NO_2 at 30 ppm for 2 h (Henschler et al. 1960), dogs exposed at 20 ppm for 24 h (Hine et al. 1970), and monkeys exposed at 35 ppm for 2 h (Henry et al. 1969).

Elsayed et al. (2002) examined species variability to NO_2 through dosimetry; the calculated total inspired dose from experimental measurements in rats and sheep was compared with the theoretical dose of an average human. Whether normalized for body weight, lung volume, or alveolar surface area, the total effective dose was greater in rats then sheep then humans. Taking physiologic and anatomical factors into consideration, rats had a much higher effective dose than the larger animals. The authors concluded that NO_2 toxicity is associated with inhaled-dose distribution per unit lung volume or lung surface rather than per unit body mass (Elsayed et al. 2002).

No information was available to allow comparison of NO toxicity between species. Concentrations used in animal models of human diseases are similar to those used therapeutically in humans with no adverse effects. Because the major toxic action of NO is binding to hemoglobin resulting in methemoglobinemia, little interspecies variation is expected.

4.4.2. Susceptible Populations

For chronic, low-level exposures to NO_2, EPA (1995) has identified two populations as potentially at risk from NO_2 exposure: children (5-12 years old) and persons with pre-existing respiratory disease. Conclusions drawn from epidemiology studies were that 5-12 year-old children had an increased risk of about 20% for developing respiratory symptoms and disease with each increase of 0.015 ppm in estimated 2-week average NO_2 exposure (mean weekly concentrations in bedrooms was 0.008-0.065 ppm) and that no evidence for increased risk was found for infants <2 years old. These conclusions are supported somewhat by animal data in which adult animals were more sensitive than neonates to the effects of NO_2 (Stephens et al. 1978; Azoulay-Dupuis et al. 1983). Reduced ventilatory reserves may prevent individuals with respiratory disease from resuming normal activity following exposure to NO_2 (EPA 1995). However, it is not certain whether these populations also are at particular risk from acute exposure scenarios.

Taken together, the data summarized in Section 2.2.3.1 indicate that some asthmatic subjects exposed to NO_2 at 0.3-0.5 ppm may respond with either subjective symptoms or slight changes in pulmonary function of no clinical significance. At approximately these same concentrations of NO_2, subsequent exposure of asthmatic subjects to an agent that causes nonspecific airway responsiveness resulted in slight hyper-reactivity, but the response is not more severe than to NO_2 alone (e.g., while some asthmatic subjectss respond to

bronchial challenge and to NO_2, the response to the challenge is not additively increased from prior exposure to NO_2). In contrast, some asthmatic subjects did not respond to NO_2 with changes in pulmonary function or symptoms at concentrations of 0.5-4 ppm. The responses of healthy individuals to NO_2 also are variable, with some, but not all, having slight changes in pulmonary function at 5 ppm. All reported responses in both asthmatic and healthy subjects at the concentrations discussed were slight and of questionable biologic or clinical significance.

Conclusions regarding differences in susceptibility between healthy and asthmatic individuals are difficult to draw from the available data because of the high variability in responses among both groups. There is only one study that has measured the responses of both healthy and asthmatic individuals with the same study protocol (Linn and Hackney 1983). Dose-response patterns were not discernible at low concentrations and clear thresholds were not apparent. Some individuals reported clinical symptoms in the absence of changes in pulmonary function, while other individuals had measurable changes in pulmonary function tests but no symptoms. One proposed explanation for the variability in the responses of asthmatic subjects to inhaled NO_2 is the existence of a subgroup of "responders." From one laboratory, several asthmatic subjects were identified as equally responsive to NO_2 at 0.3 ppm in more than one study (Bauer et al. 1985, 1986). However, the investigators could find no common identifiers for these "responders," such as degree of baseline obstruction or their inherent airway reactivity to carbachol or cold air (Utell 1989). Although some individuals had a measurable response at lower concentrations, the magnitude of the reported changes was not biologically or clinically significant in either asthmatic subjects or healthy individuals.

No information was available to allow comparison of NO toxicity between individuals. Because the major toxic action of NO is binding to hemoglobin resulting in methemoglobinemia, little intraspecies variation is expected. In addition, NO is administered for extended periods of time to critically ill patients with only slight increases in methemoglobin concentrations.

4.4.3. Concentration-Response Relationship

As discussed below for AEGL-2 and -3 levels, extrapolations were made to each of the time points using the equation $C^n \times t = k$, where $n = 3.5$ (ten Berge et al. 1986). The value of n was calculated by ten Berge et al. (1986) on basis of data from Hine et al. (1970). The large value of n indicates that concentration is more important than duration for the effects of exposure to NO_2. Support for this supposition also comes from Gardner et al. (1979), who showed that short-term exposure to high concentrations resulted in greater effects (as measured by mortality in a infectivity model using mice) than exposure to lower concentrations administered over a longer duration.

4.4.4. Susceptibility to Infection

To determine the effects of NO_2 on resistance to infection, squirrel monkeys were challenged with *Klebsiella pneumoniae* within 24 h after exposure. No deaths occurred from exposure to NO_2 alone; however, 3/3 monkeys died within 72 h after exposure to NO_2 at 50 ppm 2 h, followed by challenge with *K. pneumoniae*; massive infection was present in the lungs and other organs. No death occurred in monkeys exposed at 10 ppm for 2 h and challenged with *K. pneumoniae* 3-5 days later, but bacteria were still present in lung tissue at necropsy up to 46 days after challenge indicating reduced clearance (Henry et al. 1969).

Numerous studies have reported enhanced susceptibility of mice to infectious agents following exposure to NO_2. Most of these studies have been reviewed by EPA (1993) and only a few are described here. Gardner et al. (1977) demonstrated that the concentration-time relationship was linear for 20% mortality using an infectivity model in mice challenged with *Streptococcus pyogenes*; NO_2 exposures ranged from 0.5 to 28 ppm for 6 min to 12 months. Similarly, mortality was increased in mice challenged with *S. pyogenes* in response to short-term exposure to a high concentration of NO_2 compared with a lower concentration administered over a longer duration when the concentration × time product was held constant. A single 3-h exposure to NO_2 at 2.0 or 3.5 ppm enhanced the susceptibility of three strains of mice to streptococcal pneumonia and influenza infection, as seen by excess mortality and reduced survival time (Ehrlich 1978). Mice exercised in a motorized wheel during exposure to NO_2 at 3 ppm for 3 h and challenged with *S. pyogenes* had significantly increased mortality compared with nonexercised animals (Illing et al. 1980). Pulmonary bacterial defenses against *Staphylococcus aureus* were suppressed following exposure of Swiss mice to concentrations of NO_2 at ≥4 ppm for 4 h (Jakab 1987). Significantly decreased pulmonary bactericidal activity was shown in Swiss mice infected with *S. aureus* then exposed to NO_2 at 7, 9.2, or 14.8 ppm for 4 h, or exposed at 2.3 or 6.6 ppm for 17 h prior to infection. Histologically the lungs of mice exposed at ≥9.2 ppm for 4 h showed vascular hyperemia, while those from mice exposed at ≥2.3 ppm for 17 h had minor vascular hyperemia and interstitial edema (Goldstein et al. 1973). Enhanced susceptibility to infection was observed in CD-1 mice exposed to NO_2 at 5 ppm for 6 h/day on two consecutive days prior to inoculation with murine cytomegalovirus, followed by exposure at 5 ppm for 6 h/day for 4 consecutive days; there was no histologic evidence of lung injury (Rose et al. 1989). Continuous exposure of mice to NO_2 at 20 ppm for 4 days resulted in impairment of acquired resistance (decreased ED_{50}) in C57Bl/6 mice immunized prior to challenge with *K. pneumoniae* (Bouley et al. 1986).

Alterations in host-defense mechanisms have been demonstrated in rabbits. Male and female New Zealand rabbits exposed for 3 h to varying concentrations of NO_2 had an increase in polymorphonuclear neutrophils obtained by pulmonary lavage at ≥8 ppm, with the peak infiltration 6-9 h after

the end of exposure (Gardner et al. 1969). In other experiments, these authors demonstrated that the response persisted up to 72 h post-exposure and that phagocytic activity was inhibited.

Mice also have been used extensively as a model for immune function alterations following NO_2 exposure. Decreases in splenic and thymic weights, cellularity, plaque-forming cell responses, and hemagglutinins, along with decreased body weight, were observed in C56Bl/6 mice exposed to NO_2 at 20 ppm for 48 h (Azoulay-Dupuis et al. 1985). Significant suppression of primary antibody responses (hemagglutinins and plaque-forming cells) also were seen in BALB/c mice following exposure at 20 or 40 ppm for 12 h (Hidekazu and Fujio 1981). Phytohemagglutinin and bacterial-lipopolysaccharide responses were depressed in mice exposed continuously to NO_2 at 0.5 or 0.1 ppm, with daily 3-h peaks (5 days/week) of 0.25, 0.5, or 1.0 ppm (Maigetter et al. 1978). Other effects of NO_2 on cellular and humoral immunity have been reviewed by EPA (1993), but are not relevant to derivation of AEGL values.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

The evidence indicates that some asthmatic subjects exposed to NO_2 at 0.3-0.5 ppm might respond with either subjective symptoms or slight changes in pulmonary function of no clinical significance. Some asthmatic subjects exposed at approximately same concentrations might show slight hyper-reactivity to a bronchial challenge, but the response is no more severe than the response to NO_2 alone (e.g., while some asthmatic subjects respond to a bronchial challenge and to NO_2, the response to the challenge is not additively increased from prior exposure to NO_2). In contrast, some asthmatic subjects did not respond to NO_2 at concentrations of 0.5-4 ppm. The responses of healthy individuals to NO_2 exposures also are variable, with some, but not all, responding at 5 ppm.

Kerr et al. (1978, 1979) reported that 7/13 asthmatic subjects experienced slight burning of the eyes, slight headache, chest tightness, and labored breathing with exercise when exposed to NO_2 at 0.5 ppm for 2 h; at that concentration, the odor of NO_2 was perceptible but the subjects lost awareness of it after about 15 min. No changes in any pulmonary function tests were found immediately following the chamber exposure (Kerr et al. 1978, 1979). Significant group-mean reductions in FEV_1 (-17.3 vs. -10.0%) and specific airway conductance (-13.5 vs. -8.5%) occurred in asthmatic subjects after exercise when exposed at 0.3 ppm for 4 h, and 1/6 individuals experienced chest tightness and wheezing (Bauer et al. 1985). The onset of effects was delayed when exposures were by oral-nasal inhalation compared with oral inhalation. This delay may result from scrubbing within the upper airway. In a similar study, asthmatic subjects exposed at 0.3 ppm for 30 min at rest, followed by 10 min of exercise, had significantly greater reductions in FEV_1 (10% vs. 4% with air) and partial expiratory flow rates at 60% of total lung capacity, but no

symptoms were reported (Bauer et al. 1986). In a preliminary study with 13 asthmatic subject exposed at 0.3 ppm for 110 min, slight cough, dry mouth and throat, and significantly greater reduction (11% vs. 7%) in FEV_1 occurred after exercise; however, in a larger study, no changes in pulmonary function were measured and no symptoms were reported when 21 asthmatic subjects were exposed at concentrations up to 0.6 ppm for 75 min (Roger et al. 1990). The mean drop in FEV_1 for asthmatic subjects during a 3-h exposure to NO_2 at 1 ppm (2.5%) with intermittent exercise was significantly greater than the drop during air (1.3%) exposure with intermittent exercise; in bronchoalveolar lavage fluid, concentrations of 6-keto-prostaglandin$_{1\alpha}$ were decreased and thromboxane B_2 and prostaglandin D_2 were increased after NO_2 exposure (Jörres et al. 1995).

5.2. Summary of Animal Data Relevant to AEGL-1

Animal data relevant to derivation of AEGL-1 are limited. Slight irritation was noted in squirrel monkeys exposed to NO_2 at 10 and 15 ppm for 2 h (Henry et al. 1969) and mild sensory effects occurred in dogs exposed at 125 ppm for 5 min, 52 ppm for 15 min, or 39 ppm for 60 min (Carson et al. 1962).

5.3. Derivation of AEGL-1

AEGL values were based on studies of NO_2, the predominant form of the nitrogen oxides, and the values are considered applicable to all nitrogen oxides. Values for N_2O_4 in units of ppm have been calculated on a molar basis. Because conversion to NO_2 is expected to occur in the atmosphere and because NO_2 is more toxic than NO, the AEGL values for NO_2 are recommended in emergency planning for NO. However, short-term exposures below an NO concentration of 80 ppm should not constitute a health hazard.

The study by Kerr et al. (1978, 1979) was considered the most appropriate to use as the basis for AEGL-1 values. Asthmatic subjects exposed to NO_2 at 0.5 ppm 2 h showed clinical signs but no changes in pulmonary function. Since asthmatic subjects are potentially the most susceptible population, no uncertainty factor was applied. Therefore, a concentration of 0.94 mg/m^3 (NO_2 or NO at 0.50 ppm or N_2O_4 at 0.25 ppm) was adopted for all time points (see Table 4-9), because adaptation to mild sensory irritation occurs. In addition, animal responses to NO_2 have demonstrated a much greater dependence on concentration than on time; therefore, extending the 2-h concentration to 8 h should not exacerbate the human response.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Human data relevant to AEGL-2 values are limited but consistent. Henschler et al. (1960) performed several experiments on healthy, male volunteers

and found that exposure to NO_2 at 30 ppm for 2 h caused definite discomfort. Three individuals exposed at 30 ppm for 2 h perceived an intense odor on entering the chamber, but odor detection quickly diminished and was completely absent after 25-40 min. One individual experienced a slight tickling of the nose and throat mucous membranes after 30 min, and others after 40 min. From 70 min, all subjects experienced a burning sensation and an increasingly severe cough for the next 10-20 min, but coughing decreased after 100 min. However, the burning sensation continued and moved into the lower sections of the airways and was finally felt deep in the chest. At that time, marked sputum secretion and dyspnea were noted. Toward the end of the exposure, the subjects' condition was described as bothersome and barely tolerable. A sensation of pressure and increased sputum secretion continued for several hours after cessation of exposure (Henschler et al. 1960). In a similar experiment (Henschler and Lütge 1963), groups of four or eight healthy male volunteers were exposed at 10 ppm for 6 h or at 20 ppm for 2 h. All subjects noted the odor on entering the chamber, but detection diminished rapidly. At 20 ppm, minor scratchiness of the throat was felt after about 50 min and three of eight subject experienced slight headaches near the end of the exposure period.

6.2. Summary of Animal Data Relevant to AEGL-2

Several animal studies are relevant to AEGL-2 derivation. Hine et al. (1970) noted lacrimation, reddening of the conjunctivae, and increased respiration in five species exposed to NO_2 at ≥40 ppm for varying durations. Lethality did not occur until concentrations and durations reached 75 ppm for 4 h in the dog and 1 h in the rabbit, 50 ppm for 1 h in the guinea pig, and 50 ppm for 24 h in the rat and mouse. At 20 ppm for 24 h, all species showed minimal signs of irritation and changes in behavior with histopathologic lesions described as questionable evidence of lung congestion and interstitial inflammation.

Exposure of monkeys to NO_2 at 35 ppm for 2 h resulted in irritation as measured by changes in lung function and microscopic lesions in the lung (Henry et al. 1969). The histologic lesions in the lung were characterized by Siegel et al. (1989) following exposure of mice at 140 ppm for 1 h. Carson et al. (1962) conducted a series of experiments in dogs and rats. Mild irritation and some respiratory effects, but no gross or microscopic lesions, were noted in dogs exposed to NO_2 at 53 or 39 ppm for 1 h, while rats exposed at 72 ppm for 1 h showed signs of severe respiratory distress and ocular irritation as well as gross lesions in the lung and evidence of infection.

TABLE 4-9 AEGL-1 Values for Nitrogen Dioxide, Nitric Oxide, and Nitrogen Tetroxide

Chemical	10 min	30 min	1 h	4 h	8 h
NO_2 and NO	0.50 ppm (0.94 mg/m^3)	0.50 ppm (0.94 mg/m^3)	0.50 ppm (0.94 mg/m^3)	0.50 ppm (0.94 mg/m^3)	0.50 ppm (0.94 mg/m^3)
N_2O_4	0.25 ppm (0.94 mg/m^3)	0.25 ppm (0.94 mg/m^3)	0.25 ppm (0.94 mg/m^3)	0.25 ppm (0.94 mg/m^3)	0.25 ppm (0.94 mg/m^3)

Developmental delays and disturbances in neuromotor development were reported for rat pups following maternal exposure to NO_2 (Tabacova et al. 1985). However, these effects were reported to have occurred at levels near ambient concentrations and are well below those of most other studies in both humans and animals.

6.3. Derivation of AEGL-2

AEGL values were based on studies of NO_2, the predominant form of the nitrogen oxides, and the values are considered applicable to all nitrogen oxides. Values for N_2O_4 in units of ppm were calculated on a molar basis. Because conversion to NO_2 is expected to occur in the atmosphere and because NO_2 is more toxic than NO, the AEGL values for NO_2 are recommended in emergency planning for NO.

On the basis of both human and animal data, it appears that NO_2 at concentrations of ≥30 ppm are required before marked irritation, discomfort, and respiratory effects occur. Therefore, 30 ppm for a 2-h exposure in humans (Henschler et al. 1960) was used to derive AEGL-2 values. The point-of-departure was considered a threshold for AEGL-2 effects, because the effects noted by the subjects would not impair the ability to escape and the effects were reversible after cessation of exposure. Values were scaled for 10- and 30-min and 1-, 4-, and 8-h AEGL-2 end points using the equation $C^n \times t = k$ using $n = 3.5$ (ten Berge et al. 1986). The value of n was calculated by ten Berge et al. (1986) from data on all species tested by Hine et al. (1970). An intraspecies uncertainty factor of 3 was applied to account for sensitive subpopulations because the mechanism of action for a direct-acting irritant is not expected to differ greatly among individuals (see Section 4.2 for detailed information regarding the mechanism of respiratory toxicity). The application of additional uncertainty factors would make the values inconsistent with some of the experimental data on asthmatic subjects, such as the no-adverse-effect concentration of 4 ppm in the study by Linn and Hackney (1984). AEGL-2 values are presented in Table 4-10.

These levels are not expected to cause severe effects because coal miners were exposed to peak NO_2 concentrations of 14 ppm without adverse consequences (Robertson et al. 1984), and it can be assumed that the peak levels were not sustained longer than a few minutes. Similar AEGL-2 values are derived from a study of mice exposed NO_2 at 140 ppm for 1 h (Siegel et al. 1989), with the application of an uncertainty factor of 10, and from a study of monkeys exposed at 35 ppm for 2 h (Henry et al. 1969), with the application of an uncertainty factor of 3. If the animal data from either Hine et al. (1970) or Carson et al. (1962) are used, the AEGL-2 values are even more conservative than those derived with the use of human data.

TABLE 4-10 AEGL-2 Values for Nitrogen Dioxide, Nitric Oxide, and Nitrogen Tetroxide

Chemical	10 min	30 min	1 h	4 h	8 h
NO_2 and NO	20 ppm (38 mg/m^3)	15 ppm (28 mg/m^3)	12 ppm (23 mg/m^3)	8.2 ppm (15 mg/m^3)	6.7 ppm (13 mg/m^3)
N_2O_4	10 ppm (38 mg/m^3)	7.6 ppm (28 mg/m^3)	6.2 ppm (23 mg/m^3)	4.1 ppm (15 mg/m^3)	3.5 ppm (13 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

A welder was hospitalized with pulmonary edema after exposure to NO_2 at approximately 90 ppm for 30-40 min (Norwood et al. 1966). It is possible that without medical intervention, the exposure could have been fatal.

Concentrations of NO_2 greater than150 ppm are probably fatal to humans because of bronchospasm and pulmonary edema (NRC 1977; Douglas et al. 1989). A human 1-h LC_{50} of 174 ppm was estimated from data on five animal species (Book 1982); however, the data were not considered valid experimental data on which to base AEGL-3 values. No other human data were relevant to derivation of AEGL-3 values.

7.2. Summary of Animal Data Relevant to AEGL-3

Squirrel monkeys (n = 2-6/group) were exposed to NO_2 at 10-50 ppm for 2 h, and respiratory function was monitored during exposure (Henry et al. 1969). NO_2 alone resulted in a markedly increased respiratory rate and decreased tidal volume at concentrations of 50 or 35 ppm, but caused only slight effects at 15 and 10 ppm. Mild histopathologic changes in the lungs were noted after exposure at 10 and 15 ppm; however, marked changes in lung structure were observed at 35 and 50 ppm. At 35 ppm, areas of the lung were collapsed with basophilic alveolar septa; in other areas, the alveoli were expanded with septal-wall thinning, and the bronchi were moderately inflamed with some proliferation of the surface epithelium. At 50 ppm, extreme vesicular dilatation or total collapse of alveoli, lymphocyte infiltration with extensive edema, and surface erosion of the bronchial epithelium were observed. In addition to the effects on the lungs, interstitial fibrosis (35 ppm) and edema (50 ppm) of cardiac tissue, glomerular tuft swelling in the kidney (35 and 50 ppm), lymphocyte infiltration in the kidney and liver (50 ppm), and congestion and centrilobular necrosis in the liver (50 ppm) were observed.

Rats exposed at 72 ppm for 60 min (approximately 50% of the LD_{50}) showed signs of severe respiratory distress and ocular irritation lasting about 2

days; lung-to-body-weight ratios were significantly increased during the first 48 h after exposure (Carson et al. 1962).

Lethality from NO_2 in five animal species first occurred at 75 ppm for 4 h in the dog and 1 h in the rabbit, 50 ppm for 1 h in the guinea pig, and 50 ppm for 24 h in the rat and mouse (Hine et al. 1970). In general, the larger animals, including humans, are less susceptible to toxicity from NO_2 inhalation than rodents.

7.3. Derivation of AEGL-3

AEGL values were based on studies of NO_2, the predominant form of the nitrogen oxides, and values are considered applicable to all nitrogen oxides. Values for N_2O_4 in units of ppm have been calculated on a molar basis. Because conversion to NO_2 is expected to occur in the atmosphere and because NO_2 is more toxic than NO, the AEGL values for NO_2 are recommended in emergency planning for NO.

The data from the monkey are considered the best available for derivation of AEGL-3 values. Signs of marked irritation and severe lung histopathology were observed from exposure to NO_2 at 50 ppm for 2 h. This exposure scenario was extrapolated to the 10- and 30-min and 1-, 4-, and 8-h time points using the equation $C^n \times t = k$ where $n = 3.5$ (ten Berge et al. 1986). The value of n was calculated by ten Berge et al. (1986) from the data on all species studied by Hine et al. (1970). A total uncertainty factor of 3 was applied, which includes a 3 for intraspecies variability and a 1 for interspecies variability. Use of a greater intraspecies uncertainty factor was considered unnecessary, because the mechanism of action for direct-acting respiratory irritants is not expected to differ greatly among individuals (see Section 4.2 for detailed information regarding the mechanism of respiratory toxicity). Because the end point in the monkey study is below the definition of AEGL-3, human data support the point-of-departure and derived values, and the respiratory tracts of humans and monkeys are similar, an interspecies uncertainty factor is not considered necessary. The mechanism of action of NO_2 does not vary between species with the target at the alveoli. AEGL-3 values for NO_2, NO, and N_2O_4 are presented in Table 4-11.

TABLE 4-11 AEGL-3 Values for Nitrogen Dioxide, Nitric Oxide, and Nitrogen Tetroxide

Chemical	10 min	30 min	1 h	4 h	8 h
NO_2 and NO	34 ppm (64 mg/m^3)	25 ppm (47 mg/m^3)	20 ppm (38 mg/m^3)	14 ppm (26 mg/m^3)	11 ppm (21 mg/m^3)
N_2O_4	17 ppm (64 mg/m^3)	13 ppm (47 mg/m^3)	10 ppm (38 mg/m^3)	7.0 ppm (26 mg/m^3)	5.7 ppm (21 mg/m^3)

The AEGL-3 values are supported by human data from a welder. Pulmonary edema, confirmed on x-ray, resulted from exposure to NO_2 at approximately 90 ppm for up to 40 min (Norwood et al. 1966). If this exposure scenario is used for derivation of AEGL-3 values and an uncertainty factor of 3 is applied, the 10- and 30-min and 1-, 4-, and 8-h values are 45, 33, 27, 18, and 15 ppm, respectively. Similar results are obtained from a study in rats exposed to NO_2 at 72 ppm for 1 h (Carson et al. 1962), and an uncertainty factor of 3 is applied. In addition, the AEGL-3 values are below the concentrations at which lethality first occurred in five animal species (Hine et al. 1970).

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

AEGL values for NO_2 and NO are summarized in Table 4-12, and the values for N_2O_4 are in Table 4-13. Values were derived on the basis of data on NO_2, and are considered applicable to the other oxides of nitrogen. Values for N_2O_4 in units of ppm have been calculated on a molar basis.

8.2. Comparison with Other Standards and Criteria

Standards and guidelines for workplace and community exposures to NO_2 are presented in Table 4-14. No standards or guidelines for exposure to N_2O_4 were found. The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a Threshold Limit Value (TLV) of 3 ppm for workers (ACGIH 2003), and the Occupational Safety and Health Administration's Permissible Exposure Limit (PEL) is a ceiling concentration of 5 ppm (29 CFR§1910.1000[1999]). The Immediately Dangerous to Life or Health (IDLH) value of the National Institute for Occupational Safety and Health (NIOSH) is 20 ppm (NIOSH1994a), which is exactly between the 30-min AEGL-2 and AEGL-3 values. The IDLH is reportedly based on acute inhalation data in humans, but no primary references were listed in the documentation; NIOSH notes that the IDLH may be a conservative value because of the lack of relevant acute toxicity data on workers exposed at concentrations above 20 ppm. Emergency Response Planning Guidelines (ERPGs) (AIHA 2003), based on human and animal data, are similar to the 1-h AEGL values. The National Research Council 1-h Emergency Exposure Guidance Level (EEGL) is 1 ppm for workplace conditions (NRC 1985). The occupational exposure limits of ACGIH, Germany, The Netherlands, and Sweden are 2-5 ppm.

In addition to the standards in Table 4-14, air-quality standards also have been developed for NO_2. The National Ambient Air Quality Standard is 0.053 ppm (40 CFR §50.11[1997]) with Significant Harm Levels of 2 ppm for a 1-h average and 0.5 ppm for a 24-h average (40 CFR §51.151[1987]). The Level of Concern is 5 ppm (EPA 1987). California has adopted 0.25 ppm as the standard for a 1-h exposure to NO_2 to protect sensitive individuals (CalEPA 2007).

TABLE 4-12 Summary of AEGL Values for Nitrogen Dioxide and Nitric Oxide

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	0.50 ppm (0.94 mg/m^3)	0.50 ppm (0.94 mg/m^3)	0.50 ppm (0.94 mg/m^3)	0.50 ppm (0.94 mg/m^3)	0.50 ppm (0.94 mg/m^3)
AEGL-2 (disabling)	20 ppm (38 mg/m^3)	15 ppm (28 mg/m^3)	12 ppm (23 mg/m^3)	8.2 ppm (15 mg/m^3)	6.7 ppm (13 mg/m^3)
AEGL-3 (lethal)	34 ppm (64 mg/m^3)	25 ppm (47 mg/m^3)	20 ppm (38 mg/m^3)	14 ppm (26 mg/m^3)	11 ppm (21 mg/m^3)

TABLE 4-13 Summary of AEGL Values for Nitrogen Tetroxide

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	0.25 ppm (0.94 mg/m^3)	0.25 ppm (0.94 mg/m^3)	0.25 ppm (0.94 mg/m^3)	0.25 ppm (0.94 mg/m^3)	0.25 ppm (0.94 mg/m^3)
AEGL-2 (disabling)	10 ppm (38 mg/m^3)	7.6 ppm (28 mg/m^3)	6.2 ppm (23 mg/m^3)	4.1 ppm (15 mg/m^3)	3.5 ppm (13 mg/m^3)
AEGL-3 (lethal)	17 ppm (64 mg/m^3)	13 ppm (47 mg/m^3)	10 ppm (38 mg/m^3)	7.0 ppm (26 mg/m^3)	5.7 ppm (21 mg/m^3)

TABLE 4-14 Extant Standards and Guidelines for Nitrogen Dioxide

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	0.50 ppm	0.50 ppm	0.50 ppm	0.50 ppm	0.50 ppm
AEGL-2	20 ppm	15 ppm	12 ppm	8.2 ppm	6.7 ppm
AEGL-3	34 ppm	25 ppm	20 ppm	14 ppm	11 ppm
ERPG-1 (AIHA)[a]			1 ppm		
ERPG-2 (AIHA)			15 ppm		
ERPG-3 (AIHA)			30 ppm		
EEGL (NRC)[b]			1 ppm	0.25 ppm	0.12 ppm
IDLH (NIOSH)[c]		20 ppm			
TLV-STEL (ACGIH)[d]	5 ppm				
REL-STEL (NIOSH)[e]	1 ppm				
PEL-STEL (OSHA)[f]	1ppm				
TLV-TWA (ACGIH)[g]					3 ppm
PEL-C (OSHA)[h]					5 ppm
MAK (Germany)[i]					5 ppm
MAK Peak Exposure (Germany)[j]	5 ppm				
MAC (The Netherlands)[k]					2.0 ppm
OEL-LLV (Sweden)[l]					2 ppm
OEL-CLV (Sweden)[m]	5 ppm				

[a]ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association) (AIHA 2003).

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) 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]IDLH (Immediately Dangerous to Life or Health, National Institute of Occupational Safety and Health) (NIOSH 1994a) 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 NO_2 is based on acute inhalation toxicity data in humans.
[d]TLV-STEL (Threshold Limit Value-Short-Term Exposure Limit, American Conference of Governmental Industrial Hygienists) (ACGIH 2003) is defined as a 15-minTWA 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 4 times per day. There should be at least 60 min between successive exposures in this range.
[e]REL-STEL (Recommended Exposure Limits-Short Term Exposure Limit, National Institute of Occupational Safety and Health) (NIOSH 2010a) is defined analogous to the ACGIH TLV-STEL.
[f]PEL-STEL (Permissible Exposure Limits-Short Term Exposure Limit, Occupational Health and Safety Administration) (NIOSH 2010 3) is defined analogous to the ACGIH TLV-STEL.
[g]TLV-TWA (Threshold Limit Value - Time-Weighted Average, American Conference of Governmental Industrial Hygienists) (ACGIH 2003) is the TWA 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]PEL-C (Permissible Exposure Limits-Ceiling, Occupational Health and Safety Administration) (29CFR§1910.1000[1999]) is a value that must not be exceeded during any part of the workday.
[i]MAK (Maximale Argeitsplatzkonzentration [Maximum Workplace Concentration]) (Deutsche Forschungsgemeinschaft [German Research Association](DFG 2002) is defined analogous to the ACGIH TLV-TWA.
[j]MAK Spitzenbegrenzung (Peak Limit [Category I, 1]) (German Research Association (DFG 2002) constitutes the average concentration to which workers can be exposed for up to 15 min, with no more than 1 excursion per work shift and a minimum of 1 h between excursions.
[k]MAC (Maximaal Aanvaaarde Concentratie [Maximal Accepted Concentration]) (Dutch Expert Committee for Occupational Standards, The Netherlands (MSZW 2004 is defined analogous to the ACGIH TLV-TWA.

[l]OEL-LLV (Occupational Exposure Limits - Level Limit Value) (Swedish Work Environment Authority 2005) is an occupational exposure limit value for exposure during 1 working day.
[m]OEL-CLV (Occupational Exposure Limits - Ceiling Limit Value) (Swedish Work Environment Authority 2005) is an occupational exposure limit for exposure during a reference period of 15 min.

Standards and guidance levels for workplace and community exposures to NO are presented in Table 4-15. An occupational time-weighted average of 25 ppm has been adopted by several groups (29CFR§1910.1000[1999]; ACGIH 2003; NIOSH 2010b). International standards also are 25 ppm for a workday (MSZW 2004; Swedish Work Environmental Authority 2005). In addition, Sweden has adopted 50 ppm as a short-term exposure limit, and the IDLH of 100 ppm (NIOSH 1994b) is based on human and animal studies of oxides of nitrogen because of the lack of useful data on NO.

8.3. Data Adequacy and Research Needs

Data on the effects of NO_2 on asthmatic subjects and individuals with respiratory disease were inconsistent and inconclusive. Additional studies that correlate severity of disease with individual responses would be helpful.

TABLE 4-15 Extant Standards and Guidelines for Nitric Oxide

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
IDLH (NIOSH)[a]		100 ppm			
TLV-TWA (ACGIH)[b]					25 ppm
PEL-TWA (OSHA)[c]					25 ppm
REL-TWA (NIOSH)[d]					25 ppm
MAC (The Netherlands)[e]					25 ppm
OEL-LLV (Sweden)[f]					25 ppm
OEL-CLV (Sweden)[g]	50 ppm				

[a]IDLH (Immediately Dangerous to Life or Health, National Institute of Occupational Safety and Health) (NIOSH 1994b) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms, or any irreversible health effects.
[b]TLV-TWA (Threshold Limit Value - Time Weighted Average, American Conference of Governmental Industrial Hygienists) (ACGIH 2003) is the TWA 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.
[c]PEL-TWA (Permissible Exposure Limits – Ceiling, Occupational Health and Safety Administration) (29 CFR§1910.1000 [1999]) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week.

[d]REL-TWA (Recommended Exposure Limits - time weighted average, National Institute of Occupational Safety and Health) (NIOSH 2010b) is defined analogous to the ACGIH TLV-TWA.
[e]MAC (Maximaal Aanvaaarde Concentratie [Maximal Accepted Concentration]) (Dutch Expert Committee for Occupational Standards, The Netherlands (MSZW 2004) is defined analogous to the ACGIH TLV-TWA.
[f]OEL-LLV (Occupational Exposure Limits - Level Limit Value) (Swedish Swedish Work Environment Authority 2005) is an occupational exposure limit value for exposure during 1 working day.
[g]OEL-CLV (Occupational Exposure Limits - Ceiling Limit Value) (Swedish Swedish Work Environment Authority 2005) is an occupational exposure limit value for exposure during a reference period of 15 min.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR NITROGEN OXIDES

Derivation of AEGL-1 Values

Key Studies:	Kerr, H.D., T.J. Kulle, M.L. McIlhany, and P. Swidersky. 1978. Effects of Nitrogen Dioxide on Pulmonary Function in Human Subjects: An Environmental Chamber Study. EPA/600/1-78/025. Health Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC. Kerr, H.D., T.J. Kulle, M.L. McIlhany, and P. Swidersky. 1979. Effects of nitrogen dioxide on pulmonary function in human subjects: An environmental chamber study. Environ. Res. 19(2):392-404.
Toxicity end point:	Slight burning of the eyes, slight headache, chest tightness, or labored breathing with exercise in 7/13 asthmatic subjects exposed to NO_2 at 0.5 ppm for 2 h
Time scaling:	Not applied
Uncertainty factors:	None
Modifying factor:	None
Calculations:	0.50 ppm applied across AEGL-1 exposure durations AEGL values were developed on the basis of data on NO_2, the predominant form of nitrogen oxide, and values are considered applicable to all nitrogen oxides. Values for N_2O_4 in units of ppm have been calculated on a molar basis. Because conversion to NO_2 is expected to occur in the atmosphere and because NO_2 is more toxic than NO, the AEGL values for NO_2 are recommended for emergency planning for NO. However, that short-term exposures to NO below 80 ppm should not constitute a health hazard.

Derivation of AEGL-2 for Nitrogen Oxides

Key Study:	Henschler, D., A. Stier, H. Beck, and W. Neumann. 1960. The odor threshold of some important irritant gasses (sulfur dioxide, ozone, nitrogen dioxide) and the manifestations of the effect of small concentrations on man [in German] Arch. Gewerbepathol. Gewerbehyg. 17:547-570.
Toxicity end points:	Burning sensation in nose and chest, cough, dyspnea, and sputum production in normal volunteers exposed to NO_2 at 30 ppm for 2 h
Time scaling:	$C^{3.5} \times t = k$; the value of n was calculated by ten Berge et al. (1986) from the data of Hine et al. (1970). $k = (30 \text{ ppm}/3)^{3.5} \times 2 \text{ h} = 6{,}324.56 \text{ ppm-h}$
Uncertainty factors:	3 for intraspecies variability
Modifying factor:	None AEGL values were developed on the basis of data on NO_2, the predominant form of nitrogen oxide, and values are considered applicable to all nitrogen oxides. Values for N_2O_4 in units of ppm have been calculated on a molar basis. Because conversion to NO_2 is expected to occur in the atmosphere and because NO_2 is more toxic than NO, the AEGL values for NO_2 are recommended for emergency planning for NO.
Calculations:	
10-min AEGL-2:	$C = (6{,}324.56 \text{ ppm-h}/0.167 \text{ h})^{1/3.5}$ $C = 20 \text{ ppm}$
30-min AEGL-2:	$C = (6{,}324.56 \text{ ppm-h}/0.5 \text{ h})^{1/3.5}$ $C = 15 \text{ ppm}$
1-h AEGL-2:	$C = (6{,}324.56 \text{ ppm-h}/1 \text{ h})^{1/3.5}$ $C = 12 \text{ ppm}$

4-h AEGL-2:	$C = (6{,}324.56 \text{ ppm-h}/4 \text{ h})^{1/3.5}$ $C = 8.2$ ppm
8-h AEGL-2:	$C = (6{,}324.56 \text{ ppm-h}/8 \text{ h})^{1/3.5}$ $C = 6.7$ ppm

Derivation of AEGL-3 for Nitrogen Oxides

Key study:	Henry, M.C., R. Ehrlich, and W.H. Blair. 1969. Effect of nitrogen dioxide on resistance of squirrel monkeys to *Klebsiella pneumoniae* infection. Arch. Environ. Health 18(4):580-587.
Toxicity end point:	Signs of marked irritation, but no deaths in monkeys exposed to NO_2 at 50 ppm for 2 h
Time scaling:	$C^{3.5} \times t = k$; the value of n was calculated by ten Berge et al. (1986) from the data of Hine et al. (1970) $k = (50 \text{ ppm}/3)^{3.5} \times 2 \text{ h} = 37{,}801$ ppm-h
Uncertainty factors:	3 for intraspecies variability; 1 for interspecies variability
Modifying factor:	None
	AEGL values were based on studies of NO_2, the predominant form, and values are considered applicable to all nitrogen oxides. Values for N_2O_4 in units of ppm have been calculated on a molar basis. Because conversion to NO_2 is expected to occur in the atmosphere and because NO_2 is more toxic than NO, the AEGL values for NO_2 are recommended for use with emergency planning for NO.
Calculations:	
10-min AEGL-3:	$C = (37{,}801 \text{ ppm-h}/0.1667 \text{ h})^{1/3.5}$ $C = 34$ ppm
30-min AEGL-3:	$C = (37{,}801 \text{ ppm-h}/0.5 \text{ h})^{1/3.5}$ $C = 25$ ppm

1-h AEGL-3: $C = (37{,}801 \text{ ppm-h}/1 \text{ h})^{1/3.5}$
$C = 20$ ppm

4-h AEGL-3: $C = (37{,}801 \text{ ppm-h}/4 \text{ h})^{1/3.5}$
$C = 14$ ppm

8-h AEGL-3: $C = (37{,}801 \text{ ppm-h}/8 \text{ h})^{1/3.5}$
$C = 11$ ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR NITROGEN OXIDES

Derivation Summary for Nitrogen Oxides

AEGL-1 VALUES

Chemical	10 min	30 min	1 h	4 h	8 h
NO_2/NO	0.50 ppm	0.50 ppm	0.50 ppm	0.50 ppm	0.50 ppm
N_2O_4	0.25 ppm	0.25 ppm	0.25 ppm	0.25 ppm	0.25 ppm

References:
Kerr, H.D., T.J. Kulle, M.L. McIlhany, and P. Swidersky. 1978. Effects of Nitrogen Dioxide on Pulmonary Function in Human Subjects: An Environmental Chamber Study. EPA/600/1-78/025. Health Effects Research Laboratory, U.S. Environmental Protection Agency, Reserch Triangle Park, NC.
Kerr, H.D., T.J. Kulle, M.L. McIlhany, and P. Swidersky. 1979. Effects of nitrogen dioxide on pulmonary function in human subjects: An environmental chamber study. Environ. Res. 19(2):392-404.

Test species/Strain/Number: Human subjects; sex not given; 13 asthmatic subjects with exercise

Exposure route/Concentrations/Durations: Inhalation of NO_2 at 0.5 ppm for 2 h

Effects: Slight burning of the eyes, slight headache, chest tightness, or labored breathing in 7/13 subjects

End point/Concentration/Rationale: Mild symptoms of discomfort in asthmatic subjects

Uncertainty factors/Rationale:
Total uncertainty factor: 1
Interspecies: Not applied because human data were used
Intraspecies: 1 was applied because asthmatics subjects were the test population

Modifying factor: None

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: Extrapolation was not conducted because adaptation to mild sensory irritation occurs. In addition, animal responses to NO_2 have demonstrated a much greater dependence on concentration than on time; therefore, extending the 2-h concentration to 8 h should not exacerbate the human response.

Data quality and support for the AEGL values: AEGL-1 values are considered conservative and should be protective of the toxic effects of NO_2 outside the expected AEGL-1 effects.

AEGL-2 VALUES

Chemical	10 min	30 min	1 h	4 h	8 h
NO_2/NO	20 ppm	15 ppm	12 ppm	8.2 ppm	6.7 ppm
N_2O_4	10 ppm	7.6 ppm	6.2 ppm	4.1 ppm	3.5 ppm

Reference:
Henschler, D., A. Stier, H. Beck, and W. Neumann. 1960. The odor threshold of some important irritant gasses (sulfur dioxide, ozone, nitrogen dioxide) and the manifestations of the effect of small concentrations on man [in German] Arch. Gewerbepathol. Gewerbehyg. 17:547-570.

Test species/Strain/Number: Human, healthy male, 10-14

Exposure route/Concentrations/Durations: Inhalation, 0.5-30 ppm for up to 2 h

Effects:
0.5 ppm: metallic taste
1.5 ppm: dryness of the throat
4 ppm: sensation of constriction
25 ppm: prickling of the nose
30 ppm: burning sensation in nose and chest, cough, dyspnea, sputum production

End point/Concentration/Rationale: Humans exposed to NO_2 at 30 ppm for 2 h experienced pronounced irritation. The point-of-departure is considered a threshold for AEGL-2 because the effects would not impair the ability to escape and were reversible after cessation of exposure.

Uncertainty factors/Rationale:
Total uncertainty factor: 3
Interspecies: Not applied because human data were used
Intraspecies: 3 applied because the mechanism of action of a direct-acting irritant is not expected to differ greatly among individuals (see Section 4.2 for detailed information regarding the mechanism of respiratory toxicity).

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: $C^n \times t = k$, where n = 3.5 (ten Berge et al. 1986)

Data quality and support for the AEGL values: AEGL-2 values should be protective of the toxic effects of NO_2 outside the expected AEGL-2 effects. The values are supported by occupational monitoring data.

AEGL-3 VALUES

Chemical	10 min	30 min	1 h	4 h	8 h
NO_2/NO	34 ppm	25 ppm	20 ppm	14 ppm	11 ppm
N_2O_4	17 ppm	13 ppm	10 ppm	7.0 ppm	5.7 ppm

Reference:
Henry, M.C., R. Ehrlich, and W.H. Blair. 1969. Effect of nitrogen dioxide on

(Continued)

AEGL-3 VALUES Continued

Chemical	10 min	30 min	1 h	4 h	8 h
NO_2/NO	34 ppm	25 ppm	20 ppm	14 ppm	11 ppm
N_2O_4	17 ppm	13 ppm	10 ppm	7.0 ppm	5.7 ppm

(continued)

resistance of squirrel monkeys to *Klebsiella pneumoniae* infection. Arch. Environ. Health 18(4):580-587.

Test species/Strain/Number: Monkeys, 2-6/group

Exposure route/Concentrations/Durations: Inhalation, 10, 15, 35, or 50 ppm for 2 h

Effects:
50 ppm: marked increase in respiratory rate, decrease in tidal volume, microscopic lesions in lung (determinate for AEGL-3)
35 ppm: increase in respiratory rate, decrease in tidal volume, microscopic lesions in lung 10 and 15 ppm: slight changes in lung function

End point/Concentration/Rationale: 50 ppm resulted in marked effects on lung function but no deaths

Uncertainty factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1 applied because the end point in the monkey study is below the definition of AEGL-3 effects, human data support the AEGL-3 point-of-departure and derived values, the mechanism of action does not vary between species with the target at the alveoli, and because of the similarities of the respiratory tract between humans and monkeys.
Intraspecies: 3 applied because the mechanism of action of a direct-acting irritant is not expected to differ greatly among individuals (see Section 4.2 for detailed information regarding the mechanism of respiratory toxicity).

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: $C^n \times t = k$, where n = 3.5 (ten Berge et al. 1986)

Data quality and support for the AEGL values: The study is of high quality and the AEGL-3 values are supported by human data.

APPENDIX C

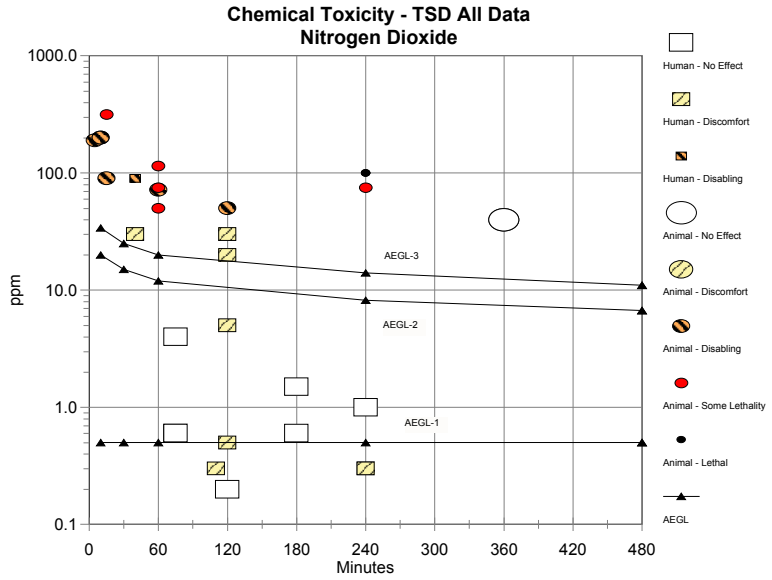

FIGURE C-1 Category plot of toxicity data and AEGLs values for nitrogen dioxide.

TABLE C-1 Data Used in Category Graph

Source	Species	ppm	Minutes	Category
NAC/AEGL-1		0.5	10	AEGL
NAC/AEGL-1		0.5	30	AEGL
NAC/AEGL-1		0.5	60	AEGL
NAC/AEGL-1		0.5	240	AEGL
NAC/AEGL-1		0.5	480	AEGL
NAC/AEGL-2		20	10	AEGL
NAC/AEGL-2		15	30	AEGL
NAC/AEGL-2		12	60	AEGL
NAC/AEGL-2		8.2	240	AEGL
NAC/AEGL-2		6.7	480	AEGL
NAC/AEGL-3		34	10	AEGL
NAC/AEGL-3		25	30	AEGL
NAC/AEGL-3		20	60	AEGL

(Continued)

TABLE C-1 Continued

Source	Species	ppm	Minutes	Category
NAC/AEGL-3		14	240	AEGL
NAC/AEGL-3		11	480	AEGL
Norwood et al. 1966	Human	90	40	2
Morley and Silk 1970	Human	30	40	1
Henschler et al. 1960	Human	30	120	1
Multiple studies	Human	0.6	180	0
Frampton et al. 1991	Human	1.5	180	0
Linn and Hackney 1983, 1984	Human	4.0	75	0
von Nieding et al. 1979	Human	5.0	120	1
Kleinman et al. 1983	Human	0.2	120	0
Sackner et al. 1981	Human	1.0	240	0
Kerr et al. 1978	Human	0.5	120	1
Roger et al. 1990	Human	0.3	110	1
Roger et al. 1990	Human	0.6	75	0
Hine et al. 1970	Dog	75	240	PL
Hine et al. 1970	Rat	100	240	3
Hine et al. 1970	Mouse	100	240	3
Hine et al. 1970	Rabbit	75	60	PL
Henry et al. 1969	Monkey	50	120	2
Hine et al. 1970	Dog	20	1,440	1
Carson et al. 1962	Rat	190	5	2
Carson et al. 1962	Rat	90	15	2
Carson et al. 1962	Rat	72	60	2
Hine et al. 1970	Rat	20	1,440	1
Henschler and Lutge 1963	Human	20	120	1
Bauer et al. 1985	Human	0.3	240	1
Hine et al. 1970	Guinea pig	50	60	PL
Carson et al. 1962	Rabbit	315	15	PL
Carson et al. 1962	Rat	115	60	PL
Meulenbelt et al. 1992	Rat	200	10	2
Hidekazu and Fujio 1981	Mouse	40	720	PL
Henschler and Lutke 1963	Dog	40	360	0
Hine et al. 1970	Guinea pig	20	1,440	1
Hine et al. 1970	Mouse	20	1,440	1

5

Vinyl Chloride[1]

Acute Exposure Guideline Levels

PREFACE

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

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, 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 or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain 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 Fritz Kalberlah (Forschungs- und Beratungsinstitut Gefhtoffe GmbH), Chemical Manager Bob Benson (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (U.S. Environmental Protection Agency). 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 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 concentrations 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 idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Vinyl chloride (VC) is a colorless, flammable gas with a slightly sweet odor. It is heavier than air and accumulates at the bottom of rooms and tanks. Worldwide production of VC is approximately 27,000,000 tons. Most VC is polymerized to polyvinyl chloride. Combustion of VC in air produces carbon dioxide and hydrogen chloride. Odor thresholds of VC range from 10 to 25,000 ppm. Validated studies that provide quantitative data on odor recognition and detection are not available; therefore, a level of odor awareness (LOA) could not be derived.

VC is an anesthetic compound. After a 5-min exposure to VC at 16,000 ppm, volunteers experienced dizziness, lightheadedness, nausea, and visual and auditory dulling (Lester et al. 1963). Mild headache and some dryness of the eyes and nose were the only complaints of volunteers exposed at 491 ppm for several hours (Baretta et al. 1969). No data on the developmental or reproductive toxicity of VC in humans after acute exposure are available. Chromosomal aberrations in human lymphocytes were associated with accidental exposure to VC. After chronic occupational exposure, VC is a known human carcinogen that induces liver angiosarcoma, possibly hepatocellular carcinoma, and brain tumors. Evidence of tumors at other sites is contradictory. Two epidemiologic studies (Mundt et al. 2000; Ward et al. 2001) found no increase in standardized mortality ratios (SMRs) after 5 years of occupational exposure to VC, whereas a third study suggested an increase after 1-5 years of exposure (Boffetta et al. 2003).

Acute exposure to VC results in narcotic effects (Mastromatteo et al. 1960), cardiac sensitization (Clark and Tinston 1973, 1982), and hepatotoxicity (Jaeger et al. 1974) in laboratory animals. Prodan et al. (1975) reported 2-h LC_{50} values (lethal concentration, 50% lethality) for mice, rats, rabbits, and guinea pigs of 117,500, 150,000, 240,000, and 240,000 ppm, respectively. No studies of reproductive or developmental toxicity after a single exposure are available. In repeated-exposure studies, developmental toxicity (e.g., delayed ossification) in mice, rats, and rabbits was observed only at maternally toxic concentrations. Embryo-fetal development of rats was not affected by VC at concentrations up to 1,100 ppm for 2 weeks (6 h/day) (Thornton et al. 2002). Positive results for genotoxicity after in vitro and single and repeated in vivo treatment have been reported for VC. Elevated etheno-adducts were observed after single and short-term exposure and were associated with mutational events (Barbin 2000; Swenberg et al. 2000). Adduct levels in young animals were greater than in adult animals after identical treatment (Laib et al. 1989; Ciroussel et al. 1990; Fedtke et al. 1990; Morinello et al. 2002). A study of adult rats exposed to VC at 45 ppm for 6 h found no increase in relevant etheno-adducts above background (Watson et al. 1991).

Induction of liver tumors has been reported in rats after short-term (5 weeks and 33 days) exposure (Maltoni et al. 1981, 1984; Froment et al. 1994). VC induces lung tumors in mice after a single exposure to high concentrations of VC (Hehir et al. 1981). Short-term exposure experiments by Drew et al. (1983), Maltoni et al. (1981), and Froment et al. (1994) indicated newborn and young animals are more susceptible to tumor formation than adult animals.

The cancer risk from exposure to VC for 30 min to 8 h was estimated on the basis of laboratory animal data. However, there is great uncertainty in those estimates, and they conflict with epidemiologic data on occupational exposure to VC.

AEGL-1 values are based on a study of four to seven volunteers exposed to VC (Baretta et al. 1969). Two individuals experienced mild headache when exposed to VC at 491 ppm for 3.5 h and 7.5 h (two exposures for 3.5 h, with a 0.5 h break between exposures). The time of onset of headaches was not specified, so it was assumed to be after 3.5 h. A total uncertainty factor of 3 was used. Because the AEGL-1 values are based on human data no interspecies uncertainty factor was used. The effects are probably from VC in the blood and not a metabolite. Only small interindividual differences in the pharmacokinetics of VC are expected, as the concentration of VC required to elicit the AEGL-1 effect is greater than that required for saturation of the metabolic pathways. An intraspecies uncertainty factor of 3 is used to account for toxicodynamic differences among individuals. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of n = 3 for shorter exposure periods and n = 1 for longer exposure periods; there were no suitable experimental data for deriving the value of n. The default values were used because the mechanism for the induction of headache is unknown, but is unlikely to be a simple function of VC in the

blood. The extrapolation from a 3.5 h exposure to 10 min is justified because humans exposed at 4,000 ppm for 5 min did not experience headaches (Lester et al. 1963).

The AEGL-2 values are based on prenarcotic effects observed in human volunteers. After exposure to VC at 16,000 ppm for 5 min, five of six persons experienced dizziness, lightheadedness, nausea, and visual and auditory dulling. At 12,000 ppm, one of six persons experienced dizziness and "swimming head, reeling." No effects were reported at 4,000 ppm. A single person reported slight effects ("slightly heady") of questionable meaning at 8,000 ppm (this volunteer also felt slightly heady when given a sham exposure and reported no response when exposed at 12,000 ppm) (Lester et al. 1963). VC at 12,000 ppm was considered the no-effect level for impaired ability to escape. An intraspecies uncertainty factor of 3 was used to account for toxicodynamic differences among individuals. The effects are probably from VC in the blood and not a metabolite. Only small interindividual differences in pharmacokinetics of VC are expected, as the concentration of VC required to elicit AEGL-2 effects is greater than that required for saturation of the metabolic pathways. By analogy with other anesthetics, the effects are assumed to be solely concentration dependent. Thus, after reaching steady state after about 2 h, no increase in effect is expected. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, with $n = 2$, based on a study by Mastromatteo et al. (1960). This study reported various time-dependent prenarcotic effects in mice and guinea pigs after less than steady-state exposure conditions. Time extrapolation was performed from 5 min to 10-min, 30-min, 60-min, and 2-h exposures. The steady state concentration at 2 h is used for the 4- and 8-h values.

The AEGL-3 values are based on cardiac sensitization and the no-effect level for lethality. Short-term exposure (5 min) to VC induced cardiac sensitization in dogs (effective concentration producing 50% response [EC_{50}] was 50,000 and 71,000 ppm in two independent experiments) (Clark and Tinston 1973, 1982). Severe cardiac sensitization is a life-threatening effect, but at 50,000 ppm no animals died. The cardiac-sensitization model with the dog is considered an appropriate model for humans and is highly sensitive because the response is optimized by the exogenous administration of epinephrine (Brock et al. 2003; ECETOC 2009). This protocol is conservative and has built-in safety factors; thus, no additional uncertainty factors were considered necessary (ECETOC 2009). Accordingly, an interspecies uncertainty factor of 1 was applied. Only small interindividual differences in pharmacokinetics of VC are expected, as the concentration of VC required to elicit the effect is greater than that required for saturation of the metabolic pathways. An intraspecies uncertainty factor of 3 is used to account for toxicodynamic differences among individuals. By analogy with other halocarbons (e.g., Halon 1211, HFC 134a) that are cardiac sensitizer, the effects are assumed to be solely dependent on the concentration of VC in the blood. Thus, after reaching steady state after about 2 h, no increase in effect is expected. The other exposure duration-specific values were derived by time

scaling according to the dose-response regression equation $C^n \times t = k$, with n = 2, based on data from Mastromatteo et al. (1960). Time extrapolation was performed from 5 min to 10-min, 30-min, 60-min, and 2-h exposures. The steady state concentration at 2 h is used for the 4- and 8-h values.

The AEGLs values for VC are presented in Table 5-1.

1. INTRODUCTION

VC is a colorless, flammable gas with a slightly sweet odor. It is heavier than air and accumulates at the bottom of rooms and tanks. Its worldwide production is approximately 27,000,000 tons. Most VC is polymerized to polyvinyl chloride, which subsequently is used to produce packaging materials, building materials, electric appliances, medical-care equipment, toys, agricultural piping and tubing, and automobile parts. The largest single use of polyvinyl chloride is in the building sector (WHO 1999). About 10,000 tons are used in the production of 1,1,1-trichloroethane and other chlorinated solvents on an annual basis (Kielhorn et al. 2000).

TABLE 5-1 Summary of AEGL Values for Vinyl Chloride[a]

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	450 ppm (1,200 mg/m^3)	310 ppm (800 mg/m^3)	250 ppm (650 mg/m^3)	140 ppm (360 mg/m^3)	70 ppm (180 mg/m^3)	Mild headaches in 2/7 humans (Baretta et al. 1969); no-effect level for notable discomfort.
AEGL-2 (disabling)	2,800 ppm (7,300 mg/m^3)	1,600 ppm (4,100 mg/m^3)	1,200 ppm (3,100 mg/m^3)	820 ppm (2,100 mg/m^3)	820 ppm (2,100 mg/m^3)	Mild dizziness in 1/6 humans (Lester et al. 1963); no-effect level for impaired ability to escape.
AEGL-3 (lethal)	12,000 ppm[b] (31,000 mg/m^3)	6,800 ppm[b] (18,000 mg/m^3)	4,800 ppm[b] (12,000 mg/m^3)	3,400 ppm (8,800 mg/m^3)	3,400 ppm (8,800 mg/m^3)	Cardiac sensitization (Clark and Tinston 1973, 1982); no-effect level for lethality.

[a]Derivation of the AEGL values excludes potential mutagenic or carcinogenic effects after a single exposure, which might occur at lower concentrations based on laboratory animal data (see Appendix C).

[b]The explosion limits for VC in air range from 38,000 ppm to 293,000 ppm. The 10-min, 30-min, and 1-h AEGL-3 values exceed 10% of the lower explosion limit. Therefore, safety considerations against explosion should be taken into account.

Most VC is produced either by hydrochlorination of acetylene, mainly in Eastern European countries, or by thermal cracking of 1,2-dichloroethane. VC is stored either under pressure at ambient temperature or refrigerated at atmospheric pressure (WHO 1999). Since it does not polymerize readily, VC is stored without additives. Combustion of VC in air produces carbon dioxide and hydrogen chloride (WHO 1999).

The chemical and physical properties of VC are presented in Table 5-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Danziger (1960) describes two worker deaths from accidental exposure to VC. The concentration and exposure duration were not specified, but circumstances suggest inhalation of very high concentrations of VC. Autopsy results show cyanosis, congestion of lung and kidneys, and failure of blood coagulation. Citing results from Schaumann (1934), 12% VC (120,000 ppm) is reported as "dangerous concentrations" (Danziger 1960; Oster et al. 1947).

At very high concentrations, VC causes asphyxia, probably from narcosis-induced respiratory failure (HSDB 2005).

TABLE 5-2 Chemical and Physical Properties of Vinyl Chloride

Parameter	Value	Reference
Synonyms	Vinyl chloride monomer, monochlorethene, monochlorethylene, 1-chloroethylene, chlorethylene, chloroethene	WHO 1999
CAS Reg. No.	75-01-4	WHO 1999
Chemical formula	C_2H_3Cl	WHO 1999
Molecular weight	62.5 g/mol	WHO 1999
Physical state	Gaseous (at room temperature)	WHO 1999
Color	Colorless	WHO 1999
Melting point	-153.8°C	WHO 1999
Boiling point	-13.4°C	WHO 1999
Density	0.910 g/cm^3 at 20°C	WHO 1999
Solubility in water	Soluble in almost all organic solvents, slightly soluble in water	WHO 1999
Vapor pressure	78 kPa at -20°C 165 kPa at 0°C 333 kPa at 20°C	WHO 1999
Odor	Slightly sweet	WHO 1999
Explosion limits in air	3.8-29.3 vol% in air at 20°C; 4-22 vol%	WHO 1999
Conversion factors	1 ppm = 2.59 mg/m^3 at 20°C, 101.3 kPa 1 mg/m^3 =0.386 ppm	WHO 1999

2.2. Nonlethal Toxicity

A summary of the acute effects in humans after exposure to VC is presented in Table 5-3.

TABLE 5-3 Summary of Acute Effects in Humans after Inhalation of Vinyl Chloride

Concentration	Duration	Effects	Reference
Very high	Unknown	Ocular irritation	Danziger 1960
25,000 ppm	3 min	Dizziness, disorientation with regard to space and size, burning sensation in feet, persistent headache.	Patty et al. 1930
20,000 ppm	5 min	6/6 dizziness, lightheadedness, nausea, visual and auditory dulling, 1/6 persistent headache.	Lester et al. 1963
16,000 ppm	5 min	5/6 dizziness, lightheadedness, nausea, visual and auditory dulling; no effects in one volunteer.	Lester et al. 1963
12,000 ppm	5 min	1/6 "swimming head, reeling," 1/6 "unsure" of effects (somewhat dizzy in the middle of exposure).	Lester et al. 1963
8,000 ppm	5 min	1/6 "slightly heady" (volunteer also felt slightly heady at sham exposure and reported no effects at 12,000 ppm).	Lester et al. 1963
4,000 ppm	5 min	No effects.	Lester et al. 1963
3,000 ppm	Unknown	Odor threshold (geometric averages of three studies, omitting extreme points and duplicate quotations).	Amoore and Hautala 1983
High, not specified	Unknown	Prenarcotic and narcotic effects; repeated exposure caused headaches, asthenovegetative syndrome, cardiovascular effects, hepatomegaly.	Suciu et al. 1975
491 or 459 ppm	3.5 h	2/7 reported mild headache and dryness of the eyes and nose.	Baretta et al. 1969
261 ppm	Unknown	Detection of VC odor by 4/4 subjects.	Baretta et al. 1969
20 ppm	Unknown	Odor threshold in polyvinyl chloride production workers.	Hori et al.1972
10 ppm	Unknown	Odor threshold in workers from a polyvinyl chloride facility not working in polyvinyl chloride production.	Hori et al. 1972

2.2.1. Neurotoxicity

VC was considered a potential anesthetic. A narcotic limit concentration for man is 7-10% (70,000-100,000 ppm) (Lehmann and Flury 1938; Oster et al. 1947; Danziger 1960). Schauman (1934) reported narcosis at somewhat higher concentrations. Exposure to unknown, high concentrations of VC (e.g., during cleaning of autoclaves) also resulted in narcotic effects (Suciu et al. 1975).

Acute Exposure

Lester et al. (1963) exposed six volunteers (three men and three women) to VC at 0, 0.4, 0.8, 1.2, 1.6, or 2% (0, 4,000, 8,000, 12,000, 16,000, or 20,000 ppm, nominal concentration) for 5 min using a plastic breathing mask that covered the mouth and nose. The total gas flow was 50 liters per minute (L/min). The desired concentrations were obtained by metering air and VC (gas chromatography of the liquid phase indicated more than 99% VC) through flow meters and passing the appropriate flows through a 2-L mixing chamber. The concentration was continuously monitored by a thermal conductivity meter (less than 5% deviation from the desired concentration). All volunteers were exposed to every concentration in a randomized fashion, separated by a 6-h interval. Dizziness ("slightly heady") was experienced by one volunteer at 8,000 ppm (the subject also reported slight dizziness at sham exposure and reported no response at 12,000 ppm). At 12,000 ppm, four people reported no response, one subject reported reeling and swimming head, and another subject was unsure of some effects. The latter person had a somewhat dizzy feeling in the middle of exposure. Dizziness, nausea, headache, and dulling of visual and auditory cues were reported by five people exposed to VC at 16,000 ppm and by all subjects exposed at 20,000 ppm. All symptoms disappeared shortly after termination of exposure; headache persisted for 30 min in one subject after exposure at 20,000 ppm.

Two experimenters were exposed to VC at 25,000 ppm (nominal concentration) for 3 min by entering an exposure chamber. They reported dizziness, slight disorientation with regard space and size of surrounding objects, and a burning sensation in the feet. The subjects immediately recovered on leaving the chamber and complained only of a slight headache that persisted for 30 min. No further details were presented (Patty et al. 1930).

Baretta et al. (1969) exposed four to six volunteers to VC at 59, 261, and 491 ppm (analytic concentrations) for 7.5 h (including a 0.5 h lunch period). The corresponding time-weighted average concentrations were 48, 248, and 459 ppm over 7.5 h. Seven people were exposed at 491 ppm for only 3.5 h. The subjects were exposed in an exposure chamber (41 feet × 6 feet, 7.5 feet high) with a continuous positive air supply and exhaust system. Air was recirculated with a squirrel cage fan through a series of inlet and outlet ducts spanning the length of the chamber. VC concentration was monitored by an infrared spectrophotometer. The vapors were introduced from a pressurized storage cylinder through 6 feet of 1/8 inch in diameter stainless-steel tubing into a rotometer prior to enter-

ing the circulating air duct. A heating tape wrapped around the stainless-steel tubing prevented condensation of VC. Subjective and neurologic responses of the volunteers, as well as clinical parameters, were measured. Two subjects reported mild headache and some dryness of their eyes and nose after exposure to the highest concentration. The time of onset of headaches is not clearly stated, so it was assumed that headaches occurred in both experiments after 3.5 h and during or after 7.5 h.

According to a literature review, acute human exposure to VC at 1,000 ppm for 1 h leads to fatigue and vision disturbances (Lefaux 1966). Exposure at 5,000 ppm for 60 min has lead to nausea and disorientation (Oettel 1954), with similar effects reported at 6,000 ppm for 30 min (Patty et al. 1930). VC concentrations of 6,000 to 8,000 ppm are reported to result in prenarcotic symptoms (von Oettingen 1964). Examination of the primary literature did not show how those values were derived. No experimental background or observational data were provided. Thus, the referred results might not be used for risk assessment.

Occupational Exposure

Suciu et al. (1975) reported acute effects after 1,684 workers from two factories were exposed to VC. When air concentrations of VC were high (1963-1964), acute and subacute poisonings occurred. After the first breaths of "a high concentration of VC," pleasant taste in the mouth, euphoric conditions, slow movements, giddiness, and inebriety-like condition were reported. Continued exposure caused more pronounced symptoms of somnolence and complete narcosis. After repeated exposures to unknown high concentrations, workers complained of headaches, irritability, diminution of memory, insomnia, general asthenia, paresthesia, tingling, and loss of weight. In addition to an "onset of an asthenovegetative syndrome," other systemic and local effects included cardiovascular effects, hepatomegaly, digestive responses, and respiratory changes. Workplace concentrations of VC in the factory were 2,300 mg/m^3 (about 890 ppm) in 1963 and decreased in subsequent years. This VC concentration may have been an average exposure (not specified in the report). No information on peak concentrations and duration of episodes with short-term high concentrations of VC exposure was provided. Some of the reported activities, such as cleaning autoclaves, are associated with very high exposures.

Several authors have reported headache in workers chronically exposed to VC. Exposure concentration and duration were not specified, but always were characterized as "high" (Lilis et al. 1975; Suciu et al. 1975; EPA 1987).

2.2.2. Odor

A wide range of odor thresholds (10-25,000 ppm [26-65,000 mg/m^3]) have been reported in the literature. Hori et al. (1972) reported a threshold of 20 ppm in production workers and 10 ppm in workers from other departments of

polyvinyl-chloride facilities (number of workers not specified). VC odor was perceived by 50% of the "non-production" workers at 200 ppm and by 50% of the "production" workers at 350 ppm. Odor threshold was tested by two methods. Polyvinyl chloride was diluted with air at fixed concentrations and was supplied from a glass injector to the subject's nostrils at a rate of 100 mL over 5 to 10 seconds. This procedure was repeated using gradually higher concentrations of VC until the subject perceived an odor. The second method involved measuring atmospheric concentrations of VC. Production workers were less sensitive to VC than workers from other departments. When workers from different facilities were compared, even greater ranges on odor threshold were observed. However, interindividual differences and measurement techniques were not strictly controlled. The odor thresholds reported by Hori et al. (1972) were reviewed by the American Industrial Hygiene Association and were rejected because there was no calibration of panel odor sensitivity, it was not clear whether the limit was based on recognition or detection, and the number of trials was not stated in the study (AIHA 1997).

Baretta et al. (1969) reported that none of six subjects perceived odor after entering an exposure chamber with VC at 59 ppm, whereas at 261 ppm all four subjects detected a very slight odor. Five of seven subjects were able to detect the odor of VC at 491 ppm, but after 5 min the odor was no longer perceived (study details described earlier).

Two people exposed to VC at 25,000 ppm (nominal concentration) for 3 min in an experimental exposure chamber reported a "fairly pleasant odor" (Patty et al. 1930).

Amoore and Hautala (1983) reported an odor threshold for VC of 3,000 ppm. This value reportedly represents the geometric average of three literature studies (individual studies not mentioned); studies reporting extreme points and duplicate quotations were omitted. It was not stated whether the value was a detection or recognition threshold.

2.2.3. Irritation

Acute Exposure

Irritating effects of VC are only observed after exposure to very high concentrations. Lesions of the eyes (wedge-shaped brown discoloration of the bulbar conjunctiva, palpebral slits, and conjunctiva and cornea appeared dry) were observed at autopsy in a worker who died from inhalation of very high concentrations of VC. Intensely hyperemic lungs, with desquamation of the alveolar epithelium also were observed (Danziger 1960).

Chronic Exposure

Tribukh et al. (1949) reported mucous irritation of the upper respiratory tract and chronic bronchitis in polyvinyl-chloride workers; however, Lilis et al. (1975) and Marsteller et al. (1975) did not mention these effects.

Suciu et al. (1975) describe coughing and sneezing after exposure of workers to VC during one shift; no other acute pulmonary effects or irritation were mentioned. These workers had been regularly exposed to VC for an extended duration.

In chronically exposed VC workers, evidence for adverse respiratory disease is conflicting. Lung function (respiratory volume, vital capacity, and oxygen and carbon dioxide transfer) deteriorates over time. Emphysema, chronic obstructive pulmonary disease (COPD), respiratory insufficiency, dyspnea, and pulmonary fibrosis have been described (Suciu et al. 1975; Walker 1976; Lloyd et al. 1984). Some of these observations have been attributed to smoking as a possible confounder.

2.2.4. Cardiovascular Effects

A slight decrease in blood pressure in VC workers has been attributed to the narcotic effects of VC (Suciu et al. 1975). In older experiments in human volunteers, no cardiovascular parameters have been measured (Lester et al. 1963).

Raynaud's disease has been correlated with extended occupational exposure to high concentrations of VC (ATSDR 1997), with histologic alterations of small vessels (Veltman et al. 1975). Other symptoms observed in VC workers are splenomegaly, hypertension, portal hypertension, generally increased cardiovascular mortality, and vasospastic symptoms (Suciu et al. 1975; Byron et al. 1976; ATSDR 1997). According to Kotseva, elevated occupational exposure to VC increases the incidence of arterial hypertension, but there is no conclusive evidence that it is associated on its own with an increased risk of coronary heart disease (Beck et al. 1973).

2.2.5. Other End Points

Hematology and Immunology

Blood tests of two workers that died from exposure to VC indicated failure of blood coagulation (Danziger et al. 1960).

Hepatotoxicity

More or less pronounced hepatitis and enlargement of the liver have been reported in chronically exposed workers (Marsteller et al. 1975; ECB 2000). In another study, impaired liver function and periportal liver fibrosis was found in workers at a polyvinyl chloride producing plant (no further details presented) (Lange et al. 1974). Liver function disturbances have been reported in workers from polyvinyl chloride producing factories (Fleig and Thiess 1978). Focal

hepatocellular hyperplasia and focal mixed hyperplasia has been observed in VC exposed workers; some of the individuals with focal mixed hyperplasia developed liver angiosarcoma (Tamburro et al. 1984). No data on liver effects after acute exposure are available.

2.3. Developmental and Reproductive Toxicity

No data on developmental or reproductive toxicity in humans after single exposure to VC were found.

2.4. Genotoxicity

Huettner and Nikolova (1998) investigated chromosomal aberrations in the lymphocytes of 29 people exposed to VC its combustion byproducts after a train accident in Schoenebeck, Germany, and 29 unexposed people. Blood samples were drawn 2-4 months after the accident. The authors found increased incidences of chromosomal aberrations (gaps, chromatid breaks, and acentric chromosomes). The health complaints of 60% of the exposed individuals were ascribed to the pollutants. More than 15 h after the accident, atmospheric VC concentrations were 1-8 ppm (Huettner and Nikolova 1998). Hahn et al. (1998) reported a maximum VC concentration of 30 ppm near the center of the accident. The personal exposure to VC and its combustion products experienced by individuals is highly uncertain. In a follow-up study of the same cohort of people 2 years later, Becker et al. (2001) found enhanced chromosome aberrations in peripheral lymphocytes as an indicator of clastogenic activity of VC, while no increased mutagenic activity (as measured by mutations in the hypoxanthine-guanine-phosphoribosyl-transferase was observed in exposed persons.

Clastogenic DNA damage has been detected by various tests in workers exposed chronically to VC. Chromosomal defects (inversions, translocations, rings) and micronuclei have been detected at exposure concentrations around 1 ppm (Fucic et al. 1995; short exposure spikes up to 300 ppm were reported) and 5 ppm (Graj-Vrhovac et al. 1990). Also increased frequencies of sister-chromatid exchanges were reported (Sinués et al. 1991; Fucic et al. 1992). Awara et al. (1998) observed an increased incidence of DNA damage (detected by single-cell gel electrophoresis) in workers exposed to VC. The amount of DNA-damage increased with exposure duration. Average VC concentrations were highest in the production area (about 3 ppm).

Covalent binding of VC to macromolecules in humans has not been directly assessed. However, gene mutations were found in human tumors associated with exposure to etheno-adduct-forming chemicals such as VC. Specifically, in angiosarcoma of the human liver, G→A transitions of the Ki-*ras* gene were found in five of six cases and A→T transitions of *p53* were observed in three of six cases, which may be attributed to the formation of ethenobases in DNA (Barbin 2000).

2.5. Carcinogenicity

No data about cancer induction in humans after a single exposure to VC have been reported. Two large epidemiologic studies of occupational exposure of adult workers (Mundt et al. 1999; Ward et al. 2000) show some evidence that risk for liver cancer or biliary-tract cancer was only increased after extended exposure duration. However, some studies have provided conflicting results (Weber et al. 1981), demonstrating a steep increase of in the SMR after very limited exposure duration (for details, see Appendix D). No epidemiologic studies have included newborn children as specific risk group.

There are sufficient epidemiologic data demonstrating a statistically significant elevated risk of liver cancer, specifically angiosarcomas, from chronic exposure to VC (summarized in WHO 1999; EPA 2000a,b; Boffetta et al. 2003). The possible association of brain, soft-tissue, and nervous-system cancer with VC exposure also has been reported. However, the evidence supporting a causal link between brain cancer and VC exposure is limited (EPA 2000a,b). Other studies have found an association between VC exposure and cancer of the hematopoetic and lymphatic systems (Greiser and Weber 1982; Simonato et al. 1991). Lung cancer also has been associated with VC, but the increased risk of lung cancer observed in some cohorts could be from exposure to polyvinyl chloride dust rather than VC monomer (Mastrangelo et al. 2003). In angiosarcoma of the human liver, mutations were observed which might be attributed to the formation of ethenobases in DNA (Barbin 2000).

Cancer risk estimates (unit risk) for VC based on epidemiologic studies have been estimated at 1×10^{-6} per $\mu g/m^3$ by the Netherlands (Anonymous 1987), 1×10^{-6} per $\mu g/m^3$ by the World Health Organization (WHO 1987, 2000), and $0.2\text{-}1.7 \times 10^{-6}$ by Clewell et al. (2001).

2.6. Summary

Odor thresholds of VC were reported in the range of 10 to 25,000 ppm (Patty et al. 1930; Baretta et al. 1969; Hori et al. 1972; AIHA 1997). Amoore and Hautala (1983) reported an odor threshold for VC of 3,000 ppm. This value represents the geometric average of three studies. Validated studies for determining the recognition and detection limit for VC were not available. VC is an anesthetic compound. Effects observed in acutely exposed VC workers and human volunteers indicate a characteristic sequence of symptoms starting with euphoria and dizziness, followed by drowsiness and loss of consciousness. After a 5-min exposure, health effects have been described at concentrations ≥8,000 ppm, and no effects were observed at 4,000 ppm (Lester et al. 1963). At 25,000 ppm, a 3-min exposure to VC caused dizziness, slight disorientation, and a burning sensation in the feet in two people (Patty et al. 1930). Mild headache and some dryness of the eyes and nose were the only complaints of volunteers exposed to VC at 491 ppm (the onset of headaches was not specified but was as-

sumed to have occurred after 3.5 h of exposure) (Baretta et al. 1969). Irritation of the eyes was reported in the context of an accidental exposure to lethal concentrations of VC (exposure concentration unknown) (Danziger et al. 1960).

No data on developmental or reproductive toxicity of VC in humans after acute exposure were found.

Huettner and Nikolova (1998) reported chromosomal aberrations in lymphocytes of humans accidentally exposed to VC more than 15 h after the accident. Atmospheric concentrations of VC were 1-8 ppm. Clastogenic changes were still detected 2 years later (Becker et al. 2001).

VC is a known human carcinogen that induces liver angiosarcomas and possibly brain tumors. Evidence for other tumors, including hepatocellular carcinoma, is contradictory (EPA 2000a,b). Mutations were found in human angiosarcomas of the liver, which might be attributed to the formation of ethenobases in DNA (Barbin 2000). Unit risk estimates based on epidemiologic studies have been published (Anonymous 1987; WHO 1987, 2000; Clewell et al. 2001).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Acute inhalation toxicity tests were performed in rats, mice, rabbits, and guinea pigs. However, none of LC_{50} studies would comply with modern testing standards. The lethality data are summarized in Table 5-4.

3.1.1. Rats

Mastromatteo et al. (1960) exposed rats (five per group) to VC (purity 99.5% maximum) at 10, 20, 30, or 40% (100,000 to 400,000 ppm) for up to 30 min. The animals were exposed in a 56.6-L inhalation chamber. The VC concentrations were adjusted by mixing it and air in a flow meter outside of the exposure chamber. The mixture was passed into to the animal chamber inlet to deliver a continuing stream (flow not given, VC concentrations not determined in the test chamber). Observations were made continuously and are summarized in Table 5-4. No animals died after exposure at 100,000 and 200,000 ppm. All animals exposed to VC at 300,000 ppm died after 15 min; their lungs, liver, and kidneys were congested and the lungs also had hemorrhagic areas.

Prodan et al. (1975) exposed rats (strain not specified) to VC for 2 h in exposure chambers (Pravdin type, with 580 L capacity). A total of 70 rats were used, with at least 10 animals per group. The animals were exposed (using Krakov's method) to variable concentrations of VC. Gas was first introduced at the lower part of the exposure chamber, without any ventilation. The gas was stirred by an inside pellet and was measured volumetrically with a Zimmermann-type spirometer. At VC concentrations of 15, 16, 17, 20, and 21% (150,000 to 210,000 ppm, nominal concentration), lethality was 23, 80, 90, 90, and 100%, respectively. The authors calculated an LC_{50} of 15% (about 150,000 ppm) and an

LC_{100} of 21% (about 210,000 ppm). All of the LC_{50}s and LC_{100}s reported in this study were 2-h values irrespective of the time of death. Findings shortly before death were general convulsions, respiratory failure, exopthalmia, and deflection of the head on the abdomen. Surviving animals rapidly recovered after exposure ended. Autopsy of the animals that died showed general congestion of the internal organs (lungs, liver, kidney, brain, and spleen); some animals (number not given) had pulmonary edema, marmorated liver, and kidney swelling.

TABLE 5-4 Summary of Acute Lethality Data on Vinyl Chloride in Laboratory Animals

Species	Concentration (ppm)	Duration	Number of Animals	Effect	Reference
Mouse	500	7 h/day, several days	29	LC_{17}	John et al. 1977, 1981
Mouse	1,000	At least 3 × 6 h	72	LC_{low}	Lee et al. 1977
Mouse	1,500	8 h	20	LC_0	Tátrai and Ungváry 1981
Mouse	1,500	12 h	60	LC_{90}	Tátrai und Ungváry 1981
Mouse	1,500	24 h	20	LC_{100}	Tátrai und Ungváry 1981
Mouse	100,000	2 h	40	LC_0	Prodan et al. 1975
Mouse	117,500	2 h	39	LC_{50}	Prodan et al. 1975
Mouse	150,000	2 h	61	LC_{100}	Prodan et al. 1975
Mouse	300,000	10 min	5	LC_{100}	Mastromatteo et al. 1960
Rat	100,000	8 h	18	LC_0	Lester et al. 1963
Rat	150,000	2 h	10	LC_{50}	Prodan et al. 1975
Rat	150,000	2 h	2	LC_{50}	Lester et al. 1963
Rat	200,000	30 min	5	LC_0	Mastromatteo et al. 1960
Rat	210,000	2 h	10	LC_{100}	Prodan et al. 1975
Rat	300,000	15 min	5	LC_{100}	Mastromatteo et al. 1960
Rabbit	200,000	2 h	4	LC_0	Prodan et al. 1975
Rabbit	240,000	2 h	4	LC_{50}	Prodan et al. 1975
Rabbit	280,000	2 h	4	LC_{100}	Prodan et al. 1975
Guinea pig	100,000	6 h	NR	LC_0	Patty et al. 1930
Guinea pig	200,000	2 h	4	LC_0	Prodan et al. 1975
Guinea pig	240,000	2 h	12	LC_{50}	Prodan et al. 1975
Guinea pig	150,000 to 250,000	18-55 min	NR	LC_{100}[a]	Patty et al. 1930
Guinea pig	280,000	2 h	4	LC_{100}	Prodan et al. 1975
Guinea pig	300,000	30 min	5	LC_{20}	Mastromatteo et al. 1960
Guinea pig	400,000	10-20 min	NR	LC_{100}[a]	Patty et al. 1930
Guinea pig	400,000	30 min	5	LC_{40}	Mastromatteo et al. 1960

[a]Number of animals per group and animals that died not specified.
Abbreviations: LC_x, lethal concentration with x% mortality; LC_{low}, lowest lethal concentration; NR, not reported.

In the context of a teratology study, John et al. (1981) exposed Sprague-Dawley rats intermittently with VC at 500 or 2,500 ppm for 7 days. At 2,500 ppm, 1/17 rats died, but the day of death was not specified by the authors (for study details see Section 3.3.).

Exposure of 18 Sherman rats (nine of each sex) to VC at 100,000 ppm for 8 h resulted in deep anesthesia, with consciousness regained 5 to 10 min after exposure ended. One female rat died after two exposures, and the remaining rats showed signs of chronic toxicity (not specified) prompting the authors to lower the VC concentration to 80,000 ppm to minimize mortality. Despite the lower concentration, mortality was considerable, especially in male rats exposed for more than 8 days. The animals were exposed in a 1,100-L steel chamber. The concentration in the chamber was initially raised rapidly to the desired level by admitting VC alone into the chamber until the effluent in the mixing chamber attained the desired level, as noted on the thermal conductivity meter. A fan mixed the VC with the air within the mixing chamber. Thereafter, the effluent from the 2-L mixing vessel was admitted to the chamber, the throughput was 20 L/min (Lester et al. 1963).

Exposure of two Sherman rats in a 10-L glass exposure chamber to VC at 150,000 ppm resulted in deep anesthesia within 5 min. One of two animals died from respiratory failure after 42 min (Lester et al. 1963) (for study details see earlier description).

3.1.2. Mice

Five mice were exposed to VC at 10, 20, 30, or 40% (100,000 to 400,000 ppm, nominal concentration) for up to 30 min (for study details see Section 3.1.1.) (Mastromatteo et al. 1960). One mouse exposed at 200,000 ppm died after 25 min, and all mice exposed at 300,000 ppm died after 10 min. No death occurred at 100,000 ppm. At 300,000 ppm, the lungs of the animals that died exhibited congestion of the lungs with hemorrhagic areas. Congestion of the liver and the kidney also were observed.

In ventilated exposure chambers of the Pravdin type, VC at 100,000 ppm for 2 h was not lethal to mice. VC at 150,000 ppm killed 46/61 mice within 1 h, and all animals died within 2 h. The authors calculated a 2-h LC_{50} of 117,500 ppm and a 2-h LC_{100} of 150,000 ppm (for study details and symptoms before death see Section 3.1.1.). When VC was administered to mice unmixed at 42,900 ppm, 70% (13 of 20) died less than an hour after exposure (Prodan et al. 1975).

Tátrai and Ungváry (1981) exposed CFLP mice to VC at 1,500 ppm for 2, 4, 8, 12, or 24 h (n = 20). Animals were observed for 24 h after exposure. An additional 40 animals were exposed for 12 h and survivors were evaluated 2 months after the exposure. Animals were exposed in dynamic exposure chambers with vertical airflow. The volume of the exposure chambers was 0.3 m^3; the vertical flow rate of the air was 3 m^3/h, at 20-23°C and 50-55% relative humid-

ity. Mortality was 100% in animals exposed for 24 h, and 90% in those exposed for 12 h. No deaths were reported in animals exposed for shorter durations. Exposure caused hemorrhages and vasodilatation characteristic of shock in the lungs. Additionally, shock-liver developed. The authors did not comment on the concentration difference between their experiment and earlier reports indicating much higher total VC concentrations as lethal. However, asphyxia is given as the cause of death in this study, which was not seen in other studies.

In a study designed to investigate long-term hepatic effects of VC, Lee et al. (1977) exposed CD-1 mice at 1,000 ppm for 6 h/day. Three of 72 mice died between day 3 and 9; all other mice, as well as replacement mice, appeared healthy throughout 12 months of exposure to VC. Autopsy showed acute toxic hepatitis with diffuse coagulation-type necrosis of hepatocytes, as well as tubular necrosis in the renal cortex.

In the context of a teratology study, John et al. (1981) exposed mice to VC at 50 or 500 ppm for 7 h/day on gestation days 6-15. At 500 ppm, 5/29 mice died, but the day of death was not specified by the authors.

3.1.3. Guinea Pigs

Patty et al. (1930) found VC at 15-25% (150,000-250,000 ppm) was lethal to guinea pigs within 1 h, and 40% (400,000 ppm) was lethal within 10-20 min. Gross pathology examinations revealed intense congestion and edema of the lungs, and hyperaemia of the kidneys and liver. The lungs were light pink, the cut section was uniformly light red, and bled freely. The authors concluded that VC is irritating to the lungs. No ocular or nasal irritation was described. However, it was unclear whether the atmosphere had been sufficiently mixed, and the number of animals per group was not specified.

Prodan et al. (1975) reported a 2-h LC_{50} for VC of 238,000 ppm and a 2-h LC_{100} of 280,000 ppm for guinea pigs exposed in a exposure chamber of the Pravdin type (the gas was permanently stirred by an inside pellet; study details are described in Section 3.1.1.). No animals died within 2 h at 200,000 ppm.

Yant (cited by Prodan et al. 1975) determined a 10-min lethal concentration for VC of 400,000 ppm in guinea pigs.

Exposure of guinea pigs to VC at 10, 20, or 30% (100,000-300,000 ppm) (5/group) did not result in death within 30 min, but one animal in the 300,000-ppm group died within 24 h after exposure. A 30-min exposure to VC at 40% (400,000 ppm) resulted in the death of one guinea pig, another animal died within 24 h, and the remaining three animals recovered (Mastromatteo et al. 1960; for study details see Section 3.1.1.). The liver of the animal from the 300,000-ppm group that died had severe fatty degeneration, was distended and very friable. In guinea pigs exposed at 400,000 ppm, liver effects were less pronounced. There was marked congestion of the lungs with hemorrhages in the dead animals.

3.1.4. Rabbits

Rabbits (n = 4) were exposed to VC at various concentrations for 2 h in exposure chambers (Pravdin type). No deaths occurred at 200,000 ppm, 50% mortality occurred at 240,000 ppm within the first hour of exposure, and all animals died when exposed at 280,000 ppm (Prodan et al. 1975) (for details see Section 3.1.1.).

In the context of a teratology study, John et al. (1981) exposed rabbits intermittently to VA at 500 or 2,500 ppm for 7 days. At 2,500 ppm, one of seven rabbits died, but the authors did not specify the day of death. For study details see Section 3-3.

3.2. Nonlethal Toxicity

Inhalation toxicity tests of VC were performed in dogs, mice, rats, guinea pigs, rabbits, and monkeys. A summary of the nonlethal effects of VC are summarized in Table 5-5.

3.2.1. Dogs

Oster et al. (1947) exposed two beagle dogs to VC at 50% in oxygen for induction of anesthesia (no duration given) and subsequently with 7% VC (70,000 ppm) in oxygen to maintain narcosis (no further study details described). Narcosis induction was rapid, and all animals showed salivation. Muscle relaxation was incomplete; good relaxation of the abdomen was found, but rigidity and uncoordinated movements of the legs was observed. The recovery period was quick but accompanied by violent excitation. In four dogs anesthetized with VC at 10% (100,000 ppm), no effects on blood pressure were observed, but cardiac irregularities (intermittent tachycardia, extraventricular systoles, and vagal beats) occurred. All symptoms disappeared rapidly when the dogs were exposed ethyl ether, as well as after termination of narcosis.

The cardiac-sensitizing potential of VC was tested in beagle dogs (Clark and Tinston 1973, 1982). Only summary data were presented in the publications. Conscious dogs (four to seven per dose group) were exposed to VC by a face mask for 5 min. Oxygen was added when high concentrations were used. During the last 10 seconds of exposure, a bolus injection of epinephrine (5 μg/kg) was given via a cephalic vein and electrocardiograph changes were recorded. Another injection of adrenaline was given 10 min after the end of exposure. Cardiac sensitization was deemed to have occurred when ventricular tachycardia or ventricular fibrillation resulted from the challenge injection of epinephrine. An increased number of ventricular ectopic beats was not considered evidence of sensitization because such effects could often be produced by a challenge injection of epinephrine during control air exposures. The EC_{50} for cardiac sensitization was 50,000 ppm (95% confidence interval [CI]: 37,000-68,000 ppm). The postexposure injection of epinephrine did not result in arrhythmias (Clark and Tinston 1973).

TABLE 5-5 Summary of Nonlethal Effects of Vinyl Chloride in Laboratory Animals

Species	Concentration (ppm)	Duration	Effect	Reference
Dog	50,000	5 min	EC_{50}, cardiac sensitization in response to epinephrine.	Clark and Tinston 1973
Dog	71,000	5 min	EC_{50}, cardiac sensitization in response to epinephrine.	Clark and Tinston 1982
Dog	100,000	Not specified	Anesthesia and cardiac arrhythmia.	Oster et al. 1947
Mouse	1,500	2 h	Stasis of blood flow, decreasing enzyme activities in liver, subcellular liver damage, centrilobular necrosis.	Tátrai and Ungváry 1981
Mouse	5,000	1 h	No clinical signs of toxicity.	Hehir et al. 1981
Mouse	50,000	40 min	Twitching, ataxia, hyperventilation, hyperactivity.	Hehir et al. 1981
Mouse	100,000	6 min	No cardiac arrhythmia.	Aviado and Belej 1974
Mouse	100,000	6 min	Cardiac sensitization in response to adrenaline.	Aviado and Belej 1974
Mouse	100,000	15 min	Pronounced tremor, unsteady gait, and muscular incoordination.	Mastromatteo et al. 1960
Mouse	100,000	30 min	Unconsciousness, side position after 20 min, lung hyperemia persisting for >2 wk.	Mastromatteo et al. 1960
Mouse	100,000	2 h	Intense salivation and lacrimation immediately after onset of exposure, narcosis within 1 h.	Prodan et al. 1975
Mouse	200,000	6 min	Cardiac arrhythmia (second-degree block, ventricular ectopics).	Aviado and Belej 1974
Mouse	200,000	30 min	Deep narcosis, side position after 5 min, pulmonary congestion for >2 wk.	Mastromatteo et al. 1960
Rat	500	10 × 7 h	No effects on liver weight in rats exposed on days 6-15 of gestation (LOAEL: 2,500 ppm)	John et al. 1977
Rat	1,500	24 h	No acute toxicity.	Tátrai and Ungváry 1981
Rat	1,500	9 × 24 h	Increased relative and absolute liver weight, increased number of resorbed fetuses and fetal losses in rats exposed on days 1-9 of gestation.	Ungváry et al. 1978
Rat	30,000	4 h	Slightly soporific.	Viola 1970
Rat	50,000	1 h	No clinical signs of toxicity.	Viola et al. 1971; Hehir et al. 1981
Rat	50,000	2 h	Moderate intoxication (not further specified), loss of righting reflex.	Lester et al. 1963

(Continued)

TABLE 5-5 Coninued

Species	Concentration (ppm)	Duration	Effect	Reference
Rat	50,000	6 h	No clinical or histologic signs of hepatic toxicity.	Jaeger et al. 1974
Rat	60,000	2 h	Intense intoxication, righting reflex still present.	Lester et al. 1963
Rat	100,000	15 min	Tremor, ataxia.	Mastromatteo et al. 1960
Rat	100,000	30 min	Deep narcosis, lung hyperemia persisting for >2 wk.	Mastromatteo et al. 1960; Jaeger et al. 1974
Rat	100,000	2 h	Deep anesthesia, loss of corneal reflex, no gross pathology changes.	Lester et al. 1963
Rat	100,000	6 h	Anesthesia, liver centrilobular vacuolization, slight increase in AKT and SDH activity in serum.	Jaeger et al. 1974
Rat	100,000	8 h	Deep anesthesia.	Lester et al. 1963
Rat	200,000	2 min	Muscular incoordination.	Mastromatteo et al. 1960
Rat	200,000	30 min	Deep narcosis, fatty liver infiltration, pulmonary congestion for >2 wk.	Mastromatteo et al. 1960
Guinea pig	10,000	8 h	No visible effects.	Patty et al. 1930
Guinea pig	25,000	5 min	Ataxia, unsteadiness.	Patty et al. 1930
Guinea pig	25,000	90 min	Quiet, apparent unconsciousness.	Patty et al. 1930
Guinea pig	25,000	6-8 h	Narcosis, slow and shallow respiration, unsteadiness.	Patty et al. 1930
Guinea pig	100,000	15 min	Unsteady gait and muscular incoordination.	Mastromatteo et al. 1960
Guinea pig	100,000	30 min	Unconsciousness, slightly hyperemic lungs for 2 wk after exposure.	Mastromatteo et al. 1960
Guinea pig	200,000	30 min	Pulmonary congestion persisting 2 wk after exposure.	Mastromatteo et al. 1960
Guinea pig	200,000	2 h	Deep narcosis.	Prodan et al. 1975
Rabbit	200,000	2 h	Deep narcosis.	Prodan et al. 1975
Monkey	25,000-100,000	5 min	Myocardial depression.	Belej et al. 1974

Abbreviations: AKT, alanine-α-ketoglutarate transaminase; ED_{50}, effective concentration eliciting 50% response; LOAEL, lowest-observed-adverse-effect level; SDH, sorbitol dehydrogenase.

Clark and Tinston (1982) conducted a second study on cardiac sensitization to epinephrine in beagle dogs (six male or female, not further specified) after 5 min of exposure to VC. Methods were appeared identical to the study published in 1973 (Beck et al. 1973). The EC_{50} for cardiac sensitization was 71,000 ppm (95% CI: 61,000-83,000 ppm). The effect concentrations were above the concentration that caused effects on the central nervous system in rats (EC_{50}: 38,000 ppm after 10 min). The authors did not comment on their earlier findings, which indicated a lower EC_{50} for cardiac sensitization. The authors discussed that cardiac sensitization is unlikely to occur in man in the absence of effects on the central nervous system and that dizziness should act as an early warning that a dangerous concentration was reached.

3.2.2. Rats

Effects after Single Exposure

In rats exposed to VC at 100,000 ppm, increased motor activity occurred after 5 min; pronounced tremor, unsteady gait, and muscular incoordination occurred after 15 min; side position occurred at 20 min; and deep narcosis occurred after 30 min. When the concentration was increased, deep narcosis occurred at 200,000 ppm after 15 min and at 300,000 ppm after 5 min, and muscular incoordination was observed after 2 or 1 min, respectively. At autopsy, the lungs of the animals in the 100,000-ppm group showed a very slight hyperemia even 2 weeks after exposure; in the 200,000-ppm group, congestion of the lungs in all animal and some fatty infiltration in the liver of one rat were observed. Irritation (not further explained) was reported to occur immediately after onset of exposure to VC at 10, 20, or 30% (Mastromatteo et al. 1960).

Lester et al. (1963) exposed Sherman rats for up to 2 h to VC at 50,000-150,000 ppm. The total gas flow was 50 L/min. The desired concentrations were obtained by metering air and VC (gas chromatography of the liquid phase indicated more than 99% VC) through flow meters and passing the appropriate flows through a 2-L mixing chamber. The desired concentration was passed through a 10-L all-glass exposure chamber containing two rats. The concentration was continuously monitored by a thermal conductivity meter (less than 5% deviation from the desired concentration). At a VC concentration of 50,000 ppm for 2 h, moderate intoxication was observed and the righting reflex was lost. At 60,000 ppm for 2 h, intoxication was more intense but the righting reflex was still present (lost at 70,000 ppm). The corneal reflex was lost at 100,000 ppm. On removal from the chamber, the animals returned to the pre-exposure state rapidly. Exposure to VC at 150,000 resulted in deep anesthesia within 5 min, and one of two animals died from respiratory failure after 42 min. Autopsy revealed edema and congestion of the lungs. The second rat recovered quickly after removal from the exposure chamber.

Exposure of 18 Sherman rats to VC at 100,000 for 8 h resulted in deep anesthesia, with consciousness regained 5 to 10 min after removal from the exposure chamber. One female rat died after two exposures, and the remaining rats showed signs of toxicity (not specified) (Lester et al. 1963; study details presented in Section 3.1.1.).

Male Holtzman rats were exposed once to VC at 0.5, 5, or 10% (5,000, 50,000, or 100,000 ppm, respectively) for 6 h in a dynamic inhalation chamber. Animals were killed 24 h after the exposure (no further details described). Exposure at 0.5 or 5% for a single 6-h period did not cause a substantial rise in serum alanine-α-ketoglutarate transaminase or sorbitol dehydrogenase, two cytoplasmic liver enzymes that correlate with liver injury. A slight increase in these parameters of hepatoxic response and centrilobular hepatocellular vacuolization were found only after exposure to VC at 10%. At the lower concentrations, the livers were histologically normal. Exposure to VC at 10% appeared anesthetize the animals (Jaeger et al. 1974).

Rats exposed to VC at 30,000 ppm for 4 h were slightly soporific (Viola 1970). No other acute toxicity data were reported; animals were exposed for total of 12 months.

Tátrai and Ungváry (1981) exposed CFY rats to VC at 1,500 ppm VC for 24 h (n = 20; study details are presented in Section 3.1.2.). No morphologic changes of the liver were observed.

F344 and Sprague-Dawley rats were treated for 1 h with VC at 50, 500, 5,000, or 50,000 ppm (about 90 rats/group). The chambers were Rochester-type, stainless steel, 1,000 L, and constructed to provide laminar airflow to ensure uniform exposure of test animals. The concentration of gas in the inhalation chamber was monitored by a gas chromatograph. No remarkable signs of toxicity were observed. When removed from the test atmosphere, all animals recovered to normal appearance within 24 h (Hehir et al. 1981). Viola et al. (1971) also reported no toxicity in rat exposed to VC at 50,000 ppm for 1 h.

Effects after Repeated Exposure

Pregnant rats exposed to VC at 1,500 ppm for 7 or 9 days (day 1-9 or 8-14 of gestation) had increased absolute and relative liver weights, but no visible changes when examined by light microscopy. The liver-to-body-weight ratio of rats exposed on days 1-9 of gestation was 4.25% compared with 3.71% in the controls, but such an increase was not observed in animals treated on days 14-21 of gestation. Additionally, an increased number of resorbed fetuses and fetal losses were observed in animals exposed during the first 9 days of pregnancy (Ungváry et al. 1978, for study details see Section 3.3.).

Intermittent exposure of rats to VC at 500 or 2,500 ppm on days 6-15 of pregnancy resulted in increased relative and absolute liver weights and an increased number of resorbed fetuses and fetal losses at 2,500 ppm (the no-observed-adverse-effect level [NOAEL] was 500 ppm). The absolute liver

weight was 15.55 grams (g) in the 2,500-ppm group and 14.27 g in the control group, and the relative liver weight was 37.8 mg/g in the 2,500-ppm group and 34.4 mg/g in the control group. One dam died at 2,500 ppm (John et al. 1977, 1981; see Section 3.3 for details).

After repeated inhalation exposure to VC at 5,000 ppm (7 h/day, 5 days/week) for 4 weeks, vacuolized hepatocytes with swollen mitochondria were found in male and female rats (Feron et al. 1979). After 13 weeks of inhalation exposure, an increase in relative liver weight was seen in male rats and centrilobular hypertrophy in females even at the lowest VC concentration of 10 ppm (Thornton et al. 2002).

3.2.3. Mice

Mice exposed to VC at 100,000 ppm for 30 min showed increased motor activity after 5 min; twitching of extremities after 10 min; pronounced tremor, unsteady gait, and muscular incoordination occurred after 15 min; side position at 20 min; and deep narcosis occurred after 30 min. When the VC concentration was increased, deep narcosis occurred at 200,000 ppm after 15 min (side position after 5 min) and at 300,000 ppm after 5 min (lethal after 10 min). The 100,000-ppm group had slight hyperemia of the lungs. One of five animals showed degenerative changes in the tubular epithelium of the kidney with hydropic swelling. Exposure to VC at 200,000 ppm for 30 min resulted in congestion of the lungs that persisted for 2 weeks. Irritation (no further details) occurred immediately after onset of exposure to VC at 10, 20, or 30% (Mastromatteo et al. 1960).

Prodan et al. (1975) exposed white mice (strain not specified) for 2 h to VC at 90,000 to 200,000 ppm with ventilation in an exposure chamber (for study details see Section 3.1.1.). Salivation and lacrimation appeared shortly after onset of exposure, with narcosis reached within less than 1 h in the majority of the animals. Typical narcosis stages of excitement with tonic-clonic convulsions and muscular contractions, tranquility and relaxation were described. Other symptoms were accelerated respiration, proceeding to bradypnea, Cheyne-Stokes type of respiration, and respiratory failure. No differentiation of the symptoms according to VC concentration was made. Concentrations of 110,000 ppm and greater were lethal. All symptoms were rapidly reversible in surviving mice.

Male mice exposed to VC at 50,000 ppm for 1 h exhibited hyperventilation after 45 min, with twitching and ataxia. Female mice became hyperactive after 40 min of exposure. Respiratory difficulty and ataxia were observed in approximately 25% of female mice after 55 min. At 5,000 ppm, no mice were visibly affected. Study details are presented in Section 3.2.2 (Hehir et al. 1981).

Tátrai and Ungváry (1981) exposed CFLP-mice to VC at 1,500 ppm for 2-24 h. Histology examination found circulation stasis in the liver, with concomitant decreases in enzyme activities (succinic dehydrogenase and acid phos-

phatase), subcellular damage, and centrilobular necrosis were found after 2 h. After 24 h, shock liver developed. Severity of changes increased with exposure duration. After 12 h, signs of circulatory disturbances included pulmonary hemorrhages and vasodilatation. No changes were observed in brain or kidney. Ninety percent of the animals died after 12 h and 100% died after 24 h.

Kudo et al. (1990) exposed male ICR mice (4-5/group) to VC for 4 h at 5,000 and 10,000 ppm on 5 and 6 successive days, respectively. Basophilic stippled erythrocytes (indicating disturbances in erythropoiesis) appeared in peripheral blood smears on the second day, indicating possible bone marrow damage after a single exposure; no difference was observed between the test concentrations. Reticulocyte numbers also were increased, but were not statistically significant. The authors discuss that the increase was partly from repeated blood sampling and was not entirely from exposure to VC. Exposure at lower concentrations (30-40 ppm) induced basophilic stippled erythrocytes after 3 days.

Lee et al. (1977) exposed CD-1 mice to VC at 1,000 ppm for 6 h/day in the context of a long-term hepatotoxicity and carcinogenicity study. Five percent of the mice died within the first days from acute toxic hepatitis, but no signs of toxicity were observed in the other animals.

Aviado and Belej (1974) reported that exposure of male Swiss mice to VC at 100,000 ppm for 6 min did not cause arrhythmia, but 200,000 ppm induced a second-degree block and ventricular ectopics (animals were anesthetized with sodium pentobarbital). Cardiac sensitization was observed after 6-min exposure to VC at 100,000 ppm (animals were anesthetized with sodium pentobarbital). Mice were exposed by face mask which was in contact with a 6-L flaccid bag. The inhalation gas was balanced with oxygen to prevent asphyxia. The number of animals tested was not specified. For testing cardiac sensitization, the animals received were injected intravenously with adrenaline hydrochloride (6 μg/kg).

3.2.4. Guinea Pigs

Guinea pigs exposed to VC at 100,000 ppm for 30 min showed increased motor activity after 5 min, unsteady gait and muscular incoordination occurred after 15 min, tremors and twitching of extremities after 20 min, and side position with tremors after 30 min and unconsciousness in one animal. When the VC concentration was increased deep narcosis occurred at 200,000 and 300,000 ppm after 30 min and at 400,000 ppm after 5 min. Guinea pigs in the 100,000-ppm group showed only slightly hyperemic lungs 2 weeks after exposure. At 200,000 ppm, congestion of the lungs was observed. At 300,000 and 400,000 ppm, survivors showed marked pulmonary congestion with hemorrhagic areas and edema. In one animal in the 400,000-ppm group, the tracheal epithelium was completely absent and the animal was unable to clot. Irritation (no further details) occurred immediately after onset of exposure to VC at 400,000 ppm, but irritation was not reported at lower dose levels (Mastromatteo et al. 1960).

Prodan et al. (1975) exposed guinea pigs (strain not specified) to VC at 20-28% (200,000-280,000 ppm) for 2 h. Symptoms of progressing anesthesia as described for mice were observed in a time-dependent manner; muscular contractions were more pronounced in guinea pigs than in mice. Lethality increased with VC concentration, and all symptoms were rapidly reversible in surviving animals. VC at 200,000 ppm were not lethal within 2 h (n = 4). Observation of the animals did not exceed 2 h.

Guinea pigs exposed to VC at 5,000 or 10,000 ppm for up to 8 h did not show any visible symptoms. Unconsciousness and deep narcosis occurred at 25,000 ppm after 90 min, and slow, shallow respiration was observed within 6-8 h. No deaths were observed within 8 h. Similar symptoms were observed at 50,000 ppm (unconsciousness within 50 min; slow, shallow respiration within 360 min; no death within 6 h). At 100,000 ppm, there was incomplete narcosis 2 min after onset of exposure, and none of the animals died within the 6-h exposure period (Patty et al. 1930).

3.2.5. Rabbits

Prodan et al. (1975) exposed rabbits (strain not specified) to VC at 20-28% (200,000-280,000 ppm) for 2 h. Symptoms of progressing anesthesia as described for mice were observed in a time-dependent manner; rabbits showed heavy respiration, salivation, and muscular contractions. Lethality increased with VC concentration, and all symptoms were rapidly reversed in survivors. No death was observed within 2 h (n = 4).

Tátrai and Ungváry (1981) exposed 20 New Zealand rabbits to VC at 1,500 ppm for 24 h. No acute clinical effects or pathologic changes of the liver were found 24 h after exposure.

3.2.6. Monkeys

Rhesus monkeys were anesthetized by intravenous injection of sodium pentobarbital (30 mg/kg). An electrocardiograph was implanted for continuous monitoring. Three monkeys were exposed to VC at 2.5, 5, or 10% for 5 min, and the exposure was alternated with room air for 10 min. Myocardial force was reduced by 2.3, 9.1, and 28.5%, respectively. The effect was significant with VC at 10%. There was no effect on the heart rate in comparison with controls. It was unclear whether an additional challenge with epinephrine was applied (Belej et al. 1974).

3.3. Developmental and Reproductive Toxicity

John et al. (1977, 1981) exposed pregnant CF-1 mice to VC at 50 or 500 ppm and Sprague-Dawley rats and New-Zealand rabbits at 500 or 2,500 ppm

during organogenesis (days 6-15 of gestation for mice and rats and days 6-18 in rabbits, 7 h/day). Exposure was conducted in 3.7 m^3 stainless-steel chambers of under dynamic conditions. The atmosphere of VC was generated by diluting gaseous VC with filtered room air at a rate calculated to give the desired concentration. The actual atmosphere was measured with an infrared spectrophotometer (no further details presented). Animals were sacrificed on day 18 (mice), 21 (rats), or 29 (rabbits) and a variety of parameters assessed.

VC at 500 ppm was maternally toxic to mice (five of 29 bred females died); weight gain, food consumption, and the absolute liver weight were decreased. Maternal toxicity was not evident in mice exposed at 50 ppm. In mice exposed at 500 ppm, the number of live fetuses per litter and fetal weight were decreased, probably from increased maternal toxicity, and fetal resorptions were increased. Moreover, fetal resorptions were within the range of historical control values. Fetal crown-rump length was significantly increased in mice exposed to VC at 50 ppm, but not those at 500 ppm. Delayed ossifications in the skull and sternum bones and unfused sternebrae were observed in the fetuses of the 500-ppm group.

Rats exposed at 500 ppm gained less weight than controls, but body weight was not significantly different from the controls. At 2,500 ppm, one maternal death occurred among 17 females and decreased food consumption and an increase in absolute and relative liver weight were observed. No significant changes were observed in rat fetuses, except for reduced fetal body weight and increased crown-crump length at 500 ppm (neither effect observed at 2,500 ppm). The incidence of dilated ureter was significantly increased in the 2,500-ppm group compared with the control group, and the number of lumbar spurs was increased at 500 ppm but not at 2,500 ppm.

One of seven bred female rabbits exposed to VC at 2,500 ppm died. Rabbits exposed at 500 ppm had decreased food consumption, but body weight was not significantly affected. The number of live fetuses per litter was slightly decreased in the 500-ppm group compared with controls (7 vs. 8 fetuses/litter), but no effect on litter size resulted from exposure at 2,500 ppm. Ossification of the sternebrae was delayed at 500 ppm, but not at 2,500 ppm.

Most of the observed effects were exaggerated when 15% ethanol was added to the drinking water, indicating an additive fetotoxic effect of ethanol and VC. The difference between species should be correlated with the concentrations that in rats and rabbits exceed the threshold for metabolic saturation whereas, in mice, this threshold probably has not been reached. The authors attribute the observed developmental changes to maternal toxicity: "exposure to VC did not cause significant embryonal or fetal toxicity and was not teratogenic."

CFY rats were exposed to VC at 1,500 ppm for 24 h/day during the first (days 1-9), second (days 8-14), or third trimester (days 14 to 21) of gestation. The volume of the inhalation chambers was 0.13 m^3, the vertical flow rate was 2 m^3/h at a regulated temperature of 24-25°C and 50-55% relative humidity. The concentration of VC in the inhalation chamber was determined by a gas chro-

matograph. Section was performed on the day 21 of gestation. Treatment resulted in significantly increased frequency of resorptions in the group exposed during the first trimester (two fetuses resorbed in the control group vs. 12 fetuses in the exposed group; fetal loss was 1.7% in the control group and 5.5% in the exposed group). Two cases of central-nervous-system malformations were recorded in treated animals (not significant), and no increase in other malformations were detected. The absolute and relative maternal liver weights were increased in animals treated during the first and second week of pregnancy, but not in animals exposed during the third week, and there were no visible changes when examined by light microscopy (Ungváry et al. 1978).

Thornton et al. (2002) conducted a study investigating developmental toxicity and reproduction (two generation). In the developmental toxicity study, Sprague-Dawley rats were exposed during days 6-19 of gestation to VC at 0, 10, 100, or 1,100 ppm for 6 h/day. The animals were exposed in stainless-steel, wire-mesh cages within a 6,000-L stainless-steel and glass exposure chamber. Placement of the animals was rotated at each exposure. No feed was provided during exposure, but water was available ad libitum. The temperature was 16-28°C, the relative humidity was 29-79%, and the air-flow rate was 1,200 L/min. VC was delivered from a compressed gas cylinder to a Scott Specialty Gases regulator equipped with inlet and outlet back pressure gauges, and gas test atmosphere was analyzed hourly with an ambient-air analyzer equipped with a strip chart recorder. Maternal body-weight gains were slightly, but statistically significantly, suppressed at all concentration during gestation days 15-20 and 6-20. Statistically significant increases in relative kidney weight were found in dams exposed to VC at 100 ppm, and in relative kidney and liver weights at 1,100 ppm. No other adverse effects were observed in this study.

In the two-generation study, exposure to VC started 10 weeks before mating. Other experimental details are provided above. One male rat in the 10-ppm group and one female rat in the control group died. Mating indices and pregnancy rates for the F_0 generation were comparable between the control and exposed groups. The live-birth index was significantly decreased whereas the number of stillborn pups was significantly increased in the F_0 generation exposed to VC at 1,100 ppm. These effects were regarded by the authors to be unrelated to exposure, because they were not dose dependent and were in the range of the historical control values. In male rats of the F_0-generation, absolute and relative liver weights were significantly increased in all exposure groups. Absolute epididymis and kidney weights were increased in male rats exposed at 100 ppm group. Although there were no changes in the liver weight of female F_0 rats, there were histologic alterations in the liver at all concentrations (hepatocytes were enlarged with increased acidophilic cytoplasm within the centrilobular areas of the liver). Centrilobular hypertrophy was observed in male and female rats exposed at 100 and 1,100 ppm and in two females of the 10-ppm group (Thornton et al. 2002).

One male rat in the F_1 control group died from unknown reasons. In the F_2 litters, there was a statistically significant decrease in the mean number of pups

delivered in the 1,100-ppm group. The authors considered this effect to be unrelated to exposure, because the values were lower than those of the F_1 control-group values but comparable to those of the F_0 control group. In the F_1 generation, there was a statistically significant increase in the absolute and relative liver weights of male rats exposed at 100 and 1,100 ppm (absolute liver weight also was increased in female rats, but was not statistically significant). Absolute and relative spleen weights were increased in male rats exposed at the highest concentration. Male (100 and 1,100 ppm) and female (all concentrations) rats had centrilobular hypertrophy. Additionally, altered foci (acidophilic, basophilic, and clear-cell foci) were observed in male and female F_1 rats exposed at 1,100 ppm, and sometimes at 100 ppm (foci also were observed in two F_0 male rats at 1,100 ppm).

3.4. Genotoxicity

The mutagenic properties of VC have been tested in a variety of bacteria with the Ames test. Positive results were obtained with *Salmonella typhimurium* TA100 and TA1535 when VC was tested at high concentrations and long exposure durations, especially with metabolic activation. VC is genotoxic only after metabolic activation in other tests, such as forward-mutation assays, gene-conversion assays in yeast, cell-transformation assays, unscheduled DNA synthesis, and sister-chromatid exchange assays in mammalian cells (summarized in WHO 1999). Tests were performed with VC at 5-100% in the atmosphere or at 0.025-50 mM in culture medium.

In vivo assays of VC for genotoxicity were performed with mice, rats, and hamsters. VC also has been tested in *Drosophila melanogaster*. Increased host-mediated forward mutations were observed after oral exposure to VC, whereas negative results were obtained in dominant-lethal assays with mice exposed by inhalation and in rat and mouse spot tests. Micronucleus formation in mice (VC at 50,000 ppm for 4-6 h; 1,000 ppm for 4 h, two exposures), cytogenetic aberrations in rats (1,500 ppm for 1-12 weeks) and hamsters (25,000 ppm for 6-24 h), and loss of sex chromosomes in *D. melanogaster* (50,000 ppm for 48 h) indicated dose-related chromosomal abnormalities. Also, increased DNA damage was demonstrated by alkaline elution assays in mice and sister-chromatid exchange formation in hamsters (summarized in WHO 1999). Further experiments with known metabolites of VC indicate that genotoxic effects are probably mediated by reactive intermediates with chloroethylene oxide being most effective.

DNA adducts of VC metabolites with miscoding properties have been directly detected after incubation of bacterial or phage DNA in vitro or in *Escherichia-coli* cells with DNA-adduct indicator systems in vivo with activated VC (summarized in WHO 1999). Covalent binding has been frequently observed after single- and short-term exposure.

Bolt et al. (1980) detected irreversible attachment of radioactive [1,2-^{14}C]VC to hepatic macromolecules in the rat. After a single exposure of adult

rats to [^{14}C]VC at 250 ppm for 5 h, the total amount metabolized per individual rat was 37 µmol. VC metabolites at 23 pmol/100 mg of liver wet weight were irreversibly bound to DNA. Alkylation products of d-guanosine amounted to 0.35 pmol.

Laib et al. (1989) exposed adult Wistar rats to [1,2-^{14}C]VC at 700 ppm. The animals received either a single 6-h exposure or two 6-h exposures separated by a treatment-free interval of 15 h. The following amounts of [^{14}C]VC-derived radioactivity in liver DNA was observed: 3.6 ± 0.2 pmol 7-(2'-oxoethyl)guanine (OEG)/mg DNA in male rats after a single exposure and 5.2 ± 0.5 pmol OEG/mg DNA in female rats after two exposures.

Watson et al. (1991) exposed adult male F344 rats (nose only) for 6 h to atmospheres containing [1,2-^{14}C]VC at nominal concentrations of 1, 10, or 45 ppm. The alkylation frequencies of OEG in liver DNA were 0.026, 0.28, and 1.28 residues OEG per 10^6 nucleotides, respectively. These data indicate a linear relationship between exposure and DNA adducts in rats. There was no evidence to indicate the formation of the cyclic adducts 1,N^6-ethenoadenine (εA) or 3,N^4-ethenocytosine (εC). The threshold for detecting these adducts were about 1 adduct per 1×10^8 nucleotides.

Swenberg et al. (2000) reported dose-dependent data on etheno-adducts using a combination of immunoaffinity and gas-chromatography high-resolution mass spectrometry. Adult F344-rats were exposed to VC at 0, 10, 100, or 1,100 ppm for 6 h/day, 5 days/week for 1 or 4 weeks. The mean for N^2,3-ethenoguanine (εG) in a mixed liver cell suspension from unexposed control rats was 90 ± 40 fmol/µmol guanine. Exposure to VC at 10 ppm for 1 or 4 weeks resulted in εG concentrations of 200 ± 50 and 530 ± 11 fmol/µmol guanine, while exposure at 100 ppm resulted in 680 ± 90 and 2,280 ± 180 fmol/µmol guanine at 1 or 4 weeks, respectively. A much lesser effect was evident for the 11-fold greater exposure of 1,100 ppm because of metabolic activation was saturated, with 1,250 ± 200 and 3,750 ± 550 fmol/µmol guanine present in liver.

In addition to these studies, there are several investigations of the differences in sensitivity of young (preweaned) vs. adult animals. Laib et al. (1989) tested 11-day-old and adult Wistar rats by with [1,2-^{14}C]VC at 700 ppm. Adult rats received either a single 6-h exposure or two 6-h exposures separated by a treatment-free interval of 15 h. Pups received two 6 h exposures, according to the same treatment schedule. The following amounts of [^{14}C]VC in liver DNA were found after two exposures (female adults, male and female pups): 5.2 ± 0.5 pmol OEG/mg DNA (adults) and 25.5 ± 3.0 pmol OEG/mg DNA (pups). After a single exposure of adult male rats, the activity (3.6 ± 0.2 pmol OEG/mg DNA) was close to that found after two exposures.

After a 5-day exposure of F344 rats to VC at 600 ppm (4 h/day), the adduct levels in the liver were 162 ± 36 pmol OEG/µmol guanine and 1.81 ± 0.25 pmol εG/µmol guanine for the pups and 43 ± 7 pmol OEG/µmol guanine and 0.47 ± 0.14 pmol εG/µmol guanine for the adult animals (Swenberg et al. 1999).

Ciroussel et al. (1990) compared the concentrations of 1,N^6-ethenodeoxyadenosine (εdAdo) and 3,N^4-ethenodeoxycytidine (εdCyd) in BD

VI rats (7 day old pups and 13-week-old adults) treated with VC. The rats were exposed to VC at 500 ppm for 2 weeks (7 h/day, 7 days/week). Analyses (two for the pups, one for adults) of the liver adducts indicated molar ratios ($\times 10^{-7}$) of 1.30 and 1.31 (εdAdo/dAdo) and 4.92 and 4.67 (εdCyd/dCyd) in pups compared with 0.19 (εdAdo/dAdo) and 0.8 (εdCyd/dCyd) in adult rat.

Fedtke et al. (1990) measured the εG content in the liver of lactating Sprague-Dawley rats and their 10-day-old pups exposed to VC (600 ppm, 4 h/day for 5 days). εG concentrations found in liver DNA were 470 ± 140 fmol/μmol (dams) compared with 1,810 ± 250 fmol/μmol (pups). The mean background concentration of the control DNA was 60 ± 40 fmol/μmol (background subtracted from εG concentration). Similarly, Morinello et al. (2002) demonstrated higher εG-adduct concentrations in hepatocytes after weanling rats were exposed to VC at 10 ppm for 1 week (6 h/day) compared with adult animals. Control animals had εG concentrations of 0.55 ± 0.14 (adults) and 0.16 ± 0.01 (pups) mol/10^7 mol guanine; VC-treated animals had 1.4 ± 0.4 (adult) and 4.1 ± 0.8 (pups) mol/10^7 mol guanine. Adducts largely persisted over the 5-week recovery period.

Etheno adducts may be repaired by DNA glycolases. However, the incidence of these adducts did not fully return to background levels after an exposure-free period of 14 days (εG was 1.8 pmol/μmol immediately after exposure, 0.47 pmol/μmol after 14 days, and 90 fmol/μmol for controls). Etheno adducts also have a miscoding potential in vitro and in vivo (Swenberg et al. 1999).

Gene mutations were found in animal tumors associated with exposure to etheno-adduct-forming chemicals such as VC. Specifically, A→T mutations of the Ha-*ras* gene were found in seven of eight rat hepatocellular carcinomas, and various base-pair substitutions as mutations of *p53* were observed in 10 of 25 cases of angiosarcoma in the rat liver, which may be attributed to the formation of ethenobases in DNA (Barbin 2000).

3.5. Carcinogenicity

Inhalation exposure to VC causes liver tumors, especially angiosarcomas, hepatocellular carcinoma, and neoplastic liver nodules, in rats. Angiosarcomas at other sites also have been reported. Additionally, tumors at other locations have been found, such as Zymbal-gland tumors, neuroblastoma, and nephroblastoma in rats; lung tumors in mice; mammary-gland tumors in rats, mice, and hamsters; and skin tumors in rabbits and hamsters (summarized in ATSDR 1997; WHO 1999). Similar tumor types and sites also are observed after oral exposure. There is evidence that liver tumors are induced in female rats at lower doses than in males. There is also evidence that animals are more susceptible to tumor induction early in life (WHO 1999).

Short-term exposure experiments indicate increased susceptibility of newborn and young animals to VC (Maltoni et al. 1981; Drew et al. 1983). Drew et

al. (1983) found increased incidences of tumors in rats, mice, and hamsters exposed to VC during the first 6 month of life but when exposed later in life. For example, the incidence of liver hemangiosarcomas was 5.3% in rats exposed at ages 0-6 months and 3.8% in rats exposed at 6-12 months, but no tumors occurred in when rats were exposed at ages of 12-18 months or 18-24 months.

Maltoni et al. (1981, 1984) exposed newborn Sprague-Dawley rats to VC at 6,000 ppm or 10,000 ppm by inhalation (4 h/day, 5 days/week) from 1-day to 5-weeks of age. Forty-two rats (18 male, 24 female) were exposed at 6,000 ppm, and 44 (24 male, 20 female) were exposed at 10,000 ppm. Six dams were tested at each concentration. No direct control group was used; however, data from dams and newborn animals not exposed to VC in parallel experiments were included. Newborn animals were simultaneously exposed to milk from exposed dams (D. Soffritti, Laboratory of Prof. Maltoni, personal commun., August 2003). The authors found liver angiosarcomas in 17/42 and 15/44 newborn rats exposed to VC at 6,000 ppm or 10,000 ppm, respectively, but no tumors were found in the dams that had identical treatment. No angiosarcomas were found in a control group of 304 rats (parallel experiment). Additionally, hepatoma incidence was increased in newborn rats (20/42 and 20/44 in the 6,000-ppm and 10,000-ppm groups, respectively), but no hepatomas were not observed in their mothers. Only 1 hepatoma was found in a control group of 304 rats (parallel experiment). Results were determined after 124 weeks of observation. The internal dose of VC might have been influenced by oral uptake from milk of exposed dams. However, because of the very high inhalation exposure and saturation of metabolism, oral uptake of VC via contaminated milk might have contributed only a limited amount to the overall organ concentration of VC metabolites.

Maltoni et al. (1981, 1984) also exposed pregnant rats (30/concentration) to VC at 6,000 or 10,000 ppm for 1 week (4 h/day, days 12-18 of pregnancy). Thirty-two (13 male, 19 female) and 51 (22 male, 29 female) offspring were evaluated after exposure at the lower or the higher concentration, respectively. The incidence of hepatic angiosarcomas and hepatomas was not increased in transplacentally-exposed offspring. However, the incidence of Zymbal-gland carcinoma and nephroblastoma were increased after transplacental exposure.

Differences between pre- and post-natal exposure and carcinogenic outcome might be explained by hepatic CYP2E1 activity, which is lower prenatally than postnatally in rats (Carpenter et al. 1997) and humans (Cresteil 1998).

Froment et al. (1994) exposed four female Sprague-Dawley rats and their pups (22 males, 22 females) to VC at 500 ppm for 8 h/day, 6 days/week, from day 3 of gestation until 28 days after birth. At day 28 postpartum, the animals were weaned, and the males and females were separated and exposed for another 2 weeks (total exposure was 33 days). Surviving animals were killed at 19 month of age. In the VC-exposed rats, 66 hepatic lesions were identified, including nodular hyperplasia, endothelial-cell hyperplasia, peliosis, adenomas, benign cholangiomas, angiosarcoma of the liver, and hepatocellular carcinoma. Liver

tumors included eight hepatocellular carcinomas, 15 angiosarcomas of the liver, and two benign cholangioma. No further details were provided. It was assumed that oral exposure via mother's milk and inhalation exposure occurred simultaneously.

Hehir et al. (1981) found an increased incidence in lung tumors in ICR mice exposed once to VC for 1 h (age of mice not specified). Animals were exposed in an inhalation chamber to VC at concentrations of 50-50,000 ppm (Rochester-type inhalation chambers, 1,000 L with laminar air flow), and were observed for their lifetime. Tumor response was dose related: adenomas of the lung were found in 12/120, 14/139, 18/139, 24/143, and 45/137 mice exposed to VC at 0, 50, 500, 5,000, and 50,000 ppm, respectively. For carcinomas of the lung, the incidence was 0/120, 0/139, 1/143, and 3/137 (data from both sexes), respectively. A slight increase in hepatic-cell carcinoma occurred in male mice, but without a dose response (2/50, 2/64, 9/67, 6/68, and 4/63). No increase in tumor incidence was observed in the liver or lungs of rats treated in an identical fashion. Additional studies in A/J mice exposed to VC for 1 h/day at 500 ppm for 10 days or at 50 ppm VC for 100 days showed that for short-term exposure the concentration might be the most critical factor. In both experiments, primarily pulmonary adenomas were observed. However, the incidence of adenomas and progression to carcinoma were considered only marginal and not statistically significant in mice exposed at 50 ppm for 100 days (44.1% in exposed, 34.5% in control) whereas a significant increase of pulmonary adenomas was observed in animals exposed at 500 ppm for 10 days (about 74% in exposed, 34.4% in control).

Suzuki (1983) also reported that short-term exposure to VC (6 h/day, 5 days/week for 4 weeks) resulted in tumor formation in young CD1 mice (5-6 weeks old at first exposure). When the animals were killed after 12 weeks, pulmonary tumors were observed in the group exposed to the two highest concentrations (300 and 600 ppm). Forty or 41 weeks after exposure, pulmonary tumors were observed in all exposed animals (1-600 ppm) but not in control mice. In addition, subcutaneous and hepatic hemangiosarcoma were found. Angiosarcoma of the liver was found at necropsy (56 weeks after exposure) in one animal exposed to VC at 600 ppm for 4 weeks (Suzuki 1981).

TABLE 5-6 Carcinogenic Potency of Vinyl Chloride Based on Animal Experiments

Unit Risk, per $\mu g/m^3$	Reference
6.5×10^{-7} to 1.4×10^{-6}	Chen und Blancato 1989
8.8×10^{-6}	EPA 2000a,b
6×10^{-7} to 2×10^{-6}	Clewell et al. 1995
1.1×10^{-6}	Clewell et al. 2001
5.7×10^{-7}	Reitz et al. 1996

A hepatocellular adenoma developed after a single 12-h exposure of rats to VC at 1,500 ppm. That concentration was lethal to most of the animals (Tátrai and Ungváry 1981). However, the observed effect (asphyxiation) was not observed in other studies with similar concentrations.

In addition to angiosarcoma of the liver, several studies with limited exposure duration to VC confirm the occurrence of hepatocellular carcinomas and other preneoplastic parenchymal changes in adult animals (Feron et al. 1979; Thornton et al. 2002). However, these changes were seen to a much lesser extent than angiosarcoma in adult animals or hepatocellular changes in young animals (see below).

In accordance with these investigations in newborn rats, Laib et al. (1985a,b) reported that hepatocellular ATPase-deficient foci (premalignant stages) were observed in rats exposed to VC early in life. The exposure regimens were: (1) Wistar rats exposed at 10-2,000 ppm for 8 h/day, 5 days/week for 10 weeks, starting 1 day after birth (Laib et al. 1985a); (2) Wistar and Sprague-Dawley rats exposed at 2.5-80 ppm for 8 h/day for 3 weeks, starting 3 days after birth (Laib et al. 1985a); and (3) Wistar rats exposed at 2,000 ppm immediately after birth for 8 h/day, 7 days/week for 5, 11, 17, 47, or 83 days. The animals were exposed immediately after birth or starting at 7 or 21 days of age (Laib et al. 1985b). Exposure at 2,000 ppm did not result in ATPase deficient foci in very young (1-5 days of age) or in adult animals (90-160 days of age). However, relevant foci areas were found when animals were exposed to VC for short periods during growth (e.g., at 1-11 or 7-28 days of age). The foci persisted until evaluation at the age of 4 months (Laib et al. 1985b). After 10 weeks, induction of ATPase-deficient foci was dose dependent (nearly linear) at concentrations of 10-500 ppm in both Wistar and Sprague-Dawley rats. This finding is consistent with the findings that VC-metabolism follows first-order kinetics until saturation occurs at high concentrations (Laib et al. 1985a).

Quantitative cancer risk assessments based on animal experiments have been published by several authors and are summarized in Table 5-6. These estimates are based on experimental studies in adult animals exposed for a lifetime by Maltoni et al. (1981, 1984). There are only slight differences in the cancer risk estimated by Clewell et al. (1995, 2001) and Reitz et al. (1996), who both used physiologically-based pharmacokinetic models to extrapolate animal data to the humans. These data are in agreement with the unit risk estimates derived from epidemiologic data, confirming the order of magnitude. However, these risk estimates were only validated with data from adult animals and epidemiologic data from the workplace. A higher sensitivity of children was not incorporated into quantification (see data from Maltoni et al. 1981; Drew et al. 1983).

The estimates from Chen and Blancato (1989) were based on pharmacokinetic models and a modified multistage model of liver tumors. Additionally, increased sensitivity in early life stages was considered. Data from female and male animals were evaluated separately.

The most recently published risk estimate by EPA (2000a,b) is based on the animal experiments by Maltoni et al. (1981, 1984). Differences in the me-

tabolism between animals and humans were taken into consideration by use of a pharmacokinetic model. The increased sensitivity of children was taken into consideration. Additionally, tumors in sites other than the liver were considered. Unit-risk estimates based on epidemiologic studies were considered uncertain because of shortcomings in the epidemiologic studies. Besides the unit-risk estimate for full lifetime exposure (birth through death) of 8.8×10^{-6} per $\mu g/m^3$, EPA provided an estimate of risk for early life exposure of 4.4×10^{-6} per $\mu g/m^3$ and for adult exposure of 4.4×10^{-6} per $\mu g/m^3$. The unit risk for adults is based on the physiologically-based pharmacokinetic modeling of Clewell et al. (2001), with slight modifications of some parameters.

3.6. Summary

Acute exposure of experimental animals to VC results in narcotic effects, cardiac sensitization, and hepatotoxicity. Narcotic effects are characterized by a typical sequence of symptoms starting with euphoria and dizziness, followed by drowsiness and loss of consciousness. Finally, animals died from respiratory failure. Prodan et al. (1975) reported 2-h LC_{50} values for mice, rats, rabbits, and guinea pigs of 117,500, 150,000, 240,000, and 240,000 ppm, respectively. Dead animals had congested internal organs (especially the lungs, liver, and kidneys), pulmonary edema, and hemorrhagia (Mastromatteo et al. 1960; Prodan et al. 1975). No lethality was seen in mice after exposure to VC at 100,000 ppm for 2 h (Prodan et al. 1975). However, Tátrai and Ungváry (1981) reported that 90% and 100% of mice exposed to VC at 1,500 ppm died after 12 and 24 h of exposure, respectively. These results are not consistent with other lethality data.

Short-term exposure (up to 30 min) to VC at concentrations of 100,000-300,000 ppm resulted mainly in ataxia, increased motor activity, side position and unconsciousness, and slow and shallow respiration in laboratory aniamls (Mastromatteo et al. 1960). These are typical reactions before the onset of narcosis. Narcosis was observed in rats and mice after a 30-min exposure to VC at 200,000 ppm (Mastromatteo et al. 1960). Short-term exposure (5 min) to VC induced cardiac sensitization towards epinephrine in dogs (EC_{50}: 50,000 and 71,000 ppm in two independent experiments) (Clark and Tinston 1973, 1982). Similar effects also were seen in mice at higher concentrations of VC (Aviado and Belej 1974). In monkeys, only myocardial depression was observed with VC at 2.5-10%. It was unclear whether an addition challenge with epinephrine was administered (Belej et al. 1974). Histopathologic changes of the liver (vacuolization) were observed in rats after a single inhalation exposure to VC at 100,000 ppm for 6 h, but not at 50,000 ppm (Jaeger et al. 1974). In mice, however, Tátrai and Ungváry (1981) reported that stasis of the liver developed 2 and 4 h after exposure began. The authors observed decreasing enzyme activities in the liver and subcellular liver damage in mice exposed to VC at 1,500 ppm for 2 h; after 24 h, shock liver developed. Repeated exposure of rats to VC at 1,500 ppm for up to 9 days during pregnancy caused increased relative and absolute

liver weights, but no changes were found by light microscopy (Ungváry et al. 1978). In another developmental study, increased absolute and relative liver weights were observed in rats exposed intermittently to VC at 2,500 ppm on days 6-15 of pregnancy; the NOAEL was 500 ppm (John et al. 1977, 1981). In rats exposed at 5,000 ppm for 7 h/day, 5 days/week for 4 weeks, vacuolized liver cells were observed (Feron et al. 1979).

No studies of reproductive or developmental toxicity after single exposure to VC were found. John et al. (1977, 1981) investigated developmental effects in mice, rats, and rabbits after repeated exposure to VC. Developmental toxicity (e.g., delayed ossification) only occurred at maternally toxic concentrations. Ungváry et al. (1978) reported maternal liver toxicity in rats exposed to VC at 1,500 ppm for 24 h/day during the first or second trimester of gestation. Resorptions were significantly increased in the group exposed during the first trimester. A developmental-toxicity study in rats (exposed to VC at 10, 100, or 1,100 ppm, 6 h/day on days 6-19 of gestation) indicated that embryo-fetal development was not affected by VC at concentrations up to 1,100 ppm. The only toxic effects observed were an increased relative organ-to-body weight ratio for the kidney and liver at 1,100 ppm and for the kidney at 100 ppm in dams (Thornton et al. 2002). In a two-generation study in rats, no adverse effects on embryo-fetal development or reproductive capability were observed at concentrations up to 1,100 ppm. The primary target organ of VC, the liver, was increased in weight and had cellular alterations, such as centrilobular hypertrophy and altered hepatocellular foci, at VC concentrations of 100 and 1,000 ppm, with increased incidence in the F_1 generation (Thornton et al. 2002).

Positive results for genotoxicity after in vitro and single and repeated in vivo treatment have been reported for VC (e.g., induction of micronuclei at 50,000 ppm for 4-6 h; chromosomal aberrations at 25,000 ppm for 6-24 h) (WHO 1999). An increase in DNA adducts was seen in adult rats after a single 5-h exposure to VC at 250 ppm (Bolt et al. 1976). Watson et al. (1991) exposed adult male F344 rats for 6 h to atmospheres containing VC at 1, 10, and 45 ppm. The alkylation frequencies of OEG in liver DNA were 0.026, 0.28, and 1.28 residues per 1×10^6 nucleotides, respectively. There was no evidence of the formation of the cyclic adducts εA or εC. The threshold for detecting these adducts were about 1 adduct per 1×10^8 nucleotides. Adult rats repeatedly exposed to VC at 10 ppm for 6 h/day for 5 days showed slightly elevated etheno-adducts for εG compared with controls (200 ± 50 vs. 90 ± 40 fmol/μmol guanine) (Swenberg et al. 2000). Adduct levels were greater in young animals than in adult animals after identical treatment (Laib et al. 1989; Ciroussel et al. 1990; Fedtke et al. 1990). OEG residues are unlikely to cause mutations, however, the cyclic adducts εA, εC, and εG have miscoding potential; respective mutations (e.g., G→A transitions, A→T transitions) were observed in VC-induced tumors (Barbin 2000). Despite repair, adducts were not reduced to background levels 2 weeks after a 5-day exposure to VC at 600 ppm for 4 h/day (Swenberg et al. 2000).

Induction of liver tumors has been reported in rats after subacute (5 weeks and 33 days) exposure (Maltoni et al. 1981, 1984; Froment et al. 1994). The liver is the primary site of tumors after chronic exposure (for review see EPA 2000a,b). VC induced lung tumors in mice after a single 1-h exposure to VC at 5,000 ppm or 50,000 ppm (Hehir et al. 1981). After mice were exposed to VC at 1,500 ppm for 12 h, most of the animals died and a hepatocellular adenoma developed (Tátrai and Ungváry 1981). Suzuki (1983) reported that short-term exposure to VC (6 h/day, 5 days/week for 4 weeks) resulted in lung-tumor formation in young CD1-mice (5-6 weeks of age). Additionally, subcutaneous and hepatic hemangiosarcoma were found. Short-term exposure experiments by Drew et al. (1983), Maltoni et al. (1981), and Froment et al. (1994) also indicated increased susceptibility of newborn and young animals to tumor formation. Hepatoma (Maltoni et al. 1981) or hepatocellular carcinoma (Froment et al. 1994) developed to a greater extent in young animals compared with adults. Laib et al. (1985a,b) reported that hepatocellular ATPase-deficient foci (premalignant stages) were observed in rats exposed to VC. Relevant foci areas were found when animals were exposed to VC at 2,000 ppm for short periods during growth (e.g., at 1-11 or 7-28 days of age). The foci persisted until histologic examination at 4 months of age (Laib et al. 1985b).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Krajewski et al. (1980) estimated the retention of VC after inhalation through a gas mask in five male volunteers by measuring the difference between inhaled and exhaled concentrations. At VC concentrations of 3-24 ppm for 6 h, the average retention was 42%, independent of the VC concentration. The higher retention values (maximum 46% on average) dropped and remained relatively constant after 30 min. Interindividual retention rates varied from 20.2 to 79% at 12 ppm. Immediately after exposure was ceased, VC concentrations in expired air dropped rapidly. After 30 min, less than 5% of the initial chamber concentration could be measured. Buchter et al. (1978) determined a retention rate of 26-28% after 3-5 min of exposure to VC at 2.5 ppm in two individuals. Given the variability of VC retention found by Krajewski et al., these values might be attributed to interindividual differences. WHO (1999) reported that the average absorption of VC after inhalation exposure was 30-40%, without citing the relevant studies.

Absorption of inspired VC was calculated to be about 40% in rats (calculation based on the decline of ^{14}C-VC in a closed system) (Bolt et al. 1976). In Rhesus monkeys, VC also is efficiently absorbed after inhalation, as deduced from data on its metabolic elimination (no further quantification) (Buchter et al. 1980).

Whole-body exposure (excluding the head) of Rhesus monkeys to radioactive VC indicated that very little VC is absorbed through the skin (about 0.031 and 0.023% at 800 and 7,000 ppm, respectively, after 2-2.5 h) (ATSDR 1997). No additional data on dermal absorption of VC are available.

The percentage of VC remaining in the carcass of rats 72 h after oral exposure at 0.05, 1, and 1 00 mg/kg was 10, 11, and 2%, respectively. The data suggest almost complete elimination of VC (Watanabe et al. 1976b). In rats exposed to radioactive VC at 10 and 1,000 ppm, 14 and 15% of ^{14}C-activity, respectively, remained in the carcasses 72 h after exposure. Radioactivity was detected in the liver, skin, plasma, muscle, lung, fat, and kidneys, representing nonvolatile metabolites of VC (Watanabe et al. 1976a) or incorporation into C_1-pool (Laib et al. 1989).

Data on serum concentrations of VC are scarce. Ungváry et al. (1978) exposed pregnant rats to VC at 2,000-12,000 ppm. They determined that blood concentrations ranged from 19 µg/mL at 2,000 ppm to 48.4 µg/mL at 12,000 ppm, indicating no direct proportional relationship between VC air and blood concentrations. Feron et al. (1975) reported that blood concentrations of VC peaked at 1.9 µg/mL, 10 min after rats were administered VC by gavage at 300 mg/kg. The blood concentration of VC after oral exposure is much smaller than after inhalation; the difference might be from the effective hepatic clearance of VC after oral uptake.

Similar to other anesthetics, maximal blood concentration of VC after inhalation depends on the partial pressure of VC in the air. Blood concentrations of VC in the brain, which directly correlate with depth of narcosis (see below) and, presumably, cardiac sensitization, can be controlled by changing the concentration of VC in the air (by changing the partial pressure of VC). If equilibrium is reached between the partial pressure of VC in the air and in the blood (steady state), no further increase of VC in the blood is possible, even if the exposure duration is prolonged (Forth et al. 1987). The time necessary to establish a steady state mainly depends on the blood:air partition coefficient of the substance. The blood:air partition coefficient of VC in humans is 1.2 (Csanády and Filser 2001), similar to the partition coefficient for the anesthetic isoflurane of 1.4 (Forth et al. 1987). For isoflurane, equilibrium is reached in about 2 h, as derived by graphical extrapolation of the data on isoflurane (Goodman and Gilman 1975). For VC at much lower concentrations, the elimination half time of VC is estimated at 20.5 min (Buchter 1979; Bolt et al. 1981). Using that value, a steady state concentration for VC in blood of about 102.5 min can be calculated by standard estimation rules (5 × 20.5 min). Thus, at high or low concentrations, a relevant increase in internal concentrations of VC is not expected after more than 2 h of exposure. However, for shorter exposure durations, the relevant influence of time on the build-up of VC on internal concentrations should be taken into account.

VC is oxidized by cytochrome-P450 2E1 (CYP2E1) to the highly reactive epoxide 2-chloroethylene oxide. The epoxide can directly interact with DNA

and proteins or spontaneously rearrange to 2-chloroacetaldehyde, which might bind to proteins and DNA. 2-Chloroethylene oxide can also be transformed to glycol aldehyde by epoxide hydrolase or react with glutathione, leading to the formation *N*-acetyl-S-(2-hydroxyethyl)-cysteine. Chloroacetaldehyde is oxidized by aldehyde dehydrogenase to 2-chloroacetic acid that reacts with glutathione to form thiodiglycolic acid (which leads to the liberation of carbon dioxide). Comparison of in vitro metabolism with rat liver microsomes and in vivo experiments in rats shows that virtually all the metabolic activation of VC in vivo occurs in the liver (WHO 1999). At low concentrations, VC is metabolically eliminated and nonvolatile metabolites are excreted mainly in the urine. At doses that saturate metabolism, the major route of excretion is exhalation of unchanged VC. Excretion of metabolites via feces is only a minor route, independent of applied dose (WHO 1999).

Buchter et al. (1980) exposed Rhesus monkeys to VC at 100-800 ppm and measured the time-dependent disappearance of VC from the atmosphere. The maximum metabolic rate was 45 μmol/kg-h, which was obtained with VC at 400 ppm; no attempt was made to identify the metabolites formed. Metabolic clearance rates were calculated from the decrease in atmospheric VC. Clearance rates for monkeys, rabbit, and humans were 2.0-3.55 L/h/kg, for gerbils and rats were 11.0-12.5 L/h/kg, and for mice were 25.6 L/h/kg, indicating major species differences, which are in accordance with allometric scaling.

After oral exposure to VC at 0.05, 1.0, or 100 mg/kg, male rats metabolized VC to the epoxide, which was further metabolized (e.g., to thiodiglycolic acid; about 25% of the ^{14}C-containing urinary metabolites). Approximately 9, 13.3, or 2.5% of the total dose was excreted as CO_2 and 1.4, 2.1, or 66.6% as VC in the low-, mid-, and high-dose groups, respectively (Watanabe et al. 1976b). At 100 mg/kg, pulmonary elimination showed a biphasic clearance with an initial half-life of 15 min and a terminal half-life of 41 min. At 0.05 and 1 mg/kg, only monophasic pulmonary clearance could be observed with half-life values of 53-58 min (Watanabe et al. 1976b). Initial urinary excretion of metabolites followed first-order kinetics with half-life values of 4.5-4.6 h, followed by a slow terminal phase (Watanabe et al. 1976b). Thus, the equilibrium concentration for metabolites will not be reached within 8 h. The ratio of the metabolites excreted in the urine did not vary in dependence on dose.

VC metabolism in Rhesus monkeys is saturated at concentrations greater than 380 ppm (Buchter et al. 1980). In humans, VC at 24 ppm appears to be below the threshold of saturation (Krajewski et al. 1980) because no difference in pulmonary retention was observed at concentrations of 3, 6, 12, and 24 ppm. When exposing rats in a closed system to VC at 50-1,000 ppm, metabolic clearance was slowed at concentrations greater than 220 ppm, as evidenced by longer half-lives (Hefner et al. 1975). Bolt et al. (1977) exposed rats in a similar system and found metabolic saturation occurred at 250 ppm. These data are in accordance with the findings of Watanabe et al. (1976a); metabolism was saturated in the rat after inhalation of VC at 1,000 ppm but not at 100 ppm VC (no intermediate concentration was tested).

Saturation of metabolism also has been observed after oral exposure to VC at high doses. Watanabe et al. (1976b) reported saturation was evidenced by an increase in expired VC from 2.1% at 1 mg/kg to 66.6% at 100 mg/kg (Watanabe et al. 1976b).

VC metabolites are assumed to destroy CYP enzymes responsible for its epoxidation (Pessayre et al. 1979; Du et al. 1982). On the other hand, activity of glutathione-*S*-transferase and glutathione reductase is elevated after VC exposure in rats (glutathione content is reduced), representing an early hepatocellular adaption to VC exposure (Du et al. 1982).

4.2. Mechanism of Toxicity

Acute neurotoxicity from high concentrations of VC is probably dependent on VC concentration and independent of VC metabolism. This assumption is supported by the finding that narcotic concentrations of VC are similar in four species, including the guinea pig, mouse, rabbit, and rat (Mastromatteo et al. 1960; Prodan et al. 1975). VC has been investigated as a possible human anesthetic (Peoples and Leake 1933; Oster et al. 1947), but was abandoned because of its induction of cardiac arrhythmia.

Acute toxicity and lethality are mainly accompanied by congestion of all internal organs, pulmonary edema, and liver and kidney changes (up to necrosis) (Prodan et al. 1975). The mechanism of action has not been established; toxic effects are possibly mediated by reactive metabolites.

The genotoxicity and carcinogenicity of VC has been attributed to the formation of reactive metabolites, especially 2-chloroethylene oxide and 2-chloroacetaldehyde (see WHO 1999). 2-Chloroethylene oxide interacts directly with DNA and produces alkylation products (Fedtke et al. 1990). This alkylation results in a highly efficient base-pair substitution that leads to neoplastic transformation (ATSDR 1997). VC-DNA ethenobases have been shown to lead to miscoding and are found in VC-induced tumors in animals and humans (Barbin 2000). Despite relevant repair, no full reduction in adducts to background levels was observed 2 weeks after a 5 day exposure to VC at 600 ppm for 4 h/day (Swenberg et al. 1999). For vinyl fluoride, when all of the data on εG and hemangiosarcomas in rats and mice were compared by regression analysis, a high correlation was seen ($r^2 = 0.88$) (Swenberg et al. 1999). However, in the case of VC, there was a close correlation in the occurrence of εA, εC, and εG, and there were indications that εA also might be related to tumor formation (Barbin 1999, 2000). In adults, nonparenchymal cells have a greater rate of proliferation than hepatocytes. Thus, this cell population is more likely to convert promutagenic DNA adducts into mutations (Swenberg et al. 1999). This relationship might be changed when exposure occurs during rapid growth of the liver; young animals have a high rate of etheno-adducts and of preneoplastic foci in the liver. These foci persisted over several months even after short durations of exposure (Laib et al. 1989). In young animals, a high rate of hepatoma and hepatocellular carci-

noma have been found after short-term exposure to VC (Maltoni et al. 1981, 1984; Froment et al. 1994).

"Vinyl chloride disease" (characterized by Raynaud's phenomena and scleroderma) is a common finding after prolonged occupational exposure to VC. No similar observations have been made in experimental animals in single-exposure experiments. The effects in humans are probably from immunologic abnormalities caused by interaction of reactive VC metabolites with proteins, as has been proposed by Grainger et al. (1980) and Ward et al. (1976); however, no definitive mechanism has been elucidated to date.

4.3. Other Relevant Information

4.3.1. Physiology-based Pharmacokinetic Modeling

Physiology-based pharmacokinetic models have been proposed to predict VC metabolism and cancer risk (Clewell et al. 1995, 2001; Reitz et al. 1996). Such models have been developed to account for physiologic differences between species relevant to VC uptake, distribution, metabolism, and excretion, and should allow better comparison across species.

Current models use four compartments (liver, fat, slowly-perfused tissues, and richly-perfused tissues) and partition coefficients determined in vitro. Metabolism is modeled by one (Reitz et al. 1996) or two (Clewell et al. 1995) saturable pathways. The model of Clewell et al. (1995, 2001) uses one high-affinity, low-capacity pathway likely pertaining to CYP2E1, and one low-affinity, high-capacity pathway tentatively assigned to CYP2C11/6 and CYP1A1/2. Because VC readily reacts with glutathione and is known to deplete hepatic glutathione stores, description of the glutathione kinetics also was included.

4.3.2. Interspecies Variability

A comparison of the metabolic activity across species indicates that mice are the most metabolically active, having a first-order metabolic clearance rate of 25.6 L/h/kg at VC concentrations below metabolic saturation (Buchter et al. 1980). Clearance in rats, Rhesus monkey, rabbits, and humans is lower (11.0, 3.55, 2.74, and 2.02 L/h/kg, respectively). Because the metabolism of VC is perfusion limited (Filser and Bolt 1979), comparison of clearance rates on a body-weight basis is not appropriate. If clearance is compared on a body-surface-area basis, these mammalian species exhibit similar clearance rates (WHO 1999).

Comparison of lethal concentrations of VC (lethality occurring in the context of narcosis) in mice, rats, rabbits, and guinea pigs indicate certain interspecies variations (see Table 5-7). The guinea pig and rabbit are less sensitive to VC than mice and rats. Comparing the most sensitive species (mouse) with the least sensitive species (rabbit and guinea pig) suggest a difference of a factor of 2.

TABLE 5-7 Lethal Concentrations of Vinyl Chloride in Laboratory Animals

Species	LC_{50}	Reference
Mouse	117,500 ppm	Prodan et al. 1975
Rat	150,000 ppm	Lester et al. 1963; Prodan et al. 1975
Rabbit	240,000 ppm	Prodan et al. 1975
Guinea pig	240,000 ppm	Prodan et al. 1975

Marginal interspecies differences are observed with nonlethal, prenarcotic effects. Rats and mice are a little more sensitive than guinea pigs. For example, exposure to VC at 100,000 ppm for 30 min resulted in similar symptoms in mice, rats, and guinea pigs: unconsciousness (in all rats and mice but only in 1/5 guinea pigs), pulmonary hyperaemia persisting for more than 2 weeks, and side position in rats and mice after 20 min and in guinea pigs after 30 min (Mastromatteo et al. 1960). No comparable data in humans are available. Mice appear to be more sensitive than rats and rabbits to hepatic effects. Exposure of mice to VC at 1,500 ppm for 2 h caused severe liver effects, resulting in shock liver and death of the mice, but no hepatic or lethal effects were observed in rats and rabbits treated identically for 24 h (Tátrai and Ungvary 1981). The reason for these interspecies differences is not known. Data on acute hepatic effects of VC in humans are not available.

With respect to lethality and VC induced prenarcotic symptoms, there appear to be only minimal interspecies differences. An extrapolation factor of 3 is recommended in this context.

4.3.3. Intraspecies Variability

CYP2E1 is the key enzyme converting VC to 2-chloroethylene oxide. CYP2E1 activity in human liver microsomes (substrate: *p*-nitrophenol) may vary up to 12-fold between individuals (Seaton et al. 1994). These data indicate a potential interindividual variability in VC metabolism.

Investigation of VC retention in the lung of human volunteers revealed large interindividual differences; the minimum retention was 20.2% and the maximum was 79% (Krajewski et al. 1980). Lester et al. (1963) reported that VC at 8,000 ppm did not cause any response in five individuals, but one person felt "slightly heady." Other subjects complained of adverse health effects at a concentration of 12,000 ppm, indicating only small interindividual differences in neurotoxic effects from VC.

Relevant interindividual differences were not described in animal experiments.

On the basis of these observations, a factor of 3 was used to characterize intraspecies variability in the context of neurotoxic effects or cardiac sensitization.

4.3.4. Concurrent Exposure Issues

Concurrent administration of ethanol and VC in rats resulted in an increase in liver angiosarcoma, compared with data from animals exposed only to VC. This difference might be from the interaction of ethanol (a known inducer of CYP2E1) with VC metabolism (WHO 1999).

Induction of certain enzymes of the mixed-function oxidase system by pretreatment with phenobarbital or a mixture of polychlorinated biphenyls enhanced acute hepatotoxicity in rats, as measured by increased activity of hepatic enzymes and focal hepatic necrosis. On the other hand, inhibitors of the mixed-function oxidase system like SKF-525A have an opposite effect (WHO 1999).

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

Odor detection of VC at 261 ppm after entering an exposure chamber was reported by Baretta et al. (1969). The authors also described that five of seven persons detected the odor at 491 ppm, but could no longer detect it after 5 min of exposure.

Amoore and Hautala (1983) reported an odor threshold for VC of 3,000 ppm. This value represents the geometric average of three studies, but the authors did not specify whether the threshold was for detection or recognition of VC.

A “fairly pleasant odor” was reported by two persons exposed to VC at 25,000 ppm for 3 min. Dizziness and slight disorientation occurred (Patty et al. 1930).

Hori et al. (1972) reported an odor threshold for VC of 10-20 ppm (20 ppm in production workers and 10 ppm in workers from other sites). These data were rejected because there was no calibration of panel odor sensitivity, it was not clear whether the limit was based on recognition or detection, and the number of trials was not stated in the study (AIHA 1997).

Irritating effects of VC are observed only at very high concentrations. Danziger (1960) reported that accidental exposure to lethal concentrations of VC was accompanied by ocular lesions.

Baretta et al. (1969) exposed four to six volunteers to VC at 59, 261, and 491 ppm (analytic concentrations) for 7.5 h (including a 0.5 h lunch period). The corresponding time-weighted average concentrations were 48, 248, and 459 ppm over 7.5 h. Seven people were exposed at 491 ppm for only 3.5 h. The only complaints were those of two subjects who reported mild headache and some dryness of their eyes and nose during exposure at the highest concentration. The time of onset of headaches was not specified but was assumed to have occurred after 3.5 h of exposure.

5.2. Summary of Animal Data Relevant to AEGL-1

Lacrimation occurred shortly after mice, rats, guinea pigs, and rabbits were exposed to VC (42,900-280,000 ppm). Lethal effects have been observed in mice and rats even at the lowest exposure concentrations (42,900 ppm without ventilation in mice and 150,000 ppm with ventilation in rats) (Prodan et al. 1975). Mastromatteo et al. (1960) described that irritation (no further details) occurred immediately after onset of exposure to VC at 100,000, 200,000, or 300,000 ppm in rats and mice. In guinea pigs, irritation was not described at concentrations below 400,000 ppm, but the animals exhibited unconsciousness at all concentrations. No other data on irritation in animals exposed to VC were found.

5.3. Derivation of AEGL-1

VC is a compound with poor odor-warning properties. Reports on odor threshold vary over a wide range (10-25,000 ppm). There are no validated studies of the detection or recognition threshold for VC. According to Baretta et al. (1969), people seem to get used to the odor of VC. In humans and animals, irritation is found at very high concentrations that are lethal or cause unconsciousness. Thus, it was not possible to derive AEGL-1 values on basis of odor detection or irritation.

Occurrence of headache has been reported by Baretta et al. (1969) in two subjects after acute exposure. These findings are supported by data from occupationally-exposed persons who developed headache after VC exposure (Lilis et al. 1975; Suciu et al. 1975). The no-effect level for notable discomfort ("mild headache") in the Baretta et al. (1969) study is 491 ppm for 3.5 h. The effects are probably from VC in the blood and not a metabolite. Only small interindividual differences in pharmacokinetics of VC are expected, as the concentration of VC required to elicit the effect is greater than that required for saturation of the metabolic pathways. An intraspecies uncertainty factor of 3 is used to account for toxicodynamic differences among individuals.

Time scaling was conducted using the default values for n = 3 for extrapolation from longer to shorter durations or n = 1 for extrapolation from shorter to longer durations (NRC 2001, see Section 2.7), as the mechanism of inducing headaches is not well understood and is unlikely to be simply due to the concentration of VC in the blood. The extrapolation to a 10-min exposure from a 3.5-h exposure is justified because people exposed at 4,000 ppm for 5 min did experience headaches (Lester et al. 1963). The AEGL-1 values for VC are presented in Table 5-8.

TABLE 5-8 AEGL-1 Values for Vinyl Chloride

10 min	30 min	1 h	4 h	8 h
450 ppm ($1,200 mg/m^3$)	310 ppm ($800 mg/m^3$)	250 ppm ($650 mg/m^3$)	140 ppm ($360 mg/m^3$)	70 ppm ($180 mg/m^3$)

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Lester et al. (1963) reported that a 5-min exposure to VC at 8,000 ppm caused dizziness in one of six subjects. (The same subject reported slight dizziness with sham exposure and no effect at 12,000 ppm.) No complaints were made by any volunteer at 4,000 ppm. At 12,000 ppm, one subject reported clear signs of discomfort (reeling, swimming head) and another subject was unsure of some effect (a "somewhat dizzy" feeling in the middle of exposure). Five of six subjects exposed at 16,000 ppm and all six subjects exposed at 20,000 ppm complained of dizziness, nausea, headache, and dulling of visual and auditory cues. All symptoms disappeared shortly after exposure was ceased; headache persisted for 30 min in one subject after exposure at 20,000 ppm.

Exposure to VC at 25,000 ppm for 3 min resulted in dizziness, slight disorientation with regard to space and size of surrounding objects, and a burning sensation in the feet in two people. They immediately recovered after leaving the exposure chamber and complained only of a slight headache that persisted for 30 min (Patty et al. 1930).

Baretta et al. (1969) exposed four to six volunteers to VC at 59, 261, and 491 ppm (analytic concentrations) for 7.5 h (including a 0.5 h lunch period). The corresponding time-weighted average concentrations were 48, 248, and 459 ppm over 7.5 h. Seven people were exposed at 491 ppm for only 3.5 h. The only complaints were those of two subjects who reported mild headache and some dryness of their eyes and nose during exposure to the highest concentration. The time of onset of headaches was not specified but was assumed to have occurred after 3.5 h of exposure.

6.2. Summary of Animal Data Relevant to AEGL-2

Animal toxicity after short-term exposure is characterized by cardiac sensitization and by prenarcotic and hepatic effects. Short-term exposure (5 min) of dogs to VC induced cardiac sensitization towards epinephrine (EC_{50} was 50,000 and 71,000 ppm in two independent experiments) (Clark and Tinston 1973, 1982). This effect was confirmed by additional experimental data on higher concentrations with VC.

Hehir et al. (1981) reported that single exposure of mice to VC at 50,000 ppm caused twitching, ataxia, hyperventilation, and hyperactivity, beginning 40 min after exposure began. Consistent with these data, Mastromatteo et al. (1960) reported that VC at 100,000 ppm induced pronounced tremor, unsteady gait, and muscular incoordination in mice 15 min after onset of exposure. Exposure of mice to VC at 1,500 ppm for 2 h resulted in stasis of blood flow, decreased enzyme activities in the liver, subcellular liver damage, and shock liver after 24 h of exposure (Tátrai and Ungváry 1981).

Viola (1970) reported that rats exposed to VC at 30,000 ppm for 4 h/day were slightly soporific (no further details). Moderate intoxication and loss of righting reflex was observed in rats exposed to VC at 50,000 ppm for 2 h, and intense intoxication was seen at 60,000 ppm (but righting reflex was still present) (Lester et al. 1963). Intoxication was not further characterized. Exposure to VC at 100,000 ppm for 2 h resulted in a loss of the corneal reflex (Lester et al. 1963). In another study, tremor and ataxia were observed 15 min after onset of exposure to VC at 100,000 ppm (Mastromatteo et al. 1960). Guinea pigs exposed at 25,000 ppm for 5 min showed motor ataxia, unsteadiness on feet, and the animals were unconscious after 90 min (the NOAEL was 10,000 ppm) (Patty et al. 1930). Mastromatteo et al. (1960) reported unsteady gait and muscular incoordination in guinea pigs exposed to VC for 15 min at 100,000 ppm.

A single inhalation exposure to VC at 100,000 ppm for 6 h resulted in histopathologic changes of the liver (vacuolization) in rats, but was not observed at 50,000 ppm (Jaeger et al. 1974). However, in mice, Tátrai and Ungváry (1981) reported that stasis of the liver developed 2 and 4 h after exposure began. The authors observed decreasing enzyme activities in the liver and subcellular liver damage at a concentration of 1,500 ppm for 2 h; after 24 h, shock liver developed and all animals died. Repeated exposure of rats to VC at 1,500 ppm for up to 9 days during pregnancy caused increased relative and absolute liver weights, but no changes in the liver were found when examined by light microscopy. Also, no histopathologic effects were observed in rabbits treated identically (Ungváry et al. 1978). In another developmental study, increased absolute and relative liver weights were found in rats exposed intermittently to VC at 2,500 ppm on days 6-15 of pregnancy; the NOAEL was 500 ppm (John et al. 1977, 1981). The results in mice (Tátrai and Ungváry 1981) suggest that this species is unusually sensitive to VC, so the results were not used to derive AEGL-2 values.

6.3. Derivation of AEGL-2

Short-term exposure (5 min) of dogs to VC induced cardiac sensitization towards epinephrine (EC_{50} was 50,000 or 71,000 ppm in two independent experiments) (Clark and Tinston 1973, 1982). A no-effect level cardiac sensitization can be reasonably estimated by using a factor of 3 with the EC_{50} of 50,000 ppm, resulting in a concentration of about 17,000 ppm. This concentration leads to effects on the central nervous system in humans after 5 min of exposure (Lester et al. 1963). Thus, cardiac sensitization would not be the critical effect for AEGL-2 derivation, but can be used to support the AEGL-2 values derived below.

Liver toxicity is a major end point after long-term exposure to VC and might possibly be linked to tumor development in young animals (see Section 4.2. for further discussion). The no-effect level for irreversible effects on the liver in rats after a single 6-h exposure to VC is 50,000 ppm. The effects seen at lower concentrations (liver weight changes) were not considered key effects for AEGL-2 derivation.

Narcotic effects seem to predominate in rats, mice, and guinea pigs acutely exposed to high concentrations of VC. These effects are relevant AEGL-2 effects because they have the potential to impair escape. Although guinea pigs appear to be less sensitive than rats and mice with regard to lethality (see Section 7.2), they are more sensitive than rats and mice with regard to early signs of narcotic effects. Guinea pigs exposed to VC at 25,000 ppm showed motor ataxia and unsteadiness on feet after 5 min, and become unconscious after 90 min (no-effect level was 10,000 ppm) (Patty et al. 1930). Rats exposed to VC at 30,000 ppm for 4 h were only slightly soporific (Viola 1970), and a single exposure of mice to 50,000 ppm caused twitching, ataxia, hyperventilation, and hyperactivity after 40 min (Hehir et al. 1981).

The observations in animals are consistent with the effects observed in humans. Dizziness, reeling, swimming head, and nausea, which can be regarded as early signs of narcosis, have been reported in humans exposed to VC in concentrations ≥12,000 ppm for 5 min. No effects were reported at 4,000 ppm (Lester et al. 1963). The effects observed at 12,000 ppm (dizziness, reeling, swimming head) were seen only in one or two of six persons (one person was unsure of an effect) and do not yet impair the ability to escape. On the other hand, effects observed at concentrations ≥16,000 ppm (dizziness, nausea, headache, and dulling of visual and auditory cues) could impair escape. Therefore, 12,000 ppm was selected as the no-effect level for impaired ability to escape and was used to derive the AEGL-2 values. The effects are from VC in the blood and not a metabolite. Only small interindividual differences in pharmacokinetics of VC are expected, as the concentration of VC required to elicit the effect is greater than that required for saturation of the metabolic pathways. An intraspecies uncertainty factor of 3 is used to account for toxicodynamic differences among individuals.

By analogy with other anesthetics, the effects of VC are assumed to be solely concentration dependent. Thus, after reaching steady state (at about 2 h of exposure), no increase in effect is expected. See Section 4.1 and Appendix B for a discussion of the duration needed for VC to reach a steady-state concentration. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using n = 2, based on data from Mastromatteo et al. (1960). Mastromatteo et al. (1960) observed various time-dependent prenarcotic effects in mice and guinea pigs after less than steady-state exposure conditions (Appendix B for details). Time extrapolations were performed from 5 min to 10-min, 30-min, 60-min, and 2-h exposures. The calculations are shown in Appendix A, and AEGL-2 values for VC are presented in Table 5-9.

TABLE 5-9 AEGL-2 Values for Vinyl Chloride

10 min	30 min	1 h	4 h	8 h
2,800 ppm (7,300 mg/m^3)	1,600 ppm (4,100 mg/m^3)	1,200 ppm (3,100 mg/m^3)	820 ppm (2,100 mg/m^3)	820 ppm (2,100 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

Only two cases of accidental death from exposure to VC are described in literature. Exposure concentrations and duration were unknown, but circumstances suggest inhalation of very high concentrations. At autopsy, cyanosis, congestion of lung and kidneys, and blood-coagulation failure were observed (Danziger 1960).

7.2. Summary of Animal Data Relevant to AEGL-3

LC_{50} values for mice, rats, rabbits, and guinea pigs indicate similar sensitivity of mice and rats and of rabbits and guinea pigs. The following LC_{50} values were obtained from the data of Prodan et al. (1975): 117,500 ppm for mice, 150,000 ppm for rats, 240,000 ppm for rabbits, and 240,000 ppm for guinea pigs. The findings in rats are supported by data from Lester et al. (1963), who reported that one of two rats died after exposure to VC at 150,000 ppm for 2 h, and the remaining rat recovered after exposure ended. No lethality was observed rats exposed to VC at 100,000 ppm for 2 h (Prodan et al. 1975), rats exposed at 100,000 ppm for 8 h (Lester et al. 1963) or at 200,000 ppm for 20 min (Mastromatteo et al. 1960), and rabbits exposed at 200,000 ppm for 2 h (Prodan et al. 1975).

In addition, relevant data on cardiac sensitization exist. EC_{50}s of 50,000 and 71,000 ppm in dogs were found in two independent experiments following 5-min exposures to VC (Clark and Tinston 1973, 1982). These effects also were seen in mice at higher concentrations (Aviado and Belej 1974). In monkeys, only myocardial depression was observed after inhalation of VC at 2.5-10% (Belej et al. 1974). It was unclear whether an addition challenge with epinephrine was applied.

7.3. Derivation of AEGL-3

Lethality data provide AEGL-3 values that are marginally higher than those derived on the basis of cardiac sensitization. Thus, animal data (Clark and Tinston 1973, 1982) on cardiac sensitization after exposure for 5 min were used to derive AEGL-3 values. Severe cardiac sensitization is a life-threatening effect, but no animals died at 50,000 ppm, so that concentration was used at the point-of-departure. The cardiac sensitization model with the dog is considered an appropriate model for humans and is highly sensitive because the response is optimized by the exogenous administration of epinephrine (Brock et al. 2003; ECETOC 2009). The protocol is designed conservatively with built-in safety factors and, thus, no additional uncertainty factors are needed to calculate AEGL-3 values (ECETOC 2009). Accordingly, an interspecies uncertainty fac-

tor of 1 was applied. Only small interindividual differences in pharmacokinetics of VC are expected, as the concentration of VC required to elicit the effect is greater than that required for saturation of the metabolic pathways. An intraspecies uncertainty factor of 3 is used to account for toxicodynamic differences among individuals.

By analogy with other halocarbons (e.g., Halon-1211, HFC-134a) that cause cardiac sensitization, the effects are assumed to be solely concentration dependent (Brock et al. 2003; ECETOC 2009). Thus, after reaching steady state in about 2 h, no increase in effect is expected. See Section 4.1 and Appendix B for a discussion of the time needed for VC to reach a steady-state concentration. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using n = 2, based on data from Mastromatteo et al. (1960). Mastromatteo et al. observed various time-dependent prenarcotic effects (muscular incoordination, side position, and unconsciousness, effects that occur immediately before death) in mice and guinea pigs after less than steady-state exposure conditions. Time extrapolation was performed from 5 min to 10-min, 30-min, 60-min, and 2-h exposures.

AEGL-3 values for VC are presented in Table 5-10.

8. SUMMARY OF PROPOSED AEGLs

8.1. AEGL Values and Toxicity End Points

The AEGL values for VC are presented in Table 5-11. AEGL-1 values were based on mild headaches observed in volunteers (Baretta et al. 1969). Odor threshold was not determined in a validated manner, and seems to vary over a wide range. AEGL-2 values are based on effects on the central nervous system, which could impair ability to escape (Lester et al. 1963). Data on cardiac sensitization (Clark and Tinston 1973, 1982) are supported by lethality data (Prodan et al. 1975) and are used for AEGL-3 derivation.

A category plot of toxicity data and AEGLs values is presented in Figure 5-1. The data were classified into severity categories chosen to fit definitions of the AEGL health effects. The category severity definitions are no effect, disabling, lethal, and AEGL.

8.2. Comparison with Other Standards and Guidelines

Other standards and guidance levels for workplace and community exposures of VC are presented in Table 5-12.

TABLE 5-10 AEGL-3 Values for Vinyl Chloride

10 min	30 min	1 h	4 h	8 h
12,000 ppm (31,000 mg/m^3)	6,800 ppm (18,000 mg/m^3)	4,800 ppm (12,000 mg/m^3)	3,400 ppm (8,800 mg/m^3)	3,400 ppm (8,800 mg/m^3)

TABLE 5-11 Summary of AEGL Values for Vinyl Chloride

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	450 ppm (1,200 mg/m^3)	310 ppm (800 mg/m^3)	250 ppm (650 mg/m^3)	140 ppm (360 mg/m^3)	70 ppm (180 mg/m^3)
AEGL-2 (disabling)	2,800 ppm (7,300 mg/m^3)	1,600 ppm (4,100 mg/m^3)	1,200 ppm (3,100 mg/m^3)	820 ppm (2,100 mg/m^3)	820 ppm (2,100 mg/m^3)
AEGL-3 (lethal)	12,000 ppm (31,000 mg/m^3)	6,800 ppm (18,000 mg/m^3)	4,800 ppm (12,000 mg/m^3)	3,400 ppm (8,800 mg/m^3)	3,400 ppm (8,800 mg/m^3)

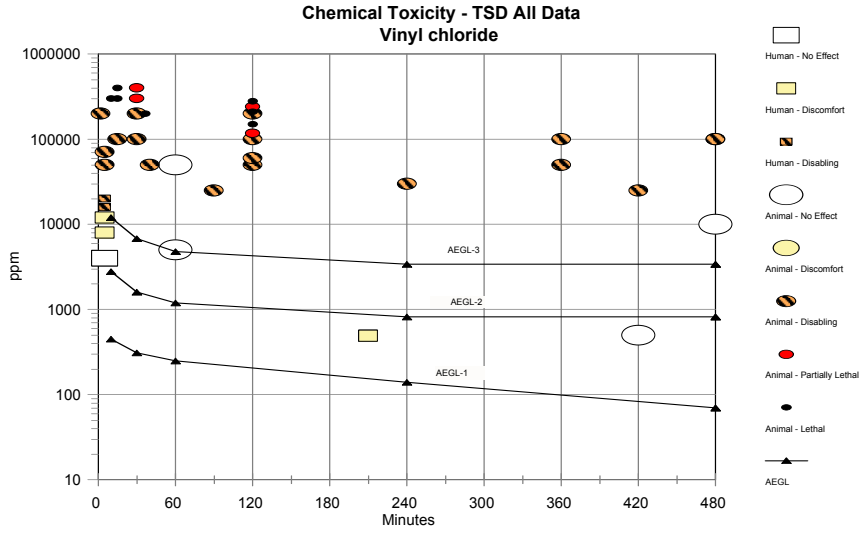

FIGURE 5-1 Category plot of animal toxicity data on vinyl chloride compared with AEGLs values. Data from studies were exposure durations exceeded 500 min were excluded.

8.3. Data Adequacy and Research Needs

Because VC has poor warning properties, the database is poor from which to derive AEGL-1 values. Additional studies with volunteers may not be performed because of ethical reasons. AEGL-2 values are based on central nervous system effects observed in human studies. The concentration range is well-established but excludes potential mutagenic or carcinogenic effects after short-term exposure, which might occur at lower concentrations. However, quantitative estimates of respective risks are highly uncertain. For derivation of AEGL-3 values, the dog studies on cardiac sensitization consistent with lethality data observed at slightly higher concentrations.

TABLE 5-12 Extant Standards and Guidelines for Vinyl Chloride

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	450 ppm	310 ppm	250 ppm	140 ppm	70 ppm
AEGL-2	2,800 ppm	1,600 ppm	1,200 ppm	820 ppm	820 ppm
AEGL-3	12,000 ppm	6,800 ppm	4,800 ppm	3,400 ppm	3,400 ppm
PEL-TWA (OSHA)[a]					1 ppm
TLV-TWA (ACGIH)[b]					1 ppm
STEL (OSHA)[c]	5 ppm (for 5 min)				
TEEL-0 (DOE)[d]			1 ppm		
TRK (Germany)[e]					2 or 3 ppm
Einsatztoleranzwerte (Greim, Germany)[f]				100 ppm	
Störfallbeurteilungswert (VCI)[j]			1,000 ppm		

[a]PEL-TWA (permissible exposure limit-time-weighted average, Occupational Safety and Health Administration, [CFR 29, Part 1910.1017 [2002]) 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.

[b] TLV-TWA (Threshold Limit Value-time-weighted average, American Conference of Governmental Industrial Hygienists [ACGIH 2010]). Is the TWA 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. VC was classified as carcinogenicity category A1 ("confirmed human carcinogen").

[c]PEL-STEL (permissible exposure limit-short-term exposure limit, Occupational Safety and Health Administration) [CFR 29, Part 1910.1017 [2002]) 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 PEL-TWA. Exposures above the PEL-TWA and 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.

[d]TEEL-0 (temporary emergency exposure limit,U.S. Department of Energy [DOE 2010]) is the threshold concentration below which most people will experience no adverse health effects.

[e]TRK (technische richtkonzentrationen [technical guidance concentration], Deutsche Forschungsgemeinschaft [German Research Association], Germany) (DFG 2001). TRK is defined as the air concentration of a substance which can be achieved with current technical standards. TRK values are given for those substances for which no maximum workplace concentration can be established. Compliance with the TRK should minimize the risk of health effects, but health effects cannot be excluded even at this concentration. (A value of 3 ppm is given for existing plants and the production of VC and polyvinyl chloride, in all other cases 2 ppm should not be exceeded.)

[f]Einsatztoleranzwert [action tolerance levels] (Vereinigung zur Förderung des deutschen Brandschutzes e.V. [Federation for the Advancement of German Fire Prevention]) (Buff and Greim 1997) constitutes a concentration to which unprotected firemen and the gen-

eral population can be exposed to for up to 4 h without any health risks. The value is based on the observation that no acute toxic effects or irritating effects have been observed during exposure to 500 ppm for 4 h.

[g]Störfallbeurteilungswert [emergency assessment value] (VCI, Verband der Chemischen Industrie, Deutschland [Association of the Chemical Industry in Germany]) (VCI 1990) are values that have been set for an exposure duration of up to 1 h. Because VC leads to anesthesia at concentrations of 7%, to prenarcotic syndromes at 0.5%, and to respiratory arrest, the emergency assessment value has been set at 1,000 ppm.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR VINYL CHLORIDE

Derivation of AEGL-1 Values

Key study:	Baretta, E.D., R.D. Stewart, and J.E. Mutchler. 1969. Monitoring exposures to vinyl chloride vapor: Breath analysis and continuous air sampling. Am. Ind. Hyg. Assoc. J. 30(6):537-544.
Toxicity end point:	Mild headache in two subjects exposed at highest concentration. The no-effect level for notable discomfort was 491 ppm for 3.5 h.
Uncertainty factors:	3 for intraspecies variability.
Modifying factor:	Not applied
Time scaling:	$C^3 \times t = k$ for extrapolation to 10 min, 30 min, and 1 h $C^1 \times t = k$ for extrapolation to 4 and 8 h $k = (491\ ppm)^3 \times 210\ min = 2.49 \times 10^{10}$ ppm^3-min $k = (491\ ppm)^1 \times 210\ min = 103{,}110$ ppm-min
Calculations:	
10-min AEGL-1:	$C^3 \times 10\ min = 2.49 \times 10^{10}$ ppm^3-min C = 1,355 ppm 1,355 ppm ÷ 3 = 450 ppm [1,200 mg/m^3]
30-min AEGL-1:	$C^3 \times 30\ min = 2.49 \times 10^{10}$ ppm^3-min C = 939.25 ppm 939 ppm ÷ 3 = 310 ppm [800 mg/m^3]
1-h AEGL-1:	$C^3 \times 60\ min = 2.49 \times 10^{10}$ ppm^3-min C = 745.48 ppm 745 ppm ÷ 3 = 250 ppm [650 mg/m^3]

4-h AEGL-1:	$C \times 240$ min = 103,110 ppm-min C = 429.63 ppm 430 ppm ÷ 3 = 140 ppm [360 mg/m^3]
8-h AEGL-1:	$C \times 480$ min = 103,110 ppm-min C = 214.81 215 ÷ 3 = 70 ppm [180 mg/m^3)]

Derivation of AEGL-2 Values

Key study:	Lester, D., L.A. Greenberg, and W.R. Adams. 1963. Effects of single and repeated exposures of humans and rats to vinyl chloride. Am. Ind. Hyg. Assoc. J. 24(3):265-275.
Toxicity end point:	Prenarcotic effects were observed in human volunteers. After exposure to VC at 16,000 ppm for 5 min, five of six persons experienced dizziness, lightheadedness, nausea, and visual and auditory dulling. At 12,000 ppm, one of six persons had "swimming head, reeling." Another individual was unsure of some effect and was somewhat dizzy. One person reported slight effects ("slightly heady") of questionable meaning at 8,000 ppm (this subject also felt slightly heady at sham exposure and reported no response at 12,000 ppm). No effects were observed at 4,000 ppm. The no-effect level for inability to escape was 12,000 ppm.
Uncertainty factors:	3 for intraspecies variability.
Modifying factor:	Not applied
Time scaling:	$C^2 \times t = k$ for extrapolation to 10 min, 30 min, 1 h, and 2 h Steady-state concentration occurs after 2 h, so flat-line response assumed for extrapolation to 4 and 8 h $k = (12{,}000 \text{ ppm})^2 \times 5 \text{ min} = 7.2 \times 10^8$ ppm^2-min

Calculations:

10-min AEGL-2:	$C^2 \times 10$ min = 7.2×10^8 ppm^2-min C = 8,485.28 ppm 8,485 ppm ÷ 3 = 2,800 ppm [7,300 mg/m^3]
30-min AEGL-2:	$C^2 \times 30$ min = 7.2×10^8 ppm^2-min C = 4,898.98 ppm 4,899 ppm ÷ 3 = 1,600 ppm [4,100 mg/m^3]
1-h AEGL-2:	$C^2 \times 60$ min = 7.2×10^8 ppm^2-min C = 3,464.11 ppm 3,464 ppm ÷ 3 = 1,200 ppm [3,100 mg/m^3]
4- and 8 -h AEGL-2:	2-h steady state = $C^2 \times 120$ min = 7.2×10^8 ppm^2-min C = 2,449.49 ppm 2,450 ppm ÷ 3 = 820 ppm [2,100 mg/m^3]

Derivation of AEGL-3 Values

Key studies:	Clark, D.G., and D.J. Tinston. 1973. Correlation of the cardiac sensitizing potential of halogenated hydrocarbons with their physicochemical properties. Br. J. Pharmacol. 49(2):355-357. Clark, D.G., and D.J. Tinston. 1982. Acute inhalation toxicity of some halogenated and nonhalogenated hydrocarbons. Hum. Toxicol. 1(3):239-247.
Toxicity end point:	Short-term exposure (5 min) of dogs induced cardiac sensitization towards epinephrine (EC_{50}: 50,000 or 71,000 ppm in two independent experiments). These effects also observed in mice at higher concentrations (Aviado and Belej 1974). The no-effect level for lethality was 50,000 ppm.
Uncertainty factors:	1 for interspecies variability 3 for intraspecies variability

Time scaling:	$C^2 \times t = k$ for extrapolation to 10 min, 30 min, 1 h, and 2 h Steady-state concentration occurs after 2 h, so flat-line response assumed for extrapolation to 4 and 8 h $k = (50{,}000 \text{ ppm})^2 \times 5 \text{ min} = 1.25 \times 10^{10}$ $\text{ppm}^2\text{-min}$
Calculations:	
10-min AEGL-3:	$C^2 \times 10 \text{ min} = 1.25 \times 10^{10}$ $\text{ppm}^2\text{-min}$ C = 35,355.34 ppm 35,355 ppm ÷ 3 = 12,000 ppm [31,000 mg/m^3]
30-min AEGL-3:	$C^2 \times 30 \text{ min} = 1.25 \times 10^{10}$ $\text{ppm}^2\text{-min}$ C = 20,412.41 ppm 20,412 ppm ÷ 3 = 6,800 ppm [18,000 mg/m^3]
1-h AEGL-3:	$C^2 \times 60 \text{ min} = 1.25 \times 10^{10}$ $\text{ppm}^2\text{-min}$ C = 14,433.76 ppm 14,434 ppm ÷ 3 = 4,800 ppm [12,000 mg/m^3]
4- and 8-h AEGL-3:	2-h steady state = $C^2 \times 120 \text{ min} = 1.25 \times 10^{10}$ $\text{ppm}^2\text{-min}$ C = 10,206.21 ppm 10,206 ppm ÷ 3 = 3,400 ppm [8,800 mg/m^3]

APPENDIX B

TIME-SCALING CALCULATIONS

The relationship between dose and exposure duration to produce a toxic effect for any given chemical is a function of the physical and chemical properties of the substance and the toxicologic and pharmacologic properties of the individual substance. Historically, the relationship according to Haber (1924), commonly called Haber's rule ($C \times t = k$, where C = exposure concentration, t = exposure duration, and k = a constant), has been used to relate exposure concentration and duration to a toxic 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) determined that 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 vs. t (NRC 2001).

Acute central-nervous-system toxicity and lethality of VC are dominated by its narcotic effects characterized by a typical sequence of effects (increased motor activity, tremor, muscular incoordination, side position, and unconsciousness, resulting in deep narcosis). The occurrence and time sequence of these effects in rats, mice, and guinea pigs has been described by Mastromatteo et al. (1960). These experimental data are used for the derivation of values of n by linear regression analysis of the log-log transformed plot of C vs. t.

Three data sets of toxic effects in mice, rats, or guinea pigs described by Mastromatteo et al. (1960) were analyzed. The time-concentration relationships for mice and rats were identical, so the following evaluation concentrates on the data obtained from mice and guinea pigs. Data were collected for the end points of unconsciousness, muscular incoordination, and side position. As the side-position data are considered more reliable from cage-side observation, these data were used to derive the value of n. Because VC is not a potent irritant, the short-term time points are considered reliable and not affected by bradypnea.

The time after which side position was observed in mice and guinea pigs is presented in Tables B-1 and B-2, respectively. Regression analysis of the data is shown in Figure B-1.

TABLE B-1 Observations of Side Position in Mice Exposed to Vinyl Chloride

Concentration	Time (min)	Log concentration	Log time
100,000	20	5	1.301
200,000	5	5.301	0.699
300,000	2	5.477	0.301

TABLE B-2 Observations of Side Position in Guinea Pigs Exposed to Vinyl Chloride

Concentration	Time (min)	Log concentration	Log time
100,000	30	5	1.477
200,000	10	5.301	1
300,000	3.5	5.477	0.544

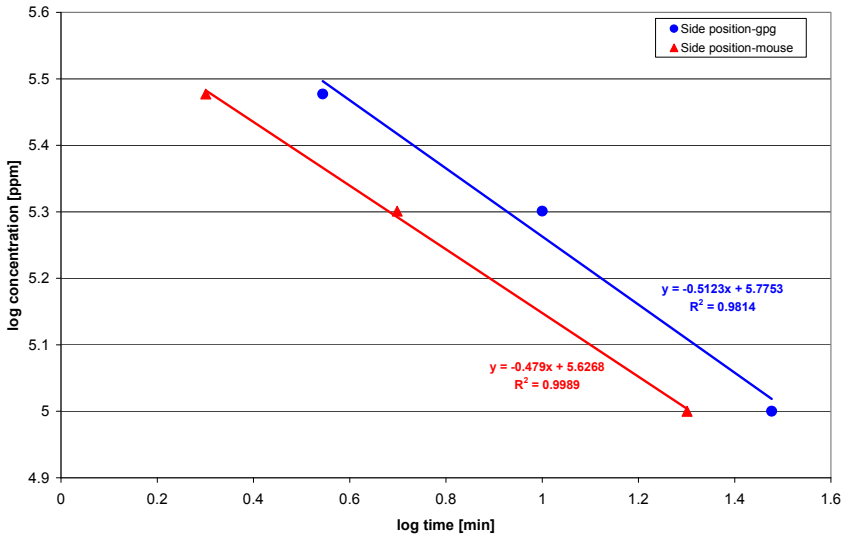

FIGURE B-1 Regression analysis of the log-log transformed concentration-time curve for side position in mice and guinea pigs exposed to vinyl chloride. Source: Data from Mastromatteo et al. 1960.

The slope of the regression line was -0.479 and -0.5123 in mice and guinea pigs, respectively, corresponding to a value of 2.1 and 2.0 for n.

The end point of side position was used to derive n = 2, which is used for the time extrapolation for AEGL-2 (central nervous system effects) and AEGL-3 (cardiac sensitization) values for up to 2 h. Concentrations for these "less-than-steady-state" durations (10, 30, 60 and 120 min) should be calculated according to $C^2 * t$ = concentrations.

Although the end points for AEGL-2 (anesthesia) and AEGL-3 (cardiac sensitization) values occur by different mechanisms (Himmel 2008), it is appropriate to use the same n value for both calculations. Anesthesia is related to the concentration of VC in the brain, and brain concentration of VC is directly related to blood concentrations. Cardiac sensitization is related to VC concentration in the blood (Brock et al. 2003; ECETOC 2009). Therefore, both end points should follow the same $C \times t$ relationship.

APPENDIX C

CANCER ASSESSMENT OF VINYL CHLORIDE

The most recently published cancer risk estimate from EPA (2000a,b) appears to be the best unit risk estimate currently available for VC. The values are 8.8×10^{-6} $(\mu g/m^3)^{-1}$ for continuous lifetime exposure, including childhood, and 4.4×10^{-6} $(\mu g/m^3)^{-1}$ for continuous exposure as an adult. These risk values indicate that exposure during childhood results in a similar tumor incidence as exposure in adulthood. EPA used the physiologically-based pharmacokinetic model of Clewell et al. (1995, 2001) to calculate the inhalation unit risk. These values are based on model-derived estimates of the internal dose of the active metabolite in animals and the continuous external exposure in humans that would result in these same internal doses of the active metabolite.

Two calculations for cancer risk are presented below. Calculation A is based on EPA's unit risk for continuous lifetime exposure (EPA 2000a,b), transformed to a single 24-h exposure estimate by the default procedure recommended in the standard operating procedures for developing AEGLs (NRC 2001). The procedure involves linear transformation, and correction by a factor of 6 to account for the relevance of sensitive stages in development. Exposures of less than 24 h are derived using the physiologically-based pharmacokinetic model of Clewell et al. (1995, 2001). Calculation B is based on the cancer incidence observed in the 5-week animal study by Maltoni et al. (1981), assuming that 5 weeks of exposure of animals is equivalent to about 150 weeks exposure of humans, with linear transformation to a single 24-h exposure without further correction for potential sensitive stages of tumor development. Exposures of less than 24 h are derived using the model of Clewell et al. (1995, 2001).

Calculation A

EPA's unit risk estimate for continuous lifetime exposure (inclusive of childhood) is 8.8×10^{-6} $(\mu g/m^3)^{-1}$. This unit risk was derived using the model of Clewell et al. (1995, 2001) which relates liver tumor incidence in animals with the lifetime average daily dose of the VC metabolite in the liver believed to be responsible for the tumor response (the internal dose of the metabolite). The model uses human parameters to transform that internal dose to an external exposure concentration for humans. With a unit risk for continuous lifetime exposure of 8.8×10^{-6} per $\mu g/m^3$, the exposure for a risk of 1 in 10,000 is 11.36 $\mu g/m^3$. To convert a 70-year exposure to a 24-h exposure, the exposure is multiplied by the number of days in 70 years:

$$11.36\ \mu g/m^3 \times 25{,}600 = 291\ mg/m^3$$

Under this strict C × t assumption, these exposures are considered equipotent.

To account for uncertainty regarding the variability in the stage of the cancer process at which VC or its metabolites may act, a multistage factor of 6 is applied (NRC 2001):

$$291 \text{ mg/m}^3 \times 1/6 = 48.5 \text{ mg/m}^3 \text{ (18.4 ppm)}$$

On the basis of this transformation, a 24-h VC exposure at this concentration would result in a 1×10^{-4} risk. For 1×10^{-5} and 1×10^{-6} risks, the value at 1×10^{-4} is reduced 10- and 100-fold, respectively. This estimate is based on the assumption of a strict C × t relationship.

Calculation B

As mentioned above for Calculation A, the basis of EPA's cancer risk estimate for VC is the internal dose, the lifetime average daily dose of VC metabolite in the liver. For numerous reasons, this metric may be quite different after a single exposure to VC of less than 24 h. Rather than make assumptions about the relationship of C × t, a physiologically-based pharmacokinetic model was used to estimate the internal dose to the liver under different external exposure regimes. These data are shown in the Table C-1 and Figure C-1.

The external 24-h exposure to VC corresponding to a 1×10^{-4} risk is 48.5 mg/m^3. Values for less than 24-h exposure are determined by interpolation using Table C-1. The internal dose metric (mg/L liver) corresponding to a 1×10^{-4} risk from a 24-h exposure to VC is 51.4 mg/L ([48.5 mg/m^3 ÷ 100 mg/m^3] × 106 mg/L). The external exposure necessary to achieve a VC concentration of 51.4 mg/L in the liver after an 8-h exposure is 147 mg/m^3 ([51.4 mg/L ÷ 35.0 mg/L] × 100 mg/m^3). A corresponding calculation was made for the other durations (0.5, 1, 4, and 8 h) and each risk level (1×10^{-4}, 1×10^{-5}, and 1×10^{-6}).

If exposure is limited to a fraction of a 24-h period, the exposure corresponding to the various cancer risk levels is presented in Table C-2. Comparison of the VC concentrations corresponding to a cancer risk of 1×10^{-4} and AEGL values are presented in Table C-3.

Calculation B is based on the cancer incidence as evident from a 5-week animal study by Maltoni et al. (1981), assuming that 5 weeks of exposure to animals is equivalent to about 150 weeks exposure to humans, with linear transformation to a single 24-h exposure without correction for potential sensitive stages of tumor development. Exposures of less than 24 h are derived using the physiologically-based pharmacokinetic model of Clewell et al. (1995, 2001).

The study was considered relevant because investigations were performed with newborn rats, which represent a sensitive subgroup for carcinogenesis, exposure was over a short period of time, and the end point (incidence of liver angiosarcoma) is relevant to humans. The data are shown in Table C-4.

TABLE C-1 Dose in the Liver of Active Metabolite 24 Hours After Exposure to Vinyl Chloride

	Dose in Liver, mg/L				
Concentration (mg/m^3)	0.5 h	1 h	4 h	8 h	24 h/70 y
1	0.022	0.044	0.176	0.352	1.07
10	0.22	0.441	1.76	3.52	10.7
100	2.19	4.38	17.5	35	106
200	4.36	8.72	34.8	69.4	211
300	6.5	13	51.8	103	313
400	8.61	17.2	68.4	136	413
500	10.7	21.3	84.5	169	510
600	12.7	25.2	100	199	604
700	14.6	29.1	115	229	692
800	16.5	32.7	129	256	775
900	18.2	36.1	142	282	850
1,000	19.9	39.3	153	304	917
2,000	30.4	57.7	211	412	1,220
3,000	35.7	65.8	231	442	1,300
4,000	39.7	71.9	243	461	1,350
5,000	43.3	77.2	254	476	1,390
6,000	46.6	82.1	264	490	1,420
7,000	49.7	86.7	273	502	1,460
8,000	52.3	91.1	279	513	1,490
9,000	54.7	95.3	284	523	1,520
10,000	57	99.3	289	533	1,540

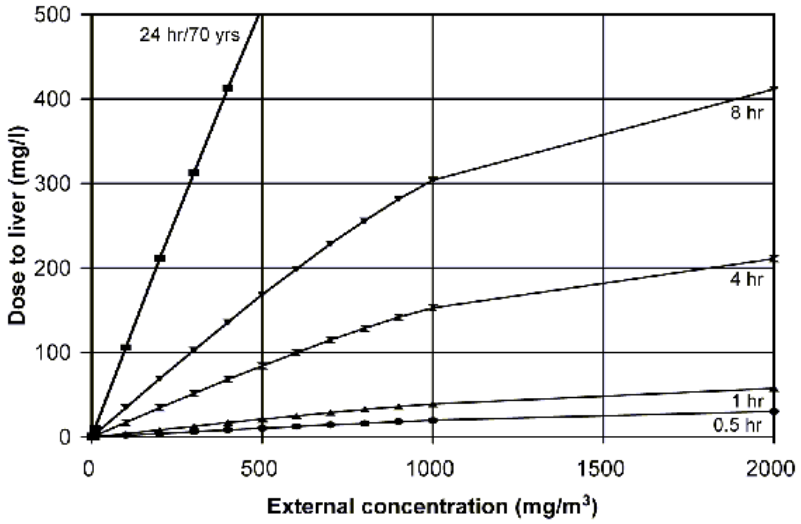

FIGURE C-1 External concentration and dose to liver of vinyl chloride calculated by physiologically-based pharmacokinetic modeling by EPA. Source: Gary Foureman, EPA, personal commun., June 2003.

TABLE C-2 Cancer Risks from Vinyl Chloride Based on Calculation A

Risk Level	30 min	1 h	4 h	8 h
1×10^{-4}	2,990 ppm 7,870 mg/m^3	676 ppm 1,780 mg/m^3	113 ppm 298 mg/m^3	55.9 ppm 147 mg/m^3
1×10^{-5}	89.7 ppm 236 mg/m^3	44.5 ppm 117 mg/m^3	11.1 ppm 29.2 mg/m^3	5.55 ppm 14.6 mg/m^3
1×10^{-6}	8.97 ppm 23.3 mg/m^3	4.45 ppm 11.6 mg/m^3	1.11 ppm 2.92 mg/m^3	0.555 ppm 1.46 mg/m^3

TABLE C-3 Comparison of AEGL Values for Vinyl Chloride and Cancer Risks Based on Calculation A

	10 min	30 min	1 h	4 h	8 h
1×10^{-4} risk	—	2,990 ppm 7,870 mg/m^3	676 ppm 1,780 mg/m^3	113 ppm 298 mg/m^3	55.9 ppm 147 mg/m^3
AEGL-1	450 ppm 1,200 mg/m^3	310 ppm 800 mg/m^3	250 ppm 650 mg/m^3	140 ppm 360 mg/m^3	70 ppm 180 mg/m^3
AEGL-2	2,800 ppm 7,300 mg/m^3	1,600 ppm 4,100 mg/m^3	1,200 ppm 3,100 mg/m^3	820 ppm 2,100 mg/m^3	820 ppm 2,100 mg/m^3
AEGL-3	12,000 ppm 31,000 mg/m^3	6,800 ppm 18,000 mg/m^3	4,800 ppm 12,000 mg/m^3	3,400 ppm 8,800 mg/m^3	3,400 ppm 8,800 mg/m^3

TABLE C-4 Incidence of Tumors in Studies by Maltoni et al. (1981)

Concentration (ppm)	Angiosarcoma	Hepatoma
Experiment BT 14: 4 h/d, 5 d/wk for 5 wk starting at day 1		
6,000	20/42 (48%), all[a] 17/42 (40.5%), LAS[b]	20/42 (47.6%)
10,000	18/44 (41%), all 15/44 (34.1%), LAS	20/44 (45.4%)
Experiment BT 1: 4 h/d, 5 d/wk for 52 wk starting at age 13 wk		
6,000	22/42 (52%), all 13/42 (31%), LAS	1/27 (3.7%)
10,000	13/46 (28%), all 7/46 (15%), LAS	1/24 (4.2%)

[a]All angiosarcomas, including angioma.
[b]Liver angiosarcoma only.
Source: EPA 2000a.

Derivation of an inhalation unit risk for exposure to young animals was based on a VC concentration of 6,000 ppm, at which there was an incidence of liver angiosarcomas of 40.5%. A concentration of 6,000 ppm corresponds to a human equivalent concentration of 51 ppm (132 mg/m^3), according to the physiologically-based pharmacokinetic model of Clewell et al. (1995). Corresponding data are shown in Table C-4 (note: exposure to rats exposure was intermittent (4 h/day, 5 days/week) compared with human equivalent concentration for continuous exposure [24 h/day]). Saturation in rats leads to only minor increases of metabolite concentrations, when exposure to VC exceeds 250 ppm (intermittent exposure). The derivation of the inhalation unit risk is based on the assumption that the tumor response is a linear function of the concentration of the active metabolite in the liver (human equivalent concentrations presented in Table C-5).

The dose associated with a risk of 1×10^{-4} is 33.0 $\mu g/m^3$

$$132\ mg/m^3 = 40.5\%$$
$$\geq 3.3\ mg/m^3 = 1\%$$
$$\geq 33\ \mu g/m^3 = 0.01\% = 1{:}10{,}000$$

To convert from a 5-week exposure to a 24-h exposure, consideration was given to the ratio between the lifespan of rats and humans. Newborn rats grow about 30 times faster than newborn humans (NRC 1993), which is similar to the ratio of a 75-year lifetime in humans to a 2.5-year lifetime in rats (30:1).

5 week × 7 days/week × 30 = 1,050 days
33.0 μg/m^3 × 1,050 days = 34.7 mg/m^3 (14 ppm)

An additional factor to adjust for uncertainties with assessing potential cancer risks under short-term exposures is not applied, as exposure was short-term in the underlying study. Therefore, on the basis of the potential carcinogenicity of VC during early life, a 24-h exposure corresponding to a 1 ×10^{-4} risk would be 34.7 mg/m^3 (13.2 ppm). For risks of 1 × 10^{-5} and 1 × 10^{-6}, the concentration associated with a risk of 1 × 10^{-4} is reduced by 10- and 100-fold, respectively.

If the exposure is limited to a fraction of a 24-h period, the exposure corresponding to the various risk levels are presented in Table C-6. These values were calculated using the physiologically-based pharmacokinetic model for VC described above for Calculation A. Comparison of the VC concentrations corresponding to a cancer risk of 1 × 10^{-4} and AEGL values are presented in Table C-7.

TABLE C-5 Human Equivalent Concentrations of Vinyl Chloride from Animal Studies

Administered Concentration (ppm)[a]	Metabolite in liver (mg/L)[b]	Human Equivalent Concentration (ppm)[c]
0	0	0
1	0.59	0.2
5	2.96	1
10	5.9	2
25	14.61	4.6
50	31.27	10.1
100	55.95	19
150	76.67	26
200	90	31
250	103.45	35
500	116.94	40
2,500	134.37	48
6,000	143.72	51

[a]Animals exposed 4 h/day, 5 days/week for 52 weeks.
[b]Dose metric (lifetime average delivered dose in female rats) calculated from physiologically-based pharmacokinetic modeling of the administered animal concentration.
[c]Continuous concentration of VC over a lifetime required to produce an equivalent concentration (mg/L) of metabolite in the liver.
Source: EPA 2000a,b.

A similar result is obtained if the tumor data from Froment et al. (1994) are used. Froment et al. exposed newborn animals to only one concentration of VC (500 ppm). Hence, fewer extrapolations were needed compared with the Maltoni et al. (1981) data (data and calculation not shown). For both calculations, there is uncertainty about the influence of exposure to VC via mother's milk. Because of metabolic saturation at high-level inhalation exposure, this influence might have been limited. However, no estimate of the quantitative consequences of this multipathway exposure can be given.

There is great uncertainty in these calculations. Appendix D summarizes a number of epidemiologic studies of occupational exposure to VC. There is no evidence from these studies that short-term exposure to VC results in an increased prevalence of tumors. For example, Ward et al. (2000) and Mundt et al. (1999) report that workplace exposures of <4 years or <6 years show no increase in the prevalence of liver or liver and biliary tract cancer. In addition, Ward et al. (2000) showed that cumulative exposures to VC of <734 ppm/year were not associated with a statistically significant increase in liver cancer. When the exposure was <287 ppm/year, there were no angiosarcomas reported in workers. A concentration of 40 ppm for 8 h (estimated from Calculation B to be associated with a cancer risk of 1×10^{-4}) is equivalent to a cumulative exposure of 0.16 ppm/year. Thus, human experience with VC is inconsistent with the cancer risk values calculated from the laboratory animal data.

TABLE C-6 Cancer Risks from Vinyl Chloride Based on Calculation B

Cancer Risk	30 min	1 h	4 h	8 h
1×10^{-4}	1,180 ppm 3,110 mg/m^3	350 ppm 922 mg/m^3	80.9 ppm 213 mg/m^3	40.3 ppm 106 mg/m^3
1×10^{-5}	64.6 ppm 170 mg/m^3	32.1 ppm 84.4 mg/m^3	7.98 ppm 21.0 mg/m^3	3.99 ppm 10.5 mg/m^3
1×10^{-6}	6.38 ppm 16.8 mg/m^3	3.19 ppm 8.40 mg/m^3	0.798 ppm 2.10 mg/m^3	0.399 ppm 1.05 mg/m^3

TABLE C-7 Comparison of AEGL Values for Vinyl Chloride and Cancer Risks Based on Calculation B

	10 min	30 min	1 h	4 h	8 h
1×10^{-4} risk	—	1,180 ppm 3,110 mg/m^3	350 ppm 922 mg/m^3	80.9 ppm 213 mg/m^3	40.3 ppm 106 mg/m^3
AEGL-1	450 ppm 1,200 mg/m^3	310 ppm 800 mg/m^3	250 ppm 650 mg/m^3	140 ppm 360 mg/m^3	70 ppm 180 mg/m^3
AEGL-2	2,800 ppm 7,300 mg/m^3	1,600 ppm 4,100 mg/m^3	1,200 ppm 3,100 mg/m^3	820 ppm 2,100 mg/m^3	820 ppm 2,100 mg/m^3
AEGL-3	12,000 ppm 31,000 mg/m^3	6,800 ppm 18,000 mg/m^3	4,800 ppm 12,000 mg/m^3	3,400 ppm 8,800 mg/m^3	3,400 ppm 8,800 mg/m^3

APPENDIX D

OCCUPATIONAL EPIDEMIOLOGIC STUDIES OF VINYL CHLORIDE

Two large studies of workers employed in industries using VC monomer and polyvinyl chloride before 1974 were evaluated. Both studies were retrospective cohort mortality studies. The first study was conducted in Europe and included study populations in Italy, Norway, Sweden, and the United Kingdom. The second study included plants in the United States and Canada. Each study was updated multiple times and has been the subject of numerous publications. Only the results from the most recent updates are discussed here. The focus is to review the liver cancer incidence in workers exposed to VC for relatively short-term periods or where the cumulative dose (ppm/year) was known to have been low. Both studies have more deaths from angiosarcomas of the liver than expected among workers with high or long-term exposure to VC (Mundt et al. 1999; Ward et al. 2000). A third study from Weber et al. (1981) conducted in Germany had results that conflict with the two other studies.

European Study

The European study included approximately 12,700 men with at least 1 year of employment in the VC or polyvinyl chloride industry from 1955 to 1974 (Ward et al. 2000). Three of the 19 plants had incomplete records, so the starting date for data from those three plants ranged from 1961 to 1974. The vital status follow-up was complete through 1997. Age- and calendar-period specific mortality rates for males from Italy, Norway, Sweden, and the United Kingdom were used to calculate the standardized mortality ratios (SMRs) and 95% confidence intervals (CIs). Typical exposure scenarios were estimated by industrial hygienists on the basis of job exposure matrices. These matrices were based primarily on job title and were reviewed by two other industrial hygienists with several years of experience in the VC industry. Information provided in the job exposure matrix was used to develop a ranked exposure index. Quantitative estimates of exposure were obtained for 82% of the cohort.

The total number of person-years at risk for the cohort was 324,701. The work force was classified by duration of employment: <3, 3-6, 7-11, 12-18, and >19 ppm-years. The SMR for liver cancer for workers with <3 years experience was 62 (95% CI: 2-345), below the expected value (see Table D-1). For workers exposed to VC for a longer duration, the incidence of liver cancer was higher than expected. In general, the incidence of liver cancer increased with years of employment in the industry.

TABLE D-1 Liver Cancer Incidence for All European Countries by Duration of Employment

Duration of Employment (years)	Number of Individuals[a]	Number of Person (years)	Incidence (observed/ expected)	SMR (95% CI)[b]
<3	10,961	91,970	1/1.61	62 (2-345)
3-6	8,999	79,747	3/1.44	208 (43-609)
7-11	6,919	65,789	7/1.35	517 (208-1,060)
12-18	4,610	55,149	5/1.42	352 (114-821)
1>9	2,006	32,050	13/1.46	893 (475-1,530)
Total	12,700	324,706	29/7.29	398 (267-572)

[a]The number of individuals cited for various employment intervals is greater than 12,700 because individuals can meet more than one criteria as defined by the author.
[b]Observed/expected × 100.
Abbreviations: CI, confidence interval; SMR, standardized mortality ratio.
Source: Adapted from Ward et al. 2000.

In addition, Ward et al. (2000) examined cumulative exposures in the cohort (see Table D-2). The work force was subdivided into 0-734, 735-2,379, 2,380-5,188, 5,189-7,531 and >7,532 ppm/years. The SMR was 107 (95% CI: 54-192) based on 11 observed liver cancers and 10.26 expected. Assuming workers are employed in the industry for up to 30 years, to be included in this first category, the highest average concentration the worker would have been exposed to was ~25 ppm. Workers with shorter work histories may have been exposed at much higher concentrations. Under this scenario there was no increase in the incidence of liver cancer. As previously noted, the incidence of liver cancer increased with cumulative exposure; the SMR was 1,140 (95% CI: 571-2,050) for workers with a cumulative exposure of >7,532 ppm/years. However, of the 11 liver cancers observed in the 0-734 ppm/year cumulative exposure group, four were angiosarcomas. These angiosarcomas occurred in individuals with 287-734 ppm/years cumulative exposure (Ward et al. 2001). There were no angiosarcomas reported in workers with less than 287 ppm/years of cumulative exposure.

North American Study

The North American study consisted of approximately 10,100 men employed for at least 1 year in the VC or polyvinyl chloride industry from 1942-1974 (Mundt et al. 1999). This group was followed through December 31, 1995. Thus, most workers were followed for at least 21 years. Because the industries were located in 16 states and one province of Canada, mortality rates for 16

states were used to calculate SMRs. For the Canadian province, mortality-rate data from Michigan was used because it is the state closest to the Canadian plant. As of December 31, 1995, 30% of the study group was deceased. Although the authors of previous studies have attempted to categorize individuals by exposures, no consistent criteria have been used and thus no attempt was made to estimate exposure levels in this study.

The age at first exposure, duration of exposure, and year of first exposure appeared to be related to cancer of the liver and biliary tract. Of these, duration of exposure had the greatest significance and appeared to be independent of age at first exposure and year of first exposure (see Table D-3). Mundt et al. (2000) categorized the cohort into groups working 1-4, 5-9, 10-19, or >20 years in the VC industry. Nearly half of the cohort worked for <5 years in the industry, with fewer workers in each of the subsequent groups. These data show that working in the VC industry for 1-4 years resulted in a slightly lower liver cancer rate than expected. Working in this industry for longer periods of time resulted in higher death rates than expected for liver and biliary tract cancer. Mundt et al. also examined the incidence of angiosarcomas in relation to duration of exposure. Three individuals working in the VC industry for 1-4 years had angiosarcomas of the liver. No further information on exposure or job classification was provided.

TABLE D-2 Liver Cancer Incidence for All European Countries by Cumulative Exposure

Cumulative Exposure (ppm-years)	Number of Individuals[a]	Number of Person (years)	Incidence (observed/ expected)	SMR (95% CI)[b]
Unknown	2,243	52,300	2/3.19	63 (8-227)
0-734	9,552	188,204	11/10.26	107 (54-192)
735-2,379	2,772	43,174	9/3.32	271 (124-515)
2,380-5,188	1,463	26,480	10/2.62	382 (183-703)
5,189-7,531	515	9,274	10/1.77	566 (271-1,040)
>7,532	215	5,274	11/0.96	1,140 (571-2,050
Total	12,700	324,706	53/22.11	240 (1,800-3,140)

[a]The number of individuals cited for various employment intervals is greater than 12,700 because individuals can meet more than one criteria as defined by the author.b
[b]Observed/expected × 100.
Abbreviations: CI, confidence interval; SMR, standardized mortality ratio.
Source: Adapted from Ward et al. 2000.

TABLE D-3 Liver and Biliary-Tract Cancer Incidence in the United States by Duration of Employment

Duration of Employment (years)	Number of Individuals	Number of Person (years)	Incidence (observed/ expected)	SMR (95% CI)[a]
1-4	4,774	136,200	7/8.43	83 (33-171)
5-9	2,383	71,806	10/4.65	215 (103-396)
10-19	1,992	69,015	39/5.74	679 (483-929)
>20	960	39,524	24/3.49	688 (440-1,023)
Total	10,109			

[a]Observed/expected × 100.
Abbreviations: CI, confidence interval; SMR, standardized mortality ratio.
Source: Adapted from Mundt et al. 1999.

Both studies have shown that people working in the VC industry for <3 years or exposed to low concentration of VC have liver-cancer rates very close to expected values. A low incidence of angiosarcomas of the liver was reported by both Ward et al. (2000) and Mundt et al. (2000), but the Ward study suggested this was related to higher cumulative exposure.

Weber et al. (1981)

Three German cohorts were investigated in a study by Weber et al. (1981): Group 1 (1,021 VC and polyvinyl-chloride production workers; 73,734 person years), Group 2 (4,910 reference persons; 76,029 person years), and Group 3 (4,007 polyvinyl-chloride processing workers; 52,896 person years). Reference mortality rates from West Germany were used for comparison. Twelve cases of malignant tumors of the liver were found in production workers (SMR = 1,523), four cases in the reference group (SMR = 401), and three cases in processing workers (SMR = 434). No confidence intervals were provided, and the VC concentrations were unknown. Subclassification according to duration of employment demonstrates increased mortality after little more than 1 year of exposure (see Table D-4). Results from this study and the ones cited above were included in a meta-analysis by Boffetta et al. (2003), which illustrated the conflicting information about the minimum exposure duration and increased tumor risk in workers (see Figure 1 in Boffetta et al. 2003).

TABLE D-4 Standardized Mortality Ratios for Malignant Tumors of the Liver by Duration of Exposure

Employment Duration (months)	Cases	SMR	Confidence Interval
<12	0	—	—
13-60	2	874	Beyond 95th confidence interval
61-120	3	1,525	Beyond 99th confidence interval
>121	7	2,528	Beyond 99th confidence interval
Total	12		

Source: Adapted from Weber et al. 1981.

APPENDIX E

ACUTE EXPOSURE GUIDELINE LEVELS FOR VINYL CHLORIDE

Derivation Summary for Vinyl Chloride

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
450 ppm	310 ppm	250 ppm	140 ppm	70 ppm

Reference: Baretta, E.D., R.D. Stewart, and J.E. Mutchler. 1969. Monitoring exposures to vinyl chloride vapor: Breath analysis and continuous air sampling. Am. Ind. Hyg. Assoc. J. 30(6):537-544.

Test species/Strain/Sex/Number: Human volunteers, male, 4-7 individuals.

Exposure route/Concentrations/Durations: Inhalation, 459-491 ppm, 3.5 h

Effects: Mild headache and dryness of eyes and nose in 2/7 subjects.

End point/Concentration/Rationale: End points relevant for the derivation of AEGL-1 values for VC are headache, odor recognition or detection, and irritation. Mild headache was reported in two subjects after acute exposure; mild headache can be regarded as no-effect level for notable discomfort. No appropriate studies of odor recognition or detection were available for VC. Irritation in humans and animals is reported only at very high concentrations that are lethal or cause unconsciousness. The mechanism by which headaches develop is not understood.

Uncertainty factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1 was applied because the study involved humans.
Intraspecies: 3 is used to account for toxicodynamic differences among individuals. The effects are probably from VC in the blood and not a metabolite. Only small interindividual differences in pharmacokinetics of VC are expected, as the concentration of VC required to elicit the effect is greater than that required for saturation of the metabolic pathways.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: The duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of $n = 3$ for shorter exposure periods and $n = 1$ for longer exposure periods, because there were no suitable experimental data for deriving the value of n. Extrapolation from a 3.5-h exposure to a 10-min exposure is justified because humans exposed to VC at 4,000 ppm for 5 min did not experience headaches (Lester et al. 1963).

Data adequacy: The study of Baretta et al. (1969) qualified for the derivation of AEGL-1 values and the end point is supported by several findings from occupational studies (Lilis et al. 1975; Suciu et al. 1975; EPA 1987). Confirmation of the observed effects in other studies with controlled exposure would be helpful, but may not be performed for ethical reasons.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
2,800 ppm	1,600 ppm	1,200 ppm	820 ppm	820 ppm

References: Lester, D., L.A. Greenberg, and W.R. Adams. 1963. Effects of single and repeated exposures of humans and rats to vinyl chloride. Am. Ind. Hyg. Assoc. J. 24(3):265-275.
Clark, D.G., and D.J. Tinston. 1973. Correlation of the cardiac sensitizing potential of halogenated hydrocarbons with their physicochemical properties. Br. J. Pharmacol. 49(2):355-357.
Mastromatteo, E., A.M. Fisher, H. Christie, and H. Danziger. 1960. Acute inhalation toxicity of vinyl chloride to laboratory animals. Am. Ind. Hyg. Assoc. J. 21:394-398.

Test species/Strain/Sex/Number: Human, male and female, 3 per sex

Exposure route/Concentrations/Durations: Inhalation, single exposure, VC at 0, 4,000, 8,000, 12,000, 16,000, or 20,000 ppm for 5 min.

Effects: After a 5-min exposure at 16,000 ppm, five of six persons had dizziness, lightheadedness, nausea, and visual and auditory dulling. At concentrations of 12,000 ppm, one of six persons reported "swimming head, reeling," and another was unsure of an effect and felt somewhat dizzy. A single person reported slight effects ("slightly heady") of questionable meaning at 8,000 ppm (this person also felt slightly heady at sham exposure and reported no response at 12,000 ppm). No effects were observed at 4,000 ppm. A concentration of 12,000 ppm was regarded as a no-effect level for impaired ability to escape.

End point/Concentration/Rationale: Severe dizziness may influence ability to escape, so is relevant as an end point for AEGL-2. No such effects were seen with VC at 12,000 ppm. AEGL-2 values are supported by the estimated no-effect level for cardiac sensitization of 17,000 ppm in dogs after epinephrine challenge (calculated by dividing the EC_{50} from the study by Clark and Tinston [1973] of 50,000 by 3).

Uncertainty factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1 was applied because the study involved humans
Intraspecies: 3 is used to account for toxicodynamic differences among individuals. The effects are probably from VC in the blood and not a metabolite. Only small interindividual differences in pharmacokinetics of VC are expected, as the concentration of VC required to elicit the effect is greater than that required for saturation of the metabolic pathways.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: By analogy to other anesthetics, the effects are assumed to be solely concentration dependent. Thus, after reaching steady state after about 2 h, no increase in effect by duration is expected at 4 and 8 h. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using a factor of n = 2 based on data from

(Continued)

AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
2,800 ppm	1,600 ppm	1,200 ppm	820 ppm	820 ppm

(continued)

Mastromatteo et al. (1960). Mastromatteo et al. observed various time-dependent prenarcotic effects in mice and guinea pigs after less than steady-state exposure conditions. Time extrapolation was performed from 5 min to 10 min, 30 min, 60 min, and 2 h.

Data adequacy: The overall quality of the key study (Lester et al. 1963) is medium. A dose-response relationship was observed that supported the quantitative estimates. Subjective reporting of effects leads to limited precision.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
12,000 ppm	6,800 ppm	4,800 ppm	3,400 ppm	3,400 ppm

References: Clark, D.G., and D.J. Tinston. 1973. Correlation of the cardiac sensitizing potential of halogenated hydrocarbons with their physicochemical properties. Br. J. Pharmacol. 49(2):355-357.
Clark, D.G., and D.J. Tinston. 1982. Acute inhalation toxicity of some halogenated and non-halogenated hydrocarbons. Hum. Toxicol. 1(3):239-247.
Aviado, D.M., and M.A. Belej. 1974. Toxicity of aerosol propellants in the respiratory and circulatory systems. I. Cardiac arrhythmia in the mouse. Toxicology 2(1):31-42.
Belej, M.A., D.G. Smith, and D.M. Aviado. 1974. Toxicity of aerosol propellants in the respiratory and circulatory systems. IV. Cardiotoxicity in the monkey. Toxicology 2(4):381-395.
Prodan, L., I. Suciu, V. Pislaru, E. Ilea, and L. Pascu. 1975. Experimental acute toxicity of vinyl chloride (monochloroethene). Ann. NY Acad. Sci. 246:154-158.
Mastromatteo, E., A.M. Fisher, H. Christie, and H. Danziger. 1960. Acute inhalation toxicity of vinyl chloride to laboratory animals. Am. Ind. Hyg. Assoc. J. 21:394-398.

Test species/Strain/Sex/Number: Dog, beagle, sex not reported, 4-7 dogs/dose (Clark and Tinston 1973)

Exposure route/Concentrations/Durations: Inhalation, several doses, 5 min (Clark and Tinston 1973)

Effects: Short-term exposure (5 min) of dogs to VC induced cardiac sensitization towards epinephrine (EC_{50}: 50,000 and 71,000 ppm in two independent experiments; Clark and Tinston 1973, 1982). The lower EC_{50} of 50,000 ppm was taken as the no-effect level for life-threatening effects. These effects also were seen in mice at higher concentrations (Aviado and Belej 1974). In monkeys, only myocardial depression after inhalation of VC at 2.5-10% was observed. It was unclear whether an additional challenge with epinephrine was applied (Belej et al. 1974). Severe cardiac sensitization is a life-threatening effect, but at 50,000 ppm no animals died.

(Continued)

AEGL-3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
12,000 ppm	6,800 ppm	4,800 ppm	3,400 ppm	3,400 ppm

End point/Concentration/Rationale: Considering possible sensitive subpopulations and increased excitement in case of emergency reaction, epinephrine-induced cardiac reactions might occur and could be enhanced by exposure to high concentrations of VC. The respective effects are well known for certain unsubstituted and halogenated hydrocarbons. The test method using beagle dogs is well established. Cardiac sensitization data are supported by lethality data at slightly higher concentrations (Prodan et al. 1975).

Uncertainty factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1 was used because the cardiac sensitization model with the dog is considered an appropriate model for humans and is highly sensitive as the response is optimized by the exogenous administration of epinephrine (Brock et al. 2003; ECETOC 2009). This protocol is designed conservatively with built in safety factors and thus no additional safety factor is needed (ECETOC 2009).
Intraspecies: 3 was used to account for toxicodynamic differences among individuals. Only small interindividual differences in pharmacokinetics of VC are expected, as the concentration of VC required to elicit the effect is greater than that required for saturation of the metabolic pathways.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Insufficient data

Time scaling: By analogy with other halocarbons (e.g., Halon 1211, HFC 134a) that induce cardiac sensitization, the effects are assumed to be solely concentration dependent. Thus, after reaching steady state after about 2 h, no increase of effect by duration is expected at 4 and 8 h. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using a factor of n = 2 based on data from Mastromatteo et al. (1960). Mastromatteo et al. observed various time-dependent prenarcotic effects (muscular incoordination, side position, and unconsciousness, effects which occur immediately before lethality) in mice and guinea pigs after less than steady-state exposure conditions. Time extrapolation was performed from 5 min to 10 min, 30 min, 60 min, and 2 h.

Data adequacy: Because of discrepancies between the two studies by Clark and Tinston (1973, 1982), the data quality is judged to be medium. Adequate data from human experience is lacking.