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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 14

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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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 fourteenth volume in that series. AEGL documents for BZ (2-quinuclidinyl benzilate), ethyl

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

phosphorodichloridate, hexane, methanesulfonyl chloride, nitric acid, propargyl alcohol, and vinyl acetate monomer 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 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 committee interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for BZ (interim reports 19a, 20a, and 21a), ethyl phosphorodichloridate (interim reports 20a and 21a), hexane (interim reports 17 and 21a), methanesulfonyl chloride (interim reports 20a and 21a), nitric acid (interim reports 15, 18, and 21a), propargyl alcohol (interim reports 16 and 19a), and vinyl acetate monomer (interim reports 18 and 21a): Harvey Clewell (The Hamner Institutes for Health Sciences), Jeffrey Fisher (U.S. Food and Drug Administration), Sam Kacew (University of Ottawa), A. Wallace Hayes (Harvard School of Public Health), Rogene Henderson (Lovelace Respiratory Research Institute [retired]), James McDougal (Wright State University [retired], Charles Reinhardt (DuPont Haskell Laboratory [retired]), Andrew Salmon (California Environmental Protection Agency), Kenneth Still, Occupational Toxicology Associates, 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 reports 15-21 was overseen by Robert Goyer (University of Western Ontario [retired]). Appointed by the NRC, he was 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 Ernest Falke and Iris A. Camacho from EPA. 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 14

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

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

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

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

As a first step in assisting the LEPCs, EPA identified approximately 400 EHSs largely on the basis of their immediately dangerous to life and health values, developed by the National Institute for Occupational Safety and Health. 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 exposure periods (10 min, 30 min, 1 h, 4 h, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

[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.

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 extrap-

olation 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 recommenda-

tions 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 thirteen reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009, 2010a,b, 2011, 2012a,b,c). This report is the fourteenth volume in that series. AEGL documents for BZ (2-quinuclidinyl benzilate), ethyl phosphorodichloridate, hexane, methanesulfonyl chloride, nitric acid, propargyl alcohol, and vinyl acetate monomer 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

Agent BZ (3-Quinuclidinyl Benzilate)[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 Robert Young (Oak Ridge National Laboratory), Lisa Ingerman (SRC, Inc.), Chemical Manager Glenn Leach (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 concentrations 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

Agent BZ (3-quinuclidinyl benzilate) is an odorless, environmentally stable, white crystalline powder with anticholinergic activity. Once considered a potential incapacitating agent for military applications, it is currently used as a pharmacological tool (a muscarinic antagonist known as QNB). It produces anticholinergic delirium, a non-specific syndrome of cognitive dysfunction, hallucinations, and inability to perform tasks. Inhalation exposure would likely involve an aerosolized solid.

No data on the lethality of BZ in humans after inhalation exposure were available. Lethal doses to humans were estimated by Ketchum (1963) using several methods, including extrapolation of data from animals on the basis of body weight, extrapolation of the lethality ratio of BZ and atropine in animals to humans, and extrapolation of the ratio of physiologic effectiveness (parasympatholytic effects) between BZ and atropine in humans. LD_{50} (lethal dose, 50% lethality) values estimated by these methods were 2-5 mg/kg, 0.3-1.4 mg/kg, and 0.2-1.2 mg/kg, respectively. Conversion of these doses to an air concentration of BZ was not provided.

Data on nonlethal effects of BZ in humans after inhalation exposure are from studies conducted by the military. Subjects in these studies were carefully screened, evaluated, and informed human volunteers (male military personnel). The results qualitatively demonstrated that BZ exerts its parasympatholytic effects (behavioral and cognitive dysfunction) regardless of exposure route.

Inhalation exposure experiments were limited to those conducted by Ketchum and colleagues (Ketchum 1963, 2006; Ketchum et al. 1967), in which responses of test subjects were characterized using a scoring system that integrated various cognitive parameters, blood pressure, and heart rate. Exposures were of short duration (minutes) and were expressed as cumulative exposures (mg-min/m^3). An ICt_{50} value (a concentration-time product causing incapacitation in 50% of the test subjects) of 60.1 mg-min/m^3 (95% confidence interval [CI]: 41.3-87.5 mg-min/m^3) was reported by Ketchum et al. (1967). Nonlethal effects of BZ are completely reversible.

Median lethal doses (LCt_{50}) have been reported for several animal species (U.S. Department of the Army 1974). All exposures were of relatively short durations (5-40 min) but the LCt_{50} values ranged from 12,000 to 123,000 mg-min/m^3 with no apparent relationship to body size. Results of animal experiments (Ketchum et al. 1967) showed that monkeys, dogs, and rabbits exhibited qualitatively similar responses to BZ. Mydriasis (excessive or prolonged dilation of the pupil) and cycloplegia (paralysis of the ciliary muscles of the eye) were consistently observed in all test species. Other effects included ataxia, lethargy, sedation, erratic behavior, weakness, and hyperactivity. Exposures were all of short duration (6-8 min).

AEGL-1 values for BZ could not be developed with scientific rigor. Although data on exposures to BZ resulting in no apparent effects in animals are available, the experiments could not assess possible cognitive and behavioral effects characteristic of BZ that are relevant to humans. Human data on BZ that define no-effect levels or that are consistent with the AEGL-1 definition were not available. Therefore, AEGL-1 values for BZ are not recommended.

For AEGL-2 values, a one-third reduction of the ICt_{50} value of 60.1 mg-min/m^3 (60.1 mg-min/m^3 ÷ 3 = 20 mg-min/m^3 or 4 mg/m^3) was considered an estimated threshold for incapacitating effects. The estimated threshold concentration is less than the lower limit of the ICt_{50} (41.3 mg-min/m^3), which was considered too severe to serve as a point of departure because it could result in incapacitation. The threshold estimate is also lower than concentrations associated with clinical signs which may impair the ability to escape (e.g., progressive deterioration of normal gait and uncomfortable paresthesias of lower extremities reported by subjects exposed to BZ at 46.0-84.7 mg-min/m^3 [or 9.2-16.4 mg/m^3] for 5 min) (Ketchum et al. 1967). An interspecies uncertainty factor of 1 was used because the data are from human studies. An uncertainty factor of 10 was used to account for intraindividual variability. Effects in the human studies are likely due to the anticholinergic properties of BZ; structures of muscarinic receptors are highly conserved and, thus, receptor affinity is not likely to vary among individuals. However, individuals with pre-existing conditions may be more sensitive to the anticholinergic effects of BZ. Because of data limitations, particularly the short exposure duration of the critical study (5 min), a modifying factor of 3 was also applied. Data with which to assess the concentration-time relationship for BZ are not available. The concentration-time relationship for many irritant and systemically acting vapors and gases may be

described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived exponent (n) and to obtain protective AEGL values, time scaling was performed using the default of n = 1 to extrapolate to the 10-min, 30-min, and 1-h durations. AEGL-2 values for the 4-h and 8-h durations are not recommended, because data on exposure to BZ for durations longer than a few minutes are lacking and the effects of longer exposures are uncertain.

No human data are available with which to develop AEGL-3 values for BZ. Several of the human exposures reported by Ketchum (1963) and Ketchum et al. (1967) were associated with high total response index (TRI) scores indicative of notable cognitive and behavioral effects and some motor-function effects but no apparent serious physiologic responses. Effects observed at all exposures were reversed 7-days post-exposure with no medical intervention. Other human studies have uncertainties inherent in the exposure-route extrapolations that would be required if using human LC_{50} estimates (Ketchum 1963) or if using the non-verifiable LCt_{50} of 200,000 mg-min/m^3 estimated by Hoenig (2007). Thus, animal studies were used as the basis for deriving AEGL-3 values.

AEGL-3 values for BZ were derived using 3,700 mg-min/m^3 as the point of departure. That value was determined by reducing the LCt_{50} for monkeys (37,000 mg-min/m^3 for 6-25 min) 10-fold (U.S. Department of the Army 1974). The LCt_{50} for the monkey is neither the highest nor lowest value of the six species tested, but the monkey was considered a better model for aerosol inhalation exposure in humans than the other species. Although a one-third reduction of the LC_{50} is often considered an appropriate estimate of the lethality threshold for chemicals with steep concentration-response relationships (NRC 2001), little is known about the concentration-response curve for BZ. An intraspecies uncertainty factor of 10 was used to account for individual variability. A factor of 10 was applied for interspecies variability because no human lethality data were available and LCt_{50} values for five animal species varied 10-fold. A modifying factor of 3 was applied because of data deficiencies. Time scaling was performed as described for the AEGL-2 values. AEGL-3 values for the 4-h and 8-h durations are not recommended, because data on longer exposure durations are lacking.

AEGL values for BZ are presented in Table 1-1.

1. INTRODUCTION

Agent BZ (3-quinuclidinyl benzilate) is an odorless, environmentally stable, white crystalline powder with anticholinergic activity. It was investigated as a potential incapacitating agent for military applications (Ketchum 1963, 2006; Ketchum et al. 1967; USACHPPM 1996), and is currently used as a pharmacological tool (a muscarinic antagonist known as QNB) (Yamamura and Snyder 1974). In general terms, its activity (by any route of exposure) is that of producing anticholinergic delirium, a non-specific syndrome of cognitive dys-

function, hallucinations, and inability to perform tasks. Most physiologic response data in humans exposed to BZ are for parenteral (intravenous and subcutaneous) or oral routes of administration, although some data on aerosol inhalation are available. Inhalation exposure would likely involve an aerosolized solid.

Chemical and physical data on BZ are presented in Table 1-2.

TABLE 1-1 AEGL Values for Agent BZ

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)[a]	NR	NR	NR	NR	NR	Insufficient data.
AEGL-2 (disabling)	0.067 mg/m^3	0.022 mg/m^3	0.011 mg/m^3	NR	NR	Estimated threshold (20 $mg\text{-}min/m^3$) for incapacitation in human volunteers (Ketchum et al. 1967).
AEGL-3 (lethal)	1.2 mg/m^3	0.41 mg/m^3	0.21 mg/m^3	NR	NR	Estimated lethality threshold (3,700 $mg\text{-}min/m^3$) in monkeys (U.S. Department of the Army 1974)

Abbreviations: NR, not recommended.
[a]Absence of AEGL-1 values does not imply that exposure to concentrations less than the AEGL-2 values is without effect.

TABLE 1-2 Chemical and Physical Data for Agent BZ

Parameter	Value	Reference
Synonyms	QNB; benzilic acid, 3-quinuclidinyl benzilate; EA2277; 3-quinuclindinyl ester; 3-hydroxyquinuclidine benzilate; agent buzz; 3-(2,2-diphenyl-2-hydroxyethanoyloxy)-quinuclidine	USACHPPM 1996; HSDB 2008; NIST 2011
CAS registry no.	6581-06-2	Hoenig 2007
Chemical formula	$C_{21}H_{23}NO_3$	Hoenig 2007
Molecular weight	337.4	Hoenig 2007
Physical state	Solid (white crystalline powder)	Hoenig 2007
Melting point	167.5°C	Hoenig 2007
Boiling point	320°C	Hoenig 2007
Relative vapor density	11.6	Hoenig 2007
Solubility	Slightly soluble in water; soluble in most organic solvents	Hoenig 2007
Vapor pressure	0.03 mm Hg at 70°C	Hoenig 2007
Conversion factors in air	1 ppm = 13.8 mg/m^3 1 mg/m^3 = 0.07 ppm	

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data regarding lethality in humans following inhalation exposure to BZ are available. Lethal exposures for humans were estimated by Ketchum (1963) using several methods, including extrapolation from animals on the basis of body weight, extrapolation of the lethality ratio of BZ and atropine in animals to humans, and extrapolation from the ratio of physiologic effectiveness (para-sympatholytic effects) between BZ and atropine in humans. Estimated LD_{50} values for BZ were 2-5 mg/kg (by species weight), 0.3-1.4 mg/kg (by atropine lethality ratio), and 0.2-1.2 mg/kg (by relative effectiveness ratio of atropine and BZ). Conversion to a concentration of BZ in air was not provided. An estimated median lethal dose (LCt_{50}) for BZ of 200,000 mg-min/m^3 was reported by Hoenig (2007), but the basis for that value was not described.

2.2. Nonlethal Toxicity

Ketchum (1963) conducted research on the effects of BZ in male volunteers. Subjects were informed military personnel who underwent medical and psychological evaluations as a prerequisite for participation. Test candidates were also selected on the basis of their evaluation by the Minnesota Multiphasic Personality Inventory and results of psychological interviews. Experiments were conducted under continuous medical supervision. Severity of BZ-induced effects (criterion for incapacitation) was evaluated using a total response index (TRI), which was calculated using the equation: ([2 × performance index] + [2 × heart rate index] + blood pressure index) ÷ 5. Cognitive function was assessed by the performance index, which was based on serial performance scores in numerical facility and speed of closure tests. Physiologic effects were assessed by blood pressure and heart rate measurements. TRI levels were:

- TRI 4.0 (mild): subjects show peak heart rate of 80-85 beats/min, systolic blood pressure elevation <10 mm Hg, moderate pupillary dilatation, slight blurring of vision and dryness of mouth, some mental slowing, minimal loss of coordination, no loss of contact with reality, lowest performance score of 60% at 7 h; recovery at approximately 48 h.
- TRI 5.0 (moderate): subjects show peak heart rate of 80-95 beats/min, systolic blood pressure elevation <20 mm Hg, sedation might be marked at 4-16 h, transient illusions/hallucinations/confusion and lapses in concentration, some metal slowing, lowest performance score of 40% at 8 h; recovery complete at approximately 72 h.
- TRI 6.0 (severe): subjects show peak heart rate of 95-110 beats/min, hallucinations/confusion, hyperactive disorganized behavior, incoherent speech, memory and attention deficit, deep sleep/stupor, performance at zero within 6 h; recovery complete at approximately 96 h.

- TRI 7.0 (maximal): peak heart rate of 110-140 beats/min within 3 h, systolic blood pressure increase of 20-60 mm Hg, onset of stupor within 3 h and performance decrement to zero within 4 h followed by protracted sleepiness, disorganized behavior, continual hallucinations, possible outbursts of fear and anger, delirium subsides within 72 h; complete recovery by120 h.

Air concentrations were established to attain estimated doses of BZ ranging from 1.4 to 26 μg/kg. Doses were estimated based on body weight and on the difference between the amount of BZ presented to the subject and the amount remaining in the exposure system. Cumulative concentration values were reported as 24-397 mg-min/m^3. Aerosol size mass median aerodynamic diameter (MMAD) ranged from <0.5 to 4.0 μm. The experiments were conducted using a series of suspensions and solutions of BZ, including an acetone solution, Freon 11 suspension, methylene chloride solution, pyrotechnic mix, and water solution. For the pyrotechnic mix (eight volunteers), breathing was regulated by reference to a visual feedback system that resulted in more uniform (± 10%) ventilation rates and tidal volumes. Cumulative exposures (CT; mg-min/m^3) to BZ ranged from 155-261 mg-min/m^3 and produced TRI values of 4.5 to 8.5.

Probit analysis for exposures associated with various TRI indices was reported by Ketchum (1963). The analysis provided an ED_{50} (a concentration-time product causing a specific TRI score in 50% of the test subjects) with 95% confidence limits for aerosol exposures (see Table 1-3) for groups of 36 volunteers. The exposure duration was not specified but was assumed to be of very short duration (<5 min) on the basis of other experiments and summaries provided in the report (U.S. Department of the Army 1974).

Ketchum et al. (1967) also reported the results of field-condition assessments (project DORK) for exposure to BZ aerosols. The assessments appeared to be an extension of the pyrotechnic exposures mentioned above. Two groups of eight volunteers (enlisted U.S. Army personnel under no coercion or enticement) participated with stringent medical safeguards in place. Subjects were evaluated using the number facility test (simple mathematics speed-accuracy test), speed of closure tests (ability to recognize words in a pseudo random array of letters), hand-eye coordination evaluations, and evaluations of ability to perform tasks typical of military situations (e.g., use of field glasses, sequential reporting of general activities, or completing tasks in routine military scenarios). Subjects were exposed to BZ aerosol generated by a Mars generator, and an ICt_{50} (concentration that will incapacitate 50% of exposed subjects) was estimated to be 60.1 mg-min/m^3 (95% CI: 41.3-87.5 mg-min/m^3) for a 165-pound man with a minute volume of 15 L (see Table 1-4). Incapacitation was determined by inability to perform at better than 10% on two consecutive tests of number facility. Neurologic signs were observed in seven of the eight subjects. Signs included symmetrical increase in deep tendon reflexes in the

TABLE 1-3 Probit Analysis for Response Criteria for Inhalation Exposure to Agent BZ

Response Criteria (TRI score)	Sample Size	ED_{50} (mg-min/m^3)	95% Confidence Limits (mg-min/m^3)
4.0	36	90.5	66.2-123.6
5.0	36	124.8	102.8-151.5
6.0	36	134.8	110.3-164.7
7.0	36	183.1	132.9-252.0

Source: Ketchum 1963.

TABLE 1-4 Cumulative Exposures and TRI Scores for Male Volunteers Exposed to Agent BZ

Subject Number	Minute Volume (L)	Body Weight	TRI Score	BZ (CT, mg-min/m^3)
1	12.4	160	4.4	64.8
2	16.8	165	7.1	84.7
3	13.8	145	6.3	68.3
4	11.9	190	4.2	46.0
5	13.8	145	4.6	71.2
6	18.8	200	5.4	82.2
7	14.8	160	6.3	54.0
8	23.1	190	6.8	72.9

Source: Ketchum et al. 1967.

lower extremities that progressed to ankle clonus and progressive deterioration of normal gait. Subjects also reported uncomfortable paresthesias of the lower extremities and diffuse, nonspecific weakness of all extremities which manifested as an unsteady gait, truncal weakness when sitting, and slow response to rebound testing. Additionally dysarthria (slow, slurred, and difficult to produce speech) was also noted in the subjects.

A maximum no-effect dose of 0.5-1.0 µg/kg for BZ in humans after intramuscular injection was reported by NRC (1982), and estimated median incapacitating inhalation concentrations of 101 mg-min/m^3 (base) and 112 mg-min/m^3 (hydrochloride) were reported by the U.S. Department of the Army (1974) for humans breathing rate at a rate of of 15 L/min.

2.3. Developmental and Reproductive Effects

No human developmental or reproductive toxicity data on BZ were available.

2.4. Genotoxicity

No human genotoxicity data on BZ were available.

2.5. Carcinogenicity

No data were found regarding the carcinogenic potential of BZ in humans.

2.6. Summary

Data regarding the health effects of BZ in humans following inhalation exposure are limited to military application studies. No lethality data are available. Results of experiments using carefully screened and evaluated informed human volunteers (male military personnel) qualitatively demonstrated that BZ would exert parasympatholytic effects (behavioral and cognitive dysfunction). Inhalation exposure experiments are limited to those conducted by Ketchum and colleagues (Ketchum 1963, 2006; Ketchum et al. 1967) in which responses of test subjects were characterized using a scoring system expressed as a TRI value on the basis of various cognitive parameters, blood pressure, and heart rate. Exposures were of short duration (minutes) and expressed as cumulative exposures (mg-min/m^3). An ICt_{50} of 60.1 mg-min/m^3 (95% CI: 41.3-87.5 mg-min/m^3) was reported by Ketchum et al. (1967).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Monkeys

An LCt_{50} of 37,000 mg-min/m^3 for monkeys has been reported for BZ (U.S. Department of the Army 1974). The value was reportedly based on exposure durations of 6-25 min. No additional information is available.

3.1.2. Dogs

An LCt_{50} of 25,000 mg-min/m^3 for dogs has been reported for BZ (U.S. Department of the Army 1974). The value was reportedly based on exposure durations of 6-16 min. No additional information is available.

3.1.3. Rats

An LCt_{50} of 64,000 mg-min/m^3 for rats has been reported for BZ (U.S. Department of the Army 1974). The value was reportedly based on exposure durations of 5-30 min. No additional information is available.

3.1.4. Mice

An LCt_{50} of 12,000 mg-min/m^3 for mice has been reported for BZ (U.S. Department of the Army 1974). The value was reportedly based on exposure durations of 5-19 min. No additional information is available.

3.1.5. Rabbits

An LCt_{50} of 32,000 mg-min/m^3 for rabbits has been reported for BZ (U.S. Department of the Army 1974). The value was reportedly based on exposure durations of 15-40 min. No additional information is available.

3.1.6. Guinea Pigs

An LCt_{50} of 123,000 mg-min/m^3 for guinea pigs has been reported for BZ (U.S. Department of the Army 1974). The value was reportedly based on exposure durations of 5-30 min. No additional information is available.

3.1.7. Summary of Animal Lethality Data

LCt_{50} values have been reported for several species (U.S. Department of the Army 1974). Details of the experimental protocol and results are not available. All exposures were of relatively short durations (5-40 min), but the LCt_{50} values ranged from 12,000 to 123,000 mg-min/m^3 with no apparent relationship to body size. The mouse and guinea pig were at the low end and high end, respectively, of the range of lethality values.

3.2. Nonlethal Toxicity

The only animal data on the effects of inhalation exposure to BZ are from a study by Ketchum et al. (1967). Studies of the effects of aerosol exposure of monkeys, dogs, rabbits, and rats were conducted prior to involvement of human volunteers. All species were exposed simultaneously, so exposure parameters were identical across species.

3.2.1. Monkeys

Five monkeys were exposed head only to aerosols of BZ at concentrations of 575 mg-min/m^3 for 6 min and 10 seconds or at 164, 70, or 40 mg-min/m^3 for 8 min (Ketchum et al. 1967). Information about the monkeys' species, sex, and body weight were not reported. Effects were assessed at 4, 8, 16, 24, 32, 40, 48, 56, 64, and 72 h and at 7-days post-exposure (see Table 1-5). Aerosols were generated by a Mars generator as was done for the human experiments. A BZ concentration of 40 mg-min/m^3 at 500 yards (equivalent to 5 mg/m^3 for the 8-

min duration) was without detectable effect. Although qualitatively similar, the effects observed at 575 mg-min/m^3 (equivalent to 93 mg/m^3) tended to persist for longer periods (up to 7 days) compared with the lower exposures (40-164 mg-min/m^3) where effects started to resolve by 72 h.

An RCt_{50} (response dose for 50% of animals tested) of less than 1,000 mg-min/m^3 was reported by McNamara (1963; cited in Rosenblatt et al. 1977) on the basis of conditioned avoidance response testing. Exposure duration was not specified.

3.2.2. Dogs

Groups of six dogs (breed, sex, and body weight were not reported) were tested as described for the monkeys (Ketchum et al. 1967). Results of the experiments are summarized in Table 1-6.

McNamara (1963; cited in Rosenblatt et al. 1977) reported RCt_{50} values for BZ of <130 mg-min/m^3 on the basis of mydriasis, 200 mg-min/m^3 on the basis of sustained physical exercise, 250 mg-min/m^3 on the basis of conditioned avoidance response, 25 mg-min/m^3 on the basis of increased heart rate, and ~500 mg-min/m^3 on the basis of weakness in dogs. Exposure durations and details regarding the experimental protocol were not available.

3.2.3. Rabbits

Ketchum et al. (1967) also tested groups of six rabbits (strain, sex, and body weight were not reported) using the same protocol as for the monkeys and dogs. Effects were similar to those observed in those species (see Table 1-7).

TABLE 1-5 Effects of Agent BZ on Monkeys

Concentration (mg-min/m^3)	Duration	Conditions	Distance (yards)	Effects[a]
575	6 min, 10 sec	41°F, 67% relative humidity	100	Mydriasis, cycloplegia, tranquility, erratic behavior, lethargy, hyperactivity, sedation, ataxia.
No data[b]			500	Mydriasis, cycloplegia.
No data[b]			1,000	Mydriasis, cycloplegia.
164			100	Mydriasis, cycloplegia.
70	8 min	32°F, 63% relative humidity	300	Mydriasis, cycloplegia.
40			500	No effects.

[a]All effects occurring in monkeys at any time during the post-exposure observation period are noted, although not all monkeys exhibited all effects.
[b]Study report indicated "no samples".
Source: Ketchum et al. 1967.

McNamara (1963; cited in Rosenblatt et al. 1977) reported RCt_{50} values of 10-50 mg-min/m^3 on the basis of mydriasis in rabbits. Details of the experimental protocol were not provided.

TABLE 1-6 Effects of Agent BZ on Dogs

Concentration (mg-min/m^3)	Duration	Conditions	Distance (yards)	Effects[a]
575	6 min, 10 sec	41°F, 67% relative humidity	100	Mydriasis, cycloplegia, tranquility, erratic behavior, lethargy, hyperactivity, sedation, ataxia, increased heart rate.
No data[b]			500	Mydriasis, cycloplegia, tranquility, erratic behavior, lethargy, hyperactivity, sedation, ataxia, increased heart rate.
No data[b]			1,000	Mydriasis, cycloplegia, increased heart rate.
164	8 min	32°F, 63% relative humidity	100	Mydriasis, cycloplegia, tranquility, erratic behavior, lethargy, hyperactivity, sedation, ataxia, increased heart rate, apprehension.
70			300	Mydriasis, cycloplegia, ataxia, lethargy, hyperactivity, increased heart rate.
40			500	No effects.

[a]All effects occurring in dogs at any time during the post-exposure observation period are noted, although not all dogs exhibited all effects.
[b]Study report indicated "no samples".
Source: Ketchum et al. 1967.

TABLE 1-7 Effects of Agent BZ on Rabbits

Concentration (mg-min/m^3)	Duration	Conditions	Distance (yards)	Effects[a]
575	6 min, 10 sec	41°F, 67% relative humidity	100	Mydriasis, cycloplegia.
No data[b]			500	Mydriasis, cycloplegia, salivation.
No data[b]			1,000	Mydriasis, cycloplegia.
164			100	Mydriasis, cycloplegia, respiratory distress, ataxia.
70	8 min	32°F, 63% relative humidity	300	Mydriasis, cycloplegia, hyperpnea, ataxia.
40			500	Mydriasis, cycloplegia.

[a]All effects occurring in rabbits at any time during the post-exposure observation period are noted, although not all rabbits exhibited all effects.
[b]Study report indicated "no samples".
Source: Ketchum et al. 1967.

3.2.4. Rats

Groups of 20 rats (strain, sex, and body weight were not reported) were exposed simultaneously with the monkeys, dogs, and rabbits in the Ketchum et al. (1967) study. With the exception of dyspnea (4/20 rats) and ataxia (1/20 rats) at 4 h post-exposure, no effects were observed in any of the rats at any exposure.

3.2.5. Summary of Nonlethal Toxicity in Animals

Information on the nonlethal toxicity of BZ in animals is limited to data from Ketchum et al. (1967) and McNamara (1963). Results of the Ketchum et al. (1967) study showed that monkeys, dogs, and rabbits exhibited qualitatively similar responses to BZ. Mydriasis and cycloplegia were consistently observed in all species. Other effects varied and included ataxia, lethargy, sedation, erratic behavior, weakness, and hyperactivity. Generally, the effects were most pronounced at 4- and 8-h post-exposure and, with the exception of cycloplegia, tended to resolve within 24-48 h. Cycloplegia was frequently observed in all species through the 7-day post-exposure observation period. Exposures to BZ were all of short duration (6-8 min). McNamara (1963) reported that dogs, rabbits, and monkeys exhibited similar responses along with some behavioral modifications at cumulative exposures of 10 to ~1,000 mg-min/m^3.

3.3. Developmental and Reproductive Effects

Data regarding the developmental and reproductive toxicity of BZ following inhalation exposures were not available.

3.4. Genotoxicity

No information regarding the genotoxicity of BZ was available.

3.5. Carcinogenicity

No data with which to evaluate the carcinogenic potential of BZ were available.

3.6. Summary

Toxicity data on BZ are extremely limited. Both the human and animal data are from experiments with short exposure durations (minutes). The only available inhalation exposure data are expressed in cumulative exposure terms (mg-min/m^3) and are not precisely characterized. Qualitatively, the effects of BZ

appear to be similar across species. The ability to detect, interpret, and quantify behavioral and cognitive dysfunction characteristic of BZ exposure in laboratory animals is difficult. On the basis of tests with human volunteers, Ketchum et al. (1967) estimated an ICt_{50} of 60.1 mg-min/m^3 (95% CI: 41.3-87.5 mg-min/m^3).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

BZ hydrolyzes in aqueous environments to benzilic acid and 3-quinuclidinol. It is reportedly excreted primarily in the urine (Byrd et al. 1992). In rats, about 3% of a dose (route not specified) is excreted unchanged in the urine.

4.2. Mechanism of Toxicity

BZ is an anticholinergic agent similar in its pharmacologic action to atropine and scopolamine although more potent than both (Ketchum and Sidell 1997). It exhibits a preferential affinity for muscarinc cholinergic receptors in the brain, heart, and smooth muscle, resulting in inhibition of functions mediated through acetylcholine activation of these receptors. For both humans and animals, there is a latency period of about 30 min to several hours or more regardless of exposure route. Longer latency periods are associated with percutaneous exposures.

4.3. Structure-Activity Relationships

No data regarding structure-activity relationships that would be instrumental in developing AEGL values for BZ were available.

4.4. Species Variability

Ketchum et al. (1967) tested monkeys, dogs, rabbits, and rats in their studies. Results of their preliminary tests suggested that rats are less sensitive than the other species tested. The U.S. Department of the Army (1974) found that guinea pigs were even less sensitive than rats.

4.5. Concurrent Exposure Issues

No relevant data regarding concurrent exposure issues were available.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No quantitative data on BZ relevant to AEGL-1 effects in humans were available.

5.2. Animal Data Relevant to AEGL-1

No animal data on BZ relevant to AEGL-1 effects in humans were available. No-effect levels in animals were reported, but assessment of cognitive and behavioral effects (major effects of BZ) were not possible.

5.3. Derivation of AEGL-1 Values

It is not possible to develop AEGL-1 values for BZ with scientific rigor. Although data on exposures resulting in no apparent effects in animals are available, the experiments could not assess possible cognitive and behavioral effects characteristic of BZ that are relevant to humans. Human data on BZ that define no-effect levels or that are consistent with the AEGL-1 definition are not available. Thus, AEGL-1 values for BZ are not recommended.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

Studies by Ketchum and colleagues (Ketchum 1963, 2006; Ketchum et al. 1967) are relevant to developing AEGL-2 values. Effects of BZ were characterized in these studies by a scoring system expressed as TRI values, which were based on cognitive parameters, blood pressure, and heart rate. All exposures were of short duration (about 20 min) and were expressed as cumulative exposures (CT; mg-min/m^3). An ICt_{50} of 60.1 mg-min/m^3 (95% CI: 41.3-87.5 mg-min/m^3) was reported by Ketchum et al. (1967). CT products of 46-261 mg-min/m^3 were associated with high TRI scores, which are indicative of effects well exceeding the severity of an AEGL-2 threshold (see Section 2.2). No human lethality data are available, but lethal exposures to humans were estimated by Ketchum (1963). Estimates were made by extrapolation of animal data on the basis of body weight, extrapolation of the lethality ratio of BZ and atropine in animals to humans, and extrapolation of the ratio of physiologic effectiveness (parasympatholytic effects) between BZ and atropine in humans. LD_{50} values were estimated to be 2-5 mg/kg (on the basis of species weight), 0.3-1.4 mg/kg

(on the basis of atropine lethality ratio), and 0.2-1.2 mg/kg (on the basis of the relative effectiveness ratio of atropine and BZ). Conversion of the doses to concentrations of BZ in air was not provided.

6.2. Animal Data Relevant to AEGL-2

Results of studies with laboratory animals (monkeys, dogs, rabbits, and rats) showed that exposure to BZ at 40-575 mg-min/m^3 for very short durations (6 and 8 min) generally produced nonlethal effects (mydriasis, cycloplegia, and salivation) consistent with exposure to a parasympatholytic agent. Rats appeared to be especially resistant, because none of the exposures resulted in notable effects. Monkeys and dogs also showed no effect when exposed to BZ at 40 mg-min/m^3. Studies in animals could not assess cognitive and behavioral effects as evaluated for human volunteer subjects. No animal lethality data are available.

6.3. Derivation of AEGL-2 Values

On the basis of tests with human volunteers, Ketchum et al. (1967) estimated an ICt_{50} of 60.1 mg-min/m^3 for a 165-pound human with a breathing rate of 15 L/min. A one-third reduction of the ICt_{50} (60.1 mg-min/m^3 ÷ 3 = 20 mg-min/m^3 or 4 mg/m^3) was considered an estimated threshold for incapacitating effects. A one-third reduction is often used to estimate a no-effect level (in this case, the highest concentration that is not expected to cause incapacitation) from an effect level (in this case, a concentration that incapacitates 50% of exposed persons). Comparison of the estimated threshold level and other possible point of departures for AEGL-2 values suggests that this estimate is likely to be protective. The point of departure of 20 mg-min/m^3 is less than the lower limit of the ICt_{50} (41.3 mg-min/m^3), which was considered too severe to serve as a point of departure because it could result in incapacitation. The threshold level is also lower than the one associated with clinical signs that might impair the ability to escape (e.g., progressive deterioration of normal gait and uncomfortable paresthesias of lower extremities reported by subjects exposed to BZ at 46.0-84.7 mg-min/m^3 [or 9.2-16.9 mg/m^3] for 5 min) (Ketchum et al. 1967) and the median incapacitation concentration of 101 mg-min/m^3 for humans breathing at a rate of 15 L/min (U.S. Department of the Army 1974). Additionally, experiments with four animal species indicated that 40 mg-min/m^3 was a no-effect level in monkeys, dogs, and rats (Ketchum et al. 1967); cycloplegia and mydriasis were observed in rabbits exposed at that concentration. Applying an inter-species uncertainty factor of 3 to the animal no-effect levels results in a CT product of 13.3 mg-min/m^3, which is similar but somewhat lower than the aforementioned point of departure of 20 mg-min/m^3. In the absence of definitive concentration-response data, this comparison supports the point of departure for development of AEGL-2 values.

Data with which to assess the concentration-time relationship for BZ are not available. Experiments conducted by Ketchum and colleagues were of short durations; 6-8 min in animal studies and possibly no more than 5 min in tests with human volunteers. The concentration-time relationship for many irritant and systemically acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived exponent (n) and to obtain protective AEGL values, time scaling was performed using the default of n = 1 to extrapolate to the longer AEGL-specific exposure durations. Nonlethal effects of BZ are totally reversible. Because of the paucity of data for longer-term exposures, AEGL-2 values for the 4-h and 8-h durations were not developed and are not recommended. Effects observed in the human studies are likely due to the anticholinergic properties of BZ; structures of muscarinic receptors are highly conserved in humans and, thus, receptor affinity is not likely to vary among individuals. For example, very few polymorphisms in the M1 receptor (associated with learning and memory) have been detected and polymorphisms at highly conserved sites that might disrupt function of the receptor are rare (Lucas et al. 2001). However, individuals with pre-existing conditions may be more sensitive to the anticholinergic properties of BZ than the healthy men tested in the Ketchum studies. An intraspecies uncertainty factor of 10 accounts for possible pharmacokinetic differences and possible increased sensitivity between individuals. A modifying factor of 3 was applied to account for uncertainties in the overall database, particularly the short exposure duration (5 min) of the critical study.

AEGL-2 values for BZ are presented in Table 1-8 and their derivation is summarized in Appendix A.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No data regarding lethality in humans resulting from inhalation exposure to BZ are available. Ketchum and colleagues estimated human LD_{50} values of 2-5 mg/kg (extrapolation by species weight), 0.3-1.4 mg/kg (extrapolation by atropine lethality ratio), and 0.2-1.2 mg/kg (extrapolation by relative effectiveness ratio of atropine and BZ). Conversion of these doses to a concentration of BZ in air was not provided.

TABLE 1-8 AEGL-2 Values for Agent BZ

10 min	30 min	1 h	4 h	8 h
0.067 mg/m^3	0.022 mg/m^3	0.011 mg/m^3	Not recommended	Not recommended

7.2. Animal Data Relevant to AEGL-3

Lethality data for several laboratory species have been reported in the form of LCt_{50} values (U.S. Department of the Army 1974). These values had little or no accompanying information. The LCt_{50} was 37,000 mg-min/m^3 in monkeys exposed for 6-25 min, 25,000 mg-min/m^3 in dogs exposed for 6-16 min, 64,000 mg-min/m^3 in rats exposed for 5-30 min, 12,000 mg-min/m^3 in mice exposed for 5-19 min, 32,000 mg-min/m^3 in rabbits exposed for 15-40 min, and 123,000 mg-min/m^3 in guinea pigs exposed for 5-30 min. No information is available regarding the concentration-response relationship for inhaled BZ. In the Ketchum et al. (1967) study, even the highest concentration (575 mg-min/m^3 for 8-min duration) was without serious effect.

7.3. Derivation of AEGL-3 Values

No human data with which to develop AEGL-3 values for BZ are available. Several of the human exposures reported by Ketchum (1963) and Ketchum et al. (1967) were associated with high TRI scores indicative of notable cognitive and behavioral effects and some motor function effects but no apparent serious physiologic responses. Effects were reversed 7-days post-exposure with no medical intervention. Other human studies have uncertainties inherent in the exposure-route extrapolations that would be required if using human LC_{50} estimates (Ketchum 1963) or if using the non-verifiable LCt_{50} of 200,000 mg-min/m^3 estimated by Hoenig (2007). Thus, animal studies were used as the basis for deriving AEGL-3 values.

LCt_{50} values for animals are based on relatively short exposure durations (5-40 min). The LCt_{50} for the monkey (37,000 mg-min/m^3) is neither the highest nor lowest value of the six species tested, but the monkey is a better model for aerosol inhalation exposure in humans than the other species. The monkey LCt_{50} was decreased 10-fold to 3,700 mg-min/m^3, as an estimate of the lethality threshold and a point of departure for AEGL-3 derivation. Although a one-third reduction of the LC_{50} is often considered an appropriate estimate of the lethality threshold for chemicals with steep concentration-response relationships (NRC 2001), little is known about the concentration-response curve for BZ. Therefore, the 10-fold reduction is considered more defensible. Time scaling was performed using the equation $C^n \times t = k$, with $n = 1$ to extrapolate to the longer AEGL-specific exposure durations. A factor of 10 was applied for interspecies differences because no lethality data are available for humans and LCt_{50} values for five animal species varied 10-fold. An intraspecies uncertainty factor of 10 was applied to account for possible pharmacokinetic differences and possible increased sensitivity between individuals. Effects observed in humans are likely due to the anticholinergic properties of BZ; structures of muscarinic receptors are highly conserved in humans and, thus, receptor affinity (and, therefore, toxicodynamics) is not likely to vary among individuals. For example, very few

polymorphisms in the M1 receptor (associated with learning and memory) have been detected and polymorphisms at highly conserved sites that might disrupt function of the receptor are rare (Lucas et al. 2001). However, individuals with pre-existing conditions may be sensitive to the anticholinergic effects of BZ. A modifying factor of 3 was applied because of uncertainties in the database, particularly a lack of incidence data (lethality studies only reported LCt_{50} values) which could be used to estimate a LC_{01} and a lack of studies involving longer exposure durations (longest duration was 40 min). AEGL-3 values for the 4- and 8-h durations are not recommended because data on exposure durations longer than 1 h are lacking.

AEGL-3 values for BZ are presented in Table 1-9 and their derivation is summarized in Appendix A.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

AEGL values for BZ are presented in Table 1-10. The available data do not allow for assessing a minimal-effect threshold appropriate for developing AEGL-1 values. For AEGL-2 values, the point of departure was selected on the basis of preventing cognitive, behavioral, or physiologic effects. Cognitive and behavioral effects resulting from the anticholinergic activity of BZ are the most relevant effects (incapacitation) regarding human exposure to this chemical. Data for the AEGL-2 assessment are from extensive experiments using informed, human volunteers who underwent extensive screening prior to participation in the studies. AEGL-3 values were developed on the basis of LCt_{50} values in laboratory animals; the monkey was selected as the best animal model for humans. The anticholinergic (parasympatholytic) effects of BZ exhibit a notable latency (several hours or more) and are long-lasting (several days) following only brief exposure, but are reversible. Estimates of lethality thresholds for humans and lethality data in animals indicate a large margin between induction of incapacitating effects and lethality.

8.2. Comparisons with Other Standards and Guidelines

No guidelines or standards were available for BZ.

8.3. Data Adequacy and Research Needs

Human exposure data from controlled experiments adequately describe the incapacitating effects of BZ. Concentration-response data for inhalation exposures are lacking compared with data on other exposure routes. Data in animals are adequate for assessing lethality, although definitive lethality threshold data are lacking and effects of exposures for several hours are uncertain.

TABLE 1-9 AEGL Values for Agent BZ

10 min	30 min	1 h	4 h	8 h
1.2 mg/m^3	0.41 mg/m^3	0.21 mg/m^3	Not recommended	Not recommended

TABLE 1-10 AEGL Values for Agent BZ

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)[a]	NR	NR	NR	NR	NR
AEGL-2 (disabling)	0.067 mg/m^3	0.022 mg/m^3	0.011 mg/m^3	NR	NR
AEGL-3 (lethal)	1.2 mg/m^3	0.41 mg/m^3	0.21 mg/m^3	NR	NR

NR: not recommended because of data deficiencies.

[a]Absence of AEGL-1 values does not imply that exposure to concentrations less than the AEGL-2 values is without effect.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR AGENT BZ

Derivation of AEGL-1 Values

Although exposures to BZ resulting in no apparent effects in animals were available, the experiments could not assess possible cognitive and behavioral effects characteristic of BZ that are relevant to humans. Human data on BZ that define no-effect levels or that are consistent with the AEGL-1 definition were not available. Thus, AEGL-1 values for BZ are not recommended.

Derivation of AEGL-2 Values

Key study:	Ketchum, J.S., B.R. Tharp, E.B. Crowell, D.L. Sawhill, and M.E. Vancil. 1967. The Human Assessment of BZ Disseminated Under Field Conditions Edgewood Arsenal Technical Report EATR 4140.U.S. Department of the Army, Medical Research Laboratory, Edgewood Arsenal, MD.
Critical effect:	Point of departure is 20 mg-min/m^3. Value was calculated as one-third of the ICt_{50} (a concentration-time product causing incapacitation of 50% of the test subjects) of 60.1 mg-min/m^3 (95% CI: 41.3-87.5 mg-min/m^3), and was considered an estimated threshold for incapacitating effects in humans. The one-third reduction was considered sufficient because it was well below the lower confidence limit of the ICt_{50}, and is lower than concentrations (46.0-84.7 mg-min/m^3) associated with clinical signs that might impair the ability to escape (e.g., progressive deterioration of normal gait and uncomfortable paresthesias of lower extremities).
Time scaling:	Data with which to assess the concentration-time relationship for BZ toxicity are not available. Experiments conducted by Ketchum and colleagues were of short durations; 6-8 min in animal studies and possibly no more than 5 min in tests with human volunteers. The concentration-time relationship for many irritant and systemically acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten

Berge et al. 1986). In the absence of an empirically derived exponent (n) and to obtain protective AEGL values, time scaling was performed using a default of n = 1 for extrapolating from shorter exposures to longer duration.

Uncertainty factors: 1 for interspecies differences, because data were from human volunteers.

10 for intraspecies variability. The structures of muscarinic receptors are highly conserved in humans and, thus, receptor affinity is not likely to vary among individuals; however, some individuals with pre-existing conditions may be sensitive to the anticholingeric effects of BZ.

Total uncertainty factor of 10

Modifying factor: 3 because of deficiencies in overall data, particularly lack of longer duration studies

Calculation:

10-min AEGL-2: $C = 20\ mg\text{-}min/m^3 \div 10\ min = 2\ mg/m^3$
$C = 2\ mg/m^3 \div 30 = 0.067\ mg/m^3$

30-min AEGL-2: $C = 20\ mg\text{-}min/m^3 \div 30\ min = 0.667\ mg/m^3$
$C = 0.667\ mg/m^3 \div 30 = 0.022\ mg/m^3$

1-h AEGL-2: $C = 20\ mg\text{-}min/m^3 \div 60\ min = 0.33\ mg/m^3$
$C = 0.33\ mg/m^3 \div 30 = 0.011\ mg/m^3$

4-h AEGL-2: Not recommended because of uncertainties regarding longer-term exposures.

8-h AEGL-2: Not recommended because of uncertainties regarding longer-term exposures.

Derivation of AEGL-3 Values

Key study: U.S. Department of the Army. 1974. Pp. 109-113 in Chemical Agent Data Sheets, Volume 1. Edgewood Arsenal Special Report AD 0030. U.S. Department of the Army, Edgewood Arsenal, Aberdeen Proving Ground, MD.

Critical effect:	Lethality threshold estimated as one-tenth of the LCt_{50} of 37,000 mg-min/m^3 for monkeys exposed to BZ for 6-25 min.
Time scaling:	Data with which to assess the concentration-time relationship for BZ toxicity are not available. The experiments conducted by Ketchum and colleagues were of short durations; 6-8 min in animal studies and possibly no more than 5 min in tests with human volunteers. 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 (ten Berge et al. 1986). In the absence of an empirically derived exponent (n) and to obtain protective AEGL values, time scaling was performed using the default of n = 1 for extrapolating from shorter exposures to longer duration.
Uncertainty factors:	10 for interspecies differences; no lethality data are available for humans and LCt_{50} values for five animal species varied 10-fold. 10 for intraspecies variability; BZ toxicity is due to an anticholinergic mechanism and the structures of muscarinic receptors are highly conserved in humans, so receptor affinity (and, therefore, toxicodynamics) is not likely to vary among individuals; however, some individuals with pre-existing conditions may be sensitive to the anticholinergic effects of BZ.
Modifying factor:	3 because of deficiencies in overall data, in particular a lack of incidence data (the available lethality studies only reported LCt_{50} values) which could be used to estimate a LC_{01} and studies involving longer exposure durations (the longest duration exposure was 40 min).
Calculation:	
10-min AEGL-3:	$C = 3{,}700$ mg-min/$m^3 \div 10$ min = 370 mg/m^3 $C = 370$ mg/$m^3 \div 300 = 1.2$ mg/m^3
30-min AEGL-3:	$C = 3{,}700$ mg-min/$m^3 \div 30$ min = 123.3 mg/m^3 $C = 123.3$ mg/$m^3 \div 300 = 0.41$ mg/m^3

1-h AEGL-3:	$C = 3{,}700$ mg-min/m^3 ÷ 60 min = 61.67 mg/m^3 $C = 61.67$ mg/m^3 ÷ 300 = 0.21 mg/m^3
4-h AEGL-3:	Not recommended because of uncertainties regarding longer-term exposures.
8-h AEGL-3:	Not recommended because of uncertainties regarding longer-term exposures.

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR AGENT BZ

Derivation Summary

AEGL-1 VALUES

Data on BZ were insufficient for deriving AEGL-1 values. Absence of AEGL-1 values does not imply that exposure below the AEGL-2 values are without adverse effects.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.067 mg/m^3	0.022 mg/m^3	0.011 mg/m^3	Not recommended	Not recommended

Reference: Ketchum, J.S., B.R. Tharp, E.B. Crowell, D.L. Sawhill, and M.E. Vancil. 1967. The Human Assessment of BZ Disseminated Under Field Conditions. Edgewood Arsenal Technical Report EATR 4140.U.S. Department of the Army, Medical Research Laboratory, Edgewood Arsenal, MD.

Test species/Strain/Sex/Number: Human volunteers, males, n = 8

Exposure route/Concentrations/Durations: Aerosol inhalation

Effects: Cognitive and behavioral effects, mild effects on heart rate and blood pressure. ICt_{50} of 60.1 mg-min/m^3 (95% CI: 41.3-87.5 mg-min/m^3; presumably for 5 min) for a 165-pound human with a breathing rate of 15 L/min. An ICt_{50} is a concentration-time product causing incapacitation of 50% of the test subjects.

End point/Concentration/Rationale: Point of departure is 20 mg-min/m^3 (one-third of the ICt_{50}). One-third of the ICt_{50} was considered an estimated threshold for incapacitating effects in humans. The reduction was considered sufficient because it was well below the lower confidence limit of the ICt_{50} and concentrations associated with clinical signs which might impair the ability to escape (e.g., progressive deterioration of normal gait and uncomfortable paresthesias of lower extremities reported by subjects exposed to BZ at 46.0-84.7 mg-min/m^3). BZ effects are totally reversible.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 1, because data were from human volunteers
Intraspecies: 10, although the anticholinergic mechanism by which BZ operates is not likely to vary between individuals because the structure of muscarinic receptors are highly conserved in humans, individuals with pre-existing conditions may be sensitive to the antimuscarinic effects of BZ.

Modifying factor: 3, incomplete data base.

Animal-to-human dosimetric adjustment: Not applicable
Time scaling: Experimental data on BZ were expressed as CT products (mg-min/m^3). For AEGL-specific exposure durations, all of which involved extrapolating to longer time frames, the concentrations were determined using the default of n = 1.
Data adequacy: Although definitive concentration-response information for inhalation exposure to BZ is lacking, data regarding human response to inhaled BZ aerosol are available and sufficient for developing AEGL-2 values.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
1.2 mg/m^3	0.41 mg/m^3	0.21 mg/m^3	Not recommended	Not recommended
Reference: U.S. Department of the Army. 1974. Pp. 109-113 in Chemical Agent Data Sheets, Volume 1. Edgewood Arsenal Special Report AD 0030. U.S. Department of the Army, Edgewood Arsenal, Aberdeen Proving Ground, MD.				
Test species/Strain/Sex/Number: Monkeys; species, gender, and number not reported.				
Exposure route/Concentrations/Durations: Aerosol inhalation; LCt_{50} of 37,000 mg-min/m^3 based on exposure durations of 6-25 min.				
Effects: LCt_{50} of 37,000 mg-min/m^3 based on exposure durations of 6-25 min.				
End point/Concentration/Rationale: Lethality threshold estimated as one-tenth of LCt_{50}; definitive information regarding the concentration-response relationship for BZ is lacking.				
Uncertainty factors/Rationale: Total uncertainty factor: 100 Interspecies: 10, no lethality data are available for humans and LCt_{50} values for five animal species varied 10-fold. Intraspecies: 10, the anticholinergic mechanism by which BZ operates is not likely to vary between individuals because the structure of muscarinic receptors are highly conserved in humans; however, individuals with pre-existing conditions may be sensitive to the anticholingeric effects of BZ.				
Modifying factor: 3, incomplete data base (e.g., incidence data and studies involving longer exposure durations).				
Animal-to-human dosimetric adjustment: Not applicable				
Time scaling: Experimental data for BZ were consistently expressed as CT products (mg-min/m^3). For AEGL-specific exposure durations, all of which involved extrapolating to longer time frames, the concentrations were determined using the default of n = 1.				
Data adequacy: LCt_{50} values are available for five species but experimental details are lacking. Data are considered sufficient for deriving AEGL-3 values which can be compared with human exposure data.				

APPENDIX C

CATEGORY PLOT FOR AGENT BZ

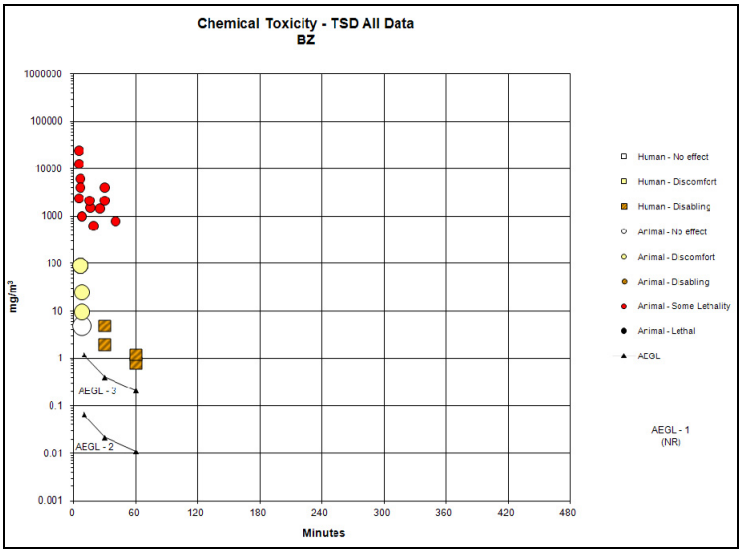

FIGURE C-1 Category plot of animal and human data and AEGL values for Agent BZ. Response data for BZ were routinely expressed as a CT products (concentration × time) of mg-min/m^3. Data points were derived for the lowest and highest exposure durations for which the CT values were determined, as well as for AEGL-specific durations within or near the respective range of the experimental exposure durations.

TABLE C-1 Data Used in Category Plot for Agent BZ

Source	Species	No. Exposures	mg/m^3	Minutes	Category	Comments
NAC/AEGL-1			NR	10	AEGL	
NAC/AEGL-1			NR	30	AEGL	
NAC/AEGL-1			NR	60	AEGL	
NAC/AEGL-1			NR	240	AEGL	
NAC/AEGL-1			NR	480	AEGL	
NAC/AEGL-2			0.067	10	AEGL	
NAC/AEGL-2			0.022	30	AEGL	
NAC/AEGL-2			0.011	60	AEGL	
NAC/AEGL-2			NR	240	AEGL	
NAC/AEGL-2			NR	480	AEGL	
NAC/AEGL-3			1.2	10	AEGL	

(Continued)

TABLE C-1 Continued

Source	Species	No. Exposures	mg/m^3	Minutes	Category	Comments
NAC/AEGL-3			1.2	10	AEGL	
NAC/AEGL-3			0.41	30	AEGL	
NAC/AEGL-3			0.21	60	AEGL	
NAC/AEGL-3			NR	240	AEGL	
NAC/AEGL-3			NR	480	AEGL	
Ketchum 1963	Human	1	2	30	2	
	Human	1	5	30	2	
	Human	1	0.8	60	2	
	Human	1	1.2	60	2	
Department of the Army 1974	Monkey	1	6,167	6	SL	LCt_{50}
	Monkey	1	1,480	25	SL	LCt_{50}
	Dog	1	4,167	6	SL	LCt_{50}
	Dog	1	1,563	16	SL	LCt_{50}
	Rat	1	12,800	5	SL	LCt_{50}
	Rat	1	2,133	30	SL	LCt_{50}
	Mouse	1	2,400	5	SL	LCt_{50}
	Mouse	1	632	19	SL	LCt_{50}
	Rabbit	1	2,133	15	SL	LCt_{50}
	Rabbit	1	800	40	SL	LCt_{50}
	Guinea pig	1	24,600	5	SL	LCt_{50}
	Guinea pig	1	4,100	30	SL	LCt_{50}
Ketchum et al. 1967	Monkey	1	93	6.17	1	Mydriasis, cycloplegia, tranquility, erratic behavior, lethargy, hyperactivity, sedation, ataxia
	Dog	1	93	6.17	1	Mydriasis, cycloplegia, tranquility, erratic behavior, lethargy, hyperactivity, sedation, ataxia, increased heart rate
	Dog	1	5	8	0	
	Rabbit	1	93	6.17	1	Mydriasis, cycloplegia
	Dog	1	1,000	8	SL	RCt_{50}
	Dog	1	25	8	1	
	Rabbit	1	10	8	1	RCt_{50}
	Rabbit	1	1,000	8	SL	

For category: 0 = no effect; 1 = discomfort; 2 = disabling; SL = some lethality; 3 = lethal.

2

Ethyl Phosphorodichloridate[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 Cheryl Bast (Oak Ridge National Laboratory), Lisa Ingerman (SRC, Inc.), Chemical Manager Dieter Heinz (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 concentrations 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

Ethyl phosphorodichloridate is a colorless liquid used as an intermediate in the preparation of the pesticide ethoprop. The vapor irritates the eyes, nose, and throat; the liquid burns skin and eyes and causes severe burns of the mouth and stomach if ingested. Ethyl phosphorodichloridate reacts with water to produce hydrogen chloride fumes.

Data were insufficient for derivation of AEGL-1 values. Therefore, AEGL-1 values are not recommended for ethyl phosphorodichloridate.

In the absence of appropriate chemical-specific data, a fractional reduction of the AEGL-3 values was used to derive AEGL-2 values. For chemicals with a steep concentration-response curve, AEGL-3 values may be divided by 3 to estimate AEGL-2 values (NRC 2001). Therefore, the AEGL-2 values for ethyl phosphorodichloridate were obtained by dividing the AEGL-3 values for ethyl phosphorodichloridate by 3.

A 4-h $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) of 38.0 ppm (Bayer 1983) for male and female rats exposed to ethyl phosphorodichloridate was used as the point of departure for calculating AEGL-3 values. The $BMCL_{05}$ is considered a threshold for lethality, and is supported by the fact that no mortality was observed in rats exposed to ethyl phosphorodichloridate at 37 ppm for 4 h. Values were scaled across time using the equation $C^n \times t = k$, where n = 3 when extrapolating to shorter durations and

n = 1 when extrapolating to longer durations in order to derive values protective of human health (NRC 2001). Extrapolating a 4-h value to a 10-min AEGL-3 value is justified because no deaths were noted in male rats exposed to ethyl phosphorodichloridate at 20,900 ppm or in female rats exposed at 16,700 ppm for 10 min (Bayer 1983). Uncertainty factors of 10 were applied to account for interspecies differences and intraspecies variability, because of the lack of information available to describe species differences in toxicity and inter-individual variability. Rat studies suggest that vapors are irritating to the eyes and nose, and that pulmonary edema increases with concentration (Bayer 1983; Rhone-Poulenc, Inc. 1990). The liquid was corrosive to the skin and eyes of rabbits (Rhone- Poulenc, Inc. 1990). It also reportedly reacts with water to produce hydrogen chloride, which supports a mechanism of primary irritation.

AEGL values for ethyl phosphorodichloridate are presented in Table 2-1.

1. INTRODUCTION

Ethyl phosphorodichloridate is a colorless liquid used as an intermediate in the preparation of the pesticide ethoprop. The vapor irritates the eyes, nose, and throat; the liquid burns the skin and eyes and causes severe burns of the mouth and stomach if ingested. Ethyl phosphorodichloridate reacts with water to produce hydrogen chloride fumes. When heated to decomposition, toxic fumes of hydrogen chloride and phosphoric acid or phosphorus oxides may be formed (HSDB 2002).

Selected physicochemical properties of ethyl phosphorodichloridate are presented in Table 2-2.

TABLE 2-1 AEGL Values for Ethyl Phosphorodichloridate

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)[a]	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (disabling)	0.37 ppm (2.4 mg/m^3)	0.25 ppm (1.7 mg/m^3)	0.20 ppm (1.3 mg/m^3)	0.13 ppm (0.86 mg/m^3)	0.063 ppm (0.40 mg/m^3)	One-third the AEGL-3 values.
AEGL-3 (lethal)	1.1 ppm (7.3 mg/m^3)	0.76 ppm (5.0 mg/m^3)	0.60 ppm (4.0 mg/m^3)	0.38 ppm (2.5 mg/m^3)	0.19 ppm (1.3 mg/m^3)	4-h threshold for lethality ($BMCL_{05}$) of 38 ppm in rats (Bayer 1983).

Abbreviations: $BMCL_{05}$, benchmark concentration, 95% lower confidence limit with 5% response; NR, not recommended.

[a]Absence of an AEGL-1 value does not imply that concentrations below the AEGL-2 are without effect.

TABLE 2-2 Chemical and Physical Data for Ethyl Phosphorodichloridate

Parameter	Value	Reference
Synonyms	Ethyl diphosphorodichloridate; ethylesterdichloride; dichloroethoxyphosphine oxide; dichlorophosphoric acid, ethyl ester	Bayer 1983; HSDB 2002
CAS registry no.	1498-51-7	HSDB 2002
Chemical formula	$C_2H_5Cl_2O_2P$	HSDB 2002
Molecular weight	162.94	HSDB 2002
Physical state	Colorless liquid	HSDB 2002
Boiling point	167°C	HSDB 2002
Specific gravity	1.35 at 19°C	HSDB 2002
Solubility in water	1.4388 g/100 mL at 20°C;	Lide 1999
Surface tension	32.8 dynes/cm at 20°C	HSDB 2002
Heat of combustion	-2,600 cal/g	HSDB 2002
Conversion factors in air	1 ppm = 6.6 mg/m^3 1 mg/m^3 = 0.15 ppm	

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Human lethality data were not found.

2.2. Nonlethal Toxicity

Human nonlethal toxicity data were not found.

2.3. Case Reports

Ocular irritation was reported in a worker exposed to ethyl phosphorodichloridate at a plant in Mount Pleasant, Tennessee (Rhone-Poulenc, Inc. 1990). No other information was available.

2.4. Developmental and Reproductive Effects

Data on the developmental and reproductive toxicity of ethyl phosphorodichloridate in humans were not available.

2.5. Genotoxicity

No information regarding the genotoxicity of ethyl phosphorodichloridate in humans was available.

2.6. Carcinogenicity

No information regarding the carcinogenicity of ethyl phosphorodichloridate in humans was available.

2.7. Summary

Ocular irritation was reported in a worker exposed to ethyl phosphorodichloridate; however, no other information regarding this case was available. No other human data were located.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

One-Hour Exposure

In a range-finding study, groups of five male and five female Sprague-Dawley rats were exposed to ethyl phosphorodichloridate (97.5% active ingredient) at 6.16, 66, or 134 ppm (analytic concentrations) for 1 h, followed by a 14-day observation period (Rhone-Poulenc, Inc. 1990). Because the test material is sensitive to oxygen and moisture, the test atmosphere was generated using a dry nitrogen-oxygen mixture. Ethyl phosphorodichloridate was delivered to the breathing zone of the animals, and exposure concentrations were determined by gas chromatographic analysis of impinger samples. Exposures were conducted in a 100-L plexiglass chamber with a glass front. Physical observations for clinical signs were recorded at 15-min intervals during exposure, and all animals received detailed physical examinations immediately prior to exposure, hourly for 2 h post-exposure, and daily thereafter. Animals were weighed just prior to exposure on day 1, on day 8, and just prior to sacrifice on day 15. All surviving animals were killed on day 15 and complete gross necropsies were performed on all rats. During exposures, labored breathing, gasping, and decreased activity were noted in all treatment groups; the time of onset was not reported. Clinical signs observed in all treatment groups during the 2 h immediately following exposure included labored breathing, gasping, decreased activity, anogenital staining, and moist rales

(anogenital staining and moist rales developed after exposure). During the 14-day observation period, surviving rats in the 66- and 134-ppm groups continued to exhibit labored breathing and rales throughout the observation period without full recovery. Rats in the 6.16-ppm group exhibited labored breathing, rales, fine tremors, and nasal discharge for a "few days" after exposure; however, the animals fully recovered during the second week post-exposure prior to sacrifice. "Significant" weight loss was noted one week following exposure in the 66- and 134-ppm groups; however, surviving rats showed some recovery prior to sacrifice. Animals in the 6.16 ppm-group gained weight during the 2 week observation period. Mortality was seen in the 66- and 134-ppm groups (see Table 2-3). All deaths occurred between days 2 and 9, with "most" being within 48-h post-exposure. There appeared to be a dose-related increase in lung weights in animals sacrificed 2-weeks post-exposure; the investigators suggest this increase may be the result of edema. No other treatment-related effects were noted at necropsy. The investigators calculated LC_{50} (lethal concentration, 50% lethality) values of 43.4 ppm for both sexes, 64.6 ppm for males, and 48.1 ppm for females.

A group of 10 male rats was exposed to ethyl phosphorodichloridate at approximately 350 ppm (nominal concentration) for 1 h, followed by a 14-day observation period (Rhone-Poulenc, Inc. 1990). The test material was metered, using a syringe infusion pump, into a stainless steel pneumatic spraying system driven by houseline air. The resulting aerosol was passed into a 40-L exposure chamber. A nominal concentration was calculated on basis of the amount of test material used and total air volume. During exposure, mild hyperemia, decreased locomotor activity, salivation, and lacrimation were noted; severe respiratory difficulty was observed during the final 15 min of exposure. Post-exposure, weight gain was reportedly slow. Seven of 10 rats died; deaths occurred on post-exposure days 2, 5, 6, 8, 10, 12, and 14.

Four-Hour Exposure

Groups of 10 male and 10 female rats (strain not specified) were exposed to ethyl phosphorodichloridate (98-99% active ingredient) at 37, 61, 75, 90, 143, or 355 ppm (analytic concentrations) for 4 h, followed by a 14-day observation period (Bayer 1983). Exposures were conducted in a 10-L glass chamber, and "minimized dermal contact". Test atmosphere concentrations were determined by absorption spectrometry. Animals were weighed before exposure and once weekly during the observation period. Gross necropsies were performed on all test animals. Clinical signs during and after exposure included disturbed behavioral patterns associated with severe respiratory problems. Ocular and nasal irritation was also noted. Clinical signs were assumed to be noted in all dose groups; however, specific signs associated with different exposure concentrations were not reported. No significant treatment-related effects on body weight were found. Necropsy findings in rats that died during the study

included severely bloated edematous lungs, spots in the lungs, brownish colored liver, pale kidneys, red renal pelvis, stomach ulcers, red intestinal wall, and dark red gastrointestinal tract contents of slimy consistency. The investigators suggested that the gastrointestinal effects were the result of ingestion. Rats killed after the 14-day observation period exhibited slightly bloated lungs at the higher concentrations. Specific necropsy findings associated with the different concentrations were not reported. The investigators calculated LC_{50} values of 91.6 ppm for both sexes, 85 ppm for males, and 99.8 ppm for females. The time of deaths was not reported. Mortality data and $BMCL_{05}$ (see Appendix B) and BMC_{01} (benchmark concentration with 1% response) values are presented in Table 2-4.

TABLE 2-3 Mortality in Rats Exposed by Inhalation to Ethyl Phosphorodichloridate for 1 Hour

	Mortality Incidence		
Concentration (ppm)	Male	Female	Total
6.16	0/5	0/5	0/10
66	5/5	3/5	8/10
134	3/5	4/5	7/10
Estimated LC_{50} (ppm)	64.6	48.1	43.4

Source: Rhone-Poulenc, Inc. 1990.

TABLE 2-4 Mortality in Rats Exposed by Inhalation to Ethyl Phosphorodichloridate for 4 Hours

	Mortality Incidence		
Concentration (ppm)	Male	Female	Total
37	0/10	0/10	0/20
61	2/10	NR	2/10
75	1/10	3/10	4/20
90	7/10	5/10	12/20
143	10/10	7/10	17/20
355	10/10	10/10	20/20
LC_{50} (ppm)	85	99.8	91.6
$BMCL_{05}$ (ppm)[a]	43.7	25.8	38.0
BMC_{01} (ppm)[a]	48.1	32.1	38.2

Abbreviations: NR, not reported; no explanation provided.
[a]Values calculated for this technical support document.
Source: Bayer 1983.

In another experiment, Bayer (1983) exposed groups of five male or five female rats to 'saturated' atmospheres of ethyl phosphorodichloridate for 10 min, 30 min, or 1 h, followed by a 14-day observation period. Exposure and analytic methods were similar to those described in the 4-h study (Bayer 1983). Clinical signs and gross necropsy results were similar to those described in the 4-h study (see Table 2-5).

Oral Exposure

An oral LD_{50} of 220 ± 41 mg/kg in rats was reported for ethyl phosphorodichloridate (Rhone- Poulenc, Inc. 1990).

3.1.2. Rabbits

A dermal LD_{50} of 2,350 ± 997 mg/kg in rabbits was reported for ethyl phosphorodichloridate (Rhone-Poulenc, Inc. 1990).

3.1.3. Summary of Animal Lethality Data

Animal lethality data on ethyl phosphorodichloridate are limited to rats. One-hour LC_{50} values of 43.4 ppm for rats of both sexes, 64.6 ppm for males, and 48.1 ppm for females were calculated (Rhone-Poulenc, Inc. 1990). In another 1-h study, seven of 10 male rats died after exposure to ethyl phosphorodichloridate at approximately 350 ppm (Rhone-Poulenc, Inc. 1990). Four-hour LC_{50} values of 85 ppm for male and 99.8 ppm for female rats were calculated (Bayer 1983). No lethality was reported in rats exposed to ethyl phosphorodichloridate at 16,700-20,900 ppm for 10 min; whereas, 90% mortality was noted in rats exposed at 10,700-14,400 ppm for 30 min and 100% mortality was noted in rats exposed at 12,000-13,700 ppm for 1 h (Bayer 1983). In all studies, clinical signs were consistent with irritation, and deaths were likely due to pulmonary edema.

3.2. Nonlethal Toxicity

3.2.1. Rabbits

A primary dermal irritation index for ethyl phosphorodichloridate of 7.16 was reported for rabbits. Ocular irritation scores of 92 at 1 h, and 100 at 1, 2, 3, 4, 7, 8, 9, 10, and 14 days were also reported (Rhone-Poulenc, Inc. 1990). These scores classify ethyl phosphorodichloridate as corrosive.

TABLE 2-5 Mortality and Clinical Findings in Rats Exposed by Inhalation to Saturated Concentrations of Ethyl Phosphorodichloridate

Concentration (ppm)	Duration	Sex	Mortality Incidence	Time of Death	Clinical Signs, Comments
20,900	10 min	Male	0/5	–	No weight gain during week 1 post-exposure; significant weight gain during week 2 post-exposure.
16,700	10 min	Female	0/5	–	
14,400	30 min	Male	5/5	Day 1	Significant weight loss throughout 14-day follow-up period in single surviving female.
10,700	30 min	Female	4/5	Days 3-4	
13,700	1 h	Male	5/5	Day 1	During exposure: audible oral noises; cramped walking; ocular and nasal irritation.
12,000	1 h	Female	5/5	Days 1-3	

Source: Bayer 1983.

3.2.2. Guinea Pigs

Ethyl phosphorodichloridate was negative in a guinea pig sensitization (Buehler) test (Rhone- Poulenc, Inc. 1990).

3.2.3. Summary of Nonlethal Toxicity in Animals

Ethyl phosphorodichloridate was corrosive to the skin and eyes of rabbits and was negative in a guinea pig sensitization test (Rhone-Poulenc, Inc. 1990).

3.3. Developmental and Reproductive Effects

No developmental or reproductive data were found.

3.4. Genotoxicity

No genotoxicity data were found.

3.5. Carcinogenicity

No carcinogenicity data were found.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Metabolism and disposition data for ethyl phosphorodichloridate in humans or animals were not available.

4.2. Mechanism of Toxicity

On the basis of clinical signs of toxicity and the physico-chemical properties of ethyl phosphorodichloridate, its mechanism of toxicity appears to be that of primary irritation. Rat lethality studies reported that vapors of ethyl phosphorodichloridate are irritating to the eyes and nose, and that the incidence of pulmonary edema increases with concentration (Bayer 1983; Rhone-Poulenc, Inc. 1990). Liquid ethyl phosphorodichloridate was corrosive to the skin and eyes of rabbits (Rhone-Poulenc, Inc. 1990).

Little information on the reactivity of ethyl phosphorodichloridate was found in the literature. It reportedly reacts with water to produce hydrogen chloride fumes, and may also produce fumes of phosphoric acid when heated (HSDB 2002). Because those products are irritating and corrosive, they may contribute to or be responsible for the irritation observed after exposure to ethyl phosphorodichloridate; however, the rate of decomposition and relative contribution of these decomposition products to the toxicity of the parent compound is unknown. Under conditions that promote aerosolization of ethyl phosphorodichloridate, transport to the deeper airways may occur, leading to greater lung injury and possibly delayed clinically manifested effects.

4.3. Structure-Activity Relationships

No structure-activity information on ethyl phosphorodichloridate was available.

4.4. Species Variability

Data are insufficient to determine species variability for ethyl phosphorodichloridate; however, because the clinical signs and physico-chemical properties suggest that its mechanism of toxicity may be primary irritation, little species variability is expected (NRC 2001).

4.5. Temporal Extrapolation

The concentration-time relationship for many irritant and systemically acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of data to allow empirical derivation of the exponent n, temporal scaling was performed using n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations (NRC 2001).

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No human data relevant to derivation of AEGL-1 values for ethyl phosphorodichloridate were available.

5.2. Animal Data Relevant to AEGL-1

No animal data relevant to derivation of AEGL-1 values for ethyl phosphorodichloridate were available.

5.3. Derivation of AEGL-1 Values

No human or animal data were available for derivation of AEGL-1 values for ethyl phosphorodichloridate. Therefore, AEGL-1 values are not recommended.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data relevant to derivation of AEGL-2 values for ethyl phosphorodichloridate were available.

6.2. Animal Data Relevant to AEGL-2

No animal data relevant to derivation of AEGL-2 values for ethyl phosphorodichloridate were available.

6.3. Derivation of AEGL-2 Values

In the absence of appropriate chemical-specific data, a fractional reduction of the AEGL-3 values may be used to derive AEGL-2 values (NRC 2001). For chemicals with a steep concentration-response curve, AEGL-3 values may be divided by 3 to estimate AEGL-2 values (NRC 2001). Therefore, AEGL-2 values will be estimated by dividing AEGL-3 values by 3. AEGL-2 values are presented in Table 2-6, and calculations are presented in Appendix A.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data relevant to derivation of AEGL-3 values for ethyl phosphorodichloridate were located.

TABLE 2-6 AEGL-2 Values for Ethyl Phosphorodichloridate

10 min	30 min	1 h	4 h	8 h
0.37 ppm (2.4 mg/m^3)	0.25 ppm (1.7 mg/m^3)	0.20 ppm (1.3 mg/m^3)	0.13 ppm (0.86 mg/m^3)	0.063 ppm (0.40 mg/m^3)

7.2. Animal Data Relevant to AEGL-3

Animal lethality data are available for rats. On the basis of a 1-h study, LC_{50} values of 64.6 ppm for male rats, 48.1 ppm for female rats, and 43.4 ppm for the sexes combined were calculated (Rhone-Poulenc, Inc. 1990). On the basis of a 4-h study, LC_{50} values of 85 ppm for males, 99.8 ppm for females, and 91.6 ppm for the sexes combined were calculated. $BMCL_{05}$ values were 43.7 ppm for males, 25.8 ppm for females, and 38.0 ppm for the sexes combined, and BMC_{01} values were 48.1 ppm, 32.1 ppm, 38.2 ppm, respectively (Bayer 1983). No deaths were noted in male rats exposed to ethyl phosphorodichloridate at 20,900 ppm or in female rats exposed at 16,700 ppm for 10 min (Bayer 1983).

7.3. Derivation of AEGL-3 Values

The 4-h $BMCL_{05}$ of 38.0 ppm for male and female rats (Bayer 1983) was used as the point of departure for AEGL-3 values. That value is considered a threshold for lethality, and is supported by the fact that no mortality was observed in rats exposed to ethyl phosphorodichloridate at 37 ppm for 4 h. The 4-h study was chosen over the 1-h study because it included more animals per exposure group and more exposure concentrations, and yielded a better concentration-response relationship. Due to the concentrations of ethyl phosphorodichloridate used in the 1-h study, the concentration-response relationship resembles a step function (1-h mortality data were 0/10 at 6.16 ppm, 8/10 at 66 ppm, 7/10 at 134 ppm, and 7/10 at 350 ppm [Rhone-Poulenc, Inc. 1990]); whereas, the 4-h study used narrower exposure intervals and yielded more variable responses (4-h mortality data were 0/20 at 37 ppm, 2/10 at 61 ppm, 4/20 at 75 ppm, 12/20 at 90 ppm, 17/20 at 143 ppm, and 20/20 at 355 ppm [Bayer 1983]). Furthermore, the goodness of fit for benchmark calculations was better for the 4-h data (p-value = 0.7465) than for the 1-h data (p-value = 0.21). Values were be scaled across time using the equation $C^n \times t = k$, where n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations to derive values protective of human health (NRC 2001). Extrapolating from a 4-h study duration to the 10-min AEGL-3 value is justified because no deaths were noted in male rats exposed to ethyl phosphorodichloridate at 20,900 ppm or in female rats exposed at 16,700 ppm for 10 min (Bayer 1983). A factor of 10 was used to account for interspecies differences and another factor of 10 was used for intraspecieis variability because of the lack information available to describe species differences in toxicity and interindividual variability. Ani-

mals exposed to ethyl phosphorodichloridate experienced labored breathing, rales, nasal discharge, salivation, lacrimation, and ocular irritation following exposure for 1 or 4 h (Bayer 1983; Rhone-Poulenc, Inc. 1990), which are signs of irritation. Liquid ethyl phosphorodichloridate was corrosive to the skin and eyes of rabbits (Rhone-Poulenc, Inc. 1990), and may also produce fumes of hydrogen chloride and phosphoric acid (HSDB 2002). Because those fumes are irritating and corrosive, they may contribute to or be responsible for the irritation observed after exposure to ethyl phosphorodichloridate; however, the relative contribution of these decomposition products to the toxicity of the parent compound is unknown, as is the rate of decomposition.

AEGL-3 values for ethyl phosphorodichloridate are presented in Table 2-7 and their derivation is summarized in Appendix A.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

AEGL values for ethyl phosphorodichloridate are presented in Table 2-8. AEGL-1 values were not recommended because insufficient data. AEGL-2 values were derived by dividing the AEGL-3 values by 3, and the AEGL-3 values are based on a threshold for lethality in rats (4-h $BMCL_{05}$).

8.2. Comparisons with Other Standards and Guidelines

No other standards or guidelines for ethyl phosphorodichloridate were found for ethyl phosphorodichloridate.

TABLE 2-7 AEGL-3 Values for Ethyl Phosphorodichloridate

10 min	30 min	1 h	4 h	8 h
1.1 ppm (7.3 mg/m^3)	0.76 ppm (5.0 mg/m^3)	0.60 ppm (4.0 mg/m^3)	0.38 ppm (2.5 mg/m^3)	0.19 ppm (1.3 mg/m^3)

TABLE 2-8 AEGL Values for Ethyl Phosphorodichloridate

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)[a]	NR	NR	NR	NR	NR
AEGL-2 (disabling)	0.37 ppm (2.4 mg/m^3)	0.25 ppm (1.7 mg/m^3)	0.20 ppm (1.3 mg/m^3)	0.13 ppm (0.86 mg/m^3)	0.063 ppm (0.40 mg/m^3)
AEGL-3 (lethal)	1.1 ppm (7.3 mg/m^3)	0.76 ppm (5.0 mg/m^3)	0.60 ppm (4.0 mg/m^3)	0.38 ppm (2.5 mg/m^3)	0.19 ppm (1.3 mg/m^3)

Abbreviations: NR, not recommended.

[a]Absence of an AEGL-1 value does not imply that concentrations below the AEGL-2 are without effect.

8.3. Data Adequacy and Research Needs

No human or animal data on ethyl phosphorodichloridate relevant to AEGL-1 or AEGL-2 end points were available. Toxicity data on this compound were limited to unpublished studies, including 1-h and 4-h lethality studies in rats exposed by inhalation (Bayer 1983; Rhone-Poulenc, Inc. 1990), LD50 estimates in rats (oral) and rabbits (dermal), dermal and ocular irritation data in rabbits, and a guinea pig sensitization study (Rhone-Poulenc, Inc. 1990). No data were available on the metabolism and disposition of ethyl phosphorodichloridate in humans or animals. Anecdotal information provided by HSDB (2002) suggests that hydrogen chloride and phosphoric acid may represent decomposition products of ethyl phosphorodichloridate, but the rate of decomposition and relative contribution of these decomposition products to the toxicity of the parent compound is unknown. Additional research on the acute inhalation toxicity of ethyl phosphorodichloridate in other species, the metabolism and disposition of ethyl phosphorodichloridate in the respiratory tract, and identification of the ultimate chemical compound(s) responsible for toxicity of this compound would enhance confidence in the AEGL values.

9. REFERENCES

Bayer AG. 1983. Ethylesterdichloride [in German]. Report No. 11439 and 11715. Bayer AG, Wuppertal-Elberfeld. Attachment in letter from Mobay Corporation, Pittsburg, PA, to U.S. EPA Submitting Toxicology Study on Ethylesterdichloride, Dated 12/31/90. EPA Document No. 86910000570, Microfiche No. OTS0530306; and EPA Document No. 86910000571, Microfiche No. OTS0530307.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR ETHYL PHOSPHORODICHLORIDATE

Derivation of AEGL-1 Values

The available data were insufficient to derive AEGL-1 values for ethyl phosphorodichloridate. Therefore, AEGL-1 values were not recommended.

Derivation of AEGL-2 Values

In the absence of appropriate chemical-specific data, a fractional reduction of the AEGL-3 values may be used to derive AEGL-2 values. For chemicals with a steep concentration-response curve, AEGL-3 values may be divided by 3 to estimate AEGL-2 values (NRC 2001).

10-min AEGL-2:	1.1 ppm ÷ 3 = 0.37 ppm
30-min AEGL-2:	0.76 ppm ÷ 3 = 0.25 ppm
1-h AEGL-2:	0.60 ppm ÷ 3 = 0.20 ppm
4-h AEGL-2:	0.38 ppm ÷ 3 = 0.13 ppm
8-h AEGL-2:	0.19 ppm ÷ 3 = 0.06 ppm

Derivation of AEGL-3 Values

Key study:	Bayer AG. 1983. Ethylesterdichloride [in German]. Report No. 11439 and 11715. Bayer AG, Wuppertal-Elberfeld. Attachment in Letter from Mobay Corporation, Pittsburg, PA, to U.S. EPA Submitting Toxicology Study on Ethylesterdichloride, Dated 12/31/90. EPA Document No. 86910000570, Microfiche No. OTS0530306; and EPA Document No. 86910000571, Microfiche No. OTS0530307.
Toxicity end point:	4-h threshold for lethality in rats ($BMCL_{05}$ = 38 ppm).

Time scaling:	Values scaled across time using the equation $C^n \times t = k$, where n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations to derive values protective of human health (NRC 2001). Extrapolating from the 4-h point of departure to the 10-min AEGL-3 value is justified because no deaths were noted in male rats exposed to ethyl phosphorodichloridate at 20,900 ppm or in female rats exposed at 16,700 ppm for 10 min (Bayer 1983). $(38 \text{ ppm})^3 \times 4 \text{ h} = 219{,}488 \text{ ppm-h}$ $(38 \text{ ppm})^1 \times 4 \text{ h} = 152 \text{ ppm-h}$
Uncertainty factors:	10 for interspecies differences 10 for intraspecies variability
Modifying factor:	None
10-min AEGL-3:	$C^3 \times 0.167 \text{ h} = 219{,}488 \text{ ppm-h}$ $C^3 = 1{,}314{,}299 \text{ ppm}$ $C = 109 \text{ ppm}$ $109 \text{ ppm} \div 100 = 1.1 \text{ ppm}$
30-min AEGL-3:	$C^3 \times 0.5 \text{ h} = 219{,}488 \text{ ppm-h}$ $C^3 = 438{,}976 \text{ ppm}$ $C = 76 \text{ ppm}$ $76 \text{ ppm} \div 100 = 0.76 \text{ ppm}$
1-h AEGL-3:	$C^3 \times 1 \text{ hr} = 219{,}488 \text{ ppm-h}$ $C^3 = 219{,}488 \text{ ppm}$ $C = 60 \text{ ppm}$ $60 \text{ ppm} \div 100 = 0.60 \text{ ppm}$
4-h AEGL-3:	$C = 38 \text{ ppm}$ $38 \text{ ppm} \div 100 = 0.38 \text{ ppm}$
8-h AEGL-3:	$C^1 \times 8 \text{ h} = 152 \text{ ppm-h}$ $C = 19 \text{ ppm}$ $19 \text{ ppm} \div 100 = 0.19 \text{ ppm}$

APPENDIX B

BENCHMARK CALCULATION FOR ETHYL PHOSPHORODICHLORIDATE

Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
Input Data File: C:\BMDS\
Mon Jan 28 09:33:17 2008

BMDS MODEL RUN

The form of the probability function is:

P[response] = Background
+ (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),

where CumNorm(.) is the cumulative normal distribution function

Dependent variable = COLUMN3
Independent variable = COLUMN1
Slope parameter is not restricted

Total number of observations = 7
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
Background = 0
Intercept = -8.25812
Slope = 1.795

Asymptotic Correlation Matrix of Parameter Estimates

	Intercept	Slope
Intercept	1	-1
Slope	-1	1

(***The model parameter(s) background have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix.)

Parameter Estimates

Variable	Estimate	Standard error
Intercept	-12.0173	2.35981
Slope	2.6604	0.526262

NA: indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Analysis of Deviance Table

Model	Log (likelihood)	Deviance Test	DF	P-value
Full model	-36.9265			
Fitted model	-38.3731	2.89329	5	0.7164
Reduced model	-88.5645	103.276	6	<0.0001

AIC: 80.7463.

Goodness of Fit

		Scaled			
Dose	Estimated probability	Expected	Observed	Size	Residual
0.0000	0.0000	0.000	0	20	0
37.0000	0.0080	0.159	0	20	-0.4006
61.0000	0.1399	1.399	2	10	0.5477
75.0000	0.2977	5.954	4	20	-0.9556
90.0000	0.4817	9.633	12	20	1.059
143.0000	0.8822	17.643	17	20	-0.4462
355.0000	0.9998	19.997	20	20	0.05588

Chi-square = 2.70; DF = 5; P-value = 0.7465.

Benchmark Dose Computation
Specified effect = 0.05

Risk Type = Extra risk
Confidence level = 0.95
BMD = 49.3439
BMDL = 37.9523

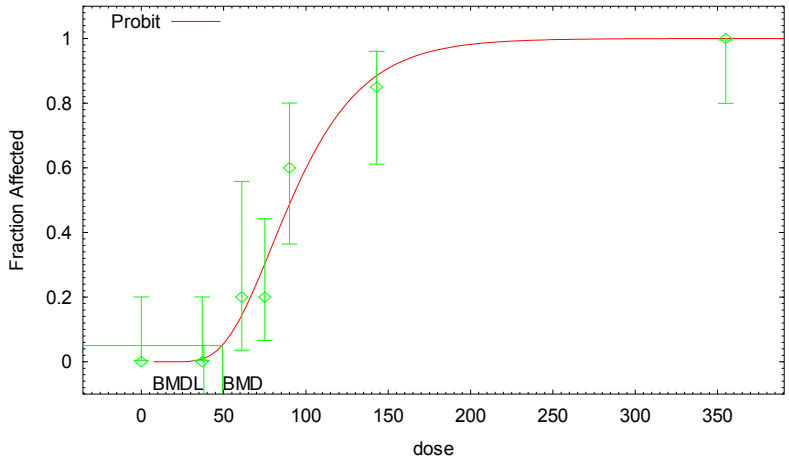

FIGURE B-1 Probit model with 0.95 confidence level.

APPENDIX C

ACUTE EXPOSURE GUIDELINE LEVELS FOR ETHYL PHOSPHORODICHLORIDATE

Derivation Summary

AEGL-1 VALUES

The available data were insufficient to derive AEGL-1 values for ethyl phosphorodichloridate. Therefore, AEGL-1 values were not recommended.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.37 ppm (2.4 mg/m^3)	0.25 ppm (1.7 mg/m^3)	0.20 ppm (1.3 mg/m^3)	0.13 ppm (0.86 mg/m^3)	0.063 ppm (0.40 mg/m^3)

Data adequacy: The available data were insufficient to derive AEGL-2 values for ethyl phosphorodichloridate. A fractional reduction of the AEGL-3 values may be used to derive AEGL-2 values. For chemicals with a steep concentration-response curve, AEGL-3 values may be divided by 3 to estimate AEGL-2 values (NRC 2001).

AEGL -3 VALUES

10 min	30 min	1 h	4 h	8 h
1.1 ppm (7.3 mg/m^3)	0.76 ppm (5.0 mg/m^3)	0.60 ppm (4.0 mg/m^3)	0.38 ppm (2.5 mg/m^3)	0.19 ppm (1.3 mg/m^3)

Reference: Bayer AG. 1983. Ethylesterdichloride [in German]. Report No. 11439 and 11715. Bayer AG, Wuppertal-Elberfeld. Attachment in Letter from Mobay Corporation to U.S. EPA Submitting Toxicology Study on Ethylesterdichloride, Dated 12/31/90.EPA Document No. 86910000570, Microfiche No.OTS05030306; and EPA Document No. 86910000571, Microfiche No. OTS05030307.

Test Species/Strain/Sex/Number: Rat, strain not specified , 10 males and 10 females per group

Exposure route/Concentrations/Durations: Inhalation; 37, 61, 75, 90, 143, or 355 ppm for 4 h

Effects: Lethality

Concentration	Mortality		
(ppm)	Male	Female	Total
37	0/10	0/10	0/20
61	0/10	Not reported	0/10
75	1/10	3/10	4/20

75	1/10	3/10	4/20
90	7/10	5/10	12/20
143	10/10	7/10	17/20
355	10/10	10/10	20/20
LC_{50}	85 ppm	99.8 ppm	91.6 ppm
$BMCL_{05}$	43.7 ppm	25.8 ppm	38.0 ppm
BMC_{01}	48.1 ppm	32.1 ppm	38.2 ppm

End point/Concentration/Rationale: 4-h $BMCL_{05}$ in rats of 38 ppm; threshold for lethality

Uncertainty factors/Rationale:
Interspecies: 10, no interspecies or mechanistic data.
Intraspecies: 10, no data on interindividual variability.

Modifying factor: None

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: $C^n \times t = k$, where n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations to derive values protective of human health (NRC 2001). Extrapolating from a 4-h point of departure to a 10-min AEGL-3 value is justified because no deaths were noted in male rats exposed to ethyl phosphorodichloridate at 20,900 ppm or in female rats exposed at 16,700 ppm for 10 min (Bayer 1983).

Data adequacy: Sparse data set.

APPENDIX D

CATEGORY PLOT FOR ETHYL PHOSPHORODICHLORIDATE

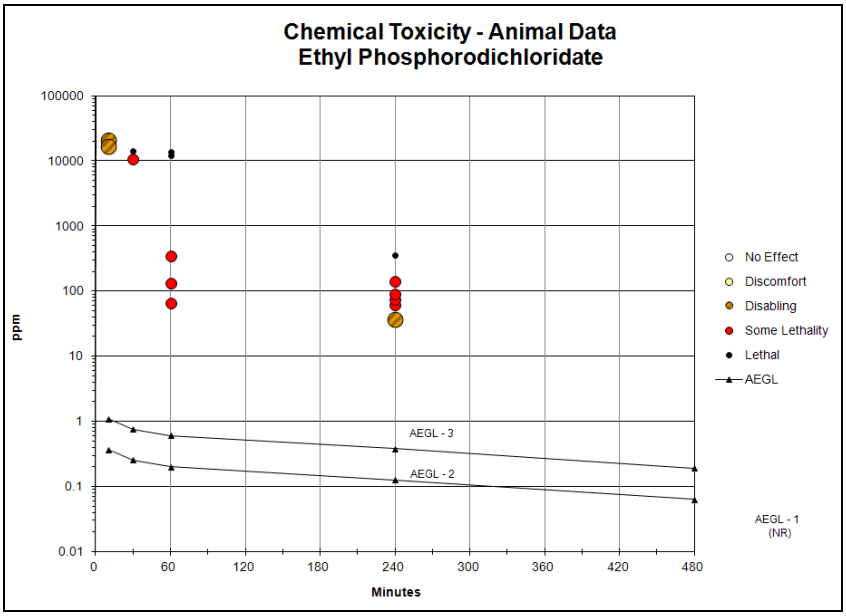

TABLE D-1 Category plot of animal toxicity data on ethyl phosphorodichloridate compared with AEGL values.

TABLE D-1 Data Used in Category Plot of AEGL Values for Ethyl Phosphorodichloridate

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Reference
NAC/AEGL-1				NR	10	AEGL	
NAC/AEGL-1				NR	30	AEGL	
NAC/AEGL-1				NR	60	AEGL	
NAC/AEGL-1				NR	240	AEGL	
NAC/AEGL-1				NR	480	AEGL	
NAC/AEGL-2				0.37	10	AEGL	
NAC/AEGL-2				0.25	30	AEGL	
NAC/AEGL-2				0.20	60	AEGL	
NAC/AEGL-2				0.13	240	AEGL	
NAC/AEGL-2				0.063	480	AEGL	
NAC/AEGL-3				1.1	10	AEGL	
NAC/AEGL-3				0.76	30	AEGL	
NAC/AEGL-3				0.60	60	AEGL	
NAC/AEGL-3				0.38	240	AEGL	
NAC/AEGL-3				0.19	480	AEGL	
	Rat		1	6.16	60	2	Labored breathing, gasping, decreased activity, rales, tremors (Rhone-Poulenc, Inc. 1990).
	Rat		1	66	60	SL	Labored breathing, gasping, decreased activity, rales, tremors, weight loss, mortality 8/10 (Rhone-Poulenc, Inc. 1990).

(Continued)

TABLE D-1 Continued

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Reference
	Rat		1	134	60	SL	Labored breathing, gasping, decreased activity, rales, tremors, weight loss, mortality 7/10 (Rhone-Poulenc, Inc. 1990).
	Rat		1	37	240	2	Severe ocular and nasal irritation, disturbed behavior, severe respiratory signs (Bayer 1983).
	Rat		1	61	240	SL	Severe ocular and nasal irritation, disturbed behavior, severe respiratory signs, mortality 2/10 (Bayer 1983).
	Rat		1	75	240	SL	Severe ocular and nasal irritation, disturbed behavior, severe respiratory signs, mortality 4/20 (Bayer 1983).
	Rat		1	90	240	SL	Severe ocular and nasal irritation, disturbed behavior, severe respiratory signs, mortality 12/20 (Bayer 1983).
	Rat		1	143	240	SL	Severe ocular and nasal irritation, disturbed behavior, severe respiratory signs, mortality 17/20 (Bayer 1983).
	Rat		1	355	240	3	Severe ocular and nasal irritation, disturbed behavior, severe respiratory signs, mortality 2/10 (Bayer 1983).
	Rat		1	350	60	SL	Hyperemia, decreased activity, salivation, lacrimation, mortality 20/20 (Rhone-Poulenc, Inc. 1990).

Rat	1	20,900	10	2	Severe ocular and nasal irritation, disturbed behavior, severe respiratory signs, no weight gain (Bayer 1983).
Rat	1	16,700	10	2	Severe ocular and nasal irritation, disturbed behavior, severe respiratory signs, no weight gain (Bayer 1983).
Rat	1	14,400	30	3	Severe ocular and nasal irritation, disturbed behavior, severe respiratory signs, weight loss, mortality 5/5 (Bayer 1983).
Rat	1	10,700	30	SL	Severe ocular and nasal irritation, disturbed behavior, severe respiratory signs, weight loss, mortality 4/5 (Bayer 1983).
Rat	1	13,700	60	3	Severe ocular and nasal irritation, oral noises, cramped walking, mortality 5/5 (Bayer 1983).
Rat	1	12,000	60	3	Severe ocular and nasal irritation, oral noises, cramped walking, mortality 5/5 (Bayer 1983).

For category: 0 = no effect, 1 = discomfort, 2 = disabling, 3 = lethal; SL = some lethality.

3

n-Hexane[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 Peter Bos (Oak Ridge National Laboratory), Julie Klotzbach (SRC, Inc.), Chemical Manager Alfred Feldt (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 concentrations 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

n-Hexane is a colorless liquid with a slightly disagreeable, gasoline-like odor. It dissolves slightly in water. The lower explosive limit of *n*-hexane is 1.1%. *n*-Hexane is produced from natural gas and crude oil. Its main use in industry is in products known as solvents. The major uses for these solvents are in food processing to extract vegetable oils from crops, as cleaning agents in the printing, textile, furniture, and shoemaking industries (used in special glues), and in the manufacture of pharmaceuticals. Because of their easily accessibility, solvents and glues containing *n*-hexane are often used in inhalant abuse.

Human data on the acute toxicity of *n*-hexane are extremely limited and are insufficient for setting AEGL values. The data show that the acute toxicity of *n*-hexane is very low. No cases of lethality were reported after inhalation of *n*-hexane or *n*-hexane-containing mixtures, not even in solvent abuse. Furthermore, no severe clinical signs were reported in human volunteers after acute exposure to *n*-hexane both at rest and during physical exercise. Genotoxic and carcinogenic effects of the chemical have not been examined in humans. Chronic exposure to *n*-hexane frequently results in degenerative distal axonopathy in the peripheral nervous system, but this effect is not relevant for acute exposures.

Two LC_{50} (lethal concentration, 50% lethality) values for *n*-hexane have been reported for rats, but the original studies from which they were derived could not be obtained. Findings in toxicokinetic studies appear to have discrepancies with the LC_{50}s. Visible signs of acute toxicity from *n*-hexane are generally associated with effects on the nervous system, such as reduced respiration, ptosis, myoclonic seizures, ataxia, decreased motor activity, sedation, laying

down in a side position, and narcosis. Rats exposed to *n*-hexane exhibited acute effects on the brain and lungs and reversible lesions in the testis. The most significant effect in developmental and reproduction studies of *n*-hexane was a transient retardation in the growth of live pups; however, this effect is considered to be a result of repeated exposure. In general, *n*-hexane is not mutagenic in vitro although some positive results were obtained. *n*-hexane is not mutagenic in mice, but morphologic alterations in sperm, as well as chromatid breaks in bone marrow cells, were reported in rats. The limited information available on the carcinogenicity found hepatocellular neoplasms in mice and papillary tumors in the bronchiolar epithelium of rabbits exposed to *n*-hexane.

Because of insufficient human and animal data addressing the level of effects defined by AEGL-1, no AEGL-1 values are recommended for *n*-hexane.

Human and animal data indicate that central nervous system (CNS) depression is the most relevant adverse effect of acute exposure to *n*-hexane. However, adequate human data for evaluating concentration-response relationships for AEGL-2 effects are not available. Reporting insufficiencies in rat studies and confounding methodologic issues in studies of mice severely limit confidence in identifying no-effect levels for AEGL-2 effects. Although data are not available to define the concentration-response curve for *n*-hexane, a steep concentration-response relationship is observed for butane, a structural analog of *n*-hexane and central nervous system depressant (NRC 2012). On this basis, at steep concentration-response relationship is also expected for *n*-hexane. For chemicals with a steep concentration-response curve, AEGL-2 values may be derived by reducing AEGL-3 values by one-third (NRC 2001).

AEGL-3 values were based on a kinetic study of male Sprague-Dawley rats exposed to *n*-hexane at an actual concentration of 86,222 ± 1,330 ppm for 10, 15, 20, 25, or 30 min (Raje et al. 1984). Although the study focused on blood *n*-hexane concentrations, some toxicity data were provided; rats exposed for 25 or 30 min showed visible signs of toxicity (ataxia and decreased motor activity), but no deaths. From these results, a 30-min exposure at 86,222 ppm in rats was chosen as the point of departure for AEGL-3 values. Considering data on humans, rats, and mice, a total uncertainty factor of 10 appears to be sufficient for toxicokinetic and toxicodynamic differences between individuals and interspecies differences. The effects are attributed to *n*-hexane itself and no relevant differences in kinetics are assumed, so only small interindividual differences are expected. Steady-state blood concentrations for *n*-hexane will be reached in approximately 30 min. Thus, the 30-min AEGL-3 value was adopted as the 1-, 4-, and 8-h AEGL-3 values. The 10-min AEGL-3 value was derived from the 30-min value by time scaling using the equation $C^n \times t = k$, with $n = 3$. All of the AEGL-3 values are higher than 50% of the lower explosive limit for *n*-hexane and the 10-min value is higher than the lower explosive limit, so safety considerations against the hazard of explosion must be taken into account.

AEGL values are summarized in Table 3-1.

TABLE 3-1 AEGL Values for *n*-Hexane

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (disabling)	4,000 ppm[a] (14,000 mg/m^3)	2,900 ppm[a] (10,000 mg/m^3)	2,900 ppm[a] (10,000 mg/m^3)	2,900 ppm[a] (10,000 mg/m^3)	2,900 ppm[a] (10,000 mg/m^3)	One-third of AEGL-3 values
AEGL-3 (lethal)	See below[b]	See below[c]	See below[c]	See below[c]	See below[c]	No lethality in rats (Raje et al. 1984)

Abbreviations: NR, not recommended because of insufficient data.
[a]The AEGL-2 value is higher than 10% of the lower explosive limit of *n*-hexane in air of 1.1% (11,000 ppm). Therefore, safety considerations against the hazard of explosion must be taken into account.
[b]The 10-min AEGL-3 value of 12,000 ppm (42,000 mg/m^3) is higher than the lower explosive limit of *n*-hexane in air of 1.1% (11,000 ppm). Therefore, extreme safety considerations against the hazard of explosion must be taken into account.
[c]The AEGL-3 values for the 30-min, 1-h, 4-h, and 8-h durations are each 8,600 ppm (30,000 mg/m^3), which is higher than 50% of the lower explosive limit of *n*-hexane in air of 1.1% (11,000 ppm). Therefore, extreme safety considerations against the hazard of explosion must be taken into account.

1. INTRODUCTION

n-Hexane is a chemical isolated from natural gas and crude oil (WHO 1991; ATSDR 1999). Pure *n*-hexane is a colorless, volatile liquid with a slightly disagreeable, gasoline-like odor. It evaporates very easily in air and dissolves only slightly in water. *N*-Hexane is highly flammable, and its vapors can be explosive (ATSDR 1999).

Pure *n*-hexane is used in laboratories (WHO 1991; ATSDR 1999). Most of the *n*-hexane used in industry is mixed with similar chemicals in products known as solvents. Common names for some of these solvents are commercial hexane, mixed hexanes, petroleum ether, and petroleum naphtha (ATSDR 1999). Commercial hexane is mainly a mixture of hexane isomers and related 6-carbon compounds, and has an *n*-hexane content varying between 20 and 80% (WHO 1991). Several hundred million pounds of *n*-hexane are produced in the United States each year in the form of these solvents (WHO 1991; ATSDR 1999). The major use for these solvents is in food processing to extract vegetable oils from crops such as soybeans, flaxseed, peanuts, safflower seed, corn germ, and cottonseed. They are also used as cleaning agents in the printing, textile, furniture, and shoemaking industries. Certain kinds of special glues used in the roofing and shoe and leather industries also contain *n*-hexane. Several other products containing *n*-hexane are gasoline, low-temperature thermometers, adhesives, and lacquers. *n*-Hexane is also present in rubber cement. It is further used in the manufacture of pharmaceuticals. Selected physical and chemical properties of *n*-hexane are presented in Table 3-2.

TABLE 3-2 Chemical and Physical Data for *n*-Hexane

Parameter	Value	Reference
Synonyms	Hexane; hexyl hydride	ATSDR 1999
CAS registry no.	110-54-3	ACGIH 2001
Chemical formula	C_6H_{14}	Lide 1999
Molecular weight	86.18	Lide 1999
Physical state	Liquid	O'Neil et al. 2006
Color	Colorless	O'Neil et al. 2006
Odor	Faint, peculiar odor	O'Neil et al. 2006
Melting point	-95 to -100°C	O'Neil et al. 2006
Boiling point	69°C	O'Neil et al. 2006
Vapor density (air = 1)	2.97	WHO 1991
Liquid density (water = 1)	0.660	O'Neil et al. 2006
Solubility in water	Insoluble; 9.5 mg/L	ATSDR 1999; O'Neil et al. 2006
Vapor pressure	138 mm Hg @ 24°C; 150 mm Hg @ 25°C	WHO 1991; ATSDR 1999
Flammability	Highly flammable	ATSDR 1999
Explosive	Lower explosive limit = 1.1%	WHO 1991
Conversion factors	1 mg/m^3 = 0.284 ppm 1 ppm = 3.52 mg/m^3	WHO 1991

Commercial hexanes are manufactured by two-tower distillation of a suitable hydrocarbon feedstock (WHO 1991). The feedstock may be straight-run gasoline distilled from crude oil or natural gas. Hexanes are also obtained from the remains of catalytic reformates after the removal of aromatics. Very pure *n*-hexane can be produced from hexane mixtures by absorption on molecular sieves.

n-Hexane evaporates easily, so the greatest potential for exposure is through inhalation. Because gasoline contains *n*-hexane, almost everyone is exposed to small amounts of the chemical in the air. A concentration of 2 ppb in the air has been reported for *n*-hexane (ATSDR 1999). Foods, drinking water, and even cooking oils processed with solvents containing *n*-hexane do not generally contain *n*-hexane or contain only very small amounts. Exposure to *n*-hexane most frequently occurs among industrial workers in occupational settings (for example, refinery workers, shoe and footwear assembly workers, ball makers, laboratory technicians, and carpenters). Some people known as "sniffers" inhale volatile chemicals deliberately for their euphoric properties (reviews of Seppäläinen [1988] and Ritchie et al. [2001]). Exposure can also occur in the home if products containing *n*-hexane are used without proper ventilation.

Concentrations of *n*-hexane measured in extraction facilities were 0.9-97 ppm (olive extraction plants) and 4.4-13.2 ppm (soybean extraction facility) (WHO 1991). Concentrations measured for outside operators and transport drivers were 0.13 ± 0.17 ppm and 0.33 ± 0.25 ppm, respectively. Maximum time-weighted average (TWA) (8 h) concentrations of *n*-hexane at an extraction facility were found to be 26 ppm.

2. HUMAN TOXICITY DATA

Many studies of toxicologic effects of *n*-hexane in humans are available. However, most of these studies concerned industrial workers or substance abusers repeatedly exposed for long periods of time to commercial hexane. Commercial hexane generally contains 20-80% *n*-hexane, in addition to hexane isomers and small amounts of related carbon compounds (e.g., cyclopentane, cyclohexane, pentane, and heptane) and other chemicals (e.g., acetone, methyl ethyl ketone, and toluene). Often co-exposure to other solvents was also present. Since most of the studies concern repeated exposure to solvents with a low percentage of *n*-hexane (not pure), they were considered of little or no relevance for deriving AEGL values for *n*-hexane are not discussed in detail. However, it is noteworthy that no lethality was reported in humans abusively exposed to *n*-hexane or commercial hexane.

The main toxic effect reported for *n*-hexane in human studies is degenerative distal axonopathy in the peripheral nervous system, which is caused by the main toxic metabolite 2,5-hexanedione (2,5-HD). Peripheral neuropathy develops in workers who are occupationally exposed to rather high concentrations of *n*-hexane for months (ATSDR 1999). Therefore, this effect is a result of chronic exposure to *n*-hexane and is not relevant for deriving AEGL values.

2.1. Acute Lethality

2.1.1. Case Reports

No case reports of human lethality from acute exposure to *n*-hexane (pure or commercial) were found.

2.2. Nonlethal Toxicity

2.2.1. Case Reports

No relevant case reports of nonlethal toxicity from *n*-hexane were found.

2.2.2. Experimental Studies

Nelson et al. (1943) exposed human volunteers in a chamber (approximately 10 subjects; both sexes) to *n*-hexane at nominal concentrations of up to

500 ppm for 3-5 min. Exposure was well tolerated and there were no subjective complaints.

Four Caucasian male volunteers (22-52 years old; no occupational exposure to organic solvents) were exposed (whole body) for 2 h to *n*-hexane (purity 99%) at an actual concentration of 54.2 (±0.8) ppm during light physical exercise (50 W) on a bicycle ergometer (Shibata et al. 2002). Subjects rated the severity (somewhat, rather, quite, and very) of 10 main symptoms frequently associated with solvent exposure in a questionnaire. Symptoms in the questionnaire included: ocular discomfort, runny nose, discomfort in throat or airways, headache, fatigue, nausea, dizziness, feeling of being intoxicated, difficulty in breathing, and odor of solvents. Ratings for all symptoms except odor were below 10% of the whole scale and corresponded to verbal ratings of "not at all" and "hardly at all".

In addition, several toxicokinetic studies with volunteers were performed. Although the studies did not focus on adverse health effects, no mention of such effects was made. These studies are briefly described.

No adverse clinical effects or subjective complaints were reported in an absorption study with 10 volunteer students (healthy Japanese men and women; 18- to 25-years old) after a 4-h exposure (whole body) to *n*-hexane (purity not specified) at actual concentrations of 87-122 ppm (Nomiyama and Nomiyama 1974).

Veulemans et al. (1982) exposed healthy male subjects (25- to 35-years old) to *n*-hexane (purity unknown) at 100 and 200 ppm (360 and 720 mg/m^3, respectively) for 4 h at rest and at 100 ppm (360 mg/m^3) for 3 h under exertion (up to 100 W). No adverse clinical effects or subjective complaints were reported.

No adverse clinical effects or subjective complaints were also reported in healthy male volunteers (19- to 26-years old) exposed twice (nose only; in a sitting position) to *n*-hexane (purity 99%) at 60 ppm with a 4-h interval (van Engelen et al. 1997). Mean exposure durations were 15.5 min and 3.91 h, respectively.

2.2.3. Occupational and Epidemiological Studies

The group of Perbellini and Brugnone has published many reports on *n*-hexane in occupational settings. In one study, grasp samples of breathing zone air were collected from 20 workers (18 men and 2 women) employed in a shoe upper factory after 60, 165, 195, and 270 min. Average *n*-hexane concentrations were 99 ppm (349 mg/m^3), 150 ppm (531 mg/m^3), 167 ppm (589 mg/m^3), and 214 ppm (755 mg/m^3), respectively (Brugnone et al. 1978). No adverse clinical symptoms were reported. In a second study, the breathing zone air of workers in a shoe factory was collected at different time points (duration of sampling not specified). An average *n*-hexane concentration of 117 ppm (411 mg/m^3) was

reported (mean of 76 air samples, with a maximum concentration of 480 ppm [1,700 mg/m^3]) (Perbellini et al. 1980).

Ten healthy workers (18-30 years old) employed in a shoe factory were shown to be exposed to *n*-hexane at an 8-h TWA of 69 ppm (243 mg/m^3) (range 2-325 ppm [8-1,143 mg/m^3]) (Mutti et al. 1984). No adverse clinical signs were reported.

No adverse clinical effects were also reported in four healthy shoe factory workers (women, 41-54 years old) exposed during four working days to a mean concentration of *n*-hexane in the breathing zone of 1.9-31 ppm (6.7-108.7 mg/m^3). The exposure period was preceded by four days without exposure and followed by two exposure-free days (Ahonen and Schimberg 1988).

2.3. Neurotoxicity

No neurotoxicity studies of acute exposure to *n*-hexane in humans were found.

2.4. Developmental and Reproductive Toxicity

No studies on developmental and reproductive toxicity of *n*-hexane in humans are available. However, it has been reported that on the basis of data from experimental animals and according to the Nordic criteria, *n*-hexane has been classified into Group 1B: "The substance should be regarded as toxic to human reproduction" (Hansen 1992).

2.5. Genotoxicity

The genotoxicity of *n*-hexane has been evaluated by two organizations (WHO 1991; ATSDR 1999). Both evaluations reported only one in vitro test of *n*-hexane in human cells; no increase in unscheduled DNA synthesis was found in an assay using human lymphocytes. Genotoxic effects have not been examined in humans after *n*-hexane exposure.

2.6. Carcinogenicity

No epidemiological studies of occupational exposure to *n*-hexane and cancer were found, which was consistent with the reviews by WHO (1991) and ATSDR (1999).

2.7. Summary of Human Data

In humans, *n*-hexane is of low acute toxicity. No cases of lethality were reported after inhalation of *n*-hexane or commercial hexane. Furthermore, no

severe clinical signs were reported by volunteers after acute exposure at the highest *n*-hexane concentrations tested (200 ppm for 4 h at rest and 100 ppm for 1 h under physical exercise [20-100W]). The only symptom reported at more than 10% on a rating scale by volunteers exposed for 2 h to *n*-hexane at an actual concentration of 54.2 ppm while performing low physical exercise (50 W) was detection of the odor of *n*-hexane.

Corresponding to the evaluations of WHO (1991) and ATSDR (1999), no studies on genotoxicity in humans were located. Only a negative unscheduled DNA synthesis assay using human lymphocytes has been reported. Although genotoxic effects have not been examined in humans after *n*-hexane exposure, genotoxicity in humans cannot be excluded because some positive results were reported in limited animal studies (polyploidy, structural aberrations, and sister chromatid exchanges in in vitro tests with mammalian cells, and morphologic alterations in sperm and chromatid breaks in bone marrow cells in studies of rats) (see Section 3.5).

Consistent with the WHO (1991) and ATSDR (1999) reviews, no epidemiologic studies of occupational exposure to *n*-hexane and cancer in humans were found. However, carcinogenicity cannot be excluded because limited studies in experimental animals have reported hepatocellular neoplasms (adenoma and carcinoma) in mice and papillary tumors in the bronchiolar epithelium of rabbits.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Little data were available on acute lethality of *n*-hexane in rats. Two LC_{50} values were reported, but lacked details on experimental conditions. A 1-h LC_{50} of 76,900 ppm for rats was reported in a neurotoxicity study by Pryor et al. 1982 (see Section 3.2.1) and a 4-h LC_{50} of 48,000 ppm is mentioned in a review by Couri and Milks (1982) without any details or a reference.

Some studies on the toxicokinetics and metabolism (exposure durations of 10 min to 10 h) were available, in which high concentrations of *n*-hexane (10,000-86,222 ppm) were used (Böhlen et al. 1973; Baker and Rickert 1981; Bus et al. 1982; Raje et al. 1984; see Section 4.1 for details). No mortality was reported in these studies, not even at concentrations as high as 86,222 ppm for 30 min (male Sprague-Dawley rats; whole-body exposure) (Raje et al. 1984) or 48,280 ppm for 10 h (female albino rats; whole-body exposure; purity of *n*-hexane not specified) (Böhlen et al. 1973).

No mortality was reported in rats exposed to *n*-hexane at 48,000 ppm for 10 min, 6 times per day (at least 50 min between exposures), 5 days per week for 10 weeks, followed by an additional 8 weeks at an increased frequency of 12

exposures per day (10-min exposure, 20-min no exposure) and another 4 weeks at a frequency of 24 times per day (10-min exposure, 5-min no exposure). In addition, one repeated exposure study on metabolism was available in which high concentrations of *n*-hexane were used. In this study, male Fischer rats were exposed (whole body) for 12 weeks to *n*-hexane (purity 95%) at a concentration of either 48,000 ppm for 10 min every 30 min, 8 h/day, 5 days/week or 40,000 ppm for 10 min every 30 min with a background of *n*-hexane at 4,000 ppm continuously, 8 h/day, 5 days/week (Howd et al. 1982). No mortality was reported for either exposure regimen.

3.1.2. Mice

Führer (1921) studied the narcotic action of *n*-hexane (pure, but percentage not specified) prepared from coal oil (initial concentrations approximately 34,800, 38,210, 41,620, 43,750, and 51,990 ppm [123, 134, 147, 154, and 183 g/m^3, respectively]) and *n*-hexane prepared from propyl iodide (initial concentrations approximately 37,640 and 40,060 ppm [132 and 141 g/m^3, respectively]) in white mice (sex and strain not specified). Animals were exposed whole-body in a so-called 'narcotic bottle' in which a watch glass was present for evaporation of required volumes of *n*-hexane. In this bottle, 1-2 mice could be exposed at the same time, but the number of animals exposed at each concentration was not specified. Animals were exposed for different durations (20-127 min) until they were removed or until they died. *n*-Hexane from coal oil induced mice to lay down in a side position without standing up after shaking the exposure chamber (narcotic action) after 34-90 min at the lowest concentration (34,800 ppm) and after 10 min at the highest concentration (51,990 ppm) (dose-dependent effect). Loss of reflexes occurred only at higher concentrations of approximately 38,210, 43,750, and 51,990 ppm after 75 min (1/1), 39 and 57 min (2/2), and 20 and 31 min (2/3), respectively. Animals losing reflexes died after exposure for 127 min (1/1), 73 and 119 min (2/2), and 51 min (1/2), respectively. At 51,990 ppm, one of three mice died very rapidly after 9 min with tetanic convulsions. The minimal fatal dose of *n*-hexane was approximately 38,210 ppm for 127 min. *n*-Hexane showed a marked depressant effect on respiration. Comparative results were obtained with *n*-hexane prepared from propyl iodide. Loss of reflexes occurred within 34 and 42 min (2/2) at 37,640 ppm and within 23 min at 40,060 ppm (dose-dependent effect). The minimal fatal concentration was 37,640 ppm; animals died after 39 and 45 min (2/2). No mortality was observed in mice exposed to *n*-hexane at 40,060 ppm for 26 min. This study could not be used for quantitative analysis, because mice were exposed in a closed system and *n*-hexane concentration as well as the oxygen concentration will have decreased during exposure while carbon dioxide will have increased; the number of animals exposed at each exposure concentration was unknown; and respiration rate steadily decreased during exposure.

These results appeared to be confirmed by Lazarew (1929) who determined a minimal narcotic concentration of *n*-hexane causing mice (sex and strain not specified) to lay down in a side position of approximately 28,000 ppm (100 g/m^3) and a minimal fatal concentration of 34,000-43,000 ppm (120-150 g/m^3). Exposures were for 2h, but the purity of the *n*-hexane and whether concentrations were actual or nominal concentrations were not specified. Reflexes in mice frequently persisted until death. These results showed a very small margin between narcotic and fatal concentration. Exposures were in a closed system, similar to the experiments by Fühner (1921).

Ten male NMRI mice were exposed to *n*-hexane under static conditions (Krämer et al. 1974); 3.2 mL of *n*-hexane was added in a 25-L glass box (equal to an initial concentration of about 24,000 ppm) and exposure was for at least 24 h. No mortality was reported under these conditions. The only adverse effect mentioned was that exposed mice suffered from body weight loss compared with controls.

Groups of four Swiss mice (sex not specified) were exposed head-only for 5 min to *n*-hexane (purity ≥99%) at nominal concentrations of 1,000, 2,000, 4,000, 8,000, 16,000, 32,000, and 64,000 ppm. No mention was made of whether concentrations were monitored during exposure (Swann et al. 1974). Test conditions were the same as those in the sensory irritation test (determination of the concentration that reduces the respiratory rate by 50% [RD_{50}]), and were considered to be screening tests. Mice were placed in individual plethysmographs to investigate effects on pulmonary physiology during exposure. Mice had light anesthesia at 16,000 ppm, whereas at 32,000 ppm they became directly anesthetized with occasional sporadic body movements. At 64,000 ppm, all mice had respiratory arrest within 4.5 min. During exposure at 64,000 ppm, respiration was highly irregular; excitation was followed by light anesthesia with body movements, irregular respiration, an increase in inspiratory effort, and a decrease in the expiratory effort. Respiratory arrest occurred at the end of inspiration. No convulsions were observed. No information on the methods used to assess anaesthesia was provided. Animals in this study were restrained, which could potentially affect assessments of *n*-hexane-induced anaesthesia, adding uncertainty to determination of effect levels for AEGL-2 value. A summary of relevant lethality data is presented in Table 3-3.

3.2. Nonlethal Toxicity

3.2.1. Rats

Three groups of 12 male Fischer rats (six or nine "intact animals" and six or three "surgically prepared animals" for neurologic testing) were intermittently exposed (whole body) to *n*-hexane (labeled; purity ≥95%) at target concentrations of 24,000 (one group) and 48,000 ppm (two groups) (Pryor et al. 1982).

TABLE 3-3 Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Duration	Effect	Reference
Rat	76,900	1 h	LC_{50}	Reported in Pryor et al. (1982)
Rat	48,000	4 h	LC_{50}	Reported in Couri and Milks (1982)
Rat	48,280	2-10 h	No lethality	Böhlen et al. 1973 (kinetic study)
Rat	10,000	0.5-6 h	No lethality	Baker and Rickert 1981 (kinetic study)
Rat	10,000	6 h	No lethality	Bus et al. 1982 (kinetic study)
Rat	86,222	30 min	No lethality	Raje et al. 1984 (kinetic study)
Rat	48,000 40,000	10 min/30 min, 8 h/d, 5 d/wk for 12 wk 10 min/30 min, on a background of 4,000 ppm continuous, 8 h/day, 5 d/wk for 12 wk	No lethality No lethality	Howd et al. 1982
Mouse	38,210[a] 43,750[a] 51,990[a]	127 min 73-119 min 9-51 min	Lethality (1/1) Lethality (2/2) Lethality (2/3)	Fühner 1921
Mouse	37,640	39-45 min	Lethality (2/2)	Fühner 1921
Mouse	28,000, 34,000, and 43,000[a] (+ other unspecified concentrations)	2 h	Minimal fatal concentration 34,000-43,000 ppm[a]	Lazarew 1929
Mouse	32,000	5 min	No lethality	Swann et al. 1974
	64,000	<4.5 min	Lethality	

[a]Initial concentration in a closed system.

Concentrations were continuously monitored and were within 10% of the target concentrations. Rats were surgically prepared for recording the brainstem auditory-evoked response and peripheral nerve conduction velocity. Animals were exposed for 10 min, six times per day (at least 50 min between exposures), 5 days per week for at least 10 weeks. One of the 48,000 ppm exposure groups was exposed for an additional 8 weeks to *n*-hexane at 48,000 ppm at an in-

creased frequency of 12 exposures per day (10-min exposure, 20-min no exposure). After 18 weeks, surgically prepared rats were exposed 24 times per day (10-min exposure, 5-min no exposure) for an additional 4 weeks, and were then were allowed to recover. Actual concentrations were monitored daily throughout the experiment. No acute behavioral effects (grip strength, conditioned avoidance response, undifferentiated motor activity) were observed with 10-min exposures to *n*-hexane at 24,000 ppm or 48,000 ppm. Furthermore, the study reported (without further detail) that 48,000 ppm was approximately the highest concentration that did not cause myoclonic seizures in most of the rats during the repeated exposures. An additional group of 15 rats continuously exposed to *n*-hexane at 1,000 ppm for 11 weeks did not show neurobehavioral effects before 3 weeks of exposure.

Six male Wistar rats (trained to avoid shock; avoidance rate >80%) were exposed (whole body) for 4 h first to air (internal control), and then to *n*-hexane (purity >99%) at target concentrations of 50, 100, 200, 400, and 800 ppm (in ascending order on different days) (Ikeda et al. 1993). Concentrations were measured several times during every exposure. The interval between exposures to the different concentrations of *n*-hexane was 14 days. Sham exposure to air (internal control) was carried out every seventh day following exposure to *n*-hexane. Rats were tested on their shock avoidance response 1 h immediately before exposure, during the 4 h of exposure, and 1 h thereafter (6-h test period). As behavioral baseline, the level of performance of the 1-h pretest was used. At 50 ppm, *n*-hexane induced a transitory decrease in lever press and avoidance rates during part of the exposure. No behavioral changes could be detected in rats exposed to *n*-hexane at 100 and 400 ppm, while large, variable changes were observed at 200 ppm. Exposure at 800 ppm induced a considerable increase in the lever press rate during part of the exposure period, while no effect on avoidance rate was observed. Considering the wide variation and fluctuations in responses during exposure, no clear conclusions can be drawn from this experiment.

Three groups of four male albino rats (SD strain, Charles River Japan) were exposed (whole body) for 8 h to *n*-hexane (purity not specified) at nominal concentrations of 0 and 4,000 ppm (no monitoring of actual concentrations during exposure) (Honma et al. 1982). Immediately after exposure, brains were irradiated by microwave to inactivate brain enzymes. Midbrain tissue was homogenized and free amino acids (Tau, Asp, Glu, Gln, Gly, GABA, Thr, Ser, and Ala) were analyzed. In midbrain tissue, only glutamine and alanine were significantly increased by exposure to *n*-hexane. Glutamine is synthesized from glutamic acid by glutamine synthetase in the presence of ammonia. The authors felt that more detailed examination of the change in ammonia content and glutamine synthetase activity is needed for explanation of the increase in glutamine content. Also, the increase in alanine content needs further investigation.

Groups of four male albino rats (SD strain) were exposed (whole body) for 8 h to *n*-hexane gas (purity not specified) at actual concentrations of 0, 2,000, 4,000, and 8,000 ppm (Honma 1983). During exposure the concentration of

n-hexane was monitored (frequency not specified). Rats were killed immediately after exposure by decapitation and their brains were irradiated with microwave to prevent post-mortem changes. Acetylcholine (ACh) content, choline acetyltransferase (ChAT), and acetylcholine esterase (AChE) activities were measured in homogenized hippocampus. ACh was somewhat increased (approximately +20%) at 2,000 ppm, but was reduced extensively (approximately -25%) at 8,000 ppm. At all concentrations tested, *n*-hexane showed a weak trend in reducing ChAT activity (<15%). AChE activity was increased by *n*-hexane (significantly at 4,000 ppm, approximately +23%), but without a dose-relationship. Because ChAT synthesizes ACh from choline and acetyl CoA at nerve endings, the decrease in ACh at 8,000 ppm might be due to both the reduced ChAT activity and the elevated AChE activity. Rats exposed to *n*-hexane showed some symptoms including sedation, hypothermia, and ptosis. The incidence and severity of symptoms were dependent on exposure concentration. However, no further details were presented.

The functional implications of the biochemical effects reported by Honma et al. are difficult to assess considering the degree of neurologic effects observed in repeat-exposure studies with much higher concentrations of *n*-hexane (e.g., Pryor et al. 1982).

Two groups of three male Wistar rats were exposed (whole body) for 18 h to *n*-hexane (purity not specified) at target concentrations of 0 and 500 ppm on three different days (Edelfors and Ravn-Jonsen 1985). Concentrations were monitored during exposure (frequency of sampling not specified). At the end of the exposure period, rats were bled with heart puncture. Synaptosome preparations were obtained from the brain, except for the cerebellum, to measure calcium uptake at 0.5, 2, 4, and 8 min. No significant effects were found.

Male Wistar rats were exposed (whole body) to *n*-hexane (purity 96-99%) at nominal concentrations of 700 ppm for 8 h (3 rats) and 10,000 ppm for 4 h (2 rats) and 8 h (3 rats) (Schnoy et al. 1982). Concentrations were calculated from the consumption of *n*-hexane per hour (measured by gas chromatography) and total air volume (variation $\leq \pm 15\%$). Lungs were examined for histopathologic changes with special attention to the pneumocytes. Light microscopy did not reveal any pathologic finding. Electron microscopy showed direct toxic effects of *n*-hexane to pneumocytes (concentration and exposure duration not specified; changes observed within 24-48 h) with definite regressive alterations, such as fatty degeneration, changes in lamellar bodies of type II pneumocytes, and increased detachment of cells. In a later report of this study, the intrapulmonary nerve system in the hilus and central and peripheral lung segments was examined histopathologically. Ultrastructurally, no alterations of the intrapulmonary nerves were found after short-term exposure to *n*-hexane (Schmidt et al. 1984).

Groups of six male Wistar rats were exposed (whole body) for 5 h to *n*-hexane (purity not specified) at nominal concentrations of 0 and 4,260 ppm (Hadjiivanova et al. 1987). No monitoring of the actual concentration *n*-hexane during exposure was performed. Animals were killed one day after exposure,

and bronchoalveolar lavage fluid (BAL) was isolated and freed of whole cells and debris and the lungs were homogenized. Lipids were extracted from BAL and from lung tissue homogenate. *n*-Hexane caused a moderate increase in the phospholipids of BAL, which was mainly due to an increase in phosphatidylserine and sphingomyeline on day 1 after exposure. In lung tissue homogenate, the total amount of phospholipids was not affected, but the relative contribution of the individual phospholipids was changed. Phosphocholine (the main and physiologically most important phospholipid) and phosphatidylserine were found to be decreased with a concomitant increase in phosphatidylethanolamine. The increased surfactant phopholipids in the alveoli (BAL) was most probably a direct effect of *n*-hexane on type II cells, enhancing the release of phospholipids (mainly phosphocholine) from their secretory granules (lamellar bodies). Effects on pulmonary surfactants are in general the early events in lung toxic injury.

A group of 17 male Sprague-Dawley rats (Charles River, Italy) was exposed (whole body) for 24 h to *n*-hexane (99% purity) at a target concentration of 5,000 ppm (De Martino et al. 1987). The concentration was regulated at approximately 5,000 ppm. A control group (no details provided) was also used. At days 0, 2, 7, 14, and 30 after exposure, 6, 3, 4, 2, and 2 rats, respectively, were killed. Testes and epididymides were examined histopathologically. The proportion of animals with lesions in the testis was 50, 67, 75, 50, and 0% and in the epididymis 67, 33, 25, 0, and 0% at day 0, 2, 7, 14, and 30, respectively. At day 0, testicular lesions were characterized by focal degeneration of spermatocytes (cytoplasmic swelling, nuclear pyknosis, kariorhexis, and kariolysis) and by mild exfoliation of elongated spermatids. Affected epididymal tubules showed several degenerating germ cells mixed with normal spermatozoa in the lumen. At days 2 and 7, effects were more pronounced (e.g., vacuolization, nuclear swelling of Sertoli cells), and numerous inflammatory cells were seen in the epididimys. Recovery from the lesions in both the testis and epididimys was observed starting at 14 day, with complete recovery by day 30.

No histopathologic lesions of the lungs or testes were found in groups of 15 male and 15 female Fischer-344 rats (Cavender et al. 1984) or in groups of 10 male and 10 female $B6C3F_1$ mice (Dunnick et al. 1989) exposed to *n*-hexane concentrations of up to 10,000 ppm for 6 h/day, 5 days/week for 13 weeks. Because effects on the testes were induced following a 24-h exposure, the effects might not manifest until the exposure lasts for much longer than 6-8 h. Repeated 6-h exposures with 18-h periods of no exposure in between are not sufficient to induce such lesions. Therefore, the effects on the testes reported by De Martino et al. (1987) are not relevant for setting AEGL values. Effects on the lung could only be traced with electronic microscopy. Since no functional lung impairment was observed even after repeated exposure, the effects described by Schnoy et al. (1982) and Schmidt et al. (1984) were considered irrelevant for deriving AEGL values.

A few toxicokinetic studies have been performed with relatively high concentrations of *n*-hexane. These studies are described briefly below.

Five groups of four male Sprague-Dawley rats were exposed (whole body) to *n*-hexane (reagent grade or higher, not further specified) at an actual concentration of 86,222 ± 1,330 ppm for 10, 15, 20, 25, and 30 min (Raje et al. 1984). Animals were killed immediately after exposure. Although the study focused on blood *n*-hexane concentrations, it was mentioned that only the animals exposed for 25 and 30 min showed visible signs of toxicity (ataxia and decreased motor activity).

In a toxicokinetic study, groups of four to six female albino rats (strain not specified) were exposed (whole body) for 2-10 h to *n*-hexane (purity not specified) at a nominal concentration of 48,280 ppm (170 g/m^3). No mention was made of clinical signs of *n*-hexane toxicity (Böhlen et al. 1973). In a similar study, groups of three male Fischer-344 rats were exposed for 0.5, 1, 2, 3, 4, and 6 h (head only) or for 6 h (whole body) to *n*-hexane (purity 95.8%) at actual concentrations of 1,000, 3,000, and 10,000 ppm. No mention was made of clinical signs of toxicity (Baker and Rickert 1981).

In groups of three male Fischer-344 rats exposed for 6 h (whole body) to [1,2-^{14}C]-*n*-hexane (purity 98.5%; diluted to the required specific activities with *n*-hexane, purity 95.8%) at actual concentrations of 500, 1,000, 3,000, and 10,000 ppm, reduced respiration associated with narcosis was observed at the highest concentration (Bus et al. 1982).

3.2.2. Mice

Führer (1921) studied the narcotic action of *n*-hexane (pure, but percentage not specified) prepared from coal oil (initial concentrations approximately 34,800, 38,210, 41,620, 43,750, and 51,990 ppm [123, 134, 147, 154, and 183 g/m^3, respectively]) and *n*-hexane prepared from propyl iodide (initial concentrations approximately 37,640 and 40,060 ppm [132 and 141 g/m^3, respectively]) in white mice (sex and strain not specified). Animals were exposed whole-body in a so-called 'narcotic bottle' in which a watch glass was present for evaporation of required volumes of *n*-hexane. In this bottle, 1-2 mice could be exposed at the same time, but the number of animals exposed at each concentration was not specified. Animals were exposed for different durations (20-127 min) until they were removed or until they died. *n*-Hexane from coal oil induced mice to lay down in a side position without standing up after shaking the exposure chamber (narcotic action) after 34-90 min at the lowest concentration (34,800 ppm) and 10 min at the highest concentration (51,990 ppm) (dose-dependent effect). Loss of reflexes occurred only at higher concentrations of approximately 38,210, 43,750, and 51,990 ppm after 75 min (1/1), 39 and 57 min (2/2), and 20 and 31 min (2/3), respectively. Animals losing reflexes died after exposure for 127 min (1/1), 73 and 119 min (2/2), and 51 min (1/2), respectively. At 51,990 ppm, one of three mice died very rapidly after 9 min with tetanic convulsions. The minimal fatal dose of *n*-hexane was approximately 38,210 ppm for 127 min. *n*-Hexane showed a marked depressant effect on respi-

ration. Comparative results were obtained with *n*-hexane prepared from propyl iodide. Loss of reflexes occurred within 34 and 42 min (2/2) at 37,640 ppm and within 23 min at 40,060 ppm (dose-dependent effect). The minimal fatal dose was 37,640 ppm. At this concentration, animals died after 39 and 45 min (2/2). Results of this study could not be used for quantitative analysis, because mice were exposed in a closed system and *n*-hexane concentration as well as the oxygen concentration will have decreased during exposure while carbon dioxide will have increased; the number of animals exposed at each exposure concentration was unknown; and respiration rate steadily decreased during exposure.

These results appeared to be confirmed by Lazarew (1929) who determined a minimal narcotic concentration of *n*-hexane causing mice (sex and strain not specified) to lay down in a side position of approximately 28,000 ppm (100 g/m^3) and a minimal fatal concentration of 34,000-43,000 ppm (120-150 g/m^3). Exposures were for 2h, but the purity of the *n*-hexane and whether concentrations were actual or nominal concentrations were not specified. Reflexes in mice frequently persisted until death. These results showed a very small margin between narcotic and fatal concentration. Exposures were in a closed system, similar to the experiments by Fühner (1921).

Groups of four Swiss mice (sex not specified) were exposed (head only) for 5 min to *n*-hexane (purity ≥99%) at target concentrations of 1,000, 2,000, 4,000, 8,000, 16,000, 32,000, and 64,000 ppm (no monitoring of actual concentrations during exposure) (Swann et al. 1974). Mice were placed in individual plethysmographs to investigate effects on pulmonary physiology during exposure. Light anesthesia occurred at 16,000 ppm. At 32,000 ppm, mice became directly anesthetized with occasional sporadic body movements. Anesthesia became deeper and irregular respirations occurred with increased expiratory effort. Apneic respirations (4-5 sec), an increase in rate and a decrease in amplitude followed this. There was a return to moderate to light anesthesia during early and late recovery, respectively. All animals survived. At 64,000 ppm, all mice had respiratory arrest within 4.5 min. During exposure, respiration was highly irregular; excitation was followed by light anesthesia with body movements, irregular respiration, an increase in inspiratory effort, and a decrease in the expiratory effort. Respiratory arrest occurred at the end of inspiration. No convulsions were observed.

The study by Swann et al. (1974) cannot be used to derive AEGL values. Mice in this study were restrained, which could potentially affect assessments of *n*-hexane-induced anaesthesia, adding uncertainty to determination of effect levels for AEGL-2 values. A summary of nonlethal toxicity data is provided in Table 3-4.

3.3. Neurotoxicity

According to ATSDR (1999), exposure to *n*-hexane produces toxicity to peripheral and sensory nerves. Neurotoxicity is due to the *n*-hexane metabolite

2,5-hexanedione, which interferes with neurofilament phosphorylation status and, thus, impairs axonal transport. *N*-Hexane-induced neurotoxicity is primarily associated with chronic exposure, so is not relevant to derivation of AEGL values. However, no data were identified to evaluate the potential for peripheral neuropathy to occur following exposure to a single high dose of *n*-hexane. Many studies reviewed in Section 3.2 (Animal Toxicity Data, Nonlethal Toxicity) included assessments of neurotoxicity outcomes associated with repeated exposure. See Section 3.2 for reviews of these studies.

3.4. Developmental and Reproductive Toxicity

Pregnant Wistar rats were exposed by inhalation (whole body) to air (control) or *n*-hexane (purity 99%) for 23 h/day, 7 days/week (Stoltenburg-Didinger et al. 1990). Exposure concentrations were 500 ppm (during gestation), 800 ppm (one group exposed during gestation and one group [both dams and pups] exposed during gestation and postnatally for 3 weeks), and 1,000 ppm (initial concentration of 1,500 ppm; one group exposed during gestation and one group [both dams and pups] exposed during gestation and postnatally for 30 days). *n*-Hexane concentrations were monitored continuously during exposure. Results were not clearly reported.

TABLE 3-4 Summary of Relevant Nonlethal Inhalation Effect of *n*-Hexane in Laboratory Animals

Species	Concentration (ppm)	Duration	Effect	Reference
Rat (n = 12)	24,000	6 times, 10 min/d, d/wk for 18 wk	No acute behavioral effects	Pryor et al. 1982
Rat (n = 12)	48,000	6 times, 10 min/d, 5 d/wk for 13 wk (n = 11) and 18 wk (n = 1)	No myoclonic seizures in most rats	
Rat (n = 4)	86,222	10, 15, and 20 min	No visible signs of toxicity	Raje et al. 1984
		25 and 30 min	Ataxia and decreased motor activity	
Rat (n = 3)	500, 1,000, and 3,000	6 h	No effects on respiration	Bus et al. 1982
Rat (n = 3)	10,000	6 h	Reduced respiration associated with narcosis	

Dams: Six of eight dams exposed to *n*-hexane at 800 ppm and four of eight dams exposed at 1,000 ppm carried pregnancy to full term compared with 100% of controls. In the dams that did not give birth, resorption of embryos or death during late fetal stage was confirmed by necropsy. No data on litter sizes were provided. Neurologic irregularities were not observed in dams exposed only during gestation, but at the two highest concentrations marked hindlimb weakness developed after giving birth. At the highest concentration, corresponding paranodal axonal swellings were recognizable on postpartum day 30.

Newborns: At all concentrations tested, exposure during gestation reduced body weight at a comparable litter size. This reduction was still present at postnatal day 25 after exposure to *n*-hexane at 500 ppm. In pups with only prenatal exposure, absolute brain weight was less reduced than body weight, resulting in an increased brain-weight to body-weight ratio. This effect was more pronounced in animals exposed during gestation and postnatally. Furthermore, a delay in the maturation of cerebellar cortex was observed (fissura prima of the vermis cerebella; delay in migration of the outer granular cells and a persistence of Purkinje cells) at all concentrations. Recovery was found on postnatal day 30 in animals exposed during gestation only. Other observations included retardation in growth and development, fur irregularities, and less activity. Recovery from these symptoms started about 2 weeks after exposure ended.

In a later publication, effects on brain biochemistry were discussed (Stoltenburg-Didinger 1991). The enzyme maturation pattern in the cerebellum of newborn animals was studied by histochemistry of succinic dehydrogenase (SDH) and NADH tetrazolium reductase (NADH-Tr). Enzyme activities were visualized by formazan deposition in the primary fissure of the cerebellar vermis (an early maturing region) on postnatal days 1, 9, and 21.

Newborns: In control animals, external and internal granular cells exhibited weak oxidative enzyme activity at all ages. Purkinje cells showed increasing oxidative enzyme activity from birth, reaching adult activity at the end of the fourth week. In all exposed animals, development of SDH and NADH-Tr activity paralleled that of normal rats with a delay. Exposure during gestation and postnatally resulted in a persisting apical cone and delayed formation of the apical dendritic tree of the Purkinje cells at day 9. Higher SDH and NADH-Tr activity was found in these cells, returning to normal levels at day 21. Also, a delay in migration of the outer granular cells was observed, even at 500 ppm administered only during gestation. No differences in SDH and NADH-Tr activity in external and internal granular cells were found.

In a well-performed study, pregnant Fischer-344 rats were exposed (whole body) for 6 h/day during various periods of gestation to *n*-hexane (purity 99%) at target concentrations of 0 and 1,000 ppm (Bus et al. 1979). Concentrations were monitored three times per hour (variation <5%). To investigate perinatal toxicity, three groups of pregnant rats were exposed at 1,000 ppm on gestation days 8-12 (n = 7), 12-16 (n = 9), and 8-16 (n = 8) and compared with control rats (n = 7, 6, and 3, respectively). On day 22, females were killed and fetuses examined. In a second experiment, pregnant rats (number not specified) were

exposed to *n*-hexane at 0 and 1,000 ppm on gestation days 8-16. Following delivery on day 23, litters (eight control litters, 14 treatment litters) were culled to six pups per litter and pups were examined weekly for up to 7 weeks. All litters were weaned 4 weeks after birth. After exposure on gestation days 8-12, 12-16, or 8-16 (first experiment), no significant alterations in fetal resorptions, fetal body weights, visible anomalies, or incidence of soft tissue or skeletal anomalies were observed in any of the treatment groups. These results indicated that *n*-hexane was not developmentally toxic at 1,000 ppm. After exposure on days 8-16 (second experiment), a significant reduction in the growth of the pups was found for up to 3 weeks after birth (no significant effect at birth, but 13.9% decrease in litter weight at postnatal day 21). Litter weights remained reduced between 4 (10.6%) and 6 (6.9%) weeks after birth, but returned to control values after 7 weeks (transient effect). No deaths or externally visible onset of neuropathy were observed.

Placental transfer of *n*-hexane may occur since *n*-hexane has been found in rat fetuses after maternal exposure (see Section 4.1). Comparison of the data reported by Bus et al. (1979) with those of Stoltenburg-Didinger et al. (1990) show that (near) continuous exposure to *n*-hexane is necessary to induce developmental toxicity. These effects are, therefore, not to be expected after exposure to *n*-hexane for up to 8 h. Bus et al. (1979) reported postnatal growth retardation following exposure to *n*-hexane during gestation day 8-16. However, in a review on the significance of developmental effects for acute exposures, it was concluded that this kind of effect is not expected to occur after a single exposure (van Raaij et al. 2003). Therefore, these effects are considered not relevant for deriving AEGL values for *n*-hexane.

3.5. Genotoxicity

The genotoxicity of *n*-hexane has been evaluated by several organizations (WHO 1991; ATSDR 1999). See ATSDR (1999) for more details and primary references.

Only limited mutagenicity testing of *n*-hexane has been conducted. In general, *n*-hexane appears to be negative in bacterial tester strains such as *Escherichia coli*, *Bacillus subtilis*, and *Salmonella typhimurium* both with and without metabolic activation. *n*-Hexane was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested with a pre-incubation protocol at doses up to 1,000 μg/plate with or without rat or hamster liver S9 fraction. *n*-Hexane was also negative in an in vitro test for induction of chromosome loss in *Saccharomyces cerevisiae*. Negative results for chromosomal aberrations, sister chromatid exchanges, and point mutation rate were generally also obtained in mammalian cells except for one observation of polyploidy in Chinese hamster lung (CHL) cells and polyploidy and structural aberrations in two studies on Chinese hamster ovary (CHO) cells exposed to undiluted *n*-hexane in the absence of S9. *n*-Hexane at concentrations up to 5,000 μg/mL in the presence or absence of rat liver S9 did not induce chromosomal aberrations in cultured CHO

cells. Sister chromatid exchanges were induced in CHO cells but only in the presence of S9 (no dose response).

In studies of in vivo genotoxicity (see Table 3-5), *n*-hexane was found to be negative in a dominant lethal test, micronucleus test, and sperm morphology test in mice. The highest ineffective dose in mice was 10,000 ppm (6 h/day, 5 days/week for 13 weeks). In contrast, morphologic alterations in sperm were noted in rats at 5,000 ppm (exposure duration not specified). This effect was reversible; no significant effects were found 5 weeks after exposure ended. Chromatid breaks were reported in rat bone marrow cells (concentration and exposure duration not specified).

3.6. Carcinogenicity

Little information was available on the carcinogenicity of *n*-hexane. Carcinogenicity was evaluated by WHO (1991) (a dermal study, not relevant for deriving AEGL values) and ATSDR (1999). ATSDR reported on an inhalation study with $B6C3F_1$ mice in which hepatocellular neoplasms (adenoma and carcinoma) were found. However, commercial hexane (51.5% purity) was used, so it was not clear what component of the *n*-hexane mixture caused the neoplasms. A parallel experiment carried out on rats showed no increase in incidence of neoplasms at any site. Papillary tumors have been reported in the bronchiolar epithelium of rabbits after a 24-week exposure to *n*-hexane at 3,000 ppm.

TABLE 3-5 Genetic Effects of *n*-Hexane in In Vivo Studies of Inhalation Exposure

Species	Tissue	Exposure (HID or LED)	End Point	Results
Mouse[a]		396 ppm[b]	Dominant lethal mutation	-
Swiss mouse		5,000 ppm; 20 h/d for 5 d	Dominant lethal mutation	-
$B6C3F_1$ mouse	Sperm	5,000 ppm; 20 h/d for 5 d	Sperm morphology	-
Mouse[a]	Peripheral blood	10,000 ppm; 6 h/day, 5 d/wk for 13 wk	Micronuclei formation	-
Mouse[a]	Peripheral blood	1,000 ppm; 22 h/d, 5 d/wk for 13 wk	Micronuclei formation	-
Rat[a]	Sperm	5,000 ppm[b]	Sperm morphology	+ (reversible)
Rat[a]	Bone marrow	Not specified	Chromatid breaks	+

Abbreviations: HID, highest ineffective dose; LED, lowest effective dose; +, positive results; -, negative results.
[a]Strain not specified.
[b]Exposure duration not specified.
Source: ATSDR 1999.

3.7. Summary of Animal Data

A summary of relevant lethality data is presented in Table 3-3. No original acute mortality studies could be retrieved. Reference has been made to two LC_{50} values in rats (a 1-h LC_{50} of 72,900 ppm and a 4-h LC_{50} of 48,000 ppm) without further details, but the original references could not be identified. Hence, these values cannot be evaluated properly. In addition, findings in toxicokinetic studies have discrepancies with these LC_{50} values. No lethality occurred in rats exposed to *n*-hexane at up to 48,280 ppm for 10 h or at 86,222 ppm for 30 min. Mice appeared to be more susceptible to *n*-hexane than rats, but the studies by Fühner (1921) and Lazarew (1929) could not be used for quantitative analysis because mice were exposed in a static system, the number of animals per exposure concentration was unknown, and respiration rate steadily decreased during exposure. Exposure for 5 min to *n*-hexane at 16,000 ppm caused light anesthesia in mice. Mice became directly anesthetized at 32,000 ppm, and exposure at 64,000 ppm caused respiratory arrest within 4.5 min (Swann et al. 1974).

A summary of nonlethal toxicity data is provided in Table 3-4. Visible signs of acute toxicity were associated with effects on the nervous system (e.g., reduced respiration, ptosis, myoclonic seizures, ataxia, decreased motor activity, sedation, laying down in a side position, and narcosis). In general, these effects were dose-related. Results showed a very small margin between concentrations causing narcotic effects (34,800 ppm for 90 min) and causing death (38,210 ppm for 127 min; 43,750 ppm for 96 min) in mice exposed in static systems. Clinical signs were found in rats exposed at 86,222 ppm for 25 min (Raje et al. 1984).

In rats, acute effects on the brain were found at concentrations of 2,000 ppm and higher for 8 h (increased glutamine and alanine content, effects on acetylcholine metabolism) but the functional implications are difficult to assess. Effects on the lung were seen after exposure to *n*-hexane at 4,260 ppm for 5 h (effects on the lung surfactant system followed by degenerative effects on the pneumocytes). Reversible lesions in the testis were found in rats exposed at 5,000 ppm for 24 h. However, no histopathologic changes in the lungs or testes were found in rats and mice exposed to *n*-hexane at 10,000 ppm for 6 h/day, 5 days/week for 13 weeks. Pulmonary effects were very minor and did not result in functional impairment after repeated exposure. An exposure duration longer than 6 h is necessary to induce the testes effects. Therefore, both types of effects are not relevant for AEGL-derivation.

Developmental and reproductive toxicity studies with *n*-hexane at up to 1,000 ppm showed no effects on dams exposed during gestation. A decreased number of litters were observed in dams exposed at 500 ppm for 23 h/day, 7 days/week throughout gestation (Stoltenburg-Didinger et al. 1990), but not in dams exposed at 1,000 ppm for 6 h/day on gestation days 8-16 (Bus et al. 1979). Therefore, a (near) continuous exposure regimen is necessary to induce these kind of effects. Postnatal growth retardation in offspring exposed during gestation was judged to be not relevant for setting AEGL values. Some transient ef-

fects on biochemical parameters and brain development were also reported by Stoltenburg-Didinger (1991).

Only limited mutagenicity testing has been conducted. In general, *n*-hexane was not mutagenic in vitro with some exceptions: polyploidy in hamster CHL cells, polyploidy and structural aberrations in CHO cells (undiluted *n*-hexane in the absence of S9), and sister chromatid exchanges in CHO cells (only in the presence of S9, no dose response). The available studies on in vivo genotoxicity are summarized in Table 3-5. *n*-Hexane was found to be not mutagenic in a dominant lethal test, micronucleus test, and sperm morphology test with mice. In rats, however, morphologic alterations in sperm and chromatid breaks in bone marrow cells were observed.

Little information was available on the carcinogenicity of *n*-hexane. Hepatocellular neoplasms (adenoma and carcinoma) were reported in mice and papillary tumors in the bronchiolar epithelium in rabbits.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Absorption

Ten volunteer students (healthy Japanese men and women, 18-25 years old) were exposed to *n*-hexane (purity not specified) at actual concentrations of 87-122 ppm for 4 h in an exposure room (Nomiyama and Nomiyama 1974). Concentrations of *n*-hexane in environmental and expired air were measured four times at a 1-h interval. Immediately after exposure, expired air was collected for 3 min following inhalation of fresh air. Respiratory retention decreased with exposure duration and reached a constant level after 2 h of exposure (saturation). Pulmonary retention was calculated to be 5.6 ± 5.7% (5.7 ± 7.1% for men, 5.4 ± 4.1% for women).

Brugnone and coworkers have published many reports on occupational exposure of shoe factory workers to *n*-hexane. In one study, grasp samples of breathing zone air and alveolar air samples were obtained from 20 workers (18 men and 2 women) employed in a shoe upper factory 60, 165, and 270 min after the start of a shift. Average *n*-hexane concentrations were 99 ppm (349 mg/m^3), 167 ppm (589 mg/m^3), and 214 ppm (755 mg/m^3), respectively (Brugnone et al. 1978). Alveolar retention of *n*-hexane was estimated to be equal to 14.9%, and the concentration in venous blood sampled after 270 min was 0.38 µg/mL.

Healthy males (25-35 years old) were exposed for 4 h to *n*-hexane (purity not specified) at 100 and 200 ppm (360 and 720 mg/m^3, respectively) at rest (four 50-min periods of exposure with 10-min non-exposed intervals) and at 100 ppm (360 mg/m^3) under increasing levels of physical exercise (peak exercise involved five consecutive 10-min periods of 20, 40, 60, 80, and 100 W or three consecutive 50-min periods with 10-min non-exposed intervals of 20, 40, and 60 W) on a bicycle ergometer (Veulemans et al. 1982). Exposure concentrations

were monitored. Experiments were conducted with at least 2-week intervals. *n*-Hexane concentrations were measured in inhaled and exhaled air. Physical exercise during exposure caused an important increase in lung clearance values from 2.30 L/min at rest to 5.36 L/min at 80 W of peak exercise. Retention decreased by more than 50% with increasing exercise from 24.1% at rest to 10.5% at 100 W of peak exercise. Uptake rate increased with exercise by more than two times the uptake at rest (from 0.84 mg/min at rest to 1.93 mg/min at 80 W of peak exercise). Steady-state concentrations of *n*-hexane in venous blood were reached within 15 min at 100 or 200 ppm at rest or under exertion. *n*-Hexane concentrations in peripheral venous blood (0.183 µg/mL) increased with increasing exercise levels, both after 10 min (0.290 µg/mL, 60 W) or 50 min of exercise (0.331 µg/mL, 100 W).

n-Hexane concentrations were measured in breathing zone air and in alveolar air of 10 young healthy workers (18-30 years old) employed in a shoe factory. The median 8-h TWA of *n*-hexane in the breathing zone was 69 ppm or 243 mg/m^3 (range 2-325 ppm or 8-1,143 mg/m^3). Alveolar retention was calculated to be about 25% (range 22.1-28.7%) of the inhaled *n*-hexane. Physical load while working was very slight (ventilation value 8 L/min). Urinary metabolites 2,5-dimethylfuran, 2-hexanol, 2,5-HD, and γ-valerolactone were found at low concentrations, but were related to *n*-hexane in the air. 2,5-HD was the main metabolite (Mutti et al. 1984).

Healthy male volunteers (19-26 years old) were exposed (nose only, in a sitting position) for 15.5 min to *n*-hexane (purity 99%) at concentration of about 60 ppm. Volunteers were exposed approximately 4 h later to *n*-hexane at 60 ppm for a mean exposure duration of 3.91 h (van Engelen et al. 1997). During and after exposure, the last part of the alveolar air was sampled after subjects held their breath for 30 seconds. During the first exposure, the mean inhaled concentration (C_i) of *n*-hexane was 64 ppm and the mean exhaled concentration (C_e) was 39 ppm, so alveolar retention was 39%. During the second exposure, the mean C_i was 63 ppm and the mean C_e was 41 ppm, so alveolar retention was 35%. Little variation in the toxicokinetics of *n*-hexane between the first and second exposure in the same subject was observed.

Distribution, Metabolism, and Excretion

Perbellini and Brugnone have published many reports on *n*-hexane metabolism, both in occupational workers and in animals. Two of the reports are discussed below. Solvents in the breathing air of workers in a shoe factory were found to contain *n*-hexane at 117 ppm (411 mg/m^3) (Perbellini et al. 1980). Metabolites 2-hexanol, 2,5-dimetylfuran, γ-valerolactone, and 2,5-HD were identified in the urine of workers sampled during the last 4 h of a work shift. 2,5-HD was the main metabolite. 2,5-Dimetylfuran and γ-valerolactone were also found in the urine of rats, but not in the urine of rabbits or monkeys (Perbellini et al. 1982). In this comparative study, male Sprague-Dawley rats, male New Zealand

rabbits, and one male monkey (*Macaca mulatta*) were subjected to a single, whole body exposure to *n*-hexane (purity 99%) at an actual concentration of 5,000 ppm for 6-24 h. Other metabolites present in the urine of rats, rabbits, and the monkey were 2-hexanol, 3-hexanol, methyl *n*-butyl ketone, and 2,5-HD. *n*-Hexane metabolites in rat blood were 2-hexanol, methyl-*n*-butyl ketone, 2,5-dimethylfuran, and 2,5-HD. Humans chronically exposed to a mixture of hexane isomers containing *n*-hexane at 10-40 ppm had urinary concentrations of 2,5-HD ranging from 0.4 to 21.7 mg/L, which is the same proportion as rats exposed once to *n*-hexane at 5,000 ppm for 6 h (1.7 mg/L) or for 12 h (12.8 mg/L).

Caucasian male volunteers (22-52 years old; no occupational exposure to organic solvents) were exposed (whole body) for 2 h to an actual concentration of *n*-hexane (purity 99%) of 54.2 ppm during light physical exercise (50 W) on an ergometer bicycle (Shibata et al. 2002). *n*-Hexane increased rapidly in arterialized capillary blood and reached a steady-state concentration of about 0.25 µg/mL (3 µmol/L) within 30-60 min of exposure. A rapid decline in the concentration of *n*-hexane occurred after exposure ended; *n*-hexane was not detected 2 h after exposure.

Urinary excretion of the *n*-hexane metabolite 2,5-HD was determined in four healthy shoe factory workers (women, 41-54 years old) during four working days (preceded by four exposure-free days and followed by two exposure-free days) (Ahonen and Schimberg 1988). Mean concentration of *n*-hexane in the breathing zone ranged from 1.9 ppm (6.7 mg/m^3) to 31 ppm (108.7 mg/m^3). Total absorption of *n*-hexane in the body was 22-352 mg, total excretion of 2,5-HD in the urine was 0.007-5.03 mg, and the relative excretion (excretion as percentage of absorption) of 2,5-HD was 2-100%, which increased as the exposure to *n*-hexane increased (100% reported for the highest exposed worker). 2,5-HD appeared to accumulate progressively in the body at the highest *n*-hexane concentration.

Female albino rats were exposed to *n*-hexane (purity not specified) at a target concentration of 48,280 ppm (170 g/m^3) for up to 10 h. *n*-Hexane concentration in blood, brain, adrenal glands, kidneys, and spleen increased until a saturation value was reached within 3-4 h (Böhlen et al. 1973). Blood concentrations of *n*-hexane reached a steady-state of about 0.15 mg/mL after 4 h, and a steady-state concentration in the brain of 0.39 mg/g was reached at the same time. Liver concentration of *n*-hexane increased linearly with inhalation duration, and did not reach saturation within 10 h. This was possibly caused by *n*-hexane-induced lipid accumulation (triglycerides) in the liver, and consequently the lower blood supply (lower access of *n*-hexane to fatty liver). Comparison of in vivo tissue/gas partition coefficients (calculated from *n*-hexane concentrations in saturated tissues) with total lipid content of these tissues showed a direct proportional relationship between *n*-hexane saturation concentration and total lipid content of brain, adrenal glands, kidneys, and spleen (saturation value 4 mg/g of lipid). Blood contained much more *n*-hexane in relation to its lipid content (saturation value 25 mg/g of lipid), which was considered to be possibly caused by protein binding. Calculated estimates of the *n*-hexane/lipid content ratio for the liver

essentially exceeded the saturation value of 4 mg/g of lipid. The exceedance was explained by the accumulation of triglycerides in the liver possessing a much higher solubility for organic solvents than other lipid fractions.

Blood from groups of four male Sprague-Dawley rats was collected immediately after whole-body exposure to *n*-hexane (purity at least reagent grade, presaturated air) for 10, 15, 20, 25, or 30 min (Raje et al. 1984). The concentration of *n*-hexane in the exposure chamber was 86,222 ppm (393 g/m^3) after introduction of the animals. Blood became saturated with *n*-hexane within 10 min, and saturation persisted through 30 min of exposure (mean saturation concentration 21 mg/mL).

Male Fischer rats were exposed to average 10-min concentrations of *n*-hexane (purity 95%) ranging from 4,800 to 21,000 ppm (Howd et al. 1982). For single exposures, animals were maintained under static conditions, and *n*-hexane concentrations reportedly decreased by 1% per min. For longer exposure durations, rats were exposed under dynamic conditions to regularly controlled concentrations of *n*-hexane. After 10-min of exposure to *n*-hexane at 4,800-21,000 ppm, *n*-hexane concentrations in blood and brain were found to be linearly related to the exposure concentration. Thereafter, *n*-hexane was rapidly eliminated ($t_{1/2}$ = 2.5 and 4 min in blood and brain, respectively). Blood concentration of *n*-hexane was approximately 10 µg/mL after 10 min of exposure at 21,000 ppm, and brain concentration was 60 µg/g. Lower concentrations were found in a second series of experiments with rats exposed at 24,500 or 46,100 ppm for 10 min. Blood concentrations of *n*-hexane immediately after exposure were approximately 4 and 8 µg/mL, respectively, and corresponding brain concentrations were less than 20 and approximately 40 µg/g. Despite rapid elimination of *n*-hexane, repeated 10-min exposures (10 min every half hour for 8 h/day) to a high concentration of *n*-hexane (48,000 ppm) resulted in an increase in 2,5-HD in blood (20 µg/mL from a 1-day exposure; 100 µg/mL from 3 or more days of exposure). The minimal sustained plasma 2,5-HD concentration resulting in neurotoxicity appeared to be 50 µg/mL.

Pregnant Fischer-344 rats (number not specified) were exposed (whole body) for 6 h to *n*-hexane (purity 99%) at target concentrations of 0 and 1,000 ppm on gestation day 12, day 20, or days 15-18 (Bus et al. 1979). Results from exposure on day 20 showed that *n*-hexane was rapidly and extensively metabolized to methyl *n*-butyl ketone (MBK) and 2,5-HD. Highest tissue concentrations were found immediately after exposure. Concentrations of *n*-hexane and the two metabolites in the fetus (µg/g wet wt) were approximately equal to those in maternal blood (0.45 µg/mL). Similar concentrations were also found immediately after exposure on day 12 and after exposure on days 15-18, indicating that the placenta was equally permeable during gestation. *n*-Hexane and MBK were rapidly eliminated (minimal to non-detectable concentrations 8 h after exposure) from all tissues examined (maternal blood, brain, kidneys, and liver and fetuses). In contrast, tissue concentrations of 2,5-HD increased between 0 and 4 h after exposure. Thereafter, 2,5-HD was eliminated significantly slower (non-detectable concentrations 24 h after exposure). The calculated half-life of 2,5-

HD in maternal blood (3.90 h) was significantly greater than for *n*-hexane (1.24 h) or MBK (0.99 h). Comparable half-lives for 2,5-HD and MBK were found for fetuses.

In male Fischer-344 rats exposed to *n*-hexane (purity 95.8%) at 500, 1,000, 3,000, and 10,000 ppm for 6 h, steady-state *n*-hexane concentrations were achieved within 30 min in blood and within 2 h in all other tissues examined (brain, liver, kidneys, lungs, testes, and sciatic nerve) (Baker and Rickert 1981). *n*-Hexane concentrations in air were regularly monitored. Steady-state *n*-hexane concentrations were lowest in blood (1, 2, 8, and 21 µg/mL, respectively) and highest in sciatic nerve (10-20 times the blood concentration). *n*-Hexane concentration in the brain was 54.2 µg/g after exposure at 10,000 ppm for 6 h. Steady-state concentrations in the other tissues were 2-5 times the blood concentration. Steady-state *n*-hexane concentrations in the blood and liver were shown to be directly proportional to exposure concentrations. The half-lives of *n*-hexane and MBK were approximately 1-2 h in all tissues except the kidneys ($t_{½}$ = 5-6 h). MBK was the first metabolite (<0.5 h) to appear in the blood and tissues. In blood, tissues, and urine, the following metabolites were demonstrated: 2,5-HD, MBK, 2,5-dimethylfuran (DMFU), 2-hexanol, and 1-hexanol. Concentrations of 2,5-HD were highest in the blood, kidneys, and sciatic nerve (in order of increasing concentrations) after exposure at 1,000 ppm. Tissue concentrations of 2,5-HD were not proportional to dose. The latter in combination with the finding that metabolism and elimination of *n*-hexane were dependent on exposure concentration indicated that severity of neuropathy might not be directly correlated to *n*-hexane exposure concentration.

Lam et al. (1990) demonstrated that 94% of the blood concentration of *n*-hexane was present in erythrocytes of Sprague-Dawley rats. Groups of four male rats were exposed to an actual *n*-hexane (purity not specified) concentration of 515 (± 25) ppm for 2 h. *n*-Hexane concentration immediately after exposure was 0.06 µg/mL in plasma and 0.86 µg/mL in erythrocytes. Very similar results were obtained with rat blood in vitro. In vitro studies of human blood showed that 66% of *n*-hexane in blood was present in erythrocytes, indicating that erythrocytes from humans and rats exhibit substantial differences in affinity for *n*-hexane. Proteins, chiefly hemoglobin, were demonstrated to be the major carriers of *n*-hexane.

In male Fischer-344 rats, the disposition of radioactivity after exposure to [1,2-^{14}C]-*n*-hexane (purity 98.5%; diluted to the required specific activities with *n*-hexane, purity 95.8%) at 500, 1,000, 3,000, and 10,000 ppm for 6 h was studied (Bus et al. 1982). A dose-dependent deposition of radioactivity was found. This finding was unlikely to be attributable to saturation of renal excretion of *n*-hexane metabolites since the estimated half-lives for excretion of urinary metabolites were similar for the groups exposed at 1,000-10,000 ppm. Inhibition of *n*-hexane metabolism at high concentrations (the metabolism of *n*-hexane to $^{14}CO_2$ and urinary metabolites was less in the 10,000-ppm than in the 3,000-ppm group) was suggested as a possible mechanism that would account for the dose-dependent disposition of *n*-hexane. The mechanism of the inhibition is un-

known. The total amount of radioactivity recovered did not increase linearly between the 3,000- and 10,000-ppm groups. This observation might be due to the reduced respiration associated with narcosis observed in the 10,000-ppm group.

Ten male NMRI mice were exposed to *n*-hexane (purity not specified) under static conditions (Krämer et al. 1974). Exposure conditions were very poorly characterized. In general, 3.2 mL of *n*-hexane was added to a 25-L glass box (initial concentration of about 24,000 ppm) and exposure was for at least 24 h. Evidence was obtained that the high turnover rate of *n*-hexane might be correlated with an inducing effect on the monooxygenase system in the liver. The following results supported this hypothesis: (1) increased microsomal protein/g liver ratio mainly caused by an increase in the proteins cytochrome P450, cytochrome b_5, and NADPH-DCPIP reductase (NADPH reductase activity specifically measured by reduction of dichlorophenolindophenol); (2) enhanced microsomal hydroxylation activity caused by an enhanced specific activity of cyclohexane hydroxylation and cyclohexane binding difference spectrum; (3) increase in the total cytochrome P450 content per body weight, liver weight, and total amount of microsomal protein; and (4) a qualitative alteration in the cytochrome P450 species.

The following metabolites were found in the urine of male Wistar rats exposed (whole body) to *n*-hexane (purity not specified) at an actual concentration of 997 ± 23 ppm for 8 h: 1-hexanol, 2-hexanol, 3-hexanol, 2-hexanone, 2,5-HD, 2,5-dimethyltetrahydrofuran, 2,5-dimethyl-2,3-dihydrofuran, and γ-valerolactone (Fedtke and Bolt 1986). Analysis of the urine of male Wistar rats exposed (whole body) to *n*-hexane (purity 99.5%) at an actual concentration of 2,096 ± 124 ppm for 8 h revealed the formation of 4,5-dihydroxy-2-hexanone via 5-hydroxy-2-hexanone or 2,5-HD (Fedtke and Bolt 1987a,b). 4,5-Dihydroxy-2-hexanone is converted to 2,5-dimethylfuran or 2,5-HD, depending on the conditions of urine treatment. Detection of 2,5-dimethylfuran after analysis of urine from workers exposed to *n*-hexane suggested that 4,5-dihydroxy-2-hexanone was formed as a precursor of 2,5-dimethylfuran in humans, too. In urine of male Wistar rats exposed (whole body) for 8 h to *n*-hexane (purity 99.5%) at mean actual concentrations of 50-3,074 ppm, the occurrence of the metabolites 1-hexanol, 2-hexanol, 3-hexanol, 2-hexanone, 2,5-HD, and 4,5-dihydroxy-2-hexanone was demonstrated (Fedtke and Bolt 1987a,b). Excretion of metabolites was linearly dependent on the exposure concentration at up to about 300 ppm; above 300 ppm, saturation kinetics occurred.

The amount of 4,5-dihydroxy-2-hexanone excreted in urine was approximately 10 times higher than that of 2,5-HD. 4,5-Dihydroxy-2-hexanone could also be demonstrated in the urine of a male volunteer (28 years old) exposed by breathing mask to *n*-hexane (purity 99.5%) at a mean actual concentration of 217 ppm for 4 h. The urinary concentration of 4,5-dihydroxy-2-hexanone 22 h after exposure was about four times higher than the concentration of 2,5-HD. Formation of 4,5-dihydroxy-2-hexanone was viewed as a route of detoxification in both rat and man.

Summary

Alveolar retention of *n*-hexane in humans is relatively low. In experimental settings, retention was 25-35%, and a lower retention of about 10% was found with exercise. Pulmonary retention of 5% reported by Nomiyama and Nomiyama (1974) appears to be very low. For men and women, comparable results were obtained. Alveolar retention in workers ranged from 15 to 25%. Blood *n*-hexane concentrations were highly correlated with environmental and alveolar concentrations. Post-exposure, alveolar excretion of *n*-hexane was about 10% of the total uptake. Steady-state *n*-hexane concentrations in blood are rapidly reached in approximately 30 min. Physical exercise resulted in an increase in lung clearance values, a decrease in alveolar retention, and an increase in blood *n*-hexane concentration. In general, a rapid decline in *n*-hexane concentrations was observed after exposure ended, with no detection after 2 h. Metabolite concentrations in urine were related to *n*-hexane concentrations in air.

In experimental animals, steady-state levels (saturation) were generally reached very rapidly in blood and other organs. Most studies indicate a steady-state concentration of *n*-hexane in blood within 30 min. Only Böhlen et al. (1973) reported that a steady-state concentration was reached in female albino rats after 4-5 h of exposure at 48,280 ppm (170 g/m^3). A steady-state blood concentration of about 0.15 mg/mL was also rather high when compared with other studies. Concentrations of *n*-hexane in blood vary to a large extent. In rats, exposure to *n*-hexane at 10,000 ppm for 6 h resulted in blood *n*-hexane concentrations of up to 21 µg/mL, whereas a blood concentration of 150 µg/mL was reported within 5 h of exposure at 48,280 ppm and of 22 mg/mL after a 10-min exposure at 86,222 ppm. The latter value reported by Raje et al. (1984) is probably not correct; it may be that the concentrations should read µg/mL instead of mg/mL. The difference between the 150 µg/mL reported by Böhlen et al. (1973) and the blood concentrations in other studies is difficult to explain. It might be that by direct injection of a blood sample into a gas chromatograph (as done by Böhlen et al. 1973), the *n*-hexane fraction bound to hemoglobin is more precisely estimated. By injecting headspace samples or extraction solvents, as was the method of choice in the other studies, the fraction bound to hemoglobin (which is about 95% in rats, see below) might be underestimated.

n-Hexane saturation concentrations were shown to be directly proportional to the total lipid content in tissues like brain, adrenal glands, kidneys, and spleen. Blood contained much more *n*-hexane in relation to its lipid content, caused by binding to erythrocytes. In rats, about 94% of the *n*-hexane in blood appeared to be noncovalently bound to hemoglobin, whereas in humans the percentage was 66%. In addition, relatively high concentrations of *n*-hexane were found in liver, which may be explained by accumulation of triglycerides in the liver that possess a much higher solubility for *n*-hexane than other lipid fractions. High concentrations of *n*-hexane were also found in sciatic nerve tissue.

n-Hexane is rapidly eliminated by an inducing effect on the monooxygenase system in the liver in animals and is extensively metabolized to MBK and

2,5-HD, the main neurotoxic metabolite. Maximum blood concentrations of 2,5-HD are reached at 4 h post-exposure. For *n*-hexane and MKB, high turn-over rates ($t_{1/2}$ = 1-2 h) were found in all tissues except the kidneys ($t_{1/2}$ = 5-6 h). Both compounds were rapidly eliminated to minimal or not detectable concentrations at 8 h post-exposure. In contrast, 2,5-HD increased between 0-4 h after exposure and was more slowly eliminated ($t_{1/2}$ = about 4 h) to minimal concentrations at 24 h post-exposure. Exposure of pregnant rats showed comparable kinetics of *n*-hexane and its metabolites in maternal and fetal tissues.

The main urinary metabolite of *n*-hexane was 4,5-dihydroxy-2-hexanone, which was about 4 or 10 times higher than that of excreted 2,5-HD in humans and rats, respectively. Additionally, many metabolites were identified in the blood and urine of humans, rats, mice, rabbits, and monkeys. 2,5-Dimethylfuran and γ-valerolactone could be demonstrated in the urine of humans and rats, but not in the urine of rabbits or monkeys. Excretion of metabolites was linearly dependent on the exposure concentration of *n*-hexane to about 300 ppm; above 300 ppm, saturation kinetics occurred.

4.2. Mechanism of Toxicity

The role of kinetics in the acute inhalation toxicity *n*-hexane was analyzed with a physiologically based pharmacokinetic model for the rat (De Jongh et al. 1998). Model compartments included: (1) localized fat tissue; (2) a lumped compartment representing all slowly perfused tissues except fat tissue; (3) liver tissue; (4) a lumped compartment representing all rapidly perfused tissues except liver and brain tissue; and (5) brain (central nervous system [CNS]) tissue. Two CNS subcompartments were defined, representing aqueous and lipid brain components. A common form of inhalation toxicity from nonreactive, volatile organic compounds in mammals, including humans, is general anesthesia possibly followed by death. Application of an internal dose surrogate C_{bl} (concentration in the brain's lipid constituents) instead of the traditional external exposure parameter LC_{50}-t (77,000 ppm × 1 h) resulted in a more than 10-fold reduction in the toxic range of 15 nonreactive, volatile organic compounds (including *n*-hexane) (simulated dose surrogate: 70 ± 31 mM for all volatile organic compounds). These observations support the presumption that nonspecific, acute narcotic lethality is directly related to the extent of *n*-hexane distribution in the phospholipid bilayer of nerve cell membranes.

4.3. Other Relevant Information

4.3.1. Species Variability

In lethality studies (see Section 3.1 and Table 3-3), mice seemed to be more susceptible to *n*-hexane toxicity than rats. Minimal fatal doses of 37,640 ppm for 39-45 min (Fühner 1921) and 64,000 ppm for 4.5 min (Lazarew 1929)

were found for mice. However, these studies were carried out in closed exposure chambers and were, therefore, not suitable for quantitative analysis (see Section 3.1 for explanation).

Differences in the amount of the main urinary metabolite 4,5-dihydroxy-2-hexanone were demonstrated in humans and rats (see Section 4.1). Concentrations of 4,5-dihydroxy-2-hexanone were about four times higher than that of excreted 2,5-HD in humans, whereas it was about 10 times greater than 2,5-HD in the rat (Fedtke and Bolt 1987a,b). Additionally, both quantitative and qualitative differences in the metabolites present in urine and blood of humans, rats, mice, rabbits, and monkeys were observed. Animals were exposed to *n*-hexane at 5,000 ppm for up to 72 h, while humans were exposed occupationally at 10-140 ppm during work shifts. 2,5-Dimetylfuran and γ-valerolactone could be demonstrated in the urine of humans and rats, but not in the urine of rabbits or monkeys (Perbellini et al. 1982). 3-Hexanol, a major metabolite in animals, could not be detected in human urine. The significance of these metabolic differences in the acute toxicity of *n*-hexane is unclear.

4.3.2. Irritation and Sensitization

Skin and Ocular Irritation

Little information was available on skin and ocular irritation in humans and laboratory animals after acute exposure to *n*-hexane vapor. No clinical signs (rubbing, scratching, redness, lacrimation) of ocular or skin irritation were reported in acute inhalation studies (see Sections 2.2 and 3.2). In a study by Shibata et al. (2002), in which Caucasian male volunteers were asked to rate ocular discomfort (burning, irritation), the rating was below 10% of the whole scale and corresponded verbally to ratings between ‘not at all’ and ‘hardly at all’ (see Section 2.2.2 for details).

In an evaluation by WHO (1991), only one study in humans was reported in which volunteers were exposed to *n*-hexane vapor at a concentration of 500 ppm (1,760 mg/m^3) for 3-5 min. No signs of ocular irritation were noted. No skin sensitization has been reported in exposed workers and no skin sensitization was noted in a maximization test with *n*-hexane solution. However, operators at a soybean hexane-extraction facility had a higher incidence of dry or irritated skin than maintenance workers (65% vs. 20%). It could not be deduced from the WHO (1991) report whether the operators were exposed to *n*-hexane vapor or solutions of *n*-hexane.

Respiratory Tract Irritation

Several effects on the lungs of laboratory animals have been reported following acute exposure to *n*-hexane. These studies are described in detail in Section 3.2 (Nonlethal Toxicity). In summary, Schnoy et al. (1982) reported effects

on pneumocytes (fatty degeneration, changes in lamellar bodies of type II pneumocytes, and increased detachment of cells) in rats exposed to *n*-hexane at 700 ppm for 8 h, 10,000 ppm for 4 h, and at 10,000 ppm for 8 h. Hadjiivanova et al. (1987) demonstrated effects on pulmonary surfactant in rats exposed to *n*-hexane at 4,260 ppm for 5 h, which are in general the early events in lung toxicity. However, no histopathologic lesions in the respiratory tract were found in groups of 15 male and 15 female Fischer-344 rats (Cavender et al. 1984) or in groups of 10 male and 10 female B6C3F$_1$ mice (Dunnick et al. 1989) exposed to *n*-hexane concentrations of up to 10,000 ppm for 6 h/day, 5 days/week for 13 weeks. Swann et al. (1974) reported sensory irritation of the respiratory system of mice exposed to *n*-hexane at 1,000-64,000 ppm for 5 min. Irregular respiration was observed at 32,000 ppm and 64,000 ppm. This effect was accompanied by increased expiratory effort, apneic respirations, an increase in respiration rate, and a decrease in amplitude at 32,000 ppm, and an increase in inspiratory effort and a decrease in the expiratory effort at 64,000 ppm. Respiratory arrest occurred at the end of inspiration at 64,000 ppm.

Caucasian male volunteers exposed to *n*-hexane at 54.2 ppm for 2 h under physical exertion were asked to rate a running nose and discomfort in throat or airways. Their ratings were below 10% of the whole scale (Shibata et al. 2002). This corresponded verbally to ratings between ‘not at all’ and ‘hardly at all’ (see Section 2.2.2 for details).

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Human data relevant to deriving AEGL-1 values for *n*-hexane are limited. Nelson et al. (1943) did not report symptoms of irritation in volunteers exposed to the chemical at nominal concentration of 500 ppm for 5 min. Male volunteers exposed to *n*-hexane at 54 ppm for 2 h during light physical exercise did not experience any signs of discomfort. Toxicokinetic studies of *n*-hexane with volunteers included exposures up to 200 ppm for 4 h at rest and up to 100 ppm for 3 h under increasing levels of exercise (Veulemans et al. 1982). No adverse effects were described, but it was unclear whether subjects were questioned about such effects. No clinical signs were reported by workers exposed to *n*-hexane at 8-h TWA concentrations of up to 325 ppm (Mutti et al. 1984).

5.2. Animal Data Relevant to AEGL-1

Data on *n*-hexane are predominantly from studies of mice and rats. Most studies with mice are rather old and were performed in static systems (Fühner 1921; Lazarew 1929). In such systems, *n*-hexane concentrations would have decreased during testing, and oxygen concentrations would also have decreased

and the carbon dioxide concentrations would have increased making the studies difficult to interpret. Swann et al. (1974) observed light anesthesia in mice exposed to *n*-hexane at 16,000 ppm for 5 min but no CNS-effects were present at 8,000 ppm. However, no information on the methods used to assess anaesthesia was provided. In addition, animals in this study were restrained, potentially adding uncertainty regarding observations that would be indicative of *n*-hexane-induced anaesthesia. Therefore, data from the Swann et al. (1974) study were not suitable for deriving AEGL-1 values.

No clear effects on shock-avoidance rate were observed in rats exposed to *n*-hexane at 800 ppm for 4 h (Ikeda et al. 1993). Continuous exposure to *n*-hexane at 1,000 ppm did not cause changes in grip strength, conditioned avoidance response, and undifferentiated motor activity before 3 weeks of exposure. These effects were also absent in rats repeatedly exposed to *n*-hexane at 48,000 ppm (10-min exposures followed 5-min intervals without exposure, 24 times per day) for several weeks (Pryor et al. 1982). However, the latter study reported that "48,000 ppm was about the highest concentration that did not cause myoclonic seizures in most of the rats during exposure". When such effects occurred was not reported but this statement might indicate that 48,000 ppm can cause myoclonic seizures in rats. A kinetic study reported that no visible signs of toxicity were observed in rats exposed to *n*-hexane at 86,222 ppm for up to 20 min, but that ataxia and decreased motor activity was observed in rats exposed for 25 or 30 min (Raje et al. 1984). Reduced respiration associated with narcosis was reported in a kinetic study of rats exposed to *n*-hexane at 10,000 ppm for 6 h, but not in rats exposed at 3,000 ppm (Bus et al. 1982).

5.3. Derivation of AEGL-1 Values

As with other alkanes, the predominant effect in acute exposure to *n*-hexane is CNS depression. Human data do not provide adequate information to characterize a concentration-response relationship for *n*-hexane. Data obtained from studies of mice do not provide a suitable point of departure for AEGL-1 values. Experiments were performed under static conditions or under stress, conditions that can easily induce CNS-like effects in mice. Rat data on *n*-hexane also do not adequately address the level of effects defined by the AEGL-1. Therefore, no AEGL-1 values are recommended because of insufficient data.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No adequate human data that address the level of effects defined by AEGL-2 are available.

6.2. Animal Data Relevant to AEGL-2

Data on *n*-hexane relevant to AEGL-2 values are predominantly from studies of mice and rats. However, most studies with mice are rather old (1920s) and were performed in static systems (initial exposure concentrations were up to 51,990 ppm) (Fühner 1921; Lazarew 1929) or under conditions of restraint, with poorly reported methods regarding clinical observations (Swann et al. 1974). Therefore, these studies are not suitable for AEGL-2 derivation.

Clear CNS depression was absent in rats exposed to *n*-hexane at 48,000 ppm 24 times per day for several weeks (exposure for 10 min followed by 5 min of no exposure). However, it was reported that "48,000 ppm was about the highest concentration that did not cause myoclonic seizures in most of the rats during exposure" (Pryor et al. 1982). When these effects occurred was not specified but this statement might indicate that 48,000 ppm can cause myoclonic seizures in rats. A kinetic study reported that no visible signs of toxicity were seen in rats exposed to *n*-hexane at 86,222 ppm for up to 20 min; ataxia and decreased motor activity was reported in rats exposed for 25 or 30 min (Raje et al. 1984). Reduced respiration associated with narcosis (an AEGL-2 level effect) was reported in rats exposed to *n*-hexane at 10,000 ppm for 6 h, but not in rats exposed at 3,000 ppm (Bus et al. 1982). However, the Bus et al. (1979) study is a toxicokinetic study that was not designed to assess toxicity; the methods and results sections of the study report did not include any information on how toxicity (including narcosis) was assessed or specific observations related to toxicity. The observation of narcosis associated with a 6-h exposure to *n*-hexane at 10,000 ppm was a single statement in the discussion section of the publication. In addition, no information was reported regarding toxicity in rats exposed to *n*-hexane at 3,000 ppm. Because of these reporting insufficiencies, there is considerable uncertainty regarding the no-effect level for narcosis in this study, so the data are not appropriate as the basis of AEGL-2 values.

Honma (1983) reported that some symptoms of sedation, hypothermia, and ptosis were observed in rats exposed to *n*-hexane at 2,000, 4,000, or 8,000 ppm for 8 h in a dose-dependent manner (Honma 1983). However, no details were provided and the severity of effects could not be related to the exposure concentrations. Results of kinetics studies, which were not designed to assess toxicity, do not provide adequate information to define a no-effect level for AEGL-2 effects.

Acute effects on the biochemistry in the brain were in rats exposed to *n*-hexane at concentrations of 2,000 to 8,000 ppm for 8 h (Honma et al. 1982; Honma 1983), but the functional implications of these changes are difficult to assess. Effects on rat lung tissue (effects on the lung surfactant system and degenerative effects on the pneumocytes) were seen at *n*-hexane concentrations of up to 10,000 ppm for 8 h (Schnoy et al. 1982; Hadjivanova et al. 1987). Reversible lesions in the testis were found in rats exposed to *n*-hexane at 5,000 ppm for 24 h (De Martino et al. 1987). However, no histopathologic changes in

these organs were found in rats (Cavender et al. 1984) or mice (Dunnick et al. 1989) exposed to *n*-hexane at 10,000 ppm for 6 h/day, 5 days/week for 13 weeks, and the animals did not appear to show any functional impairment related to these effects. Therefore, these effects were not considered relevant for setting AEGL-2 values.

Developmental and reproductive toxicity studies of *n*-hexane showed no effects on dams exposed during gestation at concentrations up to 1,000 ppm. A decreased number of litters was observed in dams exposed to *n*-hexane at 500 ppm for 23 h/day, 7 days per week during the entire gestation period (Stoltenburg-Didinger et al. 1990), but not in dams exposed at 1,000 ppm for 6 h/day on days 8-16 of gestation (Bus et al. 1979). On the basis of these studies, the possible effects of acute exposure to *n*-hexane on the fetus were considered not relevant for setting AEGL-2 values.

6.3. Derivation of AEGL-2 Values

CNS depression is the most relevant adverse effect from acute exposure to *n*-hexane. Adequate human data addressing the level of effects defined by the AEGL-2 were not available. Because of reporting insufficiencies in studies with rats and confounding methologic issues in studies with mice, there is considerable uncertainty regarding the no-effect level for AEGL-2 level effects. Although data are not available to define the concentration-response curve for *n*-hexane, a steep concentration-response relationship is observed for butane, a structural analog of *n*-hexane and CNS depressant (NRC 2012). Thus, a steep concentration-response relationship is also expected for *n*-hexane. For chemicals with steep concentration-response curves, AEGL-2 values may be derived by reducing AEGL-3 values by one-third (NRC 2001). AEGL-2 values for *n*-hexane are presented in Table 3-6.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No adequate human data that address the level of effects defined by the AEGL-3 are available.

TABLE 3-6 AEGL-2 Values for *n*-Hexane

10 min	30 min	1 h	4 h	8 h
4,000 ppm[a] (14,000 mg/m^3)	2,900 ppm[a] (10,000 mg/m^3)	2,900 ppm[a] (10,000 mg/m^3)	2,900 ppm[a] (10,000 mg/m^3)	2,900 ppm[a] (10,000 mg/m^3)

[a]The AEGL-2 value is higher than 10% of the lower explosive limit of *n*-hexane in air of 1.1% (11,000 ppm). Therefore, safety considerations against the hazard of explosion must be taken into account.

7.2. Summary of Animal Data Relevant to AEGL-3

Only limited animal data on mortality following acute exposure to *n*-hexane are available. Two LC_{50} values have been reported for rats: a 1-h LC_{50} of 76,900 ppm (Pryor et al. 1982) and a 4-h LC_{50} of 48,000 ppm (Couri and Milks 1982). However, because the study details are not available, the data cannot be judged on their merits. The latter value appears to be inconsistent with results of the kinetic study by Böhlen et al. (1973), in which no mortality was reported in rats were exposed to *n*-hexane at 48,280 ppm for up to 10 h. In addition, repeated daily exposure to *n*-hexane at 48,000 ppm (10-min exposures followed 5-min intervals without exposure, 24 times) for 4 weeks caused no mortality (Pryor et al. 1982). In addition, no mortality was found in rats exposed to *n*-hexane at 5,000 ppm for 24 h (De Martino et al. 1987) or in rats exposed at up to 10,000 ppm for up to 8 h (Bus et al. 1982; Schnoy et al. 1982; Honma 1983). The 1-h LC_{50} of 76,900 ppm is also inconsistent with the finding of no mortality in rats exposed to *n*-hexane at 86,222 ppm for 30 min (Raje et al. 1984).

Studies with mice are rather old (1920s) and performed in static systems (initial exposure concentrations were up to 51,990 ppm) (Fühner 1921; Lazarew 1929) or under restraint, with poorly reported methods and results (Swann et al. 1974), making these studies unsuitable for deriving AEGL-3 values.

7.3. Derivation of AEGL-3 Values

Adequate human data addressing the level of effects defined by the AEGL-3 are not available. Mouse studies are not suitable because of study flaws, including use of static exposure systems (Fühner 1921; Lazarew 1929) or exposure under restraint, with poorly reported methods and results (Swann et al. 1974). Therefore, rat data were considered to be the most reliable and well founded for AEGL-3 values. The two LC_{50} values for rats (Couri and Milks 1982; Pryor et al. 1982) could not be judged properly because of inadequate documentation, and appear to be inconsistent with other reports, as discussed above. Therefore, the study by Raje et al. (1984) was chosen to determine the best point of departure for AEGL-3 values. In that study, no deaths occurred in rats exposed to *n*-hexane at 86,222 ppm for 30 min. A total uncertainty factor of 10 was applied; a factor of 3 for interspecies differences and a factor for 3 for intraspecies variability. These factors were judged to be adequate because the effects of *n*-hexane are attributed to itself and no relevant differences in kinetics are assumed, so only small interindividual differences are expected. In addition, mortality from *n*-hexane is preceded by CNS depression. Variation in susceptibility for CNS-depressing effects is not very great in the human population. The 30-min AEGL-3 value was calculated to be approximately 8,600 ppm. The 10-min AEGL-3 value was derived from 30-min AEGL-3 value. Time scaling was performing using the equation $C^n \times t = k$, using a default value of $n = 3$.

As with other alkanes, the anesthetic effects of *n*-hexane are considered to be predominantly concentration dependent. No increase of effect-size by dura-

tion is expected for concentration-dependent effects after reaching a steady state. The majority of human data (Veulemans et al. 1982; Shibata et al. 2002) and animal data (e.g., Baker and Rickert 1981; Raje et al. 1984) indicate a rapid steady-state concentration in blood and brain, with steady-state blood concentrations reached in approximately 30 min. In addition, gases that are relatively insoluble in blood rise quickly toward equilibrium with the inhaled concentration, and the less soluble in blood the faster the narcotic action of the gas (Drummond 1993). Quick equilibrium of such gases has been confirmed for other alkanes like propane and butane as well. Hence, no increase of effect-size by exposure duration is expected from 30 min to 8 h. Therefore, AEGL-3 values for the 1-h, 4-h, and 8-h durations were set equal to the 30-min AEGL-3 value. The 8-h AEGL-3 value of 8,600 ppm appears to be conservative and protective for lethality when considered in context with the result of the study by Böhlen et al. (1973), which found no mortality in rats exposed to *n*-hexane 48,280 ppm for 10 h.

AEGL-3 values for n-hexane are presented in Table 3-7.

8. SUMMARY OF AEGL VALUES

8.1. AEGL Values and Toxicity End Points

AEGL values for *n*-hexane are presented in Table 3-8. AEGL-1values are not recommended because of insufficient data. AEGL-2 values were set at one-third of the AEGL-3 values, and the AEGL-3 values were based on a study in which no lethality was observed in rats.

8.2. Comparison with Other Standards and Guidelines

Standards and guidelines for workplace and community exposures to *n*-hexane are presented in Table 3-9. No ERPG (emergency response planning guidelines) values have been set for *n*-hexane. The 1-h IDLH (immediately dangerous to life or health) of 1,100 ppm is set at 10% of the lower explosive limit of 1.1%. AEGL values for *n*-hexane cannot be compared with these general guidelines because those values are meant for long-term exposure. For long-term exposure, the most important effect is the degenerative distal axonopathy caused by the metabolite 2,5-HD. This effect is relevant for acute exposures.

8.3. Data Quality and Research Needs

An adequate acute toxicity study on *n*-hexane is lacking, and the available data do not provide a strong basis for AEGL values. An acute toxicity study with emphasis on anesthesia, narcosis, and mortality would be very helpful. Two LC_{50} values were reported but neither the original reports nor the underlying data could be identified. These values appear to be inconsistent with other reported studies. One of the values, the 4-h LC_{50} of 48,000 ppm, appears to have

been based on a study with rats exposed to *n*-hexane concentrations ranging from 1,000 to 64,000 ppm. This could be a valuable study but the original data are not available.

TABLE 3-7 AEGL-3 Values for *n*-Hexane

10 min	30 min	1 h	4 h	8 h
See below[a]	See below[b]	See below[b]	See below[b]	See below[b]

[a]The 10-min AEGL-3 value of 12,000 ppm (42,240 mg/m^3) is higher than the lower explosive limit of *n*-hexane in air of 1.1% (11,000 ppm). Therefore, extreme safety considerations against the hazard of explosion must be taken into account.
[b]The AEGL-3 values for the 30-min, 1-h, 4-h, and 8-h durations are each 8,600 ppm (30,000 mg/m^3), which is higher than 50% of the lower explosive limit of *n*-hexane in air of 1.1% (11,000 ppm). Therefore, extreme safety considerations against the hazard of explosion must be taken into account.

TABLE 3-8 AEGL Values for *n*-Hexane

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (disabling)	4,000 ppm[a] (14,000 mg/m^3)	2,900 ppm[a] (10,000 mg/m^3)	2,900 ppm[a] (10,000 mg/m^3)	2,900 ppm[a] (10,000 mg/m^3)	2,900 ppm[a] (10,000 mg/m^3)
AEGL-3 (lethal)	See below[b]	See below[c]	See below[c]	See below[c]	See below[c]

Abbreviations: NR, not recommended because of insufficient data.
[a]The AEGL-2 value is higher than 10% of the lower explosive limit of *n*-hexane in air of 1.1% (11,000 ppm). Therefore, safety considerations against the hazard of explosion must be taken into account.
[b]The 10-min AEGL-3 value of 12,000 ppm (42,000 mg/m^3) is higher than the lower explosive limit of *n*-hexane in air of 1.1% (11,000 ppm). Therefore, extreme safety considerations against the hazard of explosion must be taken into account.
[c]The AEGL-3 values for the 30-min, 1-h, 4-h, and 8-h durations are each 8,600 ppm (30,000 mg/m^3), which is higher than 50% of the lower explosive limit of *n*-hexane in air of 1.1% (11,000 ppm). Therefore, extreme safety considerations against the hazard of explosion must be taken into account.

TABLE 3-9 Standards and Guidelines for *n*-Hexane

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	4,000 ppm[a] (14,000 mg/m^3)	2,900 ppm[a] (10,000 mg/m^3)	2,900 ppm[a] (10,000 mg/m^3)	2,900 ppm[a] (10,000 mg/m^3)	2,900 ppm[a] (10,000 mg/m^3)
AEGL-3	See below[b]	See below[c]	See below[c]	See below[c]	See below[c]

(Continued)

TABLE 3-9 Continued

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
IDLH (NIOSH)[d]		1,100 ppm (3,880 mg/m^3)			
TLV-TWA (ACGIH)[e]					50 ppm (180 mg/m^3)
REL-TWA (NIOSH)[f]					50 ppm (180 mg/m^3)
PEL-TWA (OSHA)[g]					500 ppm (1,800 mg/m^3)
REL-STEL (NIOSH)[h]	510 ppm (1,800 mg/m^3)				
MAK (Germany)[i]					50 ppm (180 mg/m^3)
MAK Peak Limit (Germany)[j]					180 ppm (630 mg/m^3)
MAC (The Netherlands)[k]					25 ppm (90 mg/m^3)

Abbreviations: NR, not recommended.

[a]The AEGL-2 value is higher than 10% of the lower explosive limit of *n*-hexane in air of 1.1% (11,000 ppm). Therefore, safety considerations against the hazard of explosion must be taken into account.

[b]The 10-min AEGL-3 value of 12,000 ppm (42,000 mg/m^3) is higher than the lower explosive limit of *n*-hexane in air of 1.1% (11,000 ppm). Therefore, extreme safety considerations against the hazard of explosion must be taken into account.

[c]The AEGL-3 values for the 30-min, 1-h, 4-h, and 8-h durations are each 8,600 ppm (30,000 mg/m^3), which is higher than 50% of the lower explosive limit of *n*-hexane in air of 1.1% (11,000 ppm). Therefore, extreme safety considerations against the hazard of explosion must be taken into account.

[d]IDLH (immediately dangerous to life or health, National Institute for Occupational Safety and Health) (NIOSH 1994) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms, or any irreversible health effects.

[e]TLV-TWA (threshold limit value - time weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 2001, 2012) 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.

[f]REL-TWA (recommended exposure limit - time weighted average, National Institute for Occupational Safety and Health) (NIOSH 2011) is defined analogous to the ACGIH TLV-TWA.

[g]PEL-TWA (permissible exposure limit - time weighted average, Occupational Safety and Health Administration) (29 CFR 1910.1000 [2006]) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week.

[h]REL-STEL (recommended exposure limit - short term exposure limit, National Institute for Occupational Safety and Health) (NIOSH 1977) is defined as a 15-min TWA exposure that should not be exceeded at any time during the workday.

[i]MAK (maximale arbeitsplatzkonzentration [maximum workplace concentration], Deutsche Forschungsgemeinschaft [German Research Association]) (DFG 2005) is defined analogous to the ACGIH TLV-TWA.
[j]MAK Spitzenbegrenzung (peak limit) (German Research Association (DFG2003) constitutes the maximum average concentration to which workers can be exposed for a period up to 30 min with no more than two exposure periods per work shift; total exposure may not exceed 8-h MAK.
[k]MAC (maximaal aanvaaarde concentratie [maximal accepted concentration], Dutch Expert Committee for Occupational Standards, The Netherlands) (MSZW 2004) is defined analogous to the ACGIH TLV-TWA.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR *n*-HEXANE

Derivation of AEGL-1 Values

Data were insufficient for deriving AGEL-1 values for *n*-hexane, so no values are recommended.

Derivation of AEGL-2 Values

In the absence of data for deriving AEGL-2 values for *n*-hexane and because *n*-hexane has a steep concentration-response curve, AEGL-2 values were calculating by dividing the AEGL-3 values by 3 (NRC 2001).

10-min AEGL-2:	12,000 ppm ÷ 3 = 4,000 ppm
30-min AEGL-2:	8,600 ppm ÷ 3 = 2,900 ppm
1-h AEGL-2:	8,600 ppm ÷ 3 = 2,900 ppm
4-h AEGL-2:	8,600 ppm ÷ 3 = 2,900 ppm
8-h AEGL-2:	8,600 ppm ÷ 3 = 2,900 ppm

Derivation of AEGL-3 Values

Key study:	Raje, R.R., M. Greening, and M.T. Fine. 1984. Blood n hexane concentration following acute inhalation exposure in rats. Res. Commun. Chem. Pathol. Pharmacol. 46(2):297-300.
Toxicity end point:	No mortality in rats exposed to *n*-hexane at 86,222 ppm for 30 min.
Time scaling:	The 10-min value was time-scaled using the equation $C^n \times t = k$, with n = 3. $(8{,}600\ \text{ppm})^3 \times 30\ \text{min} = k$ $k = 19.08 \times 10^{12}$ ppm-min Because a steady-state blood concentration will be reached within 30 min, no increase in effect-size by exposure duration is expected from 30 min to 8 h.

	Therefore, AEGL-2 values for the 1-h, 4-h, and 8-h durations were set equal to the 30-min AEGL-2 value.
Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability
10-min AEGL-3:	$C^3 \times 10$ min = 19.08×10^{12} ppm-min C ≈ 12,000 ppm (42,000 mg/m^3)
30-min AEGL-3:	86,222 ppm ÷ 10 ≈ 8,600 ppm (30,000 mg/m^3) (point of departure)
1-h AEGL-3:	Set equal to 30-min AEGL-3 of 8,600 ppm (30,000 mg/m^3)
4-h AEGL-3:	Set equal to 30-min AEGL-3 of 8,600 ppm (30,000 mg/m^3)
8-h AEGL-3:	Set equal to 30-min AEGL-3 of 8,600 ppm (30,000 mg/m^3)

APPENDIX B

CATEGORY PLOT FOR *n*-HEXANE

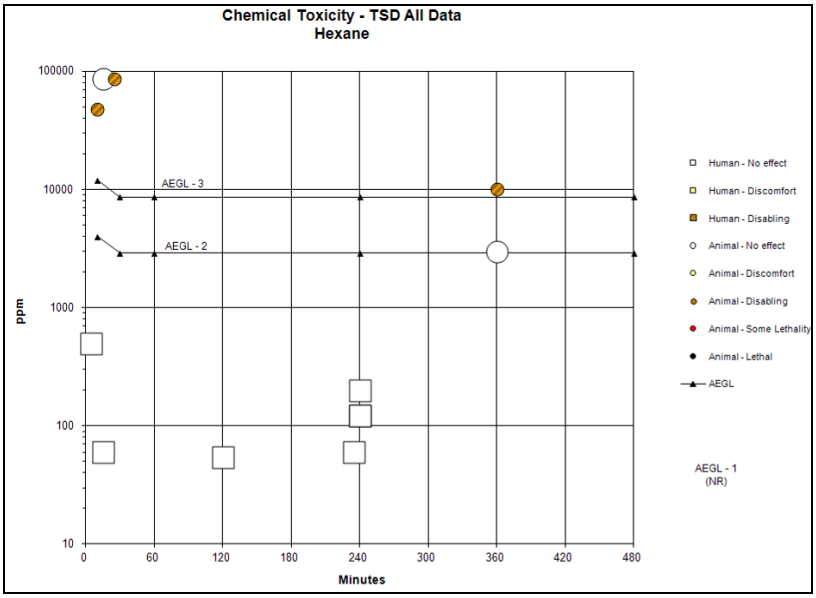

FIGURE B-1 Category plot of toxicity data on *n*-hexane compared with AEGL values. Lethal concentrations in animals were not plotted, because the available data were not reliable. Studies reporting lethality in animals used static exposure conditions or animals were exposed under restraint, and had poor descriptions of methods and results (see Section 7.2 for discussion).

TABLE B-1 Data Used in Category Plot

Source	Species	Sex	No. Exposures	ppm	Minutes	Category
NAC/AEGL-1				NR	10	AEGL
NAC/AEGL-1				NR	30	AEGL
NAC/AEGL-1				NR	60	AEGL
NAC/AEGL-1				NR	240	AEGL
NAC/AEGL-1				NR	480	AEGL
NAC/AEGL-2				4,000	10	AEGL
NAC/AEGL-2				2,900	30	AEGL
NAC/AEGL-2				2,900	60	AEGL
NAC/AEGL-2				2,900	240	AEGL

(Continued)

TABLE B-1 Continued

Source	Species	Sex	No. Exposures	ppm	Minutes	Category
NAC/AEGL-2				2,900	480	AEGL
NAC/AEGL-3				12,000	10	AEGL
NAC/AEGL-3				8,600	30	AEGL
NAC/AEGL-3				8,600	60	AEGL
NAC/AEGL-3				8,600	240	AEGL
NAC/AEGL-3				8,600	480	AEGL
Nelson et al. 1943	Human	Both	1	500	5	0
Shibata et al. 2002	Human	Male	1	54.2	120	0
Nomiyama and Nomiyama 1974	Human	Both	1	122	240	0
Nomiyama and Nomiyama 1974	Human	Both	1	122	240	0
Veulemans et al. 1982	Human	Male	1	200	240	0
van Engelen et al. 1997	Human	Male	1	60	15.5	0
	Human	Male	1	60	234.6	0
Bus et al. 1982	Rat		1	3,000	360	0
	Rat		1	10,000	360	2
Raje et al. 1984	Rat		1	86,222	15	0
	Rat		1	86,222	25	2
Pryor et al. 1982	Rat		1	48,000	10	2

For category: 0 = no effect, 1 = discomfort, 2 = disabling, 3 = lethal; L = lethality.

APPENDIX C

ACUTE EXPOSURE GUIDELINE LEVELS FOR *n*-HEXANE

Derivation Summary

AEGL -1 VALUES

Data were insufficient for deriving AGEL-1 values for *n*-hexane, so no values are recommended.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
4,000 ppm[a] (14,000 mg/m^3)	2,900 ppm[a] (10,000 mg/m^3)	2,900 ppm[a] (10,000 mg/m^3)	2,900 ppm[a] (10,000 mg/m^3)	2,900 ppm[a] (10,000 mg/m^3)

Data adequacy: Data are not available to define the concentration-response curve for *n*-hexane. A steep concentration-response relationship is observed for butane, a structural analog of *n*-hexane and CNS depressant (NRC 2012), so a similar relationship is expected for *n*-hexane. For chemicals with a steep concentration-response curve, AEGL-2 values may be derived by reducing AEGL-3 values by one-third (NRC 2001). Therefore, AEGL-2 for values *n*-hexane were calculated by dividing the AEGL-3 values by 3.

[a]The AEGL-2 value is higher than 10% of the lower explosive limit of *n*-hexane in air of 1.1% (11,000 ppm). Therefore, safety considerations against the hazard of explosion must be taken into account.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 hr
See below[a]	See below[b]	See below[b]	See below[b]	See below[b]

Key reference: Raje, R.R., M. Greening, and M.T. Fine. 1984. Blood n hexane concentration following acute inhalation exposure in rats. Res. Commun. Chem. Pathol. Pharmacol. 46(2):297-300.

Test species/Strain/Number: Rat, Sprague-Dawely, groups of 4 male

Exposure route/Concentrations/Durations: Inhalation, 86,222 ppm for 10, 15, 20, 25, or 30 min.

Effects:

Duration (min)	Effects
10	No effects
15	No effects
20	No effects
25	Ataxia, no deaths
30	Ataxia, no deaths

(Continued)

AEGL-3 VALUES Continued

End point/Concentration/Rationale: Absence of mortality.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3
Intraspecies: 3
A total uncertainty factor of 10 was considered sufficient because the effects are attributed to *n*-hexane itself and no relevant differences in kinetics are assumed. Mortality from *n*-hexane exposure is preceded by CNS depression, and variation in susceptibility for CNS-depressing effects is not very great in the human population.

Modifying factor: None

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: Because a steady-state blood concentration will be reached within 30 min of exposure, no increase in effect-size by exposure duration is expected from 30 min to 8 h. Therefore, the AEGL-3 values for the 1-h, 4-h, and 8-h durations are set equal to the 30-min AEGL-3 value. The 10-min AEGL-3 value was derived from the 30-min AEGL-3 value by time-scaling using the equation $C^n \times t = k$, with n = 3.

Data adequacy: The database is very poor. Available data for derivation of AEGL-3 values were predominantly from toxicokinetics studies. Adequate toxicity studies are lacking.

[a]The 10-min AEGL-3 value of 12,000 ppm (42,240 mg/m^3) is higher than the lower explosive limit of *n*-hexane in air of 1.1% (11,000 ppm). Therefore, extreme safety considerations against the hazard of explosion must be taken into account.
[b]The AEGL-3 values for the 30-min, 1-h, 4-h, and 8-h durations are each 8,600 ppm (30,000 mg/m^3), which is higher than 50% of the lower explosive limit of *n*-hexane in air of 1.1% (11,000 ppm). Therefore, extreme safety considerations against the hazard of explosion must be taken into account.

4

Methanesulfonyl 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 Cheryl Bast (Oak Ridge National Laboratory), Lisa Ingerman (SRC, Inc.), Chemical Manager Roberta Grant (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 concentrations 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

Methanesulfonyl chloride is a pale yellow liquid with an unpleasant odor. It is made commercially either by the chlorination of methyl mercaptan or by the sulfochlorination of methane. It is used as an intermediate in the pharmaceutical, photographic, fiber, dye, and agricultural industries. It is also used as a stabilizer, catalyst, curing agent, and chlorinating agent. Methanesulfonyl chloride causes severe ocular, dermal, and mucous membrane irritation. Chlorine gas and sulfur oxides are produced when it is heated until decomposition.

Data were insufficient to derive AEGL-1 values for methanesulfonyl chloride. Therefore, AEGL-1 values are not recommended.

Appropriate chemical-specific data were not available for deriving AEGL-2 values. In the absence of such data, chemicals with a steep concentration-response curve may be derived by dividing AEGL-3 values by 3 (NRC 2001). A steep concentration-response curve has been demonstrated for methanesulfonyl chloride; mortality in rats exposed to it for 4 h was 10% at 20 ppm and 90% at 28 ppm (Pennwalt Corporation 1987).

A 4-h rat $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) of 15.5 ppm (Pennwalt Corporation 1987) was used as the point of departure for AEGL-3 values. Values were time scaled using the equation $C^n \times t = k$, where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). An empirical value for n was sought by analyzing lethality data in rats exposed for 1-6 h by log probit analysis (see Appendix E). However, the data and modeling results were considered inadequate to define an empirical value of n, but

indicated that time is an important component of the concentration-time relationship for methanesulfonyl chloride. When an empirical value cannot be determined, default values of n = 1 for extrapolation to longer durations and n = 3 for extrapolation to shorter durations may be used to derive AEGL values protective of human health (NRC 2001). However, the log probit analyses suggested that the value of n is most likely around 1, and provided sufficient information to exclude the default value of n = 3 for scaling from longer to shorter durations. Therefore, on the basis of available data and log probit analyses, AEGL values were scaled across time using the equation $C^n \times t = k$, with n = 1. Uncertainty factors of 10 were applied to account for interspecies differences and intraspecies variability (total uncertainty factor of 100), because of the lack of information available to describe species differences in toxicity and interindividual variability. Although clinical signs and pathologic findings from the limited data set suggest contact irritation (partial eye closure, disturbed respiratory patterns, salivation, nose rubbing, blinking, nasal discharge, lacrimation, increased relative lung weight, pulmonary congestion, and corneal surface damage) and this type of portal-of-entry effect is not expected to vary greatly between species, the available data are not sufficient to conclusively describe the mechanism of toxicity. The 30-min AEGL-3 value was adopted as the 10-min value because of the added uncertainty of extrapolating a 4-h point of departure to a 10-min value.

AEGL values for methanesulfonyl chloride are presented in Table 4-1.

1. INTRODUCTION

Methanesulfonyl chloride is a pale yellow liquid with an unpleasant odor. It is made commercially either by the chlorination of methyl mercaptan or by the sulfochlorination of methane. It is used as an intermediate in the pharmaceutical, photographic, fiber, dye, and agricultural industries. It is also used as a stabilizer, catalyst, curing agent, and chlorinating agent. Methanesulfonyl chloride causes severe ocular, skin, and mucous membrane irritation. Chlorine gas and sulfur oxides are produced when methanesulfonyl chloride is heated to decomposition (Shertzer 2001). Methanesulfonyl chloride is shipped in 55 gallon drums; production in 1981 was "probably greater than 2.27×10^6 grams" (HSDB 2007). Chemical and physical data for methanesulfonyl chloride are presented in Table 4-2.

2. HUMAN TOXICITY DATA

Methanesulfonyl chloride is a strong irritant to the skin, eyes, mucous membranes, and respiratory tract and is corrosive. Its odor is described as unpleasant, although no information on an odor threshold was found (Shertzer 2001).

TABLE 4-1 AEGL Values for Methanesulfonyl Chloride

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)[a]	NR	NR	NR	NR	NR	Insufficient data.
AEGL-2 (disabling)	0.40 ppm (1.9 mg/m^3)	0.40 ppm (1.9 mg/m^3)	0.21 ppm (0.98 mg/m^3)	0.053 ppm (0.25 mg/m^3)	0.026 ppm (0.12 mg/m^3)	One third of AEGL-3 values (NRC 2001).
AEGL-3 (lethal)	1.2 ppm (5.6 mg/m^3)	1.2 ppm (5.6 mg/m^3)	0.62 ppm (2.9 mg/m^3)	0.16 ppm (0.75 mg/m^3)	0.078 ppm (0.37 mg/m^3)	4-h $BMCL_{05}$ of 15.5 ppm in rats (Pennwalt Corporation 1987)

Abbreviations: $BMCL_{05}$, benchmark concentration, 95% lower confidence limit with 5% response; NR, not recommended because of insufficient data.
[a]Absence of an AEGL-1 value does not imply that concentrations below the AEGL-2 values are without effect.

TABLE 4-2 Chemical and Physical Data for Methanesulfonyl Chloride

Parameter	Value	References
Synonyms	Chloromethyl sulfone; mesyl chloride; methanesulfonic acid chloride; methyl sulfochloride	HSDB 2007
CAS registry no.	124-63-0	HSDB 2007
Chemical formula	CH_3ClO_2S	HSDB 2007
Molecular weight	114.55	HSDB 2007
Physical state	Pale, yellow liquid	HSDB 2007
Freezing point	-32°C	HSDB 2007
Boiling point	62°C @ 18mmHg	HSDB 2007
Flash point	110°C	Shertzer 2001
Density/specific gravity	1.4805 g/L @ 18°C	HSDB 2007
Solubility in water	Insoluble; hydrolyzes slowly	HSDB 2007
Vapor pressure	3.09 mm Hg @ 25°C	HSDB 2007
Conversion factors	1 ppm = 4.68 mg/m^3 1 mg/m^3 = 0.21 ppm	

3. ANIMAL TOXICITY DATA

3.1. Acute Toxicity

Groups of five male and five female Sprague-Dawley rats were exposed to methanesulfonyl chloride at 0, 20, 28, or 54 ppm (analytic concentrations) for 4 h, followed by a 14-day observation period (Pennwalt Corporation 1987). Whole-body exposure chambers were constructed of Perspex and had an internal volume of 115 L. Test atmospheres were generated by supplying methanesulfonyl chloride from a syringe driven by a syringe pump. The compressed air supply to the generator was dried, filtered, and oil free; flow rate was 25 L/min. Test atmospheres were analyzed five times per exposure by gas chromatography flame ionization detection, and were monitored for the presence of droplets of methanesulfonyl chloride at 1.5 and 3.5 h. The study followed Good Laboratory Practice and the guidelines of Organisation for Economic Cooperation and Development for assessing acute inhalation toxicity (OECD Test 403). Clinical signs observed during exposure in all groups included closing or partial closing of the eyes, wet fur around the mouth, hunched body posture, and disturbed respiratory patterns. Clinical signs during the observation period included lethargy and disturbances of the respiratory pattern. Respiratory effects persisted for several days in rats that survived. Lung-to-body weight ratio was increased in most decedents, and pulmonary congestion and damage to the corneal surface of the eyes were also found. A 4-h LC_{50} (lethal concentration, 50% lethality) value of 25 ± 2.7 ppm, a $BMCL_{05}$ of 15.5 ppm, and BMC_{01} (benchmark concentration with 1% response) of 17.4 ppm were calculated. Mortality data from this study are summarized in Table 4-3.

TABLE 4-3 Mortality in Rats Exposed to Methanesulfonyl Chloride for 4 Hours

	Mortality		
Concentration (ppm)	Males	Females	Combined
0	0/5	0/5	0/10
20	1/5	0/5	1/10
28	4/5	5/5	9/10
54	5/5	5/5	10/10
LC_{50}			25 ppm
BMC_{01}			17.4 ppm
$BMCL_{05}$			15.5 ppm

Source: Pennwalt Corporation 1987.

Groups of five male and five female Sprague-Dawley rats were exposed to methanesulfonyl chloride at 165, 174, or 300 ppm (analytic concentrations) for 1 h, followed by a 14-day observation period (Pennwalt Corporation 1986). Animal were exposed (whole body) in 100-L Plexiglas chambers. Test atmospheres were generated by placing methanesulfonyl chloride into a bubbler fitted with an impinger. A metered, dried air supply was delivered into the bubbler and the resulting vapor laden air stream was introduced into the exposure chamber; flow rate was 25-26 L/min. Concentrations of methanesulfonyl chloride were analyzed twice per exposure. The study followed Good Laboratory Practice and U.S. Department of Transportation guidelines. Clinical signs noted during exposure and within 5-h post-exposure included secretory and pulmonary responses (not otherwise specified) and decreased activity in all groups. Rats in the 300-ppm group had closed eyes and exhibited prostration. Signs of toxicity in this group during the observation period included secretory and pulmonary responses and generally poor condition until death on the afternoon following exposure. Survivors in the 165- and 174-ppm groups showed secretory and pulmonary effects through days 4-5; these signs were noted sporadically thereafter. Corneal irregularities and opacities were found in three of nine rats in the 165-ppm group and all eight rats in the 174-ppm group at the end of the observation period. An LC_{50} value could not be calculated from the data; however, the investigators stated that the 1-h LC_{50} is most likely in the range of 175 to 250 ppm. Mortality data from this study are summarized in Table 4-4.

Groups of three rats were exposed to nominal concentrations of methanesulfonyl chloride at 2,145 ppm for up to 45 min, 29 ppm for 6 h, or 132 ppm for 6 h, followed by a 14-day observation period (TerHaar 1978). Chamber temperatures were 24-26°C. No further experimental details were provided. Methanesulfonyl chloride was described as a severe tissue irritant, capable of causing necrosis on any tissue it contacts. Results and observations of this study are presented in Table 4-5.

Oral LD_{50} values for methanesulfonyl chloride of approximately 175 mg/kg and 200 mg/kg were determined for rats and mice, respectively (TerHaar 1978). Deaths occurred immediately after dosing, except for two mice that survived a dose near the LD_{50}. Hematuria developed in surviving rats. No additional details were presented.

TABLE 4-4 Mortality in Rats Exposed to Methanesulfonyl Chloride for 1 Hour

	Mortality		
Concentration (ppm)	Males	Females	Combined
165	1/5	0/5	1/10
174	1/5	1/5	2/10
300	5/5	5/5	10/10

Source: Pennwalt Corporation 1986.

TABLE 4-5 Mortality and Clinical Signs in Rats Exposed to Methanesulfonyl Chloride

Concentration (ppm)	Duration	Mortality	Time to Death	Clinical Signs (when first observed)
2,145	45 min	3/3	1 dead in 30 min 1 dead in 40 min 1 dead in 45 min	Blinking and nose rubbing (1 min), salivation (4 min), dyspnea and piloerection (5 min), lacrimation and clear nasal discharge (10 min).
29	6 h	0/3	—	Blinking (1 min), nose rubbing (2 min), piloerection (5 min), vasodilation (15 min).
132	6 h	3/3	2 dead in 20-h post-exposure 1 dead in 3-d post-exposure	Blinking and nose rubbing (1 min), dyspnea and piloerection (10 min), clear nasal discharge (15 min), lacrimation and salivation (25 min), wheezing (265 min).

Source: TerHaar 1978.

3.2. Developmental and Reproductive Toxicity

No data on the developmental and reproductive toxicity of methanesulfonyl chloride were available.

3.3. Genotoxicity

In the presence of exogenous metabolic activation (S9 mix), methanesulfonyl chloride induced chromosome aberrations in vitro in Chinese hamster ovary (CHO) cells (Sipi et al. 1997). Without metabolic activation, no response was observed.

3.4. Chronic Toxicity and Carcinogenicity

No data on the chronic toxicity or carcinogenicity of methanesulfonyl chloride were available.

3.5. Summary

Animal toxicity data are limited. Clinical signs, including ocular and nasal irritation, respiratory difficulty, nasal discharge, wheezing, and corneal opacities, are consistent with severe irritation. Methanesulfonyl chloride induced chromosome aberrations in CHO cells only in the presence of metabolic activation. No data on the developmental, reproductive, chronic, or carcinogenic effects of methanesulfonyl chloride were available.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No information was available on the metabolism and disposition of methanesulfonyl chloride.

4.2. Mechanism of Toxicity

No information was available on the mechanism of toxicity of methanesulfonyl chloride.

4.3. Structure-Activity Relationships

Methanesulfonyl chloride (CH_3ClO_2S) is structurally similar to thionyl chloride (Cl_2OS) and sulfuryl chloride (Cl_2O_2S). However, thionyl chloride and sulfuryl chloride readily hydrolyze to SO_2 and HCl whereas methanesulfonyl chloride hydrolyzes very slowly. The health effects of these three compounds are similar but their mechanism of toxicity is likely different. Although data are limited, it appears that the effects of thionyl chloride and sulfuryl chloride result from their hydrolysis products rather than from exposure to the parent compounds; in contrast, because methanesulfonyl chloride is hydrolyzed very slowly, the effects likely result from exposure to the parent compound (EPA 2006; NRC 2011).

4.4. Other Relevant Information

4.4.1. Species Variability

No information on species variability from inhalation exposure to methanesulfonyl chloride was available. However, clinical signs are consistent with contact irritation. Therefore, effects are not expected to vary widely between species. The limited data suggest no difference in acute oral lethality between rats and mice (TerHaar 1978).

4.4.2. Susceptible Populations

No information on populations especially sensitive to methanesulfonyl chloride toxicity was available. However, clinical signs are consistent with contact irritation. Therefore, effects are not expected to vary widely among individuals.

4.4.3. Time Scaling

AEGL values were scaled using the equation $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). An empirical value for n was sought by analyzing lethality data in rats exposed for 1-6 h. Log probit analysis of the data (see Appendix E) yielded a point estimate of n = 0.7, with lower and upper bounds of 0.3 and 1.1, respectively; however, the p value of the chi-square goodness-of fit-test indicated a poor fit of the model to the data. Additional log probit analysis without the 6-h data (the two data points were associated with 0% and 100% mortality, so added little useful information to the analysis) yielded an estimate of n = 0.66, with upper and lower confidence limits of 0.61 and 0.71, respectively. For the reduced data set, which only included two durations (1 and 4 h), the p-value of the chi-square goodness-of-fit test was 1.0, indicating an exact fit to the data. Overall, the data and modeling results were considered inadequate to define an empirical value of n, but indicated that time is an important component of the concentration-time relationship for methanesulfonyl chloride. When an empirical value cannot be determined, default values of n = 1 for extrapolation to longer durations and n = 3 for extrapolation to shorter durations may be used to derive AEGL values protective of human health (NRC 2001). However, the log probit analyses suggested that the value of n is most likely around 1, and provided sufficient information to exclude the default value of n = 3 for scaling from longer to shorter durations. Therefore, on the basis of available data and log probit analyses, AEGL values were scaled across time using the equation $C^n \times t = k$, with n = 1.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No human data relevant to development of AEGL-1 values for methanesulfonyl chloride were available.

5.2. Animal Data Relevant to AEGL-1

No animal data relevant to development of AEGL-1 values for methanesulfonyl chloride were available.

5.3. Derivation of AEGL-1 Values

No human or animal data were available for derivation of AEGL-1 values for methanesulfonyl chloride. Therefore, no AEGL-1 values are recommended.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data relevant to development of AEGL-2 values for methanesulfonyl chloride were available.

6.2. Animal Data Relevant to AEGL-2

No animal data relevant to development of AEGL-2 values for methanesulfonyl chloride were available.

6.3. Derivation of AEGL-2 Values

Appropriate chemical-specific data for deriving AEGL-2 values were not available. In the absence of such data, chemicals with a steep concentration-response curve may be derived by dividing AEGL-3 values by 3 (NRC 2001). A steep concentration-response curve has been demonstrated for methanesulfonyl chloride; mortality in rats exposed to it for 4 h was 10% at 20 ppm and 90% at 28 ppm (Pennwalt Corporation 1987). AEGL-2 values are presented in Table 4-6, and calculations are presented in Appendix A.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data relevant to development of AEGL-3 values for methanesulfonyl chloride were available.

7.2. Animal Data Relevant to AEGL-3

A 4-h $BMCL_{05}$ of 15.5 ppm and $BMC_{01}$of 17.4 ppm (Pennwalt Corporation 1987) was calculated from a well-conducted acute inhalation study with rats (see Appendix D). A 1-h rat study was also available (Pennwalt Corporation 1986); however, the data did not allow for the calculation of an LC_{50} value, although the investigators stated that the 1-h LC_{50} is most likely in the range of 175 to 250 ppm. Ocular and nasal irritation, piloerection, and vasodilation were observed within the first 15 min of exposure in rats exposed to methanesulfonyl chloride at 29 ppm for 6 h, but no deaths occurred (TerHaar 1978).

7.3. Derivation of AEGL-3 Values

The 4-h rat $BMCL_{05}$ of 15.5 ppm (Pennwalt Corporation 1987) was used as the point of departure for calculating AEGL-3 values. Values were scaled

across time using the equation $C^n \times t = k$, with n = 1, on the basis of the time-scaling analysis in Section 4.4.3. The 30-min AEGL-3 value was adopted as the 10-min value because of the uncertainty of extrapolating a 4-h point of departure to a 10-min value. Uncertainty factors of 10 were applied to account for inter-species differences and intraspecies variability (total uncertainty factor of 100), because of the lack of information available to describe species differences in toxicity and interindividual variability. Although clinical signs and pathologic finding from the limited data set suggest contact irritation (partial eye closure, disturbed respiratory patterns, salivation, nose rubbing, blinking, nasal discharge, lacrimation, increased relative lung weight, pulmonary congestion, and corneal surface damage) and this type of portal-of-entry effect is not expected to vary greatly between species, the available data are not sufficient to conclusively describe the mechanism of toxicity. AEGL-3 values for methanesulfonyl chloride are presented in Table 4-7, and calculations are presented in Appendix A.

AEGL-3 values are considered adequately protective. If the study by TerHaar (1978) is used to calculate values, a point of departure of 29 ppm for a 6-h exposure would be chosen on the basis of no mortality, although severe irritation was present. Time scaling and applying the uncertainty factors described above yields higher AEGL-3 values of 3.5 ppm for the 10-min and 30-min durations, 1.7 ppm for 1 h, 0.44 ppm for 4 h, and 0.22 ppm for 8 h.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

AEGL values for methanesulfonyl chloride are presented in Table 4-8. AEGL-1 values are not recommended because of insufficient data. AEGL-2 values were derived by taking one-third of the AEGL-3 values, and AEGL-3 values were based on a 4-h rat $BMCL_{05}$ value (Pennwalt Corporation 1987).

TABLE 4-6 AEGL-2 Values for Methanesulfonyl Chloride

10 min	30 min	1 h	4 h	8 h
0.40 ppm (1.9 mg/m^3)	0.40 ppm (1.9 mg/m^3)	0.21 ppm (0.98 mg/m^3)	0.053 ppm (0.25 mg/m^3)	0.026 ppm (0.12 mg/m^3)

TABLE 4-7 AEGL-3 Values for Methanesulfonyl Chloride

10 min	30 min	1 h	4 h	8 h
1.2 ppm (5.6 mg/m^3)	1.2 ppm (5.6 mg/m^3)	0.62 ppm (2.9 mg/m^3)	0.16 ppm (0.75 mg/m^3)	0.078 ppm (0.37 mg/m^3)

TABLE 4-8 AEGL Values for Methanesulfonyl Chloride

	Exposure Duration				
Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)[a]	NR	NR	NR	NR	NR
AEGL-2 (disabling)	0.40 ppm (1.9 mg/m^3)	0.40 ppm (1.9 mg/m^3)	0.21 ppm (0.98 mg/m^3)	0.053 ppm (0.25 mg/m^3)	0.026 ppm (0.12 mg/m^3)
AEGL-3 (lethal)	1.2 ppm (5.6 mg/m^3)	1.2 ppm (5.6 mg/m^3)	0.62 ppm (2.9 mg/m^3)	0.16 ppm (0.75 mg/m^3)	0.078 ppm (0.37 mg/m^3)

Abbreviations: NR, not recommended because of insufficient data.
[a]Absence of an AEGL-1 value does not imply that concentrations below the AEGL-2 values are without effect.

8.2. Comparison with Other Standards and Guidelines

There are no other standards or guidelines for methanesulfonyl chloride.

8.3. Data Adequacy and Research Needs

There are no human data on methanesulfonyl chloride, and animal data are limited. Additional acute inhalation toxicity studies in other species would be helpful.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR METHANESULFONYL CHLORIDE

Derivation of AEGL-1 Values

Data are insufficient to derive AEGL-1 values for methanesulfonyl chloride. Therefore, AEGL-1 values are not recommended.

Derivation of AEGL-2 Values

AEGL-2 values were derived by taking one-third of the respective AEGL-3 values, because there inadequate data to derive AEGL-2 values. This approach is justified by the steep concentration-response for this chemical (NRC 2001).

10-min AEGL-2: 1.2 ppm ÷ 3 = 0.40 ppm

30-min AEGL-2: 1.2 ppm ÷ 3 = 0.40 ppm

1-h AEGL-2: 0.62 ppm ÷ 3 = 0.21 ppm

4-h AEGL-2: 0.16 ppm ÷ 3 = 0.053 ppm

8-h AEGL-2: 0.078 ppm ÷ 3 = 0.026 ppm

Derivation of AEGL-3 Values

Key study: Pennwalt Corporation. 1987. Methanesulfonyl Chloride, Acute Inhalation Toxicity in Rats, 4-Hour Exposure. Report No. PWT 45/861670. Huntingdon Research Centre. February 23, 1987 (as cited in Arkema 2007).

Toxicity end point: 4-h rat $BMCL_{05}$ of 15.5 ppm

Time scaling: AEGL values were scaled using the equation $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). An empirical value for n was sought by analyzing lethality data in rats exposed for 1-6 h. Log probit analysis yielded a point estimate of n = 0.7, with lower and upper bounds of 0.3 and 1.1, respectively; however, the p value of the chi-square

	goodness-of-fit test indicated a poor fit of the model to the data. Additional log probit analysis without the 6-h data (the two data points were associated with 0% and 100% mortality, so added little useful information to the analysis) yielded an estimate of n = 0.66, with upper and lower confidence limits of 0.61 and 0.71, respectively. For the reduced data set, which only included two durations (1 and 4 h), the p-value of the chi-square goodness-of-fit test was 1.0, indicating an exact fit to the data. Overall, the data and modeling results were considered inadequate to define an empirical value of n, but indicated that time is an important component of the concentration-time relationship for methanesulfonyl chloride. When an empirical value cannot be determined, default values of n = 1 for extrapolation to longer durations and n = 3 for extrapolation to shorter durations may be used to derive AEGL values protective of human health (NRC 2001). However, the log probit analyses suggested that the value of n is most likely around 1, and provided sufficient information to exclude the default value of n = 3 for scaling from longer to shorter durations. Therefore, on the basis of available data and log probit analyses, AEGL values were scaled across time using the equation $C^n \times t = k$, with n = 1. $(15.5 \text{ ppm})^1 \times 4 \text{ h} = 62 \text{ ppm-h}$
Uncertainty factors:	10 for interspecies differences 10 for intraspecies variability Total uncertainty factor of 100
10-min AEGL-3:	Set equal to the 30-min value of 1.2 ppm
30-min AEGL-3:	$C^1 \times 0.5 \text{ h} = 62 \text{ ppm-h}$ C = 124 ppm 124 ppm ÷ 100 = 1.2 ppm
1-h AEGL-3:	$C^1 \times 1 \text{ h} = 62 \text{ ppm-h}$ C = 62 ppm 62 ppm ÷ 100 = 0.62 ppm
4-h AEGL-3:	C = 15.5 ppm 15.5 ppm ÷ 100 = 0.16 ppm

8-h AEGL-3: $C^1 \times 8\ h = 62\ ppm\text{-}h$
$C = 7.75\ ppm$
$7.75\ ppm \div 100 = 0.078\ ppm$

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR METHANESULFONYL CHLORIDE

Derivation Summary

AEGL-1 VALUES

Data were insufficient for deriving AEGL-1 values for methanesulfonyl chloride. Therefore, AEGL-1 values are not recommended for this chemical.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.40 ppm (1.9 mg/m^3)	0.40 ppm (1.9 mg/m^3)	0.21 ppm (0.98 mg/m^3)	0.053 ppm (0.25 mg/m^3)	0.026 ppm (0.12 mg/m^3)

Data adequacy: Sparse data set for methanesulfonyl chloride. For chemicals with a steep concentration-response curve, AEGL-3 values may be divided by 3 to estimate AEGL-2 values (NRC 2001). A steep concentration-response curve has been demonstrated for methanesulfonyl chloride; mortality in rats exposed to it for 4 h was 10% at 20 ppm and 90% at 28 ppm.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
1.2 ppm (5.6 mg/m^3)	1.2 ppm (5.6 mg/m^3)	0.62 ppm (2.9 mg/m^3)	0.16 ppm (0.75 mg/m^3)	0.078 ppm (0.37 mg/m^3)

Key reference: Pennwalt Corporation. 1987. Methanesulfonyl Chloride, Acute Inhalation Toxicity in Rats, 4-Hour Exposure. Report No. PWT 45/861670. Huntingdon Research Centre. February 23, 1987 (cited in Arkema 2007).

Test species/Strain/Number: Rat, strain not specified, 10/sex/concentration

Exposure route/Concentrations/Durations: Inhalation; 20, 28, and 54 ppm for 4 h

Effects: Clinical signs of irritation in all test groups.

Concentration (ppm)	Mortality
0	0/10
20	1/10
28	9/10
54	10/10
LC_{50}	25 ppm
BMC_{01}	17.4 ppm
$BMCL_{05}$	15.5 ppm

(Continued)

AEGL-3 VALUES Continued

End point/Concentration/Rationale: 4-h $BMCL_{05}$ of 15.5 ppm (see Appendix D), considered threshold for lethality.

Uncertainty factors/Rationale: No information available to describe species differences in toxicity or interindividual variability. Although clinical signs and pathologic findings from the limited data set suggest contact irritation and this type of portal-of-entry effect is not expected to vary greatly between species, the available data are not sufficient to conclusively describe the mechanism of toxicity.
Total uncertainty factor: 100
Interspecies: 10
Intraspecies: 10

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: AEGL-3 values were scaled using the equation $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). An empirical value for n was sought by analyzing lethality data in rats exposed for 1-6 h. Log probit analysis yielded a point estimate of n = 0.7, with lower and upper bounds of 0.3 and 1.1, respectively; however, the p value of the chi-square goodness-of-fit test indicated a poor fit of the model to the data. Additional log probit analysis without the 6-h data (the two data points were associated with 0% and 100% mortality, so added little useful information to the analysis) yielded an estimate of n = 0.66, with upper and lower confidence limits of 0.61 and 0.71, respectively. For the reduced data set, which only included two durations (1 and 4 h), the p-value of the chi-square goodness-of-fit test was 1.0, indicating an exact fit to the data. Overall, the data and modeling results were considered inadequate to define an empirical value of n, but indicated that time is an important component of the concentration-time relationship for methanesulfonyl chloride. When an empirical value cannot be determined, default values of n = 1 for extrapolation to longer durations and n = 3 for extrapolation to shorter durations may be used to derive AEGL values protective of human health (NRC 2001). However, the log probit analyses suggested that the value of n is most likely around 1, and provided sufficient information to exclude the default value of n = 3 for scaling from longer to shorter durations. Therefore, on the basis of available data and log probit analyses, AEGL values were scaled across time using the equation $C^n \times t = k$, with n = 1. The 30-min AEGL-3 value was adopted as the 10-min value because of the uncertainty associated with extrapolating a 4-h point of departure to a 10-min value.

Data adequacy: Sparse data set. AEGL-3 values are considered protective. If the study by TerHaar (1978) is used to calculate values, a point of departure of 29 ppm for a 6-h exposure would be chosen on the basis of no mortality, although severe irritation was present. Time scaling and applying the uncertainty factors described above yields higher AEGL values of 3.5 ppm for the 10- and 30-min durations, 1.7 ppm for 1h, 0.44 ppm for 4 h, and 0.22 ppm for 8 h.

APPENDIX C

CATEGORY PLOT FOR METHANESULFONYL CHLORIDE

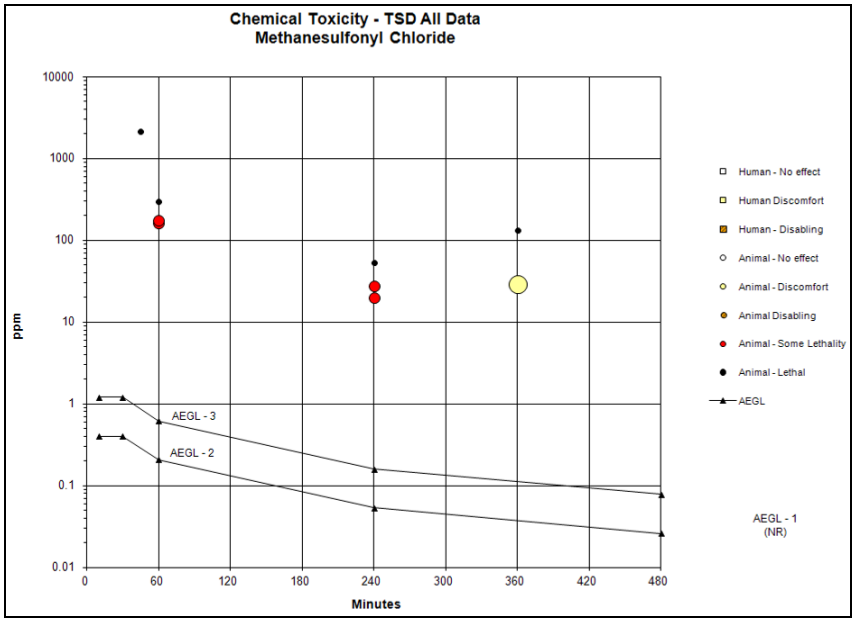

FIGURE C-1 Category plot of animal data and AEGL values for methanesulfonyl chloride.

TABLE C-1 Data Used in the Category Plot for Methanesulfonyl Chloride

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
NAC/AEGL-1				NR	10	AEGL	
NAC/AEGL-1				NR	30	AEGL	
NAC/AEGL-1				NR	60	AEGL	
NAC/AEGL-1				NR	240	AEGL	
NAC/AEGL-1				NR	480	AEGL	
NAC/AEGL-2				0.40	10	AEGL	
NAC/AEGL-2				0.40	30	AEGL	
NAC/AEGL-2				0.21	60	AEGL	
NAC/AEGL-2				0.053	240	AEGL	
NAC/AEGL-2				0.026	480	AEGL	

(Continued)

TABLE C-1 Continued

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
NAC/AEGL-3				1.2	10	AEGL	
NAC/AEGL-3				1.2	30	AEGL	
NAC/AEGL-3				0.62	60	AEGL	
NAC/AEGL-3				0.16	240	AEGL	
NAC/AEGL-3				0.078	480	AEGL	
Pennwalt Corporation 1987	Rat	Both	1	20	240	SL	Mortality (1/10); clinical signs, pulmonary function changes for several days; relative lung weight increase in decedents; damage to corneal surface of eyes
	Rat	Both	1	28	240	SL	Mortality (9/10)
	Rat	Both	1	54	240	3	Mortality (10/10)
Pennwalt Corporation 1986	Rat	Both	1	165	60	SL	Mortality (1/10); secretory and pulmonary effects through days 4-5; corneal irregularities (3/9 survivors)
	Rat	Both	1	174	60	SL	Mortality (2/10); secretory and pulmonary effects through days 4-5; corneal irregularities (8/8 survivors)
	Rat	Both	1	300	60	3	Mortality (10/10);
TerHaar 1978	Rat		1	2,145	45	3	Mortality (3/3)
	Rat		1	29	360	1	Blinking, nose rubbing, piloerection, vasodilation (3 exposed rats)
	Rat		1	132	360	3	Mortality (3/3)

For category: 0 = no effect, 1 = discomfort, 2 = disabling, 3 = lethal; SL = some lethality.

APPENDIX D

BENCHMARK DOSE CALCULATIONS FOR METHANESULFONYL CHLORIDE

Probit Model (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\UNSAVED1.(d)
Gnuplot Plotting File: C:\BMDS\UNSAVED1.plt
Wed Jul 11 10:33:08 2007

BMDS MODEL RUN - 4-hour study

The form of the probability function is:

P[response] = Background
+ (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),

where CumNorm(.) is the cumulative normal distribution function

Dependent variable = COLUMN3
Independent variable = COLUMN1
Slope parameter is not restricted

Total number of observations = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
Background = 0
Intercept = -8.60752
Slope = 2.6668

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Intercept
Background	1	-1
Intercept	-1	1

(***The model parameter(s) -background have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix)

Analysis of Deviance Table

Model	Log (likelihood)	No. Parameters	Deviance Test	DF	P-value
Full model	-6.50166	4			
Fitted model	-6.50166	2	3.41848e-009	2	1
Reduced model	-27.7259	1	42.4485	3	<0.0001

AIC: 17.0033

Parameter Estimates

Variable	Estimate	Standard Error	95.0% Wald Confidence Interval	
			Lower Confidence Limit	Upper Confidence Limit
Background	0	NA		
Intercept	-24.1018	7.1988	-38.2112	-9.99242
Slope	7.61759	2.27204	3.16448	12.0707

NA: indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Goodness of Fit

		Scaled			
Dose	Estimated Probability	Expected	Observed	Size	Residual
0.0000	0.0000	0.000	0	10	0.000
20.0000	0.1000	1.000	1	10	-0.000
28.0000	0.9000	9.000	9	10	-0.000
54.0000	1.0000	10.000	10	10	0.000

Chi-square = 0.00; DF = 2; P-value = 1.0000

Benchmark Dose Computation
Specified effect = 0.05

Risk Type = Extra risk
Confidence level = 0.95
BMD = 19.0685
BMDL = 15.5113

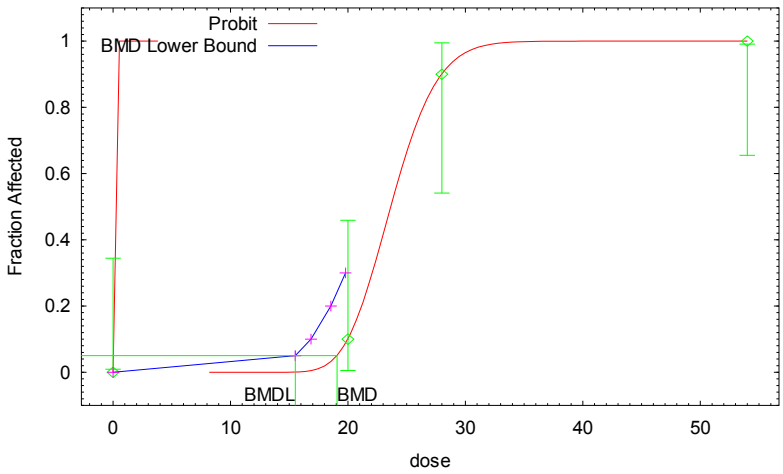

FIGURE B-1 Probit model with 0.95 confidence level.

APPENDIX E

CALCULATION OF THE TIME-SCALING EXPONENT 'n'

Log Probit Analysis of Full Dataset:

Filename: Methanesulfonyl chloride time scaling
Date: 09 February 2012 Time: 16:05:18

Sequence No.	Concentration (ppm)	Minutes	Exposed	Responded
1	165	60	10	1
2	174	60	10	2
3	300	60	10	10
4	20	240	10	1
5	28	240	10	9
6	54	240	10	10
7	29	360	3	0
8	132	360	3	3

Used Probit Equation Y = B0 + B1*X1 + B2*X2
X1 = conc mg/m^3, ln-transformed
X2 = minutes, ln-transformed

Chi-square = 48.83
Degrees of freedom = 5
Probability Model = 2.40E-09

Ln(Likelihood) = -20.30

B 0 = -2.3058E+01 Student t = -1.1494
B 1 = 2.5164E+00 Student t = 1.3933
B 2 = 3.5681E+00 Student t = 1.3718

Variance B 0 0 = 4.0242E+02
Covariance B 0 1 = -3.5556E+01
Covariance B 0 2 = -5.1770E+01
Variance B 1 1 = 3.2617E+00
Covariance B 1 2 = 4.4695E+00
Variance B 2 2 = 6.7650E+00

Estimation ratio between regression coefficients of ln(conc) and ln(minutes)
Point estimate = 0.705
Lower limit (95% CL) = 0.296
Upper limit (95% CL) = 1.114

Log Probit Analysis of Reduced Dataset:

Filename: Methanesulfonyl chloride time scaling
Date: 09 February 2012 Time: 16:07:06

Sequence No.	Concentration (ppm)	Minutes	Exposed	Responded
1	165	60	10	1
2	174	60	10	2
3	300	60	10	10
4	20	240	10	1
5	28	240	10	9
6	54	240	10	10

Used Probit Equation Y = B0 + B1*X1 + B2*X2
X1 = conc mg/m^3, ln-transformed
X2 = minutes, ln-transformed

Chi-square = 0.01
Degrees of freedom = 3
Probability Model = 1.00E+00

Ln(Likelihood) = -4.05

B 0 = -8.3259E+01 Student t = -3.5083
B 1 = 7.6810E+00 Student t = 3.5633
B 2 = 1.1669E+01 Student t = 3.7691

Variance B 0 0 = 5.6320E+02
Covariance B 0 1 = -5.1013E+01
Covariance B 0 2 = -7.3391E+01
Variance B 1 1 = 4.6466E+00
Covariance B 1 2 = 6.6254E+00
Variance B 2 2 = 9.5856E+00

Estimation ratio between regression coefficients of ln(conc) and ln(minutes)
Point estimate = 0.658
Lower limit (95% CL) = 0.611
Upper limit (95% CL) = 0.705

5

Nitric Acid[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 (SRC, Inc.), Chemical Managers Loren Koller and George Woodall (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 concentrations 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

Nitric acid is a highly corrosive, strongly oxidizing acid. Nitric acid may exist in the air as a gas, vapor, mist, fume, or aerosol. Nitric acid mist will probably be scrubbed in the mouth or nasal passages, gas and vapor in the upper respiratory tract, and fume and aerosol in the alveolar region of the lungs. Toxicity after inhalation exposure to nitric acid is similar in humans and animals. Nitric acid fumes may cause immediate irritation of the respiratory tract, pain, and dyspnea, followed by a period of recovery that may last several weeks. A relapse may occur resulting in death caused by bronchopneumonia and pulmonary fibrosis. At nonlethal concentrations, allergic or asthmatic individuals appear to be sensitive to acidic atmospheres (NIOSH 1976a; ACGIH 1991).

Both human and animal data were used to derive AEGL values. The point of departure for AEGL-1 values was selected on the basis of a study in which five healthy volunteers were exposed to nitric acid at 1.6 ppm for 10 min and had no changes in pulmonary function (vital capacity, respiratory resistance, and forced expiratory volume [FEV_1]) (Sackner and Ford 1981). That was the highest no-effect level available in humans. An uncertainty factor of 10 was applied to account for variability in the general population and possibly greater sensitivity of asthmatics to effects of a direct-acting irritant on pulmonary function. The 10-min AEGL value of 0.16 ppm was adopted for all the other AEGL durations, because the point of departure was a no-effect level for pulmonary irritation and

such irritation is generally concentration dependent but not time dependent. AEGL-1 values are higher than the odor threshold for nitric acid, which provides a warning about exposure before an individual could experience notable discomfort.

AEGL-2 and AEGL-3 values were based on a well-conducted, lethality study in rats (DuPont 1987). Groups of five male and five female Crl:CD®BR rats were exposed nose-only to nitric acid aerosol at 260-3,100 ppm for 1 h, and were observed for 14 days. Rats exposed at 470 ppm exhibited transient body weight loss 1-2 days post-exposure. At the next higher concentration, partially closed eyes (a possible sign of severe ocular irritation), which could definitely impair escape, and lung noise were reported. Thus, 470 ppm was used as the point of departure for deriving AEGL-2 values, because it is a no-effect level for impaired ability to escape. Time scaling to the 10- and 30-min and 4- and 8-h AEGL durations was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986). Because an empirical value for n could not be derived from the data, scaling was performed using default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolation to longer durations. A total uncertainty factor of 10 was applied: a factor of 3 to account for interspecies differences and another factor of 3 for intraspecies variability. Larger uncertainty factors were considered unnecessary because the mechanism of action for a direct ocular irritant and for a corrosive acid in the lung is not expected to differ greatly between species or among individuals. In addition, a modifying factor of 2 was applied because clinical observations were not well described, and AEGL-2 and AEGL-3 values overlap, suggesting a very steep concentration-response relationship.

AEGL-3 values were based on an LC_{01} (lethal concentration, 50% lethality) of 919 ppm, calculated by log-probit analysis of lethality data in rats (DuPont 1987). Time scaling was performed as was done for the AEGL-2 values, and the same uncertainty factors were applied.

AEGL values for nitric acid are presented in Table 5-1. If nitrogen dioxide is of concern, AEGL values for that chemical are available (see NRC 2012).

1. INTRODUCTION

Nitric acid is a corrosive, inorganic acid. Commercial formulations of the compound contain approximately 56-68% nitric acid. Exposure to light causes the formation of nitrogen dioxide, which gives the liquid a yellow color. Concentrated nitric acid containing dissolved nitrogen dioxide is termed fuming nitric acid, which evolves suffocating, poisonous fumes of nitrogen dioxide and nitrogen tetroxide (O'Neil et al. 2006). White fuming nitric acid contains 0.5% dissolved nitrogen dixoide while red fuming nitric acid contains 14% dissolved nitrogen dioxide (ACGIH 1991).

Inhalation of nitric acid involves exposure to nitric acid as well as nitrogen oxides, such a nitrogen dioxide and nitric oxide. Fuming nitric acid reacts with wood or metals and emits fumes of nitrogen dioxide, which form equimolar amounts of nitrous and nitric acid when in contact with steam (NIOSH 1976a;

O'Neil et al. 2006). Nitrogen oxide reacts quantitatively with oxygen in air to form nitrogen dioxide, which then reacts with water to form nitric acid. Most reports of human occupational exposure are limited to measurements of nitrogen oxides (NIOSH 1976a). If other oxides of nitrogen are of concern, NRC (2012) should be consulted for relevant AEGL values for nitrogen dioxide, nitric oxide, and nitrogen tetroxide.

Production of nitric acid atmospheres for inhalation exposure experiments potentially results in a variety of physical states (gas, fume, and vapor) depending on the production method used. For each study described in this chapter, the physical state and atmosphere-generation methods are presented as described by the study authors.

Nitric acid is used to dissolve noble metals, for etching and cleaning metals, to make nitrates and nitro compounds found in explosives, and, primarily, to make ammonium nitrate fertilizer (ACGIH 1991). Nitric acid contributes to acid deposition (or acid rain). It is a large contributor to acid deposition in the western United States compared with the eastern states (NARSTO 2004). Selected chemical and physical properties of nitric acid are presented in Table 5-2.

TABLE 5-1 AEGL Values for Nitric Acid

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	No-effect level for notable discomfort in humans (changes in pulmonary function: vital capacity, respiratory resistance, and FEV_1) (Sackner and Ford 1981).
AEGL-2 (disabling)	43 ppm (110 mg/m^3)	30 ppm (77 mg/m^3)	24 ppm (62 mg/m^3)	6.0 ppm (15 mg/m^3)	3.0 ppm (7.7 mg/m^3)	No-effect level for inability to escape; eye closure in rats exposed at 470 ppm for 1 h (DuPont 1987).
AEGL-3 (lethal)	170 ppm (440 mg/m^3)	120 ppm (310 mg/m^3)	92 ppm (240 mg/m^3)	23 ppm (59 mg/m^3)	11 ppm (28 mg/m^3)	No-effect level for lethality (estimated LC_{01}, 919 ppm) in rats (DuPont 1987).

Abbreviations: FEV_1, forced expiratory volume; LC_{01}, lethal concentration, 50% lethality).

TABLE 5-2 Chemical and Physical Data for Nitric Acid

Parameter	Value	Reference
Common name	Nitric acid	
Synonyms	Aqua fortis, azotic acid	O'Neil et al. 2006
CAS registry no.	7697-37-2	
Chemical formula	HNO_3	O'Neil et al. 2006
Molecular weight	63.01	O'Neil et al. 2006
Physical state	Colorless liquid; fumes in moist air	O'Neil et al. 2006
Melting point	-41.59°C	O'Neil et al. 2006
Boiling point	83°C	HSDB 2012
Density/specific gravity	1.51269	O'Neil et al. 2006
Vapor density (air = 1)	2-3 (estimated)	HSDB 2012
Solubility in water	Freely soluble	EPA 1993
Vapor pressure	47.9 mm Hg at 20°C	ACGIH 1991
Flammability	Noncombustible	HSDB 2012
pH (0.5% in saline)	1.6	Coalson and Collins 1985
Conversion factors in air	1 mg/m^3 = 0.388 ppm 1 ppm = 2.58 mg/m^3	EPA 1993

2. HUMAN TOXICITY DATA

Nitric acid may exist in the following airborne forms: gas, vapor, mist, fume, and aerosol. Nitric acid mist will probably be scrubbed in the mouth or nasal passages, gas and vapor in the upper respiratory tract, and fume and aerosol in the alveolar region of the lungs. For each study description below, the physical state and atmosphere-generation methods are presented as described by the study authors.

2.1. Acute Lethality

Hall and Cooper (1905) described case reports of firemen exposed to nitric acid fumes. Approximately 10 gallons of a 38% nitric acid solution were spilled and came in contact with zinc. Sawdust used to absorb the spill rapidly oxidized and burst into flame. Therefore, firemen were exposed to a mixture of nitric acid fumes and reaction products (e.g., nitrogen monoxide), which may have contributed to clinical outcomes observed. Of the 20 individuals exposed to the fumes, dyspnea was present in 100%, cough in 93%, pain in the sides, stomach, lungs,

throat, loins, and head was present in 87%, dizziness and nausea in 73%, and vomiting in 53%. Relapse of these symptoms occurred in 33% of the cases generally 3 weeks after exposure and persisted an average of 15.5 days. Four individuals died, two on the second day after exposure and two several weeks later after relapse. The two who died after relapse appeared to be recovering as well as the other survivors, however, both were exposed to cold air and almost immediately relapsed. Autopsy revealed hemorrhagic edema and coagulation necrosis. Exposure concentrations were not measured but the investigators concluded that the severity of the initial exposure was the most important factor in determining recovery or death (Hall and Cooper 1905).

Three men died of rapidly progressive pulmonary edema after inhalation of fumes from an explosion of nitric acid (Hajela et al. 1990). The men entered the area with the heaviest concentration of fumes and dust following an explosion of a tank containing approximately 1,736 L of 68% nitric acid. Escape from the building took 10-15 min. No respiratory problems were apparent during medical examination immediately after exposure; however, increasing respiratory difficulties developed 4-6 h later. On admission to the hospital, all subjects were cyanotic and had frothy fluid escaping from the nose and mouth. All died within 21 h after the accident. Pathologic evaluation of the lungs revealed degranulated and necrotic neutrophils within the alveolar capillaries. Concentrations of nitric acid or its oxides were not determined at the site of the accident.

A man cleaned a copper chandelier with a 60% nitric acid solution by placing the chemical and chandelier in a bowl. Exposure was very likely to nitrogen monoxide (a reaction product of nitric acid with silver and other metals) or a mixture of the monoxide and nitric acid. The first symptoms of respiratory distress occurred 30 min later; approximately 1 h later he entered a hospital emergency room with dyspnea, expiratory stridor, peripheral cyanosis, and general paleness. Chest X-ray showed pulmonary edema. The patient stabilized for 3 days after intense treatment and lung function improved. However, the patient died from refractory respiratory failure on the fourth day, and pulmonary edema was observed at autopsy (Bur et al. 1997).

Other lethal exposure scenarios have been summarized by others (see NIOSH 1976a; ACGIH 1991). Nitric acid fumes may cause immediate irritation of the respiratory tract, pain, and dyspnea, which are followed by a period of recovery that may last several weeks. Relapse may occur, with death caused by bronchopneumonia or pulmonary fibrosis. Nitric acid concentrations were not provided in the primary reports.

2.2. Nonlethal Toxicity

Nitric acid is described as having a characteristic choking odor (O'Neil et al. 2006). Low and high odor thresholds were reported as 0.29 and 0.97 ppm, respectively (EPA 1993).

2.2.1. Case Reports

A 42-year old man with no history of respiratory disease was exposed for 3 h to fumes from a leaking nitric acid drum (air concentrations not measured). Twelve hours post-exposure he presented with dry cough and acute dyspnea and was admitted to a hospital. Chest X-rays showed opacities compatible with pulmonary edema; he was treated with oxygen and high doses of corticosteroids. After 3 months his chest X-ray was clear and lung function tests were normal (Myint and Lee 1983).

2.2.2. Epidemiologic Studies

Ostro et al. (1991) correlated acidic aerosols and other air pollutants with respiratory symptoms in asthmatics in Denver, Colorado. Daily concentrations of several pollutants, including nitric acid were measured while a panel of asthmatics recorded respiratory symptoms, frequency of medication use, and related information. Airborne acidity, as measured by H^+, significantly correlated with such symptoms as cough and shortness of breath; however, nitric acid itself was not specifically associated with any respiratory symptom analyzed. Nitric acid concentrations ranged from 0.06 to 13.54 $\mu g/m^3$ (0.15 to 34.93 ppb) during the study period.

Health effects from exposure to acidic air pollution in children (8-12 years old) were monitored in 24 communities in the United States and Canada (Dockery et al. 1996; Raizenne et al. 1996). Air quality and meteorology were measured for 1 year in each community and parents completed a respiratory health questionnaire. At the end of the 1-year monitoring period, children were administered pulmonary function tests consisting of forced vital capacity (FVC) and forced expiratory volume (FEV) measurements. Cconcentrations of nitric acid ranged from 0.3 to 2.1 ppb, and nitrous acid ranged from 0.1 to 1.4 ppb; these were combined as gaseous acids. Gaseous acids were associated with a significantly higher risk of asthma (odds ratio = 2.00; 95% confidence interval[CI], 1.14-3.53) and showed a positive correlation with higher reporting of attacks of wheezing, persistent wheeze, and any asthmatic symptoms (Dockery et al. 1996). However, no changes in FVC or FEV were associated with gaseous acid concentrations in the communities (Raizenne et al. 1996).

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 positively correlated with concentrations of both acid and nitrogen dioxide in boys, whereas regression analysis showed that acid vapor was significantly associated with lower FVC, FEV_1, peak expiratory flow rate, and maximal midexpiratory flow in girls. When the data were further analyzed by month (Millstein et al. 2004), wheezing during the spring and summer months was not associated with either nitric acid or nitrogen dioxide. However, in asthmatics, the monthly prevalence of asthma medication use was asso-

ciated with monthly concentrations of ozone, nitric acid, and acetic acid (Millstein et al. 2004).

2.2.3. Experimental Studies

An experimental self-exposure was reported by Lehmann and Hasegawa (1913). Nitrogen oxide gas was produced by reaction of copper with nitric acid; the gas produced was collected over water and mixed with fresh air. Concentrations of total oxidation products, expressed as nitrous acid concentration, were determined analytically by either oxidation of hydrogen peroxide or by reduction using potassium iodide. Although the generated atmospheres were likely a mixture of nitrogen oxides, exposure concentrations were expressed as total nitric acid content and are reported in ppm as was done by NIOSH (1976b). One researcher exposed himself to nitric acid at 62 ppm (160 mg/m^3) for 1 h and reported irritation of the larynx, thirst, and an objectionable odor. He was then exposed at 74-101 ppm (190-260 mg/m^3) for 1 h and then at 23-43 ppm (60-110 mg/m^3) for another hour. Immediate severe irritation with cough and an increase in pulse and respiratory rates were reported after 40 min. He was able to tolerate exposure at 158 ppm (408 mg/m^3) but for only 10 min, due to coughing, severe burning in the nose and throat, lacrimation and heavy mucous secretion from the nose, a feeling of suffocation, headache, dizziness, and vomiting. On the basis of their results and comparing them with other work, the investigators estimated that the concentration causing no significant adverse effects would be below 50 ppm (130 mg/m^3).

In contrast to the above report, another researcher exposed himself and another individual to nitric acid fumes at a concentration of 11.6-12.4 ppm (30-32 mg/m^3) for 1 h (Diem 1907). Symptoms included irritation of the nasal mucosa, pressure in the chest, slight stabbing pains in the trachea and larynx, coughing, marked secretion from the nose and salivary glands, burning of the eyes and lacrimation, and burning and itching of facial skin. After 20 min, all symptoms except nasal secretion abated somewhat and a slight frontal headache developed. Some of these symptoms persisted for about 1 h post-exposure. In a second experiment, the researcher could tolerate 85 ppm (219 mg/m^3) for only 2-3 min. In these experiments, concentrations of nitric acid were produced by warming the acid and samples of the chamber air were measured by simple titration with the indicator Congo red. Differences in the methods used by Lehmann and Hasegawa (1913) and Diem (1907) for the production of nitric acid fumes as well as the detection methods probably account for the differences in effect levels.

A group of nine allergic adolescents (12-18 years old) was exposed to nitric acid gas and their pulmonary function was assessed. All subjects had exercise-induced bronchospasm defined as a greater than 15% drop in FEV_1 after 6 min of exercise at 85% maximum oxygen consumption. Five individuals also had allergic asthma. Individuals were exposed to nitric acid at 0.05 ppm (0.129

mg/m^3) through a rubber mouthpiece with nose clips for 40 min (30 min at rest, 10 min of moderate exercise on a treadmill). Each individual served as his or her own control with post-exposure pulmonary function values compared with baseline. After exposure to nitric acid, FEV_1 decreased by 4% and respiratory resistance increased by 23%. A post-exposure survey taken later that day or the following day did not indicate any correlation between exposure and symptoms of respiratory distress such as cough, pain or burning of the chest, fatigue, shortness of breath, or wheezing. On a separate testing day when subjects were exposed to only air, FEV_1 decreased by 2% and respiratory resistance increased by 7% (Koenig et al. 1989).

No changes in pulmonary function (vital capacity, respiratory resistance, and FEV_1) occurred in five healthy volunteers exposed at rest to nitric acid fumes at 1.6 ppm (4.13 mg/m^3) for 10 min (Sackner and Ford 1981). No changes in pulmonary function, lavage constituents, or bronchial biopsy specimens were found in 10 healthy, athletic subjects exposed to nitric acid gas at 0.194 ppm (0.5 mg/m^3) for 4 h during moderate exercise (Aris et al. 1993).

2.3. Developmental and Reproductive Toxicity

No information regarding the developmental or reproductive toxicity of nitric acid in humans was found.

2.4. Genotoxicity

No information regarding the genotoxicity of nitric acid in humans was found.

2.5. Carcinogenicity

No information regarding the carcinogenicity of nitric acid in humans was found.

2.6. Summary

Studies and case reports of exposure to nitric acid fumes and reaction products (e.g., nitrogen monoxide) are not directly relevant to nitric acid mists and vapor. However, the course of toxicity following inhalation exposures to atmospheres resulting from spills of nitric acid is consistent among the case reports. Nitric acid fumes may cause immediate irritation of the respiratory tract, pain, and dyspnea, followed by a period of recovery that may last several weeks. Relapse may occur, with death caused by bronchopneumonia or pulmonary fibrosis. Allergic or asthmatic individuals are the most sensitive populations when considering nonlethal concentrations of nitric acid.

3. ANIMAL TOXICITY DATA

Production of nitric acid atmospheres for inhalation exposure experiments potentially results in a variety of physical states (gas, fume, and vapor) depending on the production method used. For each study description below, the physical state and atmosphere generation methods are presented as described by the investigators.

3.1. Acute Lethality

3.1.1. Cats

Lehmann and Hasegawa (1913) conducted a series of experiments using cats exposed to nitric acid gases produced as described in Section 2.2.3. In general, as concentration or duration of exposure to nitric acid increased, death resulted from severe pulmonary edema. At concentrations less than about 388 ppm (1,000 mg/m^3), examination of the concentration and time relationship indicated that Ct products greater than about 900 ppm-h resulted in death whereas Ct products up to 760 ppm-h resulted in only a slight increase in respiration for several hours after exposure. Further, exposure at 287 ppm (740 mg/m^3) for 1.83 h (Ct = 526 ppm-h) caused no effects, whereas exposure at either 341 ppm (880 mg/m^3) for 3.83 h (Ct = 1,309 ppm-h) or 217 ppm (560 mg/m^3) for 4.25 h (Ct = 922 ppm-h) resulted in death. In contrast, at concentrations of 388 ppm (1,000 mg/m^3) or greater, severe clinical signs or death occurred at a Ct product as low as 277 ppm-h. Response probably depended on whether either the concentration of the acid or the duration of exposure was great enough to induce corrosive effects leading to edema. The data are limited because only one animal was tested at each concentration and time combination.

3.1.2. Rats

Groups of five male and five female Crl:CD®BR rats were exposed nose-only for to nitric acid aerosol at 260-3,100 ppm for 1 h, followed by a 14-day observation period (DuPont 1987). Atmospheres were generated with a nebulizer and airborne test material was dispersed with a baffle. Although an aerosol was generated, concentrations were reported in the study as ppm instead of mg/m^3. Aerosol content was assumed to be 100% at the three highest concentrations and ranged from 15-73% at the five lower concentrations as measured on a gravimetric filter sample. Except for the 2,500 and 2,700 ppm concentrations, all exposures contained 70% or more respirable particles, with a mass median aerodynamic diameter (MMAD) of 4.0 μm or less. The 2,500- and 2,700-ppm concentrations contained 59 and 61% respirable particles and had mass median aerodynamic diameters of 6.5 and 6.6 μm, respectively. Despite generation of the small particle size resulting in a high percentage of respirable particles, it is un-

clear why the concentrations were reported in ppm rather than mg/m^3. Nitrogen dioxide was not detected in the exposure atmospheres.

Clinical signs included clear nasal discharge at "some" concentrations, body weight loss for 1-2 days at 260 and 470 ppm, partially closed eyes at 1,300 ppm or higher, lung noise and gasping at 1,600 ppm or higher, and extended weight loss up to 12 days post-exposure at 1,500 ppm or higher for males and 1,600 ppm or higher for females. Mortality results are presented in Table 5-3. The 1-h LC_{50} for males and females combined was 2,500 ppm. Although males died at lower concentrations than females, no apparent differences in clinical responses or LC_{50} values were observed between males and females (DuPont 1987).

Gray et al. (1954) compared the toxicities of nitrogen dioxide, red fuming nitric acid (RFNA) (containing 8-17% nitrogen dioxide), and white fuming nitric acid (WFNA) (containing 0.1-0.4% nitrogen dioxide) by inhalation in rats. Outcomes related to exposure to RFNA and nitrogen dioxide are reported here to provide a complete description of the study; however, the chemicals are not directly relevant to nitric acid fumes. Although graphs of the dose-response curves were presented in the paper, the authors did not include the data from which those curves were plotted. Exposure concentrations for RFNA and WFNA were measured and reported as nitrogen dioxide. Thirty-minute LC_{50} values were reported to be 174 ppm (449 mg/m^3) for nitrogen dioxide, 138 ppm (356 mg/m^3) for RFNA as nitrogen dioxide, and 244 ppm (630 mg/m^3) for WFNA as nitrogen dioxide. Deaths were from pulmonary edema. The dose-response curves for nitrogen dioxide and RFNA for 30-min exposures were parallel statistically, indicating a possible similar mode of action for the two gases. But the curves were somewhat different at lower concentrations for an exposure duration of 240 min. For WFNA, the investigators reported that deaths were not as "predictable" as with the other gases. The approximate LC_{50} indicates that WFNA is much less toxic (has a higher LC_{50}) than either RFNA or nitrogen dioxide. Therefore, the investigators concluded that the main toxic component of these oxides of nitrogen is nitrogen dioxide. However, NIOSH (1976a) calculated LC_{50}s for RFNA and WFNA of 310 ppm (800 mg/m^3) and 334 ppm (862 mg/m^3), respectively, on the basis of total nitric acid concentration. The calculations were based on molecular weights and the percentage of nitrogen dioxide in RFNA and WFNA. These estimates suggest the possibility that both nitric acid vapor and nitrogen dioxide contribute to the toxicity.

3.2. Nonlethal Toxicity

3.2.1. Dogs

Mongrel dogs were used as a model of bronchial injury induced by nitric acid (Peters and Hyatt 1986; Fujita et al. 1988). One day per week, dogs were anesthetized and a catheter placed in the mainstem bronchus; nitric acid at 1% was delivered as a course spray via a nebulizer with approximately 5 mL to the

left lung and 8 mL to the right lung. For an additional two exposures per week, dogs were intubated and spontaneously breathed nitric acid mist at 1% for 2 h. This exposure regime was continued for 4 weeks and the dogs were killed either immediately or after a 5-month recovery period. Dogs developed intermittent cough and produced clear mucoid sputum within one week after treatment began. After 4 weeks, animals exhibited a decrease in total lung capacity and vital capacity with evidence of obstruction, as measured by a decrease in forced expiratory volume and expiratory flow. Increased flow resistance was observed after 14 days and continued to increase throughout the exposure period. Airway obstruction persisted for 5 months post-exposure with significant reductions in maximal expiratory flows. Necropy performed on dogs killed immediately after exposure revealed edematous lungs with areas of focal hemorrhage. Lungs appeared normal in dogs after 5 months of recovery. Histologically, chronic airway inflammation, slight epithelial changes, slight peribronchiolar fibrosis, and an increase in smooth muscle that persisted for 5 months post-exposure were found. Severity of the pathologic lesions directly correlated with decreases in pulmonary function (Peters and Hyatt 1986; Fujita et al. 1988). However, it is not possible to determine from this protocol which method of exposure was the most damaging to the airways.

Bronchiolitis obliterans was produced in dogs after instillation of nitric acid at 1% into the airways. Two instillations of three 5-mL aliquots were given approximately 2 weeks apart and pulmonary function tests performed 2 weeks later. Treated dogs had mild cough with slight hemoptysis immediately after each treatment. Several pulmonary function tests indicated increased peripheral airway resistance, and acute and chronic inflammation of the small airways were observed at necropsy (Mink et al. 1984).

TABLE 5-3 Mortality in Rats Exposed Nose-Only to Nitric Acid for 1 Hour

	Mortality	
Concentration (ppm)	Males	Females
260	0/5	0/5
470	0/5	0/5
1,300	1/5	0/5
1,500	1/5	0/5
1,600	2/5	0/5
2,500	2/5	1/5
2,700	2/5	1/5
3,100	5/5	5/5

Source: DuPont 1987.

3.2.2. Rats

Rats were treated once with 0.15 mL of nitric acid at 1% by intratracheal instillation. Focal lung damage found 1 day after administration consisted of bronchiolar inflammation with inflammatory cell infiltration. Absorption rates from the lung were significantly ($p \leq 0.05$) increased for both lipid-soluble and lipid-insoluble drugs (Gardiner and Schanker 1976).

To study the long-term effects of exposure to nitric acid, rats (about 10 per group) were exposed nose-only to nitric acid at 0, 5.1, 7.0, 13, or 19 ppm for 6 h/day on alternate days for a total of six exposures. Rats were then held for 22 months. Mortality was not affected in any group and no adverse effects were noted (Ballou et al. 1978).

3.2.3. Hamsters

Lung injury was induced in Syrian golden hamsters by a single tracheal instillation of nitric acid at 0.5% (0.5 mL saline/100 g body weight) (Coalson and Collins 1985). Several animals (number not specified) died before day 3 post-treatment and had severe hemorrhagic pulmonary edema. Airway changes in the remaining hamsters included acute bronchitis, acute bronchiolitis, obliterative bronchiolitis, bronchiolectasia, and bronchiectasis. These pathologic changes were accompanied by decreased lung volumes, decreased internal surface areas, increased lung weights, and increased elastin content. Airway dilatation and morphometric and biochemical changes persisted through day 60 post-treatment (the last day animals were examined).

In a similar experiment, hamsters were exposed via intratracheal instillation to 0.5 mL of nitric acid at 0.1 N. Up to 17 weeks post-exposure, histologic lesions in the lung included secretory cell metaplasia, interstitial fibrosis, bronchiolectasis, and diffuse extension of hyperplastic bronchiolar epithelium into adjacent alveoli (Christensen et al. 1988).

3.2.4. Sheep

Effects of nitric acid vapor on carbachol reactivity in normal and allergic sheep were investigated (Abraham et al. 1982). Allergic sheep are those with a history of developing bronchospasm after inhalation challenge with *Ascaris suum* antigen; the induced airway response is similar to that which occurs in humans with allergic airway disease. Measurements of lung resistance were taken before exposure, after 20 breaths of carbachol at 2.5% (to induce bronchoconstriction), and after exposure to nitric acid vapor at 1.6 ppm (4.13 mg/m^3) for 4 h. Immediately after treatment with nitric acid, sheep were given a second bronchial challenge with aerosolized carbachol. Nitric acid exposure alone did not

result in bronchoconstriction in either normal or allergic sheep, as measured by specific lung resistance. However, airway hyperreactivity to carbachol after nitric acid exposure occurred in allergic sheep. Pulmonary flow resistance from carbachol challenge before and after exposure to nitric acid increased by 68 and 78%, respectively, in normal sheep and 82 and 120% ($p \leq 0.05$), respectively, in allergic sheep (Abraham et al. 1982).

3.3. Developmental and Reproductive Toxicity

No information regarding the developmental or reproductive toxicity of nitric acid in animals was found.

3.4. Genotoxicity

Nitric acid at up to 0.008% was negative in mutagenicity tests with *Escherichia coli* (Demerec et al. 1951).

3.5. Carcinogenicity

No information regarding the carcinogenicity of nitric acid in animals was found. Lung damage in rats, induced by intratracheal instillation of 0.25 mL of nitric acid at 1%, did not enhance the rate of lung cancer caused by 3-methylcholanthrene (Blenkinsopp 1968).

3.6. Summary

Because of the corrosive nature of nitric acid, the chemical has been used to produce pulmonary changes in animal models of obstructive lung disease (Coalson and Collins 1985; Peters and Hyatt 1986; Fujita et al. 1988). Experiments with sheep (Abraham et al. 1982) have demonstrated the sensitivity of allergic individuals to acidic atmospheres.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No information regarding the pharmacokinetics of nitric acid was found. Because of its high water solubility and reactivity, nitric acid would be expected to undergo significant removal in the upper respiratory tract. However, in a model system, Chen and Schlesinger (1996) showed that particulates can act as vectors for adsorbed or absorbed nitric-acid transport to the lower respiratory tract.

4.2. Mechanism of Toxicity

Nitric acid is a highly corrosive, strongly oxidizing acid (O'Neil et al. 2006). Contact with the liquid causes burns on the skin and corneal opacity (NIOSH 1976a). A 4-h occluded patch test induced skin corrosion in rabbits with nitric acid at 8%, but not 6% (Vernot et al. 1977). Respiratory irritation attributed to nitric acid is almost certainly due to the corrosive properties of the chemical. Because of its high water solubility and reactivity, nitric acid would be expected to undergo significant removal in the upper respiratory tract. However, some experiments indicate that bronchial responsiveness can be altered. In a model system, Chen and Schlesinger (1996) showed that particulates can act as vectors for adsorbed or absorbed nitric-acid transport to the lower respiratory tract. Reaction with endogenous ammonia and water may also produce particulates which can act as vectors.

4.3. Structure-Activity Relationships

Inhalation exposures to nitric acid fumes involve exposure to nitric acid as well as nitrogen oxides such a nitrogen dioxide (NO_2) and nitric oxide (NO). Fuming nitric acid reacts with wood or metals and emits fumes of nitrogen dioxide, which form equimolar amounts of nitrous and nitric acid when in contact with steam (NIOSH 1976a; O'Neil et al. 2006). In the presence of light, nitric acid undergoes an oxidation-reduction reaction to produce nitrogen dioxide, water, and oxygen. Nitric oxide reacts quantitatively with oxygen in air to form nitrogen dioxide which then reacts with water to form nitric acid. Most reports of human occupational exposure are limited to measurements of nitrogen oxides (NIOSH 1976a). In animal experiments, Lehmann and Hasagawa (1913) showed that up to a concentration of about 272 ppm (700 mg/m^3), toxic response was the same whether the gas contained nitric acid alone or was a mixture of nitrous and nitric acid.

As discussed in Section 3.1.2, Gray et al. (1954) compared the toxicities of nitrogen dioxide, RFNA, and WFNA in male rats. The dose-response curves for nitrogen dioxide and RFNA for 30-min exposures were parallel statistically, indicating a similar mode of action for the two gases. For both gases, deaths were from pulmonary edema. The 30-min LC_{50} value was 174 ppm (449 mg/m^3) for nitrogen dioxide and 138 ppm as nitrogen dioxide (356 mg/m^3) for RFNA. With exposures to WFNA, the authors stated that deaths were not as "predictable as with the other gases". The approximate LC_{50} for WFNA (244 ppm as nitrogen dioxide [630 mg/m^3]) indicates it is less toxic than either RFNA or nitrogen dioxide. Therefore, the investigators concluded that the main toxic component of these oxides of nitrogen is nitrogen dioxide, and that RFNA is approximately 25% more toxic than nitrogen dioxide because of the contribution by the acid component. However, NIOSH (1976a) calculated LC_{50}s for RFNA and WFNA of 310 ppm (800 mg/m^3) and 334 ppm (862 mg/m^3), respectively,

on the basis of total nitric acid concentration. The calculations were based on molecular weights and the percentage of nitrogen dioxide in RFNA and WFNA. Because the values are very similar, it suggests the possibility of a synergistic effect between nitric acid vapor and nitrogen dioxide, because RFNA has a higher nitrogen dioxide content by weight than WFNA.

The supposition that nitric acid and nitrogen dioxide interact to cause enhanced toxicity is also supported, in part, by the inhalation toxicokinetics experiments of Goldstein et al. (1977) in Rhesus monkeys. Approximately 50-60% of inhaled nitrogen dioxide was retained by monkeys and distributed throughout the lungs. Radioactivity was retained in the lungs during a 21-min post-exposure period with extrapulmonary distribution (percent not quantified) via the bloodstream. The investigators speculate that the reaction of inhaled nitrogen dioxide with water vapor in the lungs and with liquid water in the mucous results in the formation of nitric acid and accounts for the long retention time in the lung.

It is apparent from the above discussion that the toxic action of nitric acid cannot be considered without taking into account the effects of nitrogen dioxide. However, nitric acid fumes will contain nitrogen dioxide upon contact with water, such that reports of experimental or accidental exposures to nitric acid fumes will account for the toxicity contributed by nitrogen dioxide. NIOSH (1976b) described the effects of nitrogen dioxide in humans as involving 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 nitrogen dioxide (Hine et al. 1970). This course of toxicity is identical to that described for nitric acid, but the concentrations eliciting responses are very different for the two chemicals. For example, 75 ppm is the concentration at which deaths were first observed in rats exposed to nitrogen dioxide for 1 h (Hine et al. 1970) whereas 1,300 ppm was the concentration for nitric acid (DuPont 1987). Also, on the basis of the LC_{50} values for the rat, nitrogen dioxide appears to be more toxic than nitric acid. Therefore, using data from inhalation studies of nitrogen dioxide might be an overly conservative approach for establishing AEGL values for nitric acid. If nitrogen dioxide is of concern, AEGL values for that chemical have been established (see NRC 2012).

4.4. Other Relevant Information

4.4.1. Species Variability

There are no apparent species differences in the toxic response to acute inhalation exposure to nitric acid. Nitric acid fumes may cause immediate irritation of the respiratory tract, pain, and dyspnea, which are followed by a period of recovery that may last several weeks. Relapse may occur, with death from bronchopneumonia or pulmonary fibrosis (NIOSH 1976a; ACGIH 1991). Toxic response is similar between humans and animals. Dogs (Peters and Hyatt 1986; Fujita et al. 1988) and hamsters (Coalson and Collins 1985) have been used as

models of obstructive airway disease, and experiments in sheep (Abraham et al. 1982) have demonstrated the sensitivity of allergic individuals to nitric acid.

4.4.2. Susceptible Populations

Epidemiologic studies indicate that asthmatics may be more sensitive to acidic atmospheres (Ostro et al. 1991; Dockery et al. 1996). Data from one of these studies indicates that children with a history of allergy or asthma may be a sensitive subpopulation. In 24 communities in the United States and Canada, the concentration of nitric acid ranged from 0.3 to 2.1 ppb and that of nitrous acid ranged from 0.1 to 1.4 ppb; these were combined as gaseous acids. Among children aged 8-12 years, these gaseous acids (but not nitric acid alone) were associated with a significantly higher risk of asthma (odds ratio = 2.00; 95% CI: 1.14-3.53) and showed a positive correlation with higher reporting of attacks of wheezing, persistent wheeze, and any asthmatic symptoms (Dockery et al. 1996). However, no effects in an experimental study in which allergic adolescents were exposed to nitric acid were reported (Koenig et al. 1989).

Abraham et al. (1982) showed that airway hyperreactivity to carbachol occurred in allergic sheep following a 4-h exposure to nitric acid at 1.6 ppm (4.13 mg/m^3). Specific airway resistance before and after exposure to nitric acid increased by 68 and 78%, respectively, in normal sheep and 82 and 120% ($p \leq 0.05$), respectively, in allergic sheep. These data confirm that allergic individuals are potentially a sensitive subpopulation.

4.4.3. Concentration-Exposure Duration Relationship

Little data were available to analyze the concentration-exposure duration relationship for nitric acid. The most reliable study (DuPont 1987) used a single duration over a large range of concentrations. However, lethality data in the rat indicates that 100% mortality is reached abruptly, indicating a steep concentration-response.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

A no-effect level of 1.6 ppm (4.13 mg/m^3) was reported for changes in pulmonary function (vital capacity, respiratory resistance, and FEV_1) in five healthy volunteers exposed at rest to nitric acid vapor for 10 min (Sackner and Ford 1981). That concentration is the highest no-observed-adverse-effect level available in humans. An experimental self-exposure to nitric acid at 62 ppm (160 mg/m^3) for 1 h resulted in irritation of the larynx, thirst, and an objectionable odor (Lehmann and Hasegawa 1913).

5.2. Summary of Animal Data Relevant to AEGL-1

Most animal studies of nitric acid involved lethal concentrations or were performed using intratracheal instillation, a route not comparable to inhalation exposure.

5.3. Derivation of AEGL-1 Values

The highest no-effect level for AEGL-1 effects in humans of 1.6 ppm (4.13 mg/m^3) for 10 min was used to derive AEGL-1 values. An uncertainty factor of 10 was applied to account for variability in response in the general population and possibly greater sensitivity of asthmatics to a direct-acting irritant. Time scaling was not performed because a no-effect level for irritation was used as the point of departure and such irritation is generally concentration dependent but not time dependent, so the 10-min value was applied to all the other AEGL durations. AEGL-1 values for nitric acid are presented in Table 5-4.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Human data relevant to AEGL-2 values were not found. Experimental studies in which results consistent with AEGL-2 end points were described did not expose individuals to pure nitric acid, but generated an atmosphere containing a mixture of nitrogen oxides (Diem 1907; Lehmann and Hasegawa 1913).

6.2. Summary of Animal Data Relevant to AEGL-2

The most relevant animal data for deriving AEGL-2 values were those from a study by DuPont (1987). The study was well conducted and controlled for potential nitrogen dioxide contamination. Groups of five male and five female Crl:CD®BR rats were exposed nose-only to nitric acid aerosol at 260-3,100 ppm for 1 h, followed by a 14-day observation period. Clinical signs included clear nasal discharge at "some" concentrations, body weight loss for 1-2 days at 260 and 470 ppm, partially closed eyes at concentrations of 1,300 ppm and higher, lung noise and gasping at 1,600 ppm and higher, and extended weight loss for up to 12 days post-exposure at 1,500 ppm and greater for males and 1,600 ppm and greater for females.

TABLE 5-4 AEGL-1 Values for Nitric Acid

10 min	30 min	1 h	4 h	8 h
0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)

No long-term effects from exposure to nitric acid were observed in rats exposed at up to 19 ppm for 6 h on alternate days for a total of six exposures (Ballou et al. 1978).

6.3. Derivation of AEGL-2 Values

A study of rats exposed to nitric acid at 470 ppm for 1 h (DuPont 1987) was used to derive AEGL-2 values. The point of departure is a no-effect level for impaired ability to escape. Effects observed at 470 ppm were transient body weight loss 1-2 days post-exposure. At the next higher concentration, rats exhibited partially closed eyes (a possible sign of severe ocular irritation), which could definitely impair escape, and lung noise. Time scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific value for n, scaling was performed using the default values of n = 3 for extrapolating to the shorter durations (10 and 30 min) and n = 1 for extrapolating to the longer durations (4 and 8 h). A total uncertainty factor of 10 was used: a factor of 3 for interspecies differences and 3 for intraspecies variability. Larger uncertainty factors were considered unnecessary because the mechanism of action of a direct ocular irritant and of a corrosive acid in the lung is not expected to differ greatly between species or among individuals. In addition, a modifying factor of 2 was applied because clinical observations were not well described, and the AEGL-2 values overlap AEGL-3 values, suggesting a very steep concentration-response relationship. AEGL-2 values for nitric acid are presented in Table 5-5.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

Limited human data useful for deriving AEGL-3 values are available. Case reports of lethal exposures from accidents do not contain information on exposure concentrations. An experimental self-exposure was reported by Lehmann and Hasegawa (1913). One of the researchers exposed himself to nitric acid at 74-101 ppm (190-260 mg/m^3) for 1 h and then at 23-43 ppm (60-110 mg/m^3) for another hour. He experienced immediate severe irritation with cough and an increase in pulse and respiratory rates after 40 min. Because severe symptoms were immediate, the average concentration of 88 ppm during the first hour of exposure was assumed to be close to intolerable but not lethal. The subject was able to tolerate exposure to nitric acid at 158 ppm (408 mg/m^3), but for only 10 min due to coughing, severe burning in the nose and throat, lacrimation, heavy mucous secretion from the nose, a feeling of suffocation, headache, dizziness, and vomiting.

TABLE 5-5 AEGL-2 Values for Nitric Acid

10 min	30 min	1 h	4 h	8 h
43 ppm (110 mg/m^3)	30 ppm (77 mg/m^3)	24 ppm (62 mg/m^3)	6.0 ppm (15 mg/m^3)	3.0 ppm (7.7 mg/m^3)

7.2. Summary of Animal Data Relevant to AEGL-3

Animal data relevant to derivation of AEGL-3 values are limited to the LC_{50} study by DuPont (1987). This well-conducted study controlled for potential nitrogen dioxide contamination. Groups of five male and five female Crl:CD®BR rats were exposed nose-only to nitric acid aerosol at 260-3,100 ppm for 1 h, followed by a 14-day observation period. Clinical signs included clear nasal discharge at some concentrations, body weight loss for 1-2 days at 260 and 470 ppm, partially closed eyes at 1,300 ppm and higher, lung noise and gasping at 1,600 ppm and higher, and extended weight loss for up to 12 days post-exposure at 1,500 ppm and higher for males and 1,600 ppm and higher for females. The 1-h LC_{50} for males and females combined was 2,500 ppm. Deaths occurred at concentrations of 1,300 ppm and higher (see Table 5-3).

7.3. Derivation of AEGL-3 Values

A 1-h LC_{50} in rats was calculated by DuPont (1987). In this study, mortality ratios at each concentration were determined. On the basis of these data, an LC_{01} of 919 ppm was calculated by log-probit analysis. Values were time scaled using the equation $C^n \times t = k$, where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific value for n, time scaling was performed using default values of n = 3 for extrapolating to shorter durations (10 and 30 min) and n = 1 for longer durations (4 and 8 h). A total uncertainty factor of 10 was used: a factor of 3 for interspecies differences and 3 for intraspecies variability. Use of larger uncertainty factors was considered unnecessary because the mechanism of action of a corrosive acid in the lung is not expected to differ greatly between species or among individuals. AEGL-3 values for nitric acid are presented in Table 5-6.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

AEGL values for nitric acid are presented in Table 5-7. AEGL-1 values were based on a no-effect level in humans. AEGL-2 values were based on a concentration which produced transient weight loss in rats, and AEGL-3 values on an estimated 1-h LC_{01} in rats. If nitrogen dioxide is of concern, AEGL values for that chemical are available (see NRC 2012).

8.2. Comparison with Other Standards and Guidelines

Standards and guidelines for workplace and community exposures to nitric acid are presented in Table 5-8. Some of the standards and guidelines have been developed on the basis of nitrogen dioxide or comparisons with other acids in the workplace. An occupational time weighted average (TWA) concentration of 2 ppm and a short term exposure limit (STEL) of 4 ppm have been adopted by several organizations (ACGIH 2003; OSHA [29 CFR 1910.1000 (2006)]; NIOSH 2011). ACGIH (2003) set the TWA as an intermediate value between that for hydrogen chloride and sulfuric acid and considers both the TWA and STEL to be sufficiently low to prevent ocular and upper respiratory tract irritation. International standards for nitric acid are also 2 ppm for a workday and 2-5 ppm for short-term limits (DFG 2002; Swedish Work Environment Authority 2005). The German MAK value is based on the results of a study by Diem (1907). The immediately dangerous to life or health (IDLH) value of 25 ppm (NIOSH 1994) is based on acute toxicity data in humans (conversion of lethal oral dose to an equivalent inhalation concentration) and animals (secondary source).

Emergency response planning guideline (ERPG) levels were developed for WFNA (AIHA 2001), and are based on toxicity data in animals exposed to nitric acid or nitrogen dioxide and dose-response estimates in humans exposed to nitrogen dioxide.

8.3. Data Adequacy and Research Needs

Limited inhalation data were available for determining AEGL values. Only one well-conducted study in rats was available. Most animal data administered nitric acid by intratracheal instillation, a route that does not necessarily mimic inhalation exposures. Data from human case reports lacked exposure concentrations and durations.

TABLE 5-6 AEGL-3 Values for Nitric Acid

10 min	30 min	1 h	4 h	8 h
170 ppm (440 mg/m^3)	120 ppm (310 mg/m^3)	92 ppm (240 mg/m^3)	23 ppm (59 mg/m^3)	11 ppm (28 mg/m^3)

TABLE 5-7 AEGL Values for Nitric Acid

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabliing)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)
AEGL-2 (disabling)	43 ppm (110 mg/m^3)	30 ppm (77 mg/m^3)	24 ppm (62 mg/m^3)	6.0 ppm (15 mg/m^3)	3.0 ppm (7.7 mg/m^3)
AEGL-3 (lethal)	170 ppm (440 mg/m^3)	120 ppm (310 mg/m^3)	92 ppm (240 mg/m^3)	23 ppm (59 mg/m^3)	11 ppm (28 mg/m^3)

TABLE 5-8 Standards and Guidelines for Nitric Acid

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)
AEGL-2	43 ppm (110 mg/m^3)	30 ppm (77 mg/m^3)	24 ppm (62 mg/m^3)	6.0 ppm (15 mg/m^3)	3.0 ppm (7.7 mg/m^3)
AEGL-3	170 ppm (440 mg/m^3)	120 ppm (310 mg/m^3)	92 ppm (240 mg/m^3)	23 ppm (59 mg/m^3)	11 ppm (28 mg/m^3)
ERPG-1 (AIHA)[a]			1 ppm		
ERPG-2 (AIHA)			6 ppm		
ERPG-3 (AIHA)			78 ppm		
IDLH (NIOSH)[b]		25 ppm			
TLV-TWA (ACGIH)[c]					2 ppm
REL-TWA (NIOSH)[d]					2 ppm
PEL-TWA (OSHA)[e]					2ppm
TLV-STEL (ACGIH)[f]	4ppm				
REL-STEL (NIOSH)[g]	4 ppm				
MAK (Germany)[h]					2 ppm
MAK Peak Limit (Germany)[i]	2 ppm				
OELV-LLV (Sweden)[j]					2ppm
OELV-STV (Sweden)[j]	5ppm				

[a]ERPG (emergency response planning guidelines, American Industrial Hygiene Association) (AIHA 2011).
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 or developing health effect more severe 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]IDLH (immediately dangerous to life or health, National Institute for Occupational Safety and Health) (NIOSH 1994) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms, or any irreversible health effects.
[c]TLV-TWA (threshold limit value - time weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 2003) 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.
[d]REL-TWA (recommended exposure limit - time weighted average, National Institute for Occupational Safety and Health) (NIOSH 2011) is defined analogous to the ACGIH TLV-TWA.
[e]PEL-TWA (permissible exposure limit - time weighted average, Occupational Safety and Health Administration) ((29 CFR 1910.1000 [2006]) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week.
[f]TLV-STEL (threshold limit value – short-term exposure limit, American Conference of Governmental Industrial Hygienists) (ACGIH 2003) is defined as a 15-min TWA exposure which should not be exceeded at any time during the workday even if the 8-h TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 min and should not occur more than four times per day. There should be at least 60 min between successive exposures in this range.
[g]REL-STEL (recommended exposure limit – short-term exposure limit) (NIOSH 2011) is defined analogous to the ACGIH TLV-STEL.
[h]MAK (maximale arbeitsplatzkonzentration [maximum workplace concentration], Deutsche Forschungsgemeinschaft [German Research Association]) (DFG 2002) is defined analogous to the ACGIH TLV-TWA.
[i]MAK spitzenbegrenzung (peak limit [Category I, 1], Deutsche Forschungsgemeinschaft [German Research Association]) (DFG 2002) constitutes the maximum average concentration to which workers can be exposed for a period up to 15 min with no more than four exposure periods per work shift and a minimum of 1 h between excursions.
[j]OEL-LLV (occupational exposure limit – level-limit value). OEL-STV (occupational exposure limit – short-term value) (Swedish Work Environment Authority 2005) is the maximum acceptable average concentration (time-weighted average) of an air contaminant in respiratory air. An occupational exposure limit value is either a level-limit value (1 working day) or a ceiling-limit value (15 min or some other reference time period), and a short-time value is a recommended value consisting of a time-weighted average for exposure during a reference period of 15 min.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR NITRIC ACID

Derivation of AEGL-1 Values

Key study:	Sackner, M.A., and D. Ford. 1981. Effects of breathing nitrate aerosols in high concentrations for 10 minutes on pulmonary function of normal and asthmatic adults, and preliminary results in normals exposed to nitric acid fumes. Am. Rev. Resp. Dis. 123(4Pt 2):151.
Toxicity end point:	No changes in pulmonary function (vital capacity, respiratory resistance, and FEV_1) were reported in five healthy volunteers exposed to nitric acid vapor at 1.6 ppm (4.13 mg/m^3) for 10 min at rest.
Time scaling:	Values were set equal across all AEGL durations because the point of departure is a no-effect level for irritation.
Uncertainty factors:	10 for intraspecies variability; to account for variability in response in the general population and possible greater sensitivity of asthmatics to effects of a direct-acting irritant on pulmonary function.
Modifying factors:	None
Calculations:	
10-min AEGL-1:	1.6 ppm ÷ 10 = 0.16 ppm
30-min AEGL-1:	Set equal to 10-min AEGL value of 0.16 ppm
1-h AEGL-1:	Set equal to 10-min AEGL value of 0.16 ppm
4-h AEGL-1:	Set equal to 10-min AEGL value of 0.16 ppm
8-h AEGL-1:	Set equal to 10-min AEGL value of 0.16 ppm

Derivation of AEGL-2 Values

Key study:	DuPont. 1987. One-hour Inhalation Median Lethal Concentration (LC50) Study with Nitric Acid. Report No 451-87. Haskell Laboratory, DuPont, Newark, DE. 26 pp.
Toxicity end points:	Exposure to nitric acid at 470 ppm for 1 h resulted in transient body weight loss 1-2 days post-exposure and was a no-effect level for eye closure and impairment of escape.
Time scaling:	$C^n \times t = k$ (default of n = 3 for extrapolating to the 10- and 30-min durations; default of n = 1 for extrapolating to the 4- and 8-h durations $(470 \text{ ppm} \div 20)^3 \times 1 \text{ h} = 12{,}977.875 \text{ ppm-h}$ $(470 \text{ ppm} \div 20)^1 \times 1 \text{ h} = 23.5 \text{ ppm-h}$
Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability Total uncertainty factor of 10
Modifying factor:	2, because clinical observations were not well described, and AEGL-2 and AEGL-3 values overlap suggesting a very steep concentration-response relationship.
Calculations:	
10-min AEGL-2:	$C = (12{,}977.875 \text{ ppm-h} \div 0.167 \text{ h})^{1/3}$ $C = 43 \text{ ppm}$
30-min AEGL-2:	$C = (12{,}977.875 \text{ ppm-h} \div 0.5 \text{ h})^{1/3}$ $C = 30 \text{ ppm}$
1-h AEGL-2:	$470 \text{ ppm} \div 20 = 24 \text{ ppm}$
4-h AEGL-2:	$C = (23.5 \text{ ppm-h} \div 4 \text{ h})^1$ $C = 6.0 \text{ ppm}$
8-h AEGL-2:	$C = (23.5 \text{ ppm-h} \div 8 \text{ h})^1$ $C = 3.0 \text{ ppm}$

Derivation of AEGL-3 Levels

Key study:	DuPont. 1987. One-hour Inhalation Median Lethal Concentration (LC50) Study with Nitric Acid. Report No 451-87. Haskell Laboratory, DuPont, Newark, DE. 26 pp.
Toxicity end point:	LC_{01} of 919 ppm was calculated by log-probit analysis of mortality data in rats.
Time scaling:	$C^n \times t = k$ (default of n = 3 for extrapolating to the 10- and 30-min durations; default of n = 1 for extrapolating to the 4- and 8-h durations $(919 \text{ ppm} \div 10)^3 \times 1 \text{ h} = 776{,}151.559 \text{ ppm-h}$ $(919 \text{ ppm} \div 10)^1 \times 1 \text{ h} = 91.9 \text{ ppm-h}$
Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability Total uncertainty factor of 10
Modifying factor:	None
Calculations:	
10-min AEGL-3:	$C = (776{,}151.559 \text{ ppm-h} \div 0.167 \text{ h})^{1/3}$ C = 170 ppm
30-min AEGL-3:	$C = (776{,}151.559 \text{ ppm-h} \div 0.5 \text{ h})^{1/3}$ C = 120 ppm
1-h AEGL-3:	C = 919 ppm ÷ 10 = 92 ppm
4-h AEGL-3:	$C = (91.9 \text{ ppm-h} \div 4 \text{ h})^1$ C = 23 ppm
8-h AEGL-3:	$C = (91.9 \text{ ppm-h} \div 8 \text{ h})^1$ C = 11 ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR NITRIC ACID

Derivation Summary

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)	0.16 ppm (0.41 mg/m^3)

Reference: Sackner, M.A., and D. Ford. 1981. Effects of breathing nitrate aerosols in high concentrations for 10 minutes on pulmonary function of normal and asthmatic adults, and preliminary results in normals exposed to nitric acid fumes. Am. Rev. Resp. Dis. 123(4Pt 2):151.

Test species/Strain/Number: Humans, sex not specified, 10

Exposure route/Concentrations/Durations: Inhalation, 1.6 ppm for 10 min

Effects: No effects

End point/Concentration/Rationale: No-effect level for changes in pulmonary function (vital capacity, respiratory resistance, and FEV_1); highest no-effect level available in humans.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Intraspecies: 10, to account for variability in response in the general population and possibly greater sensitivity of asthmatics to effects of a direct-acting irritant on pulmonary function.

Modifying factor: None

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: Not performed; values were set equal across all AEGL durations because the point of departure is a no-effect level for irritation.

Data adequacy: Although no dose-response data was included in the study, the values are based on human data. The point of departure is the highest no-observed-adverse-effect level in humans.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
43 ppm (110 mg/m^3)	30 ppm (77 mg/m^3)	24 ppm (62 mg/m^3)	6.0 ppm (15 mg/m^3)	3.0 ppm (7.7 mg/m^3)

Reference: DuPont. 1987. One-hour Inhalation Median Lethal Concentration (LC_{50}) Study with Nitric Acid. Report No 451-87. Haskell Laboratory, DuPont, Newark, DE. 26 pp.

(Continued)

AEGL-2 VALUES Continued

Test species/Strain/Sex/Number: Rat, Crl:CD®BR, 5 males and 5 females per group

Exposure route/Concentrations/Durations: Inhalation, 270-3,100 ppm for 1 h

Effects:

Concentration (ppm)	Effects
260 and 470	Body weight loss for 1-2 days
≥1,300	Partially closed eyes
≥1,600	Lung noise and gasping
≥1,500	Extended weight loss up to 12 days post-exposure in males
≥1,600	Extended weight loss up to 12 days post-exposure in females
3,100	100% lethality

End point/Concentration/Rationale: No-effect level for impaired ability to escape (eye closure) was 470 ppm for 1 h.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, because the mechanism of toxicity (direct reaction of nitric acid with ocular or pulmonary tissue) is not expected to vary between humans and animals.
Intraspecies: 3, because the mechanism of action of a corrosive acid in the eye or lung is not expected to differ greatly among individuals.

Modifying factor: 2, because clinical observations were not well described, and AEGL-2 and AEGL-3 values overlap suggesting a very steep concentration-response relationship.

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: $C^n \times t = k$; n = 3 for extrapolating to the 10- and 30-min durations, and n = 1 for extrapolating to the 4- and 8-h duration

Comments: Nitrogen dioxide content monitored during exposures; none measured.

AEGL -3 VALUES

10 min	30 min	1 h	4 h	8 h
170 ppm (440 mg/m^3)	120 ppm (310 mg/m^3)	92 ppm (240 mg/m^3)	23 ppm (59 mg/m^3)	11 ppm (28 mg/m^3)

Reference: DuPont. 1987. One-hour Inhalation Median Lethal Concentration (LC_{50}) Study with Nitric Acid. Report No 451-87. Haskell Laboratory, DuPont, Newark, DE. 26 pp.

Test species/Strain/Sex/Number: Rat, Crl:CD®BR, 5 males and 5 females per group

Exposure rRoute/Concentrations/Durations: Inhalation, 270-3,100 ppm for 1 h

Effects:

Concentration (ppm)	Effects
260 and 470	Body weight loss for 1-2 days; no death
1,300	1/10 died
1,500	1/10 died
1,600	2/10 died
2,500	3/10 died
2,700	3/10 died
3,100	10/10 died

End point/Concentration/Rationale: LC_{01} of 919 ppm estimated by log-probit analysis of mortality data.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, because the mechanism of toxicity (direct reaction of nitric acid with ocular or pulmonary tissue) is not expected to vary between humans and animals.
Intraspecies: 3, because the mechanism of action of a corrosive acid in the eye or lung is not expected to differ greatly among individuals.

Modifying factor: None

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: $C^n \times t = k$; n = 3 for extrapolating to the 10- and 30-min durations, and n = 1 for extrapolating to the 4- and 8-h durations

Comments: Nitrogen dioxide content monitored during exposures; none measured.

APPENDIX C

CATEGORY PLOT FOR NITRIC ACID

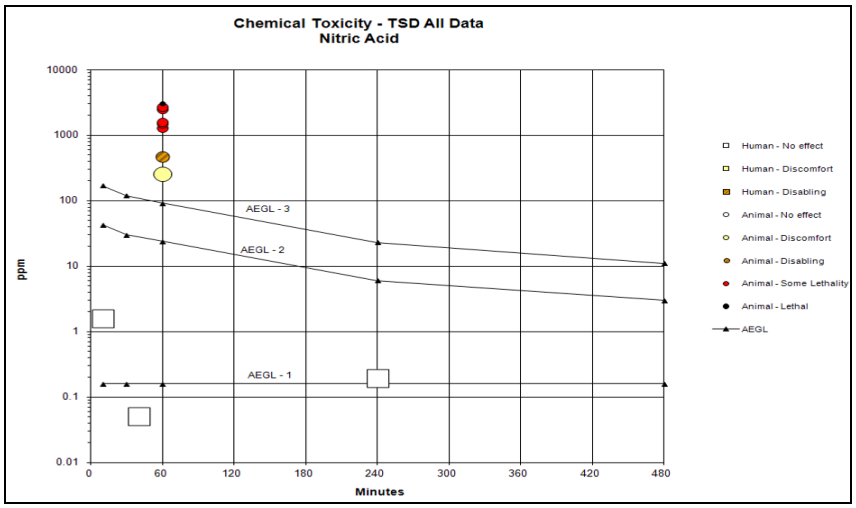

FIGURE C-1 Category plot of toxicity data and AEGL values for nitric acid.

TABLE C-1 Data Used in Category Plot for Nitric Acid

Source	Species	Sex	No. of Exposures	ppm	Minutes	Category	Comments
NAC/AEGL-1				0.16	10	AEGL	
NAC/AEGL-1				0.16	30	AEGL	
NAC/AEGL-1				0.16	60	AEGL	
NAC/AEGL-1				0.16	240	AEGL	
NAC/AEGL-1				0.16	480	AEGL	
NAC/AEGL-2				43	10	AEGL	
NAC/AEGL-2				30	30	AEGL	
NAC/AEGL-2				24	60	AEGL	
NAC/AEGL-2				6	240	AEGL	

(Continued)

TABLE C-1 Continued

Source	Species	Sex	No. of Exposures	ppm	Minutes	Category	Comments
NAC/AEGL-2				3	480	AEGL	
NAC/AEGL-3				170	10	AEGL	
NAC/AEGL-3				120	30	AEGL	
NAC/AEGL-3				92	60	AEGL	
NAC/AEGL-3				23	240	AEGL	
NAC/AEGL-3				11	480	AEGL	
Koenig et al. 1989	Human		1	0.05	40	0	
Sackner and Ford 1981	Human		1	1.6	10	0	
Aris et al. 1993	Human		1	0.194	240	0	
DuPont 1987	Rat	Both	1	260	60	1	Transient weight loss
	Rat	Both	1	470	60	2	Transient weight loss
	Rat	Both	1	1,300	60	SL	Mortality (1/10); partially closed eyes
	Rat	Both	1	1,500	60	SL	Mortality (1/10); weight loss
	Rat	Both	1	1,600	60	SL	Mortality (2/10); lung noise, gasping
	Rat	Both	1	2,500	60	SL	Mortality (3/10)
	Rat	Both	1	2,700	60	SL	Mortality (3/10)
	Rat	Both	1	3,100	60	3	Mortality (10/10)

For category: 0 = no effect, 1 = discomfort, 2 = disabling, 3 = lethal; SL = some lethality.

APPENDIX D

DERIVATION OF LC_{01} VALUE FOR NITRIC ACID

Filename: ten Berge Spreadsheet Data for Log Probit Model
Date: 01 March 2012 Time: 16:01:18

Sequence No.	Concentration (ppm)	Minutes	Exposed	Responded
1	260	60	10	0
2	470	60	10	0
3	1300	60	10	1
4	1500	60	10	1
5	1600	60	10	2
6	2500	60	10	3
7	2700	60	10	3
8	3100	60	10	10

Observations 1 through 8 considered!

Sequence No.	Concentration (ppm)	Minutes	Exposed	Responded
1	260	60	10	0
2	470	60	10	0
3	1300	60	10	1
4	1500	60	10	1
5	1600	60	10	2
6	2500	60	10	3
7	2700	60	10	3
8	3100	60	10	10

Used Probit Equation Y = B0 + B1*X1
X1 = ppm, ln-transformed

Chi-Square = 9.29
Degrees of freedom = 6
Probability Model = 1.58E-01

Ln(Likelihood) = -11.92

B 0 = -1.2890E+01 Student t = -2.7813
B 1 = 2.2809E+00 Student t = 3.7913

Variance B 0 0 = 2.1479E+01
Covariance B 0 1 = -2.7859E+00
Variance B 1 1 = 3.6193E-01

Estimation of ppm at response of 1%
Point estimate ppm = 9.192E+02 for response of 1%
Lower limit (95% CL) ppm = 3.509E+02 for response of 1%
Upper limit (95% CL) ppm = 1.273E+03 for response of 1%

6

Propargyl Alcohol[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 Robert Young (Oak Ridge National Laboratory), Lisa Ingerman (SRC, Inc.), Chemical Manager George Cushmac (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 concentrations 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

Propargyl alcohol is a moderately volatile, three-carbon acetylenic alcohol with a geranium-like odor. It is used as a chemical intermediate, solvent stabilizer, soil fumigant, and corrosion inhibitor. Annual production in the United States has been estimated at 0.5 to 2.8 million pounds.

No information on human exposure to propargyl alcohol is available. On the basis of animal data, the chemical is likely to be irritating to the eyes and respiratory tract.

Toxicity data on propargyl alcohol are available from studies of rats, mice, guinea pigs, rabbits, and cats. The studies involved acute (1-2 h) and longer-term exposures (9 days to 13 weeks). Lethality data included estimated or tested concentrations associated with 50% lethality of approximately 1,000-1,200 ppm for rats and 1,300 ppm for cats after 1-h exposures, and 850 ppm for rats and 875 ppm in mice after 2-h exposures. In longer-term studies, repeated exposure to propargyl alcohol at concentrations up to 88 ppm for 14 days or 64 ppm for 13 weeks were not lethal but resulted in notable histopathologic changes in the olfactory and respiratory epithelium of rats and mice. No reproductive toxicity, developmental toxicity, or carcinogenicity data on inhalation exposure to propargyl alcohol are available. Genotoxicity findings are equivocal. Propargyl alcohol is rapidly metabolized to propargyl aldehyde and various conjugation products; excretion is primarily via the urine.

AEGL-1 values were based on a concentration of 25.3 ppm, which was a no-effect level for histopathologic changes in the respiratory tract of mice ex-

posed to propargyl alcohol for 6 h (Zissu 1995). That concentration was considered an appropriate point of departure because a 7-h exposure of rats to propargyl alcohol at 80 ppm (the first of 59 exposures) produced signs of ocular irritation and lethargy to which the test animals subsequently adapted (Dow Chemical Co. 1964). Toxicologic response to propargyl alcohol appeared to be similar qualitatively among species tested, and individual responses are not expected to vary more than three-fold for simple direct-contact irritants. Therefore, an interspecies uncertainty factor of 3 and an intraspecies uncertainty factor of 3 were applied (total uncertainty factor of 10). Because slight direct-contact irritation is not expected to vary markedly with exposure duration, the same value was used for all AEGL-1 exposure durations.

AEGL-2 values were based on a point of departure of 88 ppm, a concentration that produced severe histologic alterations in the olfactory and respiratory epithelium of mice exposed to propargyl alcohol for 6 h/day for 4, 9, or 14 days. The point of departure is supported by observations of ocular irritation and lethargy in rats after the first of 59 exposures to propargyl alcohol at 80 ppm for 7 h (adaptation occurred during subsequent exposures) (Dow Chemical Co. 1964). An uncertainty factor of 3 was applied to account for interspecies differences because the toxic effects of propargyl alcohol do not appear to vary greatly between species. Because histopathologic lesions from propargyl alcohol are likely the result of direct-contact irritation, an uncertainty factor of 3 was applied to account for intraindividual variability. Time scaling from the 6-h experimental exposure duration to AEGL-specific exposure durations was performed using the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data on propargyl alcohol were inadequate for deriving an empirical value for n, so default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations were used. However, because of uncertainties associated with extrapolating a 6-h exposure to a 10-min value, the 30-min AEGL-2 value was adopted for the 10-min value (NRC 2001).

AEGL-3 values were based on mouse lethality data reported by Stasenkova and Kochetkova (1966). A $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) of 573 ppm (2-h exposure) was the point of departure. That $BMCL_{05}$ is consistent with the range of 1-h lethal concentrations of 1,040-1,200 ppm reported for rats (Vernot et al. 1977). Further, BASF (1965) reported no lethality in two rabbits or six guinea pigs exposed to propargyl alcohol at 1,300 ppm for 1 h, but one of two cats died from the same exposure. The available data support an interspecies uncertainty factor of 3. Animal data suggest that olfactory and respiratory-tract epithelium are the primary targets of propargyl alcohol and that damage to these tissues is likely instrumental in deaths after a single acute exposure. Studies of repeated exposures to propargyl alcohol (about 90 days) provided evidence of renal and hepatic toxicity, but the data do not support the contention that such systemic toxicity would follow a single acute exposure. Therefore, an intraspecies uncertainty factor of 3 was used. Time scaling was performed using the same method described for the AEGL-2 values.

AEGL values for propargyl alcohol are summarized in the Table 6-1.

1. INTRODUCTION

Propargyl alcohol is a moderately volatile three-carbon acetylenic alcohol with a geranium-like odor. It is used as a chemical intermediate, solvent stabilizer, soil fumigant, and corrosion inhibitor (Bevan 2001). Annual production in the United States has been estimated at 0.5 to 2.8 million pounds (J. Walker, EPA, Washington, DC, personal commun., April 26, and June 8, 1995).

Selected chemical and physical properties for propargyl alcohol isomers are presented in Table 6-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data regarding lethality in humans following inhalation exposure to propargyl alcohol were available.

2.2. Nonlethal Toxicity

Propargyl alcohol is reportedly irritating to the eyes, skin, and respiratory tract (Bevan 2001). However, definitive concentration-response data in humans are unavailable.

TABLE 6-1 AEGL Values for Propargyl Alcohol

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	2.5 ppm (5.7 mg/m^3)	2.5 ppm (5.7 mg/m^3)	2.5 ppm (5.7 mg/m^3)	2.5 ppm (5.7 mg/m^3)	2.5 ppm (5.7 mg/m^3)	No-observed-adverse-effect level for histopathologic changes in respiratory tract of mice (Zissu 1995)
AEGL-2 (disabling)	20 ppm (46 mg/m^3)	20 ppm (46 mg/m^3)	16 ppm 37 mg/m^3)	10 ppm 23 mg/m^3)	6.6 ppm 15 mg/m^3)	Lesions in olfactory and respiratory epithelium (Zissu 1995)
AEGL-3 (lethal)	130 ppm (300 mg/m^3)	91 ppm (210 mg/m^3)	72 ppm (160 mg/m^3)	29 ppm (66 mg/m^3)	14 ppm (32 mg/m^3)	Estimated lethality threshold in mice (Stasenkova and Kochetkova 1966)

TABLE 6-2 Chemical and Physical Data for Propargyl Alcohol

Parameter	Value	Reference
Synonyms	2-Propyn-l-ol; acetylene carbinol; propiolic alcohol; 2-propynol; 2-propynyl alcohol; 1-propyn-3-ol	O'Neil et al. 2006; ACGIH 2007
CAS registry no.	107-19-7	O'Neil et al. 2006
Chemical formula	C_3H_4O	O'Neil et al. 2006
Molecular weight	56.06	O'Neil et al. 2006
Physical state	Colorless to straw-colored liquid	NIOSH 2011
Freezing point	-52 to -48°C	O'Neil et al. 2006
Boiling point	114-115°C	O'Neil et al. 2006; ACGIH 2007
Density/specific gravity	0.97 at 20°C	NIOSH 2011
Solubility in water	Miscible	O'Neil et al. 2006
Vapor pressure	12 mm Hg at 20°C	NIOSH 2011
Saturated vapor pressure	15,800 ppm at 20°C	Calculated
Conversion factors in air	1 ppm = 2.29 mg/m^3 1 mg/m^3 = 0.437 ppm	NIOSH 2011

2.3. Developmental and Reproductive Effects

No human developmental or reproductive toxicity data on propargyl alcohol were available.

2.4. Genotoxicity

No human genotoxicity data on propargyl alcohol were available.

2.5. Carcinogenicity

No human data on the carcinogenic potential of propargyl alcohol were available.

2.6. Summary

No definitive information on the effects of propargyl alcohol in humans is available.

3. ANIMAL TOXICITY DATA

3.1. Lethality

3.1.1. Rats

All rats (groups of three) exposed to saturated atmospheres (about16,000 ppm) of propargyl alcohol for 0.2-2.0 h died (Dow Chemical Co. 1953). Time to death was inversely proportional to exposure duration; death occurred within 2 days from a 0.2-h exposure, within 2 h for a 0.5-h exposure, and within 2 h for a 2.0-h exposure. Two of three rats died after a 0.1-h exposure to a saturated atmosphere; deaths occurred within 4 days and the surviving rat recovered over 2 weeks. No further details of the experiment were provided.

BASF (1963) exposed rats (strain and gender not specified) to "vapor-enriched atmospheres" (likely a saturated propargyl alcohol vapor at about 16,000 ppm). Six of 12 rats died after a 3-min exposure, six of six rats died after a 10-min exposure, and six of six died after either a 1-h or 3-h exposure. Responses included mucous membrane irritation, pallor of paws and ears, and dyspnea.

BASF (1965) conducted an acute toxicity study of propargyl alcohol in multiple species. Ten rats were exposed for 1 h to propargyl alcohol at approximately 1,300 ppm (3 mg/L, purity not specified) in a closed 400-L chamber. No signs of toxicity were observed during exposure. One rat died after 3 days. Gross pathologic examination of the rat revealed evidence of liver toxicity.

A 5-day study was also conducted using one cat, one rabbits, four guinea pigs, 10 rats, and 10 mice exposed to propargyl alcohol at about 1,300 ppm for 1 h/day (BASF 1965). Similar to the single-exposure study, none of the rabbits or guinea pigs died but the cat died after 2 days, four rats after 3-4 days, and seven mice after 23 days. Gross pathologic findings in these animals revealed liver damage.

BASF (1965) also provided a brief description of a longer-term study, in which 30 rats (12 males, 18 females) were exposed to propargyl alcohol at 100 ppm (analytic concentration 90 ppm) for 6 h/day, 5 days/week, for up to a total of 75 exposures, depending on the specific treatment group. Seventeen rats died during the later stages of the study. Results of clinical chemistry test and gross pathologic examinations showed hepatic and renal damage in most of the test animals.

Vernot et al. (1977) reported 1-h LC_{50} values for propargyl alcohol of 1,200 ppm (1,180-1,220 ppm) and 1,040 ppm (970-1,120 ppm) for male and female Sprague Dawley rats, respectively. Groups of five rats were exposed to the test article in bell jars or large desiccators. LC_{50} values were determined by probit analysis (method of Finney 1971). No additional details were provided in the study report.

Hazelton Laboratories America, Inc. (1989) conducted limit tests under Good Laboratory Practices with 10 male and 10 female Sprague-Dawley rats

exposed to propargyl alcohol at 1,490 ± 159.8 ppm (time-weighted-average exposure) for 1 h. Rats were exposed in a 100-L plexiglass dynamic-flow chamber (19.2 L/min). Vapor was generated by passing filtered air through bubblers containing the propargyl alcohol, and its concentration was determined by infrared analysis (MIRAN assay). Rats were observed every 15 min during exposure. Physical examinations were performed before, immediately after, and 1 h after exposure, and daily thereafter. Treated animals exhibited hunched posture, rough hair coat, listlessness, low body temperature, prostration, and death. All rats were dead 3 days after exposure. Necropsy findings were reported to be indicative of post-mortem changes and did not reveal changes directly attributed to the test article.

Kennedy and Graepel (1991) reported a 2-h LC_{50} of 850 ppm for propargyl alcohol in a study that compared oral and inhalation acute toxicity data for rats. In their overall assessment of the acute toxicity of 108 chemicals, propargyl alcohol was classified as moderately toxic (LC_{50} range of 100-1,000 ppm). No details of experimental methods were provided in the report.

3.1.2. Mice

Three of 10 mice died 1 day after being exposed to propargyl alcohol at 3,000 ppm for 1 h (BASF 1965). Necropsy of the mice revealed signs of mucous-membrane and colon irritation. Surviving mice examined 7 days after exposure had no remarkable signs of toxicity.

A longer-term exposure study was also conducted, in which 30 male and 30 female mice were exposed to propargy alcohol at 100 ppm (analytic concentration 90 ppm) for 6 h/day, 5 days/week, for up to a total of 75 exposures, depending on the specific treatment group (BASF 1965). Results of clinical chemistry tests and gross pathologic examinations suggested both hepatic and renal damage, although the hepatic damage appeared to be reversible.

In a multiple species study by BASF (1965), 10 mice were exposed for 1 h to propargyl alcohol at approximately 1,300 ppm (3 mg/L, purity not specified) in a closed 400-L chamber. No signs of toxicity during the exposure were observed. Three of 10 mice died after 1 day. Gross pathologic examination of animals that died revealed evidence of hepatic toxicity.

Lethal effects of propargyl alcohol in mice were also reported by Stasenkova and Kochetkova (1966). Exposure of rats to propargyl alcohol for 2 h at 500, 1,500, 2,000, or 3,500 mg/m^3 (220, 655, 875, and 1,500 ppm) resulted in mortality incidences of 1/20, 1/20, 10/20, and 20/20, respectively.

3.1.3. Cats

In an experiment reported by BASF (1965), one of two cats died after a 1-h exposure to propargyl alcohol at 3,000 mg/m^3 (1,300 ppm). The time of death was not specified, but a 14-day observation period was reported. The cat was

described as lethargic, without appetite, and vomiting before death. Mucous membrane irritation, presence of urobilinogen and protein in the urine, and increased serum aminotransferase activity were reported (but it was unclear whether the effects were found in one or both animals).

In a longer-term exposure study, three cats were exposed to propargyl alcohol at 100 ppm (analytic concentration 90 ppm) for 6 h/day, 5 days/week (BASF 1965). The cats died after 29, 32, and 43 exposures.

3.1.4. Rabbits

BASF (1965) briefly described a longer-term exposure study, in which three rabbits were exposed to propargyl alcohol at 100 ppm (analytic concentration 90 ppm) for 6 h/day, 5 days/week, for up to a total of 75 exposures. One rabbit died after 45 exposures. Results of clinical chemistry tests and gross pathologic examinations showed both hepatic and renal damage in most of the test animals.

3.1.5. Summary of Animal Lethality Data

Lethality data for propargyl alcohol in various laboratory species are summarized in Table 6-3.

TABLE 6-3 Lethality of Inhaled Propargyl Alcohol in Laboratory Species

Species	Exposure Duration (min)	Exposure Concentration (ppm)	Lethality	Reference
Rat (males)	60	1,200	LC_{50}[a]	Vernot et al. 1977
Rat (females)	60	1,040	LC_{50}[a]	
Rat	60	1,490	10/10	Hazelton Laboratories America Inc. 1989
Rat	120	850	LC_{50}[b]	Kennedy and Graepel 1991
Mouse	60	3,000	3/10	BASF 1965
Mouse	120	220 655 875 1,500	1/20 1/20 10/20 20/20	Stasenkova and Kochetkova 1996
Cat	60	1,300	1/2	BASF 1965

[a]Five male and five females per exposure group.
[b]No experimental details.

3.2. Nonlethal Toxicity

3.2.1. Rats

Groups of six male and six female rats (strain not specified) were exposed to propargyl alcohol at a nominal concentration of 100 ppm (80 ppm by infrared analysis) in 160-L glass chambers (Dow Chemical Co. 1964). An additional six male and six female rats were maintained as unexposed controls. Exposure was for 7 h/day, 5 days/week, for 89 days (59 exposures). Although signs of ocular irritation and lethargy were observed during the first exposure, rats reportedly adapted and exhibited no additional responses throughout the remainder of the experiment. Gross necropsy findings consisted of enlarged livers in both sexes (females more so) with microscopic correlates indicative of degenerative changes (focal centrilobular necrosis, hydropic degeneration with cellular infiltration, and midzonal fatty metamorphosis). Severity of hepatic lesions ranged from mild to severe. Slight pneumonitis and mild degenerative changes in the kidneys were also noted. Serum enzyme activity (serum glutamic pyruvic transaminase and alkaline phosphatase) was slightly elevated. Hematologic changes (hematocrit, erythrocytes, serum urea nitrogen, hemoglobin concentration, and differential counts) were normal or only slightly altered. Bone marrow smears were normal.

BASF (1992a) conducted a 2-week study (OECD guideline 421) in which male and female Wistar rats (five per group) were exposed to propargyl alcohol (99.4% purity) at nominal concentrations of 0, 10, 50, or 200 ppm (analytic concentrations 0, 9.8, 50.4, and 199 ppm) for 6 h/day, 5 days/week. No clinical signs were observed in the control, 10-ppm, or 50-ppm groups. At the highest concentration, rats exhibited irregular breathing, lethargy, and nasal discharge during exposure (also in between exposures later in the study period). One female rat in the 200-ppm group died and the surviving rats exhibited decreased body weight gain and elevated serum alanine aminotransferase and serum alkaline phosphatase. Histopathologic findings included metaplasia of the olfactory mucosa (50 and 200 ppm) and hepatocellular hypertrophy, parenchymal single-cell necrosis, and cytoplasmic granulation (200 ppm). These findings were characterized as minimal in the 10-ppm and 50-ppm groups. Significantly increased relative liver weight was detected in males of the 200-ppm group, and significantly increased relative kidney weight was found in males and females of the 50- and 200-ppm groups.

BASF (1992b) conducted a 90-day study under Good Laboratory Practices, in which groups of 10 male and 10 female Wistar rats were exposed to propargyl alcohol vapor (99% pure) at nominal concentrations of 1, 5, or 25 ppm (analytic concentrations 1.1, 5.1, and 24.6 ppm) for 6 h/day, 5 days/week, for a total of 65 exposures; controls were exposed to clean air. No mortality or clinical signs of toxicity occurred. Clinical chemistry and hematologic assessments were negative. Results of gross pathologic and histopathologic examinations were unremarkable. Although a statistically significant reduction in body weight gain was noted for male rats during the first 2 weeks of exposure, no significant

effect on body weight gain was detected at the end of the study. Absolute renal weight and kidney-to-body weight ratio were increased in female rats exposed at 24.6 ppm. These rats also exhibited a slight decrease in serum cholinesterase activity, but no gross or histopathologic effects were found. No post-exposure period was indicated. The no-observed-adverse-effect level was 5.1 ppm and the lowest-observed-adverse-effect level was 24.6 ppm.

Exposure of groups of 10 male and 10 female Fischer 344 rats to propargyl alcohol at 0, 4, 8, 16, 32, or 64 ppm for 13 weeks did not result in any gross lesions or other significant toxic responses (NTP 2008). Chamber concentrations, monitored daily, were within the range specified in the experimental protocol and propargyl alcohol was stable throughout the experiment. Hyperplasia of the nasal epithelium was observed in male rats at all concentrations, squamous metaplasia of nasal epithelium was detected in males and females at the highest concentration, and necrosis of the olfactory epithelium occurred in males and females at the two highest concentrations (see Table 6-4). A decrease in serum cholinesterase activity ($p < 0.05$) was detected in female rats 3 days after exposure at 32 and 64 ppm; no effect was observed in males until day 23. An increase in blood urea nitrogen ($p < 0.01$) was observed in males and females 3 days after exposure to propargyl alcohol at 32 and 64 ppm. These minor alterations in clinical chemistry parameters continued through the exposure period. Hematologic parameters were unaffected.

3.2.2. Mice

Zissu (1995) exposed groups of 10 Swiss mice to propargyl alcohol at concentrations of 88 or 25.3 ppm (analytic concentrations 81.0-104.0 ppm and 22.0-31.0 ppm, respectively) for 6 h/day for 4, 9, or 14 days. Analytic concentrations were determined from chamber air samples collected with a solid adsorbent (silica gel). Breathing rates were monitored during exposure. No significant toxic effects were observed at the lower concentration. Histopathologic examinations of animals exposed at 88 ppm revealed changes in the olfactory epithelium (dorsal meatus) and respiratory epithelium (adjacent to the vestibule and characterized by rhinitis and necrosis extending into the underlying connective tissue and bone). Neither the trachea nor the lungs were affected. Lesions were most severe after 4 days of treatment and did not increase in severity after 14 days; however, there was no evidence of repair as was observed with other test chemicals (allyl alcohol, dichlorobenzene, and formaldehyde).

In a subchronic study conducted under Good Laboratory Practices, groups of 10 male and 10 female $B6C3F_1$ mice were exposed (whole-body) for 13 weeks to propargyl alcohol at nominal concentrations of 0, 4, 8, 16, 32, or 64 ppm (NTP 2008). No treatment-related deaths occurred. Mean body weight was decreased in all exposure groups, and was significantly lower in the three highest exposure groups (-8.5, -11.3, and -15.6%, respectively; $p < 0.05$) relative to the control group. Exposures resulted in significantly increased kidney-to-body

weight ratios at 8 ppm and liver-to-body weight ratios at 16 ppm and higher in male rats; however, female rats exhibited changes only in kidney weights at 32 and 64 ppm. No gross lesions were observed at necropsy. Hyperplasia of the nasal epithelium was considered the most sensitive treatment-related response. Other effects included necrosis and atrophy of respiratory epithelium, hepatic and renal weight changes, and decreased cholinesterase activity. The National Toxicology Program (NTP) considered 8 ppm a no-observed-adverse-effect level. Major pathologic findings are summarized in Table 6-5.

3.2.3. Guinea Pigs

No lethality was observed in six guinea pigs exposed to propargyl alcohol at 3,000 mg/m^3 (1,300 ppm) for 1 h (BASF 1965). Irritation of mucous membranes was the only effect reported. The duration of the post-exposure observation period was not specified.

TABLE 6-4 Effects in Fischer Rats after Exposure to Propargyl Alcohol for 13 Weeks

Effect	0 ppm	4 ppm	8 ppm	16 ppm	32 ppm	64 ppm
Males						
Olfactory epithelium necrosis	0/10	0/10	0/10	0/10	2/10	5/10
Respiratory epithelium[a]						
Hyperplasia	2/10	6/10	2/10	4/10	8/10	10/10
Squamous metaplasia	0/10	0/10	0/10	0/10	0/10	3/10
Increased kidney/body weight	-	-	-	-	-	$p < 0.01$
Increased liver weight	-	-	-	-	-	$p < 0.01$
Increased liver/body weight	-	-	-	-	$p < 0.01$	$p < 0.01$
Females						
Olfactory epithelium necrosis	0/10	0/10	0/10	0/10	3/10	5/10
Respiratory epithelium[a]						
Hyperplasia	0/10	2/10	2/10	2/10	10/10	10/10
Sqauamous metaplasia	0/10	0/10	0/10	0/10	0/10	8/10
Necrosis	0/10	0/10	0/10	0/10	0/10	2/10
Increased kidney/body weight	-	-	-	-	-	$p < 0.01$
Increased liver/body weight	-	-	-	-	-	$p < 0.01$

[a]Nasal respiratory epithelium.
Source: NTP 2008.

TABLE 6-5 Effects in $B6C3F_1$ Mice after Exposure to Propargyl Alcohol for 13 Weeks

Effect	0 ppm	4 ppm	8 ppm	16 ppm	32 ppm	64 ppm
Males						
Nasal inflammation	0/10	0/10	0/10	0/10	0/10	6/10
Olfactory epithelium						
Necrosis	0/10	0/10	1/10	0/10	1/10	0/10
Atrophy	0/10	0/10	0/10	0/10	8/10	10/10
Hyaline degeneration	0/10	0/10	0/10	0/10	3/10	9/10
Hyperplasia	0/10	0/10	0/10	3/10	9/10	9/10
Respiratory epithelium[a]						
Squamous metaplasia	0/10	0/10	0/10	0/10	5/10	10/10
Increased kidney/body weight	-	-	$p < 0.05$	$p < 0.01$	$p < 0.01$	$p < 0.01$
Increased liver/body weight	-	-	-	-	$p < 0.01$	$p < 010$
Females						
Olfactory epithelium						
Necrosis	0/10	0/10	0/10	9/10	4/10	0/10
Atrophy	0/10	0/10	0/10	0/10	7/10	10/10
Hyaline degeneration	0/10	0/10	0/10	0/10	7/10	8/10
Hyperplasia	0/10	0/10	0/10	0/10	8/10	10/10
Respiratory epithelium[a]						
Squamous metaplasia	0/10	0/10	0/10	1/10	7/10	10/10
Increased kidney/body weight	-	-	-	-	$p < 0.01$	$p < 0.01$

[a]Nasal respiratory epithelium.
Source: NTP 2008.

3.2.4. Rabbits

No deaths occurred in two rabbits exposed to propargyl alcohol at 3,000 mg/m^3 (1,300 ppm) for 1 h (BASF 1965). Over a 14-day observation period, signs of toxicity included mild irritation of mucous membranes (nonspecific), slightly elevated activity levels of serum aminotransferases, and positive tests for urobilinogen and protein in the urine.

3.2.5. Summary of Nonlethal Toxicity in Animals

Nonlethal exposure of several laboratory species to propargyl alcohol resulted in agitation and mucous membrane irritation (ocular and nasal epithelial surfaces), followed by dyspnea, lethargy, and listlessness. Hyperplasia of the

respiratory tract epithelium, evidence of hepatic and renal toxicity, and decreased serum cholinesterase activity were detected after longer-term exposure of rats to nonlethal concentrations of propargyl alcohol. In a 3-month study, rats exposed at 100 ppm for 7 h exhibited ocular irritation and lethargy after the first exposure but adaptation reportedly occurred as the experiment progressed and the responses resolved. Repeated exposure of rats to propargyl alcohol at 5.1 ppm for 6 h/day was without effect, but exposure at 24.6 ppm resulted in increased kidney-to-body weight ratio and a decrease in serum cholinesterase activity. Another study reported that repeated exposure of rats to propargyl alcohol at concentrations less than 32 ppm was without notable effect, but decreased serum cholinesterase activity and increased blood urea nitrogen were found at 32 and 64 ppm. A concentration of 8 ppm was considered a no-observed-adverse-effect level for repeated exposure to propargyl alcohol.

3.3. Developmental and Reproductive Effects

Data on the developmental and reproductive toxicity of propargyl alcohol after inhalation exposure were not available.

3.4. Genotoxicity

On the basis of tests with *Salmonella typhimurium* strains TA1535, TA1538, TA100, TA1537, and TA98, Blakey et al. (1994) concluded that propargyl alcohol was not mutagenic.

Chinese hamster ovary cells exhibited a positive trend ($p < 0.05$ at the highest concentration) in increased chromosomal aberrations 16 h after treatment with propargyl alcohol at 0.04-1.0 mM without activation (Blakey et al. 1994). With metabolic activation, frequency of aberrations became more significant ($p < 0.001$) at concentrations of 1.0-10 mM. No effect in cells was observed 10-h after treatment.

In a micronucleus assay (five male and five female NMRI mice were administered propargyl alcohol by gavage at 0 or 70 mg/kg for 24, 48, or 72 h. Female mice in the 24- and 72-h groups exhibited a small but statistically significant increase in micronucleated polychromatic erythrocytes. Because the increase was within the range of negative control values, it was considered to be of no toxicologic significance (Hoechst AG 1990). A micronucleus assay using C57BL mice (propargyl alcohol administered twice at doses of 24, 48, or 72 mg/kg and killed 36 h after the second dose) was negative (Blakey et al. 1994).

3.5. Carcinogenicity

No data to evaluate the carcinogenic potential of inhaled propargyl alcohol were available.

3.6. Summary

Lethality data in laboratory species exposed to propargyl alcohol for 1-2 h indicate that 50% morality occurs at concentration-time products of 1,000-1,750 ppm-h, as determined by LC_{50} values and raw response data: LC_{50} of 1,000-1,200 ppm-h for rats (Vernot et al. 1977), 50% lethality in mice at 1,750 ppm-h (Stasenkova and Kochetkova 1966), 30-59% lethality in mice and cats at 1,300 ppm-h (BASF 1965), and LC_{50} of 1,700 ppm-h in rats (Kennedy and Graepel 1991). Data on nonlethal responses to propargyl alcohol are primarily from repeated exposure studies (about 13 weeks) in rats and mice, which found histopathologic changes in the olfactory and respiratory epithelium at concentrations of about 25-88 ppm (6-24 h/day) and evidence of hepatic and renal changes at higher concentrations. Observations on the first observation day of a repeated exposure study are the only data on acute nonlethal toxicity.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

In studies with rats and mice, absorption of propargyl alcohol was 55-63% at concentrations of 1 or 10 ppm but only 23-33% at 100 ppm (NTP 2008). Elimination in both species was primarily via the urine. Rats orally dosed with radiolabeled propargyl alcohol (40 mg/kg) excreted about 60% of the dose in the urine within 96 h (Bevan 2001). Metabolism of propargyl alcohol appeared to be mediated by oxidation and subsequent glutathione conjugations. Metabolites identified by nuclear magnetic resonance and mass spectrophotometry included: 3-{[2-(acetyl-amino)-2-carboxyethyl]thio}-2-propenoic acid; *S*-*S'*-(3-hyroxypropylidene)-bis[*N*-acetyl-cysteine]; and 3-[[2-(acetylamino)-2-carboxyethyl]-sulfinyl]-3-[2-(acteylamino)-2-carboxyethyl]thio]1-propanol (Banijamali et al. 1999). Results of in vitro metabolism studies by DeMaster et al. (1994) using bovine liver catalase showed that this enzyme provided a higher rate of oxidative metabolism than did alcohol dehydrogenase and that the catalase pathway produced α- and β-unsaturated aldehydes, which are considered more reactive than the 2-propyn-l-al product of alcohol dehydrogenase-mediated oxidation.

4.2. Mechanism of Toxicity

Results of in vitro metabolism studies (DeMaster et al. 1994) suggested that catalase-mediated formation of α- and β-unsaturated aldehyde might explain the hepatotoxic effects of propargyl alcohol (see Section 4.1). Moridani et al. (2001), however, reported that inactivation of catalase in incubated hepatocytes only partially decreased the toxicity of propargyl alcohol, and that toxicity was also due to rapid glutathione depletion and formation of reactive oxygen species, the latter being mediated by CYP 2E1 (affirmed by induction/depletion experiments) and involving conversion of propargyl alcohol to 2-propyn-1-al.

4.3. Structure-Activity Relationships

Chemical-specific data were sufficient for deriving AEGL values for propargyl alcohol, so structure-activity relationship data were not used.

4.4. Other Relevant Information

4.4.1. Susceptible Populations

Although variability in oxidative metabolism and glutathione conjugation exist among humans, metabolism and disposition processes appear to be more relevant for longer-term exposures than for acute exposures. Therefore, the phenotypic variability known to occur for these pathways is not expected to be relevant for acute exposure situations.

4.4.2. Species Variability

On the basis of lethality data, variability among species (rats, mice, and cats) was not great. Results of acute exposure studies showed the respiratory tract to be a primary target in all species tested, and longer-term exposure studies indicated renal and hepatic effects in the all of the tested species.

4.4.3. Concentration-Exposure Duration Relationship

The concentration-time relationship for many irritant and systemically-acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data on propargyl alcohol were inadequate for deriving an empirical value for the exponent (n), so temporal scaling was performed using default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations (NRC 2001).

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No relevant human data on propargyl alcohol were available for deriving AEGL-1 values.

5.2. Animal Data Relevant to AEGL-1

Both acute and repeated exposure studies in animals describe nonlethal effects of inhaled propargyl alcohol. In a subchronic study, male and female rats had signs of ocular irritation and lethargy after the first of 59 daily 7-h exposures

to propargyl alcohol at 100 ppm (80 ppm analytic concentration) (Dow Chemical Co. 1964). Adaptation to these effects appears to have occurred, as they were not observed with subsequent exposures. A 90-day inhalation study of Wistar rats exposed to propargyl alcohol for 6 h/day, 5 days/week, identified 5.1 ppm as a no-observed-adverse-effect level and 24.6 ppm as a lowest-observed-adverse-effect level on the basis of increased kidney-to-body weight ratio and decreased serum cholinesterase activity (BASF 1992b). In subchronic studies, propargyl alcohol at 4 or 8 ppm was without effect in rats, and 8 ppm was considered a no-observed-adverse-effect level for mice after exposure for 13 weeks (NTP 2008). Zissu (1995) reported that mice exposed to propargyl alcohol at 88 ppm (6 h/day for up to 14 days) had lesions of the respiratory and olfactory epithelium. Mice exposed at 25.3 ppm under the same testing protocol did not have notable histopathologic findings.

5.3. Derivation of AEGL-1 Values

Several studies provided data indicative of little or no toxic response in test species exposed to propargyl alcohol. Rodents exposed to the chemical at 16 ppm for 13 weeks (NTP 2008) exhibited only mild hyperplasia (necrosis in female mice) of the olfactory and respiratory-tract epithelium, and rats exposed at 80 ppm for 7 h had signs of ocular irritation and lethargy (Dow Chemical Co. 1964). A 6-h exposure to propargyl alcohol at 25.3 ppm for up to 14 days was without apparent effects, on the basis of histologic assessments (Zissu 1995). Thus, 25.3 ppm was considered a concentration that would be without notable effect. Response to propargyl alcohol appeared to be similar among the species tested and individual variability is not expected to vary more than three-fold for simple direct-contact irritation. Therefore, an interspecies uncertainty factor of 3 and an intraspecies uncertainty factor of 3 were applied (total uncertainty factor of 10). The resulting value of 2.5 ppm (25.3 ppm ÷ 10) was used for all AEGL-1 exposure durations because direct-contact irritation is not expected to vary markedly with exposure duration. AEGL-1 values for propargyl alcohol are presented in Table 6-6.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data on nonlethal effects from inhalation exposure to propargyl alcohol were available.

6.2. Animal Data Relevant to AEGL-2

In subchronic studies, decreased serum cholinesterase activity was detected in female rats and increased blood urea nitrogen was detected in males and

females after 3 days of exposure to propargyl alcohol at 32 ppm (NTP 2008). After 90 days, necrosis of the olfactory epithelium and hyperplasia and squamous metaplasia of the respiratory-tract epithelium were found in rats exposed at 32 ppm or higher. Mice exhibited necrosis of the olfactory epithelium at 16 ppm for the full exposure duration. Exposure of guinea pigs and rabbits to propargyl alcohol at 1,300 ppm for 1 h resulted in irritation of mucous membranes in both species and slight elevation of serum transaminases in rabbits (BASF 1965). Although the results of subchronic studies (Dow Chemical Co. 1964; BASF 1992a,b; NTP 2008) are indicative of degenerative changes in the respiratory tract and possible renal toxicity, there is no evidence that such effects would result from a single acute exposure. Zissu (1995) reported that multiple 6-h exposures (4, 9, or 14 days) to propargyl alcohol at 88 ppm caused histologic changes in the respiratory and olfactory epithelium of mice.

6.3. Derivation of AEGL-2 Values

As shown by histologic damage to olfactory and respiratory epithelium, the upper respiratory tract appears to be the primary target after repeated exposure to propargyl alcohol. However, the available data do not provide definitive evidence of effects from a single acute exposure to propargyl alcohol. Necropsy results from repeat-exposure studies (Dow Chemical Co. 1964; BASF 1992a,b; Zissu 1995; NTP 2008) have shown concentration-related histologic changes (hyperplasia, necrosis, squamous metaplasia) in the respiratory-tract epithelium of rats and mice. Results of longer-term studies in rodents suggest possible hepatic and renal effects (increased blood urea nitrogen and serum transaminase activities and increases in kidney-to-body weight ratio and liver-to-body weight ratio). Increased urinary urobilinogen and proteinuria were reported after a single lethal exposure (1,300 ppm) in cats (BASF 1965).

Propargyl alcohol at 88 ppm (6-h/day for 4, 9, or 14 days) produced histologic alterations in the olfactory and respiratory epithelium of mice (Zissu 1995). Assuming that the alterations occurred after a single 6-h exposure, 88 ppm was selected as the point of departure for calculating AEGL-2 values. This concentration is supported by observations in the Dow Chemical Co. study (1964) of ocular irritation and lethargy in rats after the first of 59 exposures at 80 ppm for 7 h. In the Zissu (1995) study, histopathologic changes (lesions in the maxilloturbinates, nasal turbinates, and nasal septum and rhinitis with metaplasia and necrosis into underlying connective tissue and bone) observed in mice

TABLE 6-6 AEGL-1 Values for Propargyl Alcohol

10 min	30 min	1 h	4 h	8 h
2.5 ppm ($5.7\ mg/m^3$)	2.5 ppm ($5.7\ mg/m^3$)	2.5 ppm ($5.7\ mg/m^3$)	2.5 ppm ($5.7\ mg/m^3$)	2.5 ppm ($5.7\ mg/m^3$)

exposed for 4 days (88 ppm for 6 h/day) were considered very severe by the investigator. The severity of histopathologic changes after the first 6-h exposure is unknown. Assuming that a single 6-h exposure would produce changes of lesser severity, a single 6-h exposure at 88 ppm was considered an estimated threshold for AEGL-2 effects.

Time scaling was performed using the equation $C^n \times t = k$, where the exponent ranges from 0.8 to 2.5 (ten Berge et al. 1986). Data on propargyl alcohol were inadequate for deriving an empirical value for n, so default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations were used. Because the toxic effects of propargyl alcohol do not appear to vary greatly between species, an uncertainty factor of 3 was used to account for interspecies differences. An uncertainty factor of 3 was used to account for intraspecies variability because the histopathologic lesions caused by propargyl alcohol are likely the result of direct-contact irritation and are unlikely to vary by an order of magnitude among individuals. Because of uncertainties associated with extrapolating a 6-h exposure to a 10-min value, the 30-min AEGL-2 value was adopted for the 10-min AEGL value (NRC 2001). AEGL-2 values for propargyl alcohol are presented in Table 6-7 and their derivation is summarized in Appendix A.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No relevant human lethality data on propargyl alcohol were available.

7.2. Animal Data Relevant to AEGL-3

Several studies conducted in multiple species are available to assess the lethality of inhaled propargyl alcohol after acute and repeated exposures. Vernot et al. (1977) reported a 1-h LC_{50} value of 1,200 ppm for male rats and 1,040 ppm for female rats. Studies conducted by Hazelton Laboratories America, Inc. (1989) reported 100% lethality in rats exposed for 1 h to propargyl alcohol at 1,490 ppm within 3 days post-exposure. A positive relationship between exposure duration (3 min to 3 h) and lethal response in rats exposed to "vapor-enriched atmospheres" of propargyl alcohol was reported by BASF (1963). Rats exhibited signs of mucous membrane irritation, pallor of the ears and extremities, and dyspnea, suggesting that acute lethality involved respiratory-tract damage. Stasenkova and Kochetkova (1966) reported mortality incidences of 1/20, 1/20, 10/20, and 20/20 in mice exposed to propargyl alcohol for 2 h at 220, 655, 875, or 1,500 ppm, respectively. Three of 10 mice exposed at 3,000 ppm for 1 h died (BASF 1965). Necropsies revealed signs of mucous membrane irritation and colon irritation in mice that died during the study, but no signs of toxicity were found in mice that were killed 7 days post-exposure. One of two cats ex-

posed to propargyl alcohol at 1,300 ppm for 2 h died (BASF 1965). Among the species tested, cumulative exposures of 1,040-17,500 ppm-h appear to be associated with about 50% lethality.

7.3. Derivation of AEGL-3 Values

Most of the studies in which test animals died after exposure to propargyl alcohol did not provide low-incidence responses or lethality-threshold estimates. Benchmark dose analysis (EPA 2005) of the mouse mortality data from Stasenkova and Kochetkova (1966) yielded a $BMCL_{05}$ of 573 ppm (BMC_{01} [benchmark concentration with 1% response] was 621 ppm) (see Appendix D). No lethality was observed in rats exposed to propargyl alcohol at concentrations as high at 80 ppm for 90 days (Dow Chemical Co. 1964) or in guinea pigs or rabbits exposed once at 1,300 ppm for 1 h (14-day observation period) (BASF 1965).

The $BMCL_{05}$ of 573 ppm (2-h exposure) was selected as the point of departure for calculating AEGL-3 values. Although the Stasenkova and Kochetkova (1966) study is poorly detailed, both the raw exposure-response data (see Section 3.1.2) and the $BMCL_{05}$ for mice are consistent with the range of 1-h lethal concentrations of 1,040-1,200 ppm reported for rats (Vernot et al. 1977). Further, BASF (1965) reported no lethality among two rabbits or six guinea pigs exposed to propargyl alcohol at 1,300 ppm for 1 h, but one of two cats died. The available data support an interspecies uncertainty factor of 3. Animal data suggests olfactory and respiratory-tract epithelium are the primary targets of propargyl alcohol and that damage to these tissues is likely instrumental in deaths after a single acute exposures. Studies of repeated exposures to propargyl alcohol (about 90 days) provided evidence of renal and hepatic toxicity, but the data do not support the contention that such systemic toxicity would follow a single acute exposure. Therefore, an intraspecies uncertainty of 3 used. Time scaling was performed using the same method described for the AEGL-2 values. AEGL-3 values for propargyl alcohol are presented in Table 6-8 and their derivation is summarized in Appendix A.

TABLE 6-7 AEGL-2 Values for Propargyl Alcohol

10 min	30 min	1 h	4 h	8 h
20 ppm ($46\ mg/m^3$)	20 ppm ($46\ mg/m^3$)	16 ppm ($37\ mg/m^3$)	10 ppm ($23\ mg/m^3$)	6.6 ppm ($15\ mg/m^3$)

TABLE 6-8 AEGL-3 Values for Propargyl Alcohol

10 min	30 min	1 h	4 h	8 h
130 ppm ($300\ mg/m^3$)	91 ppm ($210\ mg/m^3$)	72 ppm ($160\ mg/m^3$)	29 ppm ($66\ mg/m^3$)	14 ppm ($32\ mg/m^3$)

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

No information was available regarding human exposure to propargyl alcohol. Animal data consistently showed the upper respiratory tract to be the primary target of propargyl alcohol, although hepatic and renal effects are suggested by results of repeated exposure studies. AEGL values were derived from points of departure representing data-based estimates of thresholds for each respective AEGL severity level. AEGL-1 values were based on an estimated threshold for nasal and ocular irritation, AEGL-2 values on an estimated threshold for nasal and upper respiratory tract damage, and AEGL-3 values on an estimated lethality threshold. A summary of AEGL values for propargyl alcohol are presented in Table 6-9.

8.2. Comparisons with Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures to propargyl alcohol are presented in Table 6-10.

TABLE 6-9 AEGL Values for Propargyl Alcohol

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	2.5 ppm (5.7 mg/m^3)	2.5 ppm (5.7 mg/m^3)	2.5 ppm (5.7 mg/m^3)	2.5 ppm (5.7 mg/m^3)	2.5 ppm (5.7 mg/m^3)
AEGL-2 (disabling)	20 ppm (46 mg/m^3)	20 ppm (46 mg/m^3)	16 ppm (37 mg/m^3)	10 ppm (23 mg/m^3)	6.6 ppm (15 mg/m^3)
AEGL-3 (lethal)	130 ppm (300 mg/m^3)	91 ppm (210 mg/m^3)	72 ppm (160 mg/m^3)	29 ppm (66 mg/m^3)	14 ppm (32 mg/m^3)

TABLE 6-10 Standards and Guidelines for Propargyl Alcohol

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	2.5 ppm	2.5 ppm	2.5 ppm	2.5 ppm	2.5 ppm
AEGL-2	20 ppm	20 ppm	16 ppm	10 ppm	6.6 ppm
AEGL-3	130 ppm	91 ppm	72 ppm	29 ppm	14 ppm
TLV-TWA (ACGIH)[a]					1ppm
REL-TWA (NIOSH)[b]					1 ppm
MAK (Germany)[c]					2 ppm
MAC[d] (the Netherlands)					1ppm

[a]TLV-TWA (threshold limit value - time weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 2008) 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. Skin notation for propargyl alcohol.

[b]REL-TWA (recommended exposure limit - time weighted average, National Institute for Occupational Safety and Health) (NIOSH 2011) is defined analogous to the ACGIH TLV-TWA. Skin notation for propargyl alcohol.

[c]MAK (maximale argeitsplatzkonzentration [maximum workplace concentration], Deutsche Forschungsgemeinschaft [German Research Association]) (DFG 2005) is defined analogous to the ACGIH TLV-TWA. No pregnancy risk group classification for propargyl alcohol.

[d]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.

8.3. Data Adequacy and Research Needs

Data on human exposure to propargyl alcohol are not available. Results of animal studies in several species were sufficient for identifying the adverse effects of exposure to propargyl alcohol vapor and for identifying points of departure for AEGLs development. Few data were available to definitively assess the exposure response-exposure duration relationship for propargyl alcohol, especially for identifying a threshold for innocuous effects.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR PROPARGYL ALCOHOL

Derivation of AEGL-1 Values

Key study:	Zissu, D. 1995. Histological changes in the respiratory tract of mice exposed to ten families of airborne chemicals. J. Appl. Toxicol. 15(3):207-213.
Critical effect:	No histologic changes in the respiratory tract of mice exposed to propargyl alcohol at 25.3 ppm for 6 h/day for 4 days (Zissu 1995). Point of departure is supported by the observation that rats exposed at 80 ppm for 7 h (the first of 59 exposures) exhibited only minor ocular irritation and lethargy (animals subsequently appeared to adapt) (Dow Chemical Co. 1964).
Time scaling:	Not performed
Uncertainty factors:	3 for interspecies differences; data from several species indicated quantitatively and qualitatively similar responses to propargyl alcohol. 3 for intraspecies variability; responses to direct-contact irritants are not expected to vary by an order of magnitude among individuals.
Calculations:	
All AEGL-1 values:	25.3 ppm ÷ 10 = 2.5 ppm; used for all five AEGL-1 durations, because direct-contact irritation is not expected to vary markedly with exposure duration.

Derivation of AEGL-2 Values

Key study:	Zissu, D. 1995. Histological changes in the respiratory tract of mice exposed to ten families of airborne chemicals. J. Appl. Toxicol. 15(3):207-213.

Critical effect:	Estimated threshold for histologic changes in olfactory and respiratory tissues of mice exposed at 88 ppm for 6 h.
Time scaling:	$C^n \times t = k$; data were inadequate for deriving an empirical value for n, so default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations were used. $(88 \text{ ppm})^1 \times 6 \text{ h} = 528 \text{ ppm-h}$ $(88 \text{ ppm})^3 \times 6 \text{ h} = 4{,}088{,}832 \text{ ppm-h}$ Because of uncertainties associated with extrapolating a 6-h experimental exposure duration to a 10-min value (NRC 2001), time scaling was not performed for the 10-min AEGL-2 value. Instead, the 30-min AEGL-2 value was adopted for the 10-min value.
Uncertainty factors:	3 for interspecies differences; data from several species indicated quantitatively and qualitatively similar responses to propargyl alcohol. 3 for intraspecies variability; responses to direct-contact irritants are not expected to vary by an order of magnitude among individuals.
Calculations:	
10-min AEGL-2:	Set equal to the 30-min AEGL-2 value of 20 ppm
30-min AEGL-2:	$C^3 \times 0.5 \text{ h} = 4{,}088{,}832 \text{ ppm-h}$ $C^3 = 8{,}177{,}664 \text{ ppm-h}$ $C = 201.5 \text{ ppm}$ $201.5 \text{ ppm} \div 10 = 20 \text{ ppm}$
1-h AEGL-2:	$C^3 \times 1 \text{ h} = 4{,}088{,}832 \text{ ppm-h}$ $C^3 = 4{,}088{,}832 \text{ ppm-h}$ $C = 159.9 \text{ ppm}$ $159.9 \text{ ppm} \div 10 = 16 \text{ ppm}$

4-h AEGL-2:	$C^3 \times 4$ h = 4,088,832 ppm-h C^3 = 1,022,208 ppm-h C = 100.7 ppm 100.7 ppm ÷ 10 = 10 ppm
8-h AEGL-2:	$C^1 \times 8$ h = 528 ppm-h C = 66 ppm-h 66 ppm ÷ 10 = 6.6 ppm

Derivation of AEGL-3 Values

Key study:	Stasenkova, K.P., and T.A. Kochetkova. 1966. Toxicological characteristics of propargyl alcohol [in Russian]. Toksikol. Novykh. Prom. Khim. Veshchestv. 8:97-111.
Critical effect:	Estimated lethality threshold ($BMCL_{05}$ = 573 ppm) for mice exposed for 2 h to propargyl alcohol at 500, 1,500, 2,000, or 3,500 mg/m^3 (220, 655, 875, and 1,500 ppm). Mortality incidences were 1/20, 1/20, 10/20, and 20/20, respectively. No lethality reported in repeated exposure studies (90 days) of rats exposed to propargyl alcohol at concentrations as high as 80 ppm (Dow Chemical Co. 1964) or in a study of guinea pigs and rabbits exposed at 1,300 ppm for 1 h (14-day observation period) (BASF 1965). However, a 1-h exposure at 1,300 ppm was lethal to one of two cats in the same study.
Time scaling:	$C^n \times t = k$; data were inadequate for deriving an empirical value for n, so default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations were used. $(573 \text{ ppm})^1 \times 2$ h = 1,146 ppm-h $(573 \text{ ppm})^3 \times 2$ h = 376,265,034 ppm-h
Uncertainty factors:	3 for interspecies differences; data from several species indicated quantitatively and qualitatively similar responses to propargyl alcohol.

	3 for intraspecies variability; responses to direct-contact irritants are not expected to vary by an order of magnitude among individuals. No evidence that deaths resulting from single acute exposures involved systemic toxicity or solvent narcosis.
Calculations:	
10-min AEGL-3:	$C^3 \times 0.1667$ h = 376,265,034 ppm-h C^3 = 2,257,138,776 ppm-h C = 1,311.8 ppm 1,311.8 ppm ÷ 10 = 131 ppm (rounded to 130 ppm)
30-min AEGL-3:	$C^3 \times 0.5$ h = 376,265,034 ppm-h C^3 = 752,530,068 ppm-h C = 910 ppm 910 ppm ÷ 10 = 91 ppm
1-h AEGL-3:	$C^3 \times 1$ h = 376,265,034 ppm-h C^3 = 376,265,034 ppm-h C = 722 ppm 722 ppm ÷ 10 = 72.2 ppm (rounded to72 ppm)
4-h AEGL-3:	$C^1 \times 4$ h = 1,146 ppm -h C = 287 ppm 287 ppm ÷ 10 = 28.7 ppm (rounded to 29 ppm)
8-h AEGL-3:	$C^1 \times 8$ h = 1,146 ppm -h C = 143 ppm 143 ppm ÷ 10 = 14.3 ppm (rounded to 14 ppm)

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR PROPARGYL ALCOHOL

Derivation Summary

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
2.5 ppm	2.5 ppm	2.5 ppm	2.5 ppm	2.5 ppm

Reference: Zissu, D. 1995. Histological changes in the respiratory tract of mice exposed to ten families of airborne chemicals. J. Appl. Toxicol. 15(3):207-213.

Test species/Strain/Number: Mouse, Swiss, 10 males/group

Exposure route/Concentrations/Durations: Inhalation, 25.3 or 88.0 ppm, 6 h/day for 4, 9, or 14 days.

Effects: No histopathologic effects at 25.3 ppm. Very severe lesions in olfactory and respiratory epithelium at 88.0 ppm; effects did not increase in severity with longer exposure.

End point/Concentration/Rationale: 25.3 ppm for 6 h considered a no-observed-adverse-effect level

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, data on several species indicate quantitatively and qualitatively similar responses to propargyl alcohol
Intraspecies: 3, responses to direct-contact irritants are not expected to vary by an order of magnitude among individuals.

Modifying factor: None

Animal-to-human dosimetric adjustment: None

Time scaling: None. The same value (25.3 ppm ÷ 10 = 2.5 ppm) was applied to all AEGL durations because direct-contact irritation is not expected to vary markedly with exposure duration.

Data adequacy: Data sufficient for deriving AEGL-1 values.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
20 ppm	20 ppm	16 ppm	10 ppm	6.6 ppm

Reference: Zissu, D. 1995. Histological changes in the respiratory tract of mice exposed to ten families of airborne chemicals. J. Appl. Toxicol. 15(3):207-213.

Test species/Strain/Sex/Number: Mouse, Swiss, 10 males/group

Exposure route/Concentrations/Durations: Inhalation, 25.3 or 88.0 ppm, 6 h/day for 4, 9, or 14 days

(Continued)

AEGL-2 VALUES Continued

Effects: No histopathologic effects at 25.3 ppm. Very severe lesions in olfactory and respiratory epithelium at 88.0 ppm; effects did not increase in severity with longer exposure (up to 14 days).

End point/Concentration/Rationale: A single 6-h exposure at 88.0 ppm was estimated to be a threshold for histologic changes in olfactory tissue.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, data on several species indicate quantitatively and qualitatively similar responses to propargyl alcohol
Intraspecies: 3, histopathologic effects are likely due to direct-contact irritation, which is not expected to vary by an order of magnitude among individuals.

Modifying factor: None

Animal-to-human dosimetric adjustment: None

Time scaling: $C^n \times t = k$; data were inadequate for deriving an empirical value for n, so default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations were used.

Data adequacy: Data sufficient to derive AEGL-2 values. A more robust single acute exposure-response data set would be beneficial.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
130 ppm	91 ppm	72 ppm	29 ppm	14 ppm

Reference: Stasenkova, K.P., and T.A. Kochetkova. 1966. Toxicological characteristics of propargyl alcohol [in Russian]. Toksikol. Novykh. Prom. Khim. Veshchestv. 8:97-111.

Test species/Strain/Sex/Number: Mouse, strain and gender not specified, 20/group.

Exposure route/Concentrations/Durations: Inhalation; 500, 1,500, 2,000, and 3,500 mg/m^3 (220, 655, 875, and 1,500 ppm) for 2 h.

Effects: Mortality incidences of 1/20 (220 ppm), 1/20(655 ppm), 10/20 (875 ppm), and 20/20 (1,500 ppm).

End point/Concentration/Rationale: Estimated lethality threshold, 2-h $BMDL_{05}$ of 573 ppm

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, data on several species indicate quantitatively and qualitatively similar responses to propargyl alcohol.
Intraspecies: 3, histopathologic effects are likely due to direct-contact irritation, which is not expected to vary by an order of magnitude among individuals.

Modifying factor: None

Animal-to-human dosimetric adjustment: None

Time scaling: $C^n \times t = k$; data were inadequate for deriving an empirical value for n, so default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations were used.
Data adequacy: Data sufficient to derive AEGL-3 values. Data in multiple species allowed for interspecies comparisons.

APPENDIX C

CATEGORY PLOT FOR PROPARGYL ALCOHOL

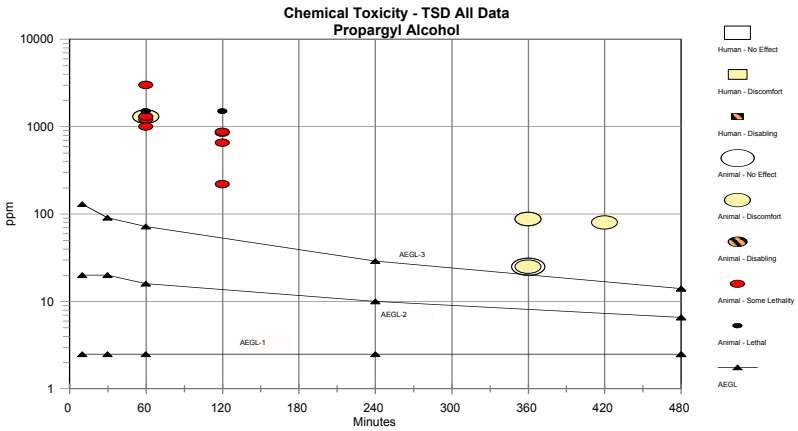

FIGURE C-1 Category plot of toxicity data and AEGL values for propargyl alcohol.

TABLE C-1 Data Used in Category Plot for Propargyl Alcohol

Source	Species	Sex	No. of Exposures	ppm	Minutes	Category	Comments
NAC/AEGL-1				2.5	10	AEGL	
NAC/AEGL-1				2.5	30	AEGL	
NAC/AEGL-1				2.5	60	AEGL	
NAC/AEGL-1				2.5	240	AEGL	
NAC/AEGL-1				2.5	480	AEGL	
NAC/AEGL-2				20	10	AEGL	
NAC/AEGL-2				20	30	AEGL	
NAC/AEGL-2				16	60	AEGL	
NAC/AEGL-2				10	240	AEGL	
NAC/AEGL-2				6.6	480	AEGL	
NAC/AEGL-3				130	10	AEGL	
NAC/AEGL-3				91	30	AEGL	
NAC/AEGL-3				72	60	AEGL	
NAC/AEGL-3				29	240	AEGL	
NAC/AEGL-3				14	480	AEGL	

(Continued)

TABLE C-1 Continued

Source	Species	Sex	No. of Exposures	ppm	Minutes	Category	Comments
	Rat	M	1	1,200	60	PL	LC_{50} (Vernot et al. 1977)
	Rat	F	1	1,000	60	PL	LC_{50} (Vernot et al. 1977)
	Rat		1	850	120	PL	LC_{50} (Kennedy and Graepel 1991); RTECS entry)
	Mouse		1	3,000	60	PL	30% lethality (BASF 1965)
	Mouse		1	220	120	PL	5% lethality (Stasenkova and Kochetkova 1966)
	Mouse		1	655	120	PL	5% lethality (Stasenkova and Kochetkova 1966)
	Mouse		1	875	120	PL	50% lethality (Stasenkova and Kochetkova 1966)
	Mouse		1	1,500	120	3	100% lethality (Stasenkova and Kochetkova 1966)
	Cat		1	1,300	60	PL	1 of 2 dead (BASF 1965)
	Rat		1	1,500	60	3	10/10 dead within 3 days (Hazelton Laboratories America, Inc. 1989)
	Rat	M/F	1	80	420	1	Irritation after first 7-h exposure of 59 exposures (Dow Chem. Co. 1964)
	Rat	M/F	1	25	360	1	No significant effects after 90 days of exposure (BASF 1965)
	Rat	M/F	1	32	1,400	0	No significant effects after 90 days of exposure (NTP 2008)
	Mouse	M/F	1	16	1,400	0	No significant effects after 90 days of exposure (NTP 2008)
	Guinea pig		1	1,300	60	1	Irritation of mucous membrane (BASF 1965)
	Rabbit		1	1,300	60	1	Irritation of mucous membrane (BASF 1965)
	Mouse		1	88	360	1	Histopathologic changes in olfactory and respiratory epithelium (Zissu 1995)
	Mouse		1	25	360	0	Histopathologic changes in olfactory and respiratory epithelium (Zissu 1995)

For category: 0 = no effect, 1 = discomfort, 2 = disabling, PL = partially lethal, 3 = lethal.

APPENDIX D

BENCHMARK CONCENTRATION ANALYSIS FOR PROPARGYL ALCOHOL

Stasenkova and Kochetkova, 1966; Propargyl alcohol; 2-h exposure; lethality study in mice.

Probit Model (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\PROPALC.(d)
Gnuplot Plotting File: C:\BMDS\PROPALC.plt
Mon Sep 14 13:38:16 2009

BMDS MODEL RUN

The form of the probability function is:

P[response] = Background
+ (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
where CumNorm(.) is the cumulative normal distribution function

Dependent variable = COLUMN3
Independent variable = COLUMN1
Slope parameter is not restricted

Total number of observations = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
Background = 0
Intercept = -11.6925
Slope = 1.75112

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Intercept	Slope
Background	1	-0.4	0.39
Intercept	-0.4	1	-1
Slope	0.39	-1	1

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance Test	d.f.	P-value
Full model	-21.8036	5			
Fitted model	-22.5131	3	1.41917	2	0.4918
Reduced model	-62.6869	1	81.7668	4	<.0001

AIC: 51.0263

Parameter Estimates

		95.0% Wald Confidence Interval		
Variable	Estimate	Standard error	Lower confidence limit	Upper confidence limit
Background	0.0252266	0.0247475	-0.0232776	0.0737309
Intercept	-45.4309	21.7571	-88.074	-2.78782
Slope	6.70209	3.21983	0.391333	13.0128

Goodness of Fit

		Scaled			
Dose	Estimated probability	Expected	Observed	Size	Residual
219.0000	0.0252	0.505	1	20	0.707
655.0000	0.0490	0.980	1	20	0.020
875.0000	0.5012	10.023	10	20	-0.010
1500.0000	0.9998	19.997	20	20	0.058
0.0000	0.0252	0.505	0	20	-0.719

Chi-square = 1.02 d.f. = 2 P-value = 0.6003

Benchmark Dose Computation

Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95

BMC = 687.589

$BMCL_{05}$ = 572.737

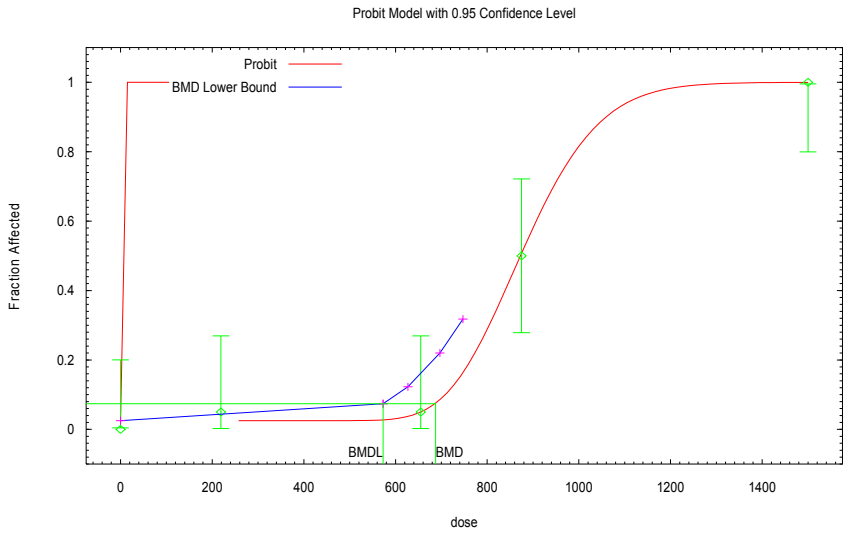

FIGURE B-1 Probit model with 0.95 confidence level.

7

Vinyl Acetate[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 Claudia Troxel (Oak Ridge National Laboratory), Heather Carlson-Lynch (SRC, Inc.), Chemical Manager Richard Thomas (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 concentrations 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 acetate is a colorless, flammable liquid with low solubility in water (Rhum 1970; O'Neil et al. 2006). It is manufactured by reacting ethylene with sodium acetate (Bisesi 2001). U.S. production of vinyl acetate in 1993 was reported to be 2.83 billion pounds (Reisch 1994). Vinyl acetate is mainly used as a monomer in the production of poly(vinyl acetate) and vinyl acetate copolymers, which in turn are used to produce water-based paints, adhesives, and other coatings and bindings (Rhum 1970). Poly(vinyl acetate) is also a precursor for the synthesis of poly(vinyl alcohol) and poly(vinyl acetate) resins, or is copolymerized with vinyl chloride or ethylene to form polymers or with acrylonitrile to form acrylic fibers.

The odor of vinyl acetate has been described as immediately pleasant, but then quickly sharp and irritating (Rhum 1970). The odor detection threshold is 0.12 ppm, and the recognition threshold is 0.4 ppm (Hellman and Small 1974; AIHA 1989; EPA 1992).

AEGL-1 values are based on a human study that reported throat irritation from inhalation of vinyl acetate. Irritation was minimal or slight after 2 min at 4-20 ppm, slight and persistent after 4 h at 20 ppm, and persistent after 2 h at 34 ppm (Smyth and Carpenter 1973). A no-effect level for notable discomfort of 20 ppm was selected as the point of departure. An intraspecies uncertainty factor of 3 was applied because throat irritation is caused by a local effect of the chemical and the response is not expected to vary greatly among individuals. Because irritation is considered a threshold effect and should not vary over time, the same AEGL-1 value of 6.7 ppm was used for all exposure durations.

AEGL-2 values are based on a no-observed-effect level (200 ppm for 6 h) for serious, long-lasting histopathologic nasal lesions in rats (Bogdanffy et al. 1997). A total uncertainty factor of 10 was applied: 3 for interspecies differences and 3 for intraspecies variability. A factor of 3 for interspecies differences was applied because nasal toxicity appears to depend on the metabolism of vinyl acetate to the metabolites acetic acid and acetaldehyde via carboxylesterase and aldehyde dehydrogenase. Metabolism studies found little difference in carboxylesterase-mediated metabolism of vinyl acetate in the nasal cavity of mice, rats, and humans, particularly in the olfactory epithelium (Bogdanffy and Taylor 1993; Bogdanffy et al. 1998). Esterase distribution in the nasal respiratory tissue of humans is believed to be similar to that of rats (Andersen et al. 2002). An intraspecies uncertainty factor of 10 would normally be applied because of the variability in the olfactory nasal tissue of humans with respect to surface area, composition of epithelial tissue layers (respiratory-type tissue can be interspersed with more characteristic olfactory tissue), and age-related changes (Andersen et al. 2002). However, a total uncertainty factor of 30 would result in an 8-h AEGL-2 value (5 ppm) lower than the AEGL-1 value of 6.7 ppm. Reducing an uncertainty factor is appropriate when the weight of evidence indicates that a higher uncertainty factor would result in AEGL values at odds with human data (NRC 2001). Therefore, the intraspecies uncertainty factor was reduced to 3.

Time scaling was performed by using the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data on vinyl acetate were insufficient for determining an empirical value of n; therefore, default values of n = 1 for extrapolating from shorter to longer durations and n = 3 for extrapolating from longer to shorter durations were used. The 10-min AEGL-2 value was set equal to the 30-min value because of the uncertainties associated with extrapolating a 6-h exposure to a 10-min AEGL value (NRC 2001).

AEGL-3 values for vinyl acetate were based on the highest nonlethal concentration (1,000 ppm) after a single 6-h exposure (Bogdanffy et al. 1997) or after repeated 6-h exposures of rats and mice (Owen 1979a,b; 1980a,b). A total uncertainty factor of 10 was applied: 3 for interspecies differences and 3 for intraspecies variability. An interspecies uncertainty factor of 3 was applied because nasal toxicity is expected to be similar between species (see rationale in discussion of AEGL-2 values above). An intraspecies uncertainty factor of 3 instead of 10 was applied because the higher value would have resulted an 8-h AEGL-3 value (25 ppm) that is lower than concentrations that, did not result in serious health effects in a human volunteer study. In that study, no life-threatening effects were observed in humans exposed to vinyl acetate at 34 ppm for 2 h or at 72 ppm for 30 min (Smyth and Carpenter 1973). Reduction of an uncertainty factor is appropriate when the weight of evidence indicates that a higher uncertainty factor would result in AEGL values at odds with human data (NRC 2001). Therefore, the intraspecies factor was reduced to 3. Time scaling was performed in the same manner as for AEGL-2 values. The 10-min AEGL-3

value was set equal to the 30-min value because of the uncertainties associated with extrapolating a 6-h exposure to a 10-min AEGL value (NRC 2001).

A level of distinct odor awareness (LOA) of 0.25 ppm was derived on the basis of the odor detection threshold for vinyl acetate reported by Hellman and Small (1974) (see Appendix C for the derivation). The LOA is the concentration above which more than half of the exposed population are predicted to perceive at least a distinct odor intensity; about 10% of the population will perceive a strong odor intensity. The LOA should help chemical emergency responders with assessing the public awareness of exposure to vinyl acetate by its odor.

A carcinogenicity assessment for vinyl acetate was not appropriate for an acute exposure scenario because the proposed mechanism of carcinogenicity suggests a nonlinear mode of action requiring continuous exposure to vinyl acetate. Therefore, a one-time exposure even to high concentrations of vinyl acetate would not be expected to result in tumor development. AEGL values for vinyl acetate are presented in Table 7-1.

1. INTRODUCTION

Vinyl acetate is a colorless, flammable liquid with low solubility in water (Rhum 1970; O'Neil et al. 2006). Its odor has been described as being immediately pleasant, but then quickly sharp and irritating (Rhum 1970). The odor detection threshold is reported to be 0.12 ppm, and the recognition threshold is 0.4 ppm (Hellman and Small 1974; AIHA 1989; EPA 1992). Other reported odor thresholds were rejected by EPA (1992) and AIHA (1989) because they were the minimum perceptible value or the result of a passive exposure.

Vinyl acetate is manufactured by reacting ethylene with sodium acetate (Bisesi 2001). U.S. production of vinyl acetate in 1993 was reported to be 2.83 billion pounds (Reisch 1994). Vinyl acetate is primarily used as a monomer in the production of poly(vinyl acetate) and vinyl acetate copolymers, which in turn are used to produce water-based paints, adhesives, and other coating and binding applications (Rhum 1970). Poly(vinyl acetate) is also a precursor for the synthesis of poly(vinyl alcohol) and poly(vinyl acetate) resins, or is copolymerized with vinyl chloride or ethylene to form polymers or with acrylonitrile for acrylic fibers.

The chemical and physical properties of vinyl acetate are presented in Table 7-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data on lethality in humans after acute exposure to vinyl acetate were found.

TABLE 7-1 AEGL Values for Vinyl Acetate

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	No effect level for notable discomfort in humans (Smyth and Carpenter 1973)
AEGL-2 (disabling)	46 ppm (160 mg/m^3)	46 ppm (160 mg/m^3)	36 ppm (130 mg/m^3)	23 ppm (81 mg/m^3)	15 ppm (53 mg/m^3)	No effect level for serious, long-lasting histopathologic nasal lesions in rats (Bogdanffy et al. 1997)
AEGL-3 (lethal)	230 ppm (810 mg/m^3)	230 ppm (810 mg/m^3)	180 ppm (630 mg/m^3)	110 ppm (390 mg/m^3)	75 ppm (260 mg/m^3)	Highest nonlethal concentration (1,000 ppm) in rats or mice (Owen 1979a,b; 1980a,b; Bogdanffy et al. 1997)

TABLE 7-2 Chemical and Physical Properties of Vinyl Acetate

Parameter	Value	Reference
Synonyms	Acetic acid ethenyl ester; acetic acid vinyl ester; 1-acetoxyethylene; ethynyl acetate; vinyl ethanoate	O'Neil et al. 2006; NIOSH 2011
CAS registry no.	108-05-4	O'Neil et al. 2006
Chemical formula	$C_4H_6O_2$	O'Neil et al. 2006
Molecular weight	86.09	O'Neil et al. 2006
Physical state	Liquid	O'Neil et al. 2006
Melting point	-100°C, -93°C	O'Neil et al. 2006
Boiling point	72.7°C	O'Neil et al. 2006
Liquid density (water = 1)	0.9317	ACGIH 2001
Vapor density (air =1)	3.0	Bisesi 2001
Solubility in water	1 g/50 mL at 20°C	O'Neil et al. 2006
Vapor pressure	115 mmHg at 25°C	ACGIH 2001
Conversion factors	1 ppm = 3.52 mg/m^3 1 mg/m^3 = 0.284 ppm	NIOSH 2011

2.2. Nonlethal Toxicity

Groups of three to nine volunteers were exposed to various concentrations of vinyl acetate for durations ranging from 2 min to 4 h (Smyth and Carpenter 1973). Vinyl acetate vapor was generated by feeding metered air through a spirally corrugated surface of a minimally heated Pyrex tube. Calculated concentration was corrected using a curve based on a gas chromatographic analysis of calculated concentrations ranging from 0.6 to 16,000 ppm. The concentrations were unknown to the volunteers, the concentrations were presented in random order, and symptoms were reported privately. No information was provided on the exposure chamber, whether the volunteers were previously exposed or naive, or how much time elapsed between exposures. The results of this study are presented in Table 7-3.

TABLE 7-3 Human Sensory Response to Controlled Exposures to Vinyl Acetate[a]

Concentration (ppm)[a]	No. of Subjects	Exposure Duration (min)	Response
0.6	9	2	None
1.3	9	2	9 immediate odor; 5 no odor at 2 min
4	9	2	9 immediate odor; 3 no odor at 2 min; 1 minimal ocular, nasal, and throat irritation
8	9	2	9 immediate odor; 1 no odor at 2 min; 2 minimal ocular, nasal, and throat irritation
20	9	2	9 immediate odor; 1 minimal ocular, nasal, and throat irritation
20	3	240	3 complete olfactory fatigue in 3-116 min (average 63 min) 1 persistent slight throat irritation
34	3	120	1 complete, 2 partial olfactory fatigue; 1 transient, 1 persistent throat irritation
72	4	30	4 strong odor, partial olfactory fatigue; 4 slight throat irritation 20-60 min after exposure; ocular irritation until 60 min after exposure; subjects expressed unwillingness to work at this concentration for 8 h

Source: Smyth and Carpenter 1973.
[a]Corrected using calibration curve.

The medical division of Union Carbide Company undertook a study to evaluate three end points: the average environmental concentrations of vinyl acetate to which chemical workers are exposed; potential chronic health effects that might have resulted from exposure to vinyl acetate; and subjective descriptions of effects from short-term exposure to vinyl acetate (Deese and Joyner 1969). To determine average environmental concentrations of vinyl acetate, air samples were measured during normal operating conditions in three different production units. Forty samples (and two blanks) were taken from the three units during two sampling periods approximately one month apart. The total sampling time was more than 18 h. Samples were taken from three to six designated sites in each of the three production units. Sampling sites were determined by the amount of time the operator spent in each area, the investigator's observation of probable exposure based on personal subjective responses, and the operator's description of duties and exposures. Short-term and long-term air samples were taken. For short-term samples (10 min), a minimum of 15 L of air was collected by scrubbing air through a fritted glass midget impinger bubbler and a standard midget impinger in series. Long-term samples (2 h) of 180 L were collected using standard Greenburg-Smith impingers. Calibrated rotometers metered the collection at a rate of 1.5 L/min, and a vacuum was maintained using appropriate equipment. Vinyl aceate was measured by gas chromatography. Concentrations ranged from 0 to 59.3 ppm; 83% of the samples were less than 10 ppm. The 8-h time-weighted averages (TWAs) for the three production facilities were 8.2, 5.2, and 7.7 ppm. Some operations, such as maintenance, resulted in brief exposures at higher concentrations. For example, concentrations measured in the breathing zone of workers as they opened the hopper door to unplug material flow were 123.3, 125.6, and 326.5 ppm. Exposures lasted for 3 min and occurred twice a day. The concentrations of vinyl acetate documented in this study were believed also represent exposures over the previous 5 years, because operating conditions, process methods, and physical equipment had not changed over that time period.

To evaluate the potential health effects resulting from long-term exposure to vinyl acetate, company medical records were evaluated and compared with a control group (Deese and Joyner 1969). Twenty-one of 26 vinyl acetate operators participated in the study. Sixteen operators had worked with vinyl acetate for more than 15 years, and six for 20 years or more. Each participant was matched by taking the next operator listed alphabetically in the medical division files who had an age within 5 years of the operator's and who had never worked in the vinyl acetate complex. The control group comprised individuals exposed to many chemicals commonly used in the petrochemical industry, but their exposures were not categorized for this study. Medical records of the participants were evaluated for the following: all sickness-related absences between January 1 and December 31 (classified according to etiology and duration); all initial visits to the medical division over the same interval; and all reported exposures to vinyl acetate. No exposure-related differences in blood

chemistry results, pulmonary pathology, work days lost, or total number of initial visits for occupational injury or illness were found. Vinyl acetate workers had a higher number of total days lost due to respiratory illness and gastrointestinal conditions. Closer examination of the records revealed that these differences were primarily because of two individuals; one operator had a recurrent upper-respiratory-tract infection and one had cholecystitis. Vinyl acetate operators completed a questionnaire at the same time as their screening examination. When asked if vinyl acetate bothers them under normal working conditions, 13 (61%) responded no, two complained of odor, two reported nasal and throat irritation, three reported dermal irritation, and one replied that it "does bother". When asked if vinyl acetate irritated their eyes, nose, or throat, 15 (71%) responded no, two responded "some", three reported ocular irritation, and one described irritation that is noticeable but worse at certain times. When asked for other comments, one individual reported he liked the odor and another reported that breathing the fumes hurt his chest (Deese and Joyner 1969).

In the third and final part of the study, individuals were asked to provide subjective descriptions about odor, ocular irritation, and upper respiratory irritation during 10-min air sampling of vinyl acetate. The individuals included one of the investigators, a laboratory analyst assisting in sampling, and one chemical operator from each of the production units. Vinyl acetate concentrations ranged from 0.4 to 21.6 ppm (exact concentrations reported at the three plant units were 0.4, 0.8, 2.7, 4.2, 4.2, 5.7, 6.8, 7.6, 7.6, 9.5, 9.9, or 21.6 ppm). Odor was generally described as slight at 0.4 to 9.9 ppm, although no odor was detected by a few subjects. At 21.6 ppm, odor was described as marked by all three individuals. Ocular irritation was not reported at concentrations of 9.9 ppm or lower, with the exception of slight ocular irritation reported by the investigator at 5.7 and 6.8 ppm. At 21.6 ppm, all three individuals agreed that the ocular irritation would be "intolerable over an extended period of time". Upper respiratory irritation (cough and hoarseness) was present at 21.6 ppm in all three subjects. Hoarseness was noted by the investigator at 4.2 and 5.7 ppm.

Data from the study of Deese and Joyner (1969) conflict with those reported by Smyth and Carpenter (1973). Three subjects in the first study reported upper respiratory irritation when exposed for 10 min at 21.6 ppm whereas three volunteers in the second study tolerated vinyl acetate at 20 ppm for 4 h with only one subject reporting olfactory fatigue and slight but persistent throat irritation. Examination of the sampling data from Deese and Joyner (1969) indicates that 21.6 ppm was measured in the production area associated with the highest concentration of vinyl acetate (49.3 ppm in a 10-min sample) measured in any part of the facility. Thus, the subjects might have been briefly exposed to a much higher concentration of vinyl acetate during the sampling period. Furthermore, Deese and Joyner (1969) noted that the odor threshold of vinyl acetate was difficult to measure in the facility because of the "intermittent and unpredictable presence of odors of other assorted chemicals in the subject's environment"; similarly, the ocular irritation reported at 21.6 ppm might have been confounded by concurrent exposure to other irritant compounds.

Air emissions around Monsanto production facilities were evaluated to assess the potential for human health effects (Monsanto Company 1989). Emission of vinyl acetate was identified as a concern at the Decatur production plant because of its carcinogenicity. Ambient air sampling at four locations in the Texas City, Texas, area revealed concentrations ranging from 0.07 to 0.57 ppm (0.25-2.0 mg/m^3). To conduct a safety assessment, the maximum annual-average concentration of vinyl acetate was estimated using a dispersion model developed by the U.S. Environmental Protection Agency. The modeled annual-average concentration for community exposure was estimated to be 1.8×10^{-3} ppb (5.52×10^{-3} µg/m^3), with the highest exposure being 8.3×10^{-2} ppb (0.25 µg/m^3).

Several studies investigating the potential health effects of workers chronically exposed to vinyl acetate were published in the Russian literature. Agaronyan and Amatuni (1980) examined the prevalence of neurotoxicity and cardiovascular effects in workers exposed at a "polyvinylacetate" plant compared with workers in a mechanical department of a different factory. Poly-vinylacetate workers were divided into three groups on the basis of neurotoxici-ty: those that had no signs of central nervous system toxicity, those that had the beginning phase of neurotoxicity (as defined by neuroasthenia), and those with asthenovegetative syndrome with pronounced autonomic-dystonia and involvement of the hypothalamic regions. Incidence of cardiovascular effects increased with increasing neurotoxicity and included: piercing pain in the area of the heart, palpitations, muffled heart sounds, systolic murmur, hypertension, and electrocardiogram findings of tachycardia, bradycardia, decreased P wave, widened QRS complex, prolonged Q-T, and decreased T wave. Amatuni and Agaronyan (1979, 1980) also investigated the same workers for potential pulmonary effects after chronic exposure to vinyl acetate. They reported a progressive and significant increase in the frequency of impaired pulmonary function in proportion to length employment (from 16.6 ± 8.7% at less than a year to 48.4 ± 5.1% ($p < 0.001$) at 15 years and longer). Pulmonary effects included decreases in vital capacity, forced expired volume in one second (FEV_1), maximal voluntary ventilation (MVV), and expiratory and inspiratory capacity (C_{exp}; C_{insp}), and clinical manifestations of chronic bronchitis. In another study, Agaronyan and Amatuni (1982) evaluated the pulmonary ventilation function of workers at the beginning of the study and after 5 years of employment. They found statistically significant decreases in ventilation parameters primarily indicative of obstructive and mixed impairment of pulmonary ventilation function. Limitations of the Russian studies include occupational exposures to multiple chemicals and of documented concentrations of vinyl acetate.

2.3. Developmental and Reproductive Toxicity

No studies of potential developmental or reproductive effects in humans after inhalation exposure to vinyl acetate were found.

2.4. Genotoxicity

In vitro incubation of vinyl acetate with human lymphocytes or leukocytes has resulted in chromosome aberrations, increased sister chromatid exchanges (SCEs), and DNA cross-linking. Human whole-blood lymphocyte cultures incubated for 48 h with vinyl acetate at 0.125, 0.25, 0.5, 1, or 2 mM exhibited a peak in the frequency of micronucleated lymphocytes at 0.5 and 1 mM (3.2 ± 1% and 3.1 ± 0.7%, respectively, vs. 0.9 ± 0.1% for controls) (Mäki-Paakkanen and Norppa 1987). A concentration of 2 mM was considered a toxic, resulting in a decreased frequency of micronucleated lymphocytes due to inhibition of mitosis. Whole blood cultures and isolated lymphocytes incubated with vinyl acetate for 48 h at 0.25, 0.5, 1, or 2 mM showed a concentration-dependent increase in chromatid-type aberrations and a slight increase in chromosome-type breaks, but no effects at 0.125 mM (Jantunen et al. 1986). Concentration-related increases in SCEs and chromosome aberrations (in first division cells) were found in human whole-blood lymphocyte cultures and purified lymphocyte cultures incubated with vinyl acetate at 0.1-1 mM for 48 h (Mäki-Paakkanen et al. 1984; Norppa et al. 1985). The most common chromosome aberration was the chromatid-type break; at 1 mM, 84% of the cells were aberrant and 38% had a chromatid-type exchange. Purified lymphocyte cultures exhibited a more pronounced effect on both SCEs and the number of aberrant cells (Norppa et al. 1985). Cultured human lymphocytes exposed to vinyl acetate at 0.1-2.4 mM exhibited a linear increase in SCEs with increasing exposure duration up to 24 h (He and Lambert 1985). A two-fold higher SCE frequency was observed in cells exposed in the late G_1 phase compared with cells exposed during the early G_1 phase. Cells treated during the first G_1 phase had a statistically significant increase in SCEs in three subsequent cell cycles. Human leukocytes incubated with vinyl acetate at 10 or 20 mM for 4 h at 37°C did not have evidence of direct DNA strand breaks, but had concentration-dependent DNA cross-linking (Lambert et al. 1985).

2.5. Carcinogenicity

A series of epidemiologic studies were conducted to investigate the potential link between employment at a Texas petrochemical plant and an increased incidence of mortality from brain cancer, specifically gliomas (Alexander et al. 1980; Austin and Schnatter 1983a,b; Leffingwell et al. 1983; Waxweiler et al. 1983). Although vinyl acetate was one of the chemicals with a greater apparent risk (Leffingwell et al. 1983), no statistically significant associations were found between exposure to specific chemicals and mortality from brain cancer (Austin and Schnatter 1983a; Leffingwell et al. 1983). Confounding factors include, but are not limited to, concurrent exposure to other chemicals, exposure to unknown concentrations of the chemicals of concern, and the use of in-plant controls (might have obscured a significant finding).

2.6. Summary

Human data on acute exposure to vinyl acetate are limited. Odor detection and recognition threshold values for vinyl acetate are 0.12 and 0.4 ppm, respectively (Hellman and Small 1974; AIHA 1989; EPA 1992). A controlled-exposure study by Smyth and Carpenter (1973) reported that a 2-min exposure to vinyl acetate at 4, 8, or 20 ppm resulted in minimal ocular, nasal, and throat irritation in one of two volunteers. One of three individuals complained of persistent throat irritation when the concentration was increased to 34 ppm for 2 h, and all four test subjects exposed at 72 ppm for 30 min reported ocular irritation and slight throat irritation for up to 60 min post-exposure. The study by Deese and Joyner (1969) did not have controlled exposure to vinyl acetate, but was simply a survey of subjective symptoms reported by three individuals during air sampling of the work environment. All three subjects reported that ocular irritation was intolerable at 21.6 ppm, and slight cough and hoarseness were noted in two individuals. Slight ocular irritation at 5.7 or 6.8 ppm was also reported by one individual.

In vitro genotoxicty studies with human lymphocytes or leukocytes have reported that vinyl acetate increased the number of chromosome aberrations, sister chromatid exchanges, and DNA-crosslinking. Epidemiologic studies have not identified any clear relationship between vinyl acetate and brain cancer.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Groups of six male and six female rats were exposed to vinyl acetate for 4 h at nominal concentrations of 2,000, 4,000, or 8,000 ppm (Smyth and Carpenter 1973). The nominal concentrations were corrected using a curve based on a gas chromatographic analysis of calculated concentrations ranging from 0.6 to 16,000 ppm; the corrected concentrations were 1,640, 3,280, and 6,560 ppm. No information was provided regarding a control group, the strain or age of the rats, or the exposure chamber. Vinyl acetate vapor was generated by feeding liquid vinyl acetate at a constant rate through a spirally corrugated surface of a minimally heated Pyrex tube, through which metered air was passed. Although not specifically stated, an observation period of 14 days was inferred from the results of the group of studies reported by Smyth and Carpenter (1973). Clinical signs, body weight changes, and mortality data are presented in Table 7-4. Gross necropsy of the animals that died revealed pulmonary congestion and hemorrhage, froth in the trachea, and opaque corneas. The LC_{50} (lethal concentration, 50% lethality) was calculated to be 3,680 (2,660-5,100) ppm using the moving average table of Weil (1952).

TABLE 7-4 Results of 4-Hour Inhalation Study of Rats Exposed to Vinyl Acetate

Concentration (ppm)	Mortality	Time of Death (no. animals)	Average Weight Change (g)	Clinical Signs
1,640	0/12	–	+60	Extremities congested at 1 h.
3,280	4/12	During exposure (3), day 9 (1)	+27	Gasping at 50 min; clonic convulsions at 150 min; death at 3 h.
6,560	12/12	During exposure (12)	–	Gasping at 10 min; prostrate at 25 min; clonic convulsions at 50 min; death at 90 min.

Source: Smyth and Carpenter 1973.

The following acute lethality studies in rats lacked adequate reporting of study details, so exposure concentrations were assumed to be nominal. Gage (1970) exposed four male and four female Alderley Park specific pathogen-free rats to air saturated with vinyl acetate for 5 min (Gage 1970). Exposure produced rapid anesthesia and death. Six Sherman rats (sex not specified) were exposed to vinyl acetate vapor at 4,000 ppm for 4 h (no details about exposure conditions were provided) and observed for 14 days for mortality (Smyth and Carpenter 1948). Three of the six rats died. Exposure concentration was not confirmed by analytical methods, and no controls were used. Rumiantsev et al. (1981) reported a 4-h LC_{50} value of 3,238 ppm in rats. Animals were observed for 30 days. No specifics were provided about the deaths other than they occurred during exposure or in the days following exposure.

3.1.2. Mice

Groups of six mice were exposed to vinyl acetate for 4 h at nominal concentrations of 500, 1,000, 2,000, 4,000, or 8,000 ppm (calculated concentrations of 410, 820, 1,640, 3,280, and 6,560 ppm as corrected using a curve based on a gas chromatographic analysis of concentrations ranging from 0.6 to 16,000 ppm) (Smyth and Carpenter 1973). No information was provided about the sex, strain, or age of the mice, the exposure chamber, or a control group. Vinyl acetate vapor was generated by feeding liquid vinyl acetate at a constant rate through a spirally corrugated surface of a minimally heated Pyrex tube, through which metered air was passed. Although not specifically stated, an observation period of 14 days was inferred from the results of the group of studies reported by Smyth and Carpenter (1973). Clinical signs, body weight changes, and mortality data are presented in Table 7-5. Gross necropsy of the animals that died revealed pulmonary congestion and excess pleural fluid. The LC_{50} was calculated to be 1,460 (925 2,305) ppm using the moving average table of Weil (1952).

TABLE 7-5 Results of 4-Hour Inhalation Study of Mice Exposed to Vinyl Acetate

Concentration (ppm)	Mortality	Time of Death	Average Weight Change (g)	Clinical Signs
410	0/6	–	+4	None
820	1/6	Day 8	+3	Labored breathing at 2 min.
1,640	4/6	During exposure	-2.5	Gasping at 5 min; clonic convulsions and death at 15 min; labored breathing in survivors.
3,280	5/6	During exposure	+1	Gasping at 5 min; clonic convulsions and death at 30 min; opaque eyes and poor coordination in one survivor.
6,560	6/6	During exposure	–	Gasping at 5 min; deaths at 15, 15, 15, 20, 20, and 65 min.

Source: Smyth and Carpenter 1973.

Rumiantsev et al. (1981) reported a 2-h LC_{50} of 3,010 ppm in mice. Animals were observed for 30 days. No specifics were provided about the deaths other than they occurred during exposure or in the days following exposure.

3.1.3. Guinea Pigs

Groups of six male guinea pigs were exposed to vinyl acetate for 4 h at nominal concentrations of 2,000, 4,000, 8,000, or 16,000 ppm (calculated concentrations of 1,640, 3,280, 6,560, and 13,120 ppm as corrected using a curve based on a gas chromatographic analysis of concentrations ranging from 0.6 to 16,000 ppm) (Smyth and Carpenter 1973). No information was provided about the age of the guinea pigs, the exposure chamber, or a control group. Vinyl acetate vapor was generated by feeding liquid vinyl acetate at a constant rate through a spirally corrugated surface of a minimally heated Pyrex tube, through which metered air was passed. Although not specifically stated, an observation period of 14 days was inferred from the group of studies reported by Smyth and Carpenter (1973). Clinical signs, body weight changes, and mortality data are presented in Table 7-6. Gross necropsy of the animals that died revealed congestion, emphysema, and scattered hemorrhages in the lungs. The LC_{50} was calculated to be 5,210 (3,500-7,740) ppm using the moving average table of Weil (1952).

TABLE 7-6 Results of 4-Hour Inhalation Exposure Study of Vinyl Acetate in Guinea Pigs

Concentration (ppm)	Mortality	Time of Death (no. animals)	Average Weight Change (g)	Clinical Signs
1,640	0/6	–	+57	Lacrimation at 30 min; eyes and noses wet at end of exposure.
3,280	1/6	During exposure (1)	+33	Labored breathing and poor coordination at 55 min; lacrimation at 90 min; death at 2 h; survivors normal.
6,560	4/6	During exposure (3); day 3 (1)	-4	Gasping at 10 min; clonic convulsions at 18 min; deaths at 55, 60, and 105 min; survivors weak.
13,120	6/6	During exposure (6)	–	Gasping and nose rubbing at 2 min; lacrimation at 10 min; prostrate at 22 min; deaths at 30, 35, 45, 75, 85, and 107 min.

Source: Smyth and Carpenter 1973.

3.1.4. Rabbits

Groups of four male rabbits were exposed to vinyl acetate for 4 h at nominal concentrations of 2,000, 4,000, or 8,000 ppm (calculated concentrations of 1,640, 3,280, or 6,560 ppm as corrected using a curve based on a gas chromatographic analysis of concentrations ranging from 0.6 to 16,000 ppm) (Smyth and Carpenter 1973). No information was provided about the strain or age of the rabbits, the exposure chamber, or a control group. Vinyl acetate vapor was generated by feeding liquid vinyl acetate at a constant rate through a spirally corrugated surface of a minimally heated Pyrex tube, through which metered air was passed. The results of the study are presented in Table 7-7. Gross necropsy of the animals that died revealed bloody nostrils, froth in the trachea, excess pleural fluid, and pulmonary hemorrhage. The LC_{50} was calculated to be 2,760 (1,800-4,200) ppm using the moving average table of Weil (1952).

3.2. Nonlethal Toxicity

3.2.1. Dogs

One male beagle dog per group was exposed to vinyl acetate for 4 h at nominal concentrations of 62.5, 125, 250, 1,000, 2,000, or 4,000 ppm (calculat-

ed concentrations of 51.25, 102.5, 205, 820, 1,640, or 3,280 ppm as corrected by using a curve based on a gas chromatographic analysis of concentrations ranging from 0.6 to 16,000 ppm) (Smyth and Carpenter 1973). Vinyl acetate vapor was generated by feeding metered air through a spirally corrugated surface of a minimally heated Pyrex tube. No controls were used, and no details were provided about the exposure chamber. All animals survived. Results of the study are presented in Table 7-8; no further details were provided.

3.2.2. Rats

Gage (1970) conducted a series of experiments in which Alderley Park specific pathogen-free rats were exposed to vinyl acetate at 100, 250, 630, or 2,000 ppm for 6 h/day for a total of 15 exposures. Animals were exposed in a glass desiccator with wire mesh separating the animals. The purity of the chemical was not determined. Appropriate nominal concentrations were produced by injecting vinyl acetate at a known rate into a metered flow of air using a controlled fluid-feed atomizer, but analytic concentrations in the chamber were not determined during the exposures. No clinical signs or abnormal necropsy findings were observed at 100 ppm. Low body weight gain was noted in females exposed at 250 or 630 ppm, but gross necropsy and blood and urine analyses were normal. Exposure to vinyl acetate at 2,000 ppm produced clinical signs of ocular and nasal irritation, respiratory difficulty, poor condition, and low body weight gain, and histopathologic examination of the lungs revealed excess macrophages. No further details were provided.

TABLE 7-7 Results of 4-Hour Inhalation Study of Vinyl Acetate in Rabbits

Concentration (ppm)	Mortality	Time of Death	Average Weight Change (g)	Clinical Signs
1,640	0/4	–	+225	None
3,280	3/4	Day 4, 7, 13	-300	Red noses at 30 min; cloudy eyes at 90 min; normal at end of exposure.
6,560	4/4	During exposure, days 2 and 4	-206	Labored breathing and poor coordination at 15 min; convulsions at 17 min; red noses and lacrimation at 55 min; cloudy eyes at 70 min; deaths at 60 and 100 min; bloody nose at 2 h.

Source: Smyth and Carpenter 1973.

TABLE 7-8 Results of 4-Hour Inhalation Exposure in Dogs

Concentration (ppm)	Clinical Signs
51.25	None
102.5	None
205	Blinking at 1 min; red sclera red at 1 h.
820	Lacrimation at 2 min; red sclera at 4 h.
1,640	Blinking and sneezing immediately; lacrimation at 5 min; inflamed eyelids at 30 min; nasal froth at 4 h.
3,280	Rubbing of eyes and nose immediately; tremors at 2.5 h; froth from nostrils at 3.5 h; red eyes.

Source: Smyth and Carpenter 1973.

To investigate the effect of vinyl acetate on nasal epithelial cell proliferation, groups of five male Sprague-Dawley rats were exposed by whole body inhalation at target concentrations of 0, 50, 200, 600, or 1,000 ppm (actual exposure concentrations 0, 50.8, 199.6, 598.5, and 1,007.3 ppm) for 6 h once or for 6 h/day for a total of 5 or 20 consecutive exposures (Bogdanffy et al. 1997). Rats were exposed in a 150-L stainless steel and glass dynamic inhalation chamber with an air flow of approximately 35 L/min. Chamber atmospheres were analyzed directly using gas chromatography. Rats were weighed three times per week and were observed for clinical signs. Animals received intraperitoneal injection of 5-bromo-2'-deoxyuridine (BrdU) 16 h after the last exposure, and were killed 2 h later. The respiratory tract of the rats was examined for gross changes, and the nasal cavities were removed and prepared for histopathologic examination. Five cross sections of the nose were examined, and sections of the duodenum were used as a positive control for the BrdU procedure. No clinical signs or gross necropsy abnormalities were reported. Body weight gain in the 1,000-ppm group was decreased, with the maximum decrease occurring on exposure day 5 (86% of controls). Histopathologic examination revealed concentration-related olfactory epithelial changes in the 600- and 1,000-ppm groups, but the incidence and severity of the lesions were low. Some rats developed degeneration, necrosis, and exfoliation after one exposure; the most affected regions were the dorsal one-third of the nasal septum and dorsolateral wall, Masera's organ, and the medial-most extent of the ethmoid turbinates (see Table 7-9 for incidence data). In a personal communication with one of the study authors, Frame (S.R. Frame, DuPont, Haskell Laboratory, Newark, DE, personal commun., December 1, 2004) concluded that the changes observed at 600 and 1,000 ppm were likely to be completely reversible both morphologically and functionally, on the basis of the focal and limited nature of the olfactory lesions and the known regenerative capacity of olfactory tissue. After 5 or 20 exposures, post-necrotic repair and adaptation were found; changes included regenerative hyperplasia of the olfactory epithelium and attenuation

and disorganization of the olfactory mucosa and occasional areas of squamous metaplasia (Bogdanffy et al. 1997). Additionally, olfactory nerve bundles in the olfactory lumina exhibited degeneration and atrophy. Cell labeling of rats after one 6-h exposure revealed a concentration-related increase in cell proliferation in the respiratory and olfactory epithelium, generally confined to the basal cells of the epithelial cell layer. Increase in the labeling index was statistically significant in the 600- and 1,000-ppm groups. No statistically significant increases in the labeling indexes were found in olfactory or respiratory epithelium of rats exposed five times. However, cell proliferation of the olfactory epithelium (primarily the basal cells) was statistically significantly increased in the 600- and 1,000-ppm groups after 20 exposures. Such an increase was not evident in the respiratory epithelium. The investigators concluded that the cell proliferation response could be a two-phase reaction, the first involving chemical insult of the tissue followed by early regenerative repair (exposure days 1-5) and the second involving cellular and biochemical adaptation.

TABLE 7-9 Histopathologic Observations in Nasal Epithelium of Rats Exposed to Vinyl Acetate for 6 Hours

Section of the Nose	Observation	Concentration (ppm)[a] 0	600	1,000
Level II	Degeneration/necrosis; respiratory epithelium			
	Minimal	–	–	1
	Degeneration/necrosis; olfactory epithelium			
	Minimal	–	2	1
	Mild	–	1	2
	Moderate	–	1	2
Level III	Degeneration/necrosis; respiratory epithelium			
	Minimal	–	–	1
	Degeneration/necrosis; olfactory epithelium			
	Minimal	–	2	–
	Mild	–	3	4
	Moderate	–	–	1
Level IV	Degeneration/necrosis; olfactory epithelium			
	Minimal	–	4	1
	Mild	–	1	3
	Moderate	–	–	–
Level V	Degeneration/necrosis; olfactory epithelium			
	Minimal	–	2	3

[a]Nasal cavities of rats exposed to vinyl acetate at 50 or 200 ppm were histologically normal.

Source: Bogdanffy et al. 1997. Reprinted with permission; copyright 1997, *Inhalation Toxicology*.

3.2.3. Mice

The RD_{50} (concentration that reduces respiratory rate by 50%) for vinyl acetate was 380 ppm in mice tested according to the ASTM E981 protocol (Dudek et al. 1996).

3.3. Developmental and Reproductive Toxicity

Vinyl acetate was administered to 24 confirmed-mated Sprague-Dawley rats by whole-body inhalation at concentrations of 0, 50, 200, or 1,000 ppm for 6 h/day on days 6 through 15 of gestation (Hurtt et al. 1995). Observations for clinical signs of maternal toxicity were made daily and body weight was recorded on gestation days (GDs) 0, 2, 4, 6, 10, 15, and 20; however, food and water consumption were not measured. On GD 20, dams were sacrificed, subjected to gross necropsy, and all fetuses were examined externally and viscerally (half by dissection and evisceration and the remaining half by Wilson's technique). The total numbers of fetuses examined (number of litters) were 322 (24), 320 (22), 345 (24), and 327 (22) for the 0-, 50-, 200-, and 1,000-ppm groups, respectively. Approximately half of the fetuses were examined for skeletal malformations and variations. Maternal toxicity was evident in the 1,000-ppm group; dams had significantly ($p < 0.05$) decreased mean absolute body weight on GDs 10, 15, and 20 (91, 88, and 89% of controls, respectively) and decreased body weight gain over GDs 6-10 (-10.3 g vs. 17.5 g for controls), GDs 10-15 (64% of controls), and GDs 6-15 (24% of controls). Weight gain in this group was comparable with controls over GDs 15-20 (96% of controls). Because food consumption was not measured, it is unknown whether the decreased body weight was an effect of decreased food consumption. Delays in fetal growth were present in the 1,000-ppm group and included significantly ($p < 0.05$) decreased mean fetal weight (72% of controls), decreased crown-to-rump length (88% of controls), and delays in ossification. Evidence of delayed ossification (number of fetuses [litter] in the 1,000-ppm group vs. controls) included incompletely ossified occipital bone (41 [12] vs. 1 [1]); unossified No. 2 sternebra (28 [10] vs. 0 [0]); unossified No. 5 sternebra (118 [22] vs. 17 [11]); unossified No. 6 sternebra (126 [22] vs. 16 [7]); and bipartite vertebra (52 [18] vs. 24 [13]). The delays in fetal growth correlate with maternal toxicity in the high-concentration group. The investigators concluded that vinyl acetate is not uniquely toxic to the fetus.

3.4. Genotoxicity and Cytotoxicity

Vinyl acetate was not mutagenic to *Salmonella typhimurium* strains TA 1535, 1537, 1538, 98, or 100 with or without metabolic activation at a maximum, nontoxic concentration of 1,000 µg/plate (Lijinsky and Andrews 1980); to *S. typhimurium* strains TA 97, 98, or 100 at 100-500 µg/mL (Brams et

al. 1987); or to *S. typhimurium* strain TA 102 (vinyl acetate concentrations not specified) (Jung et al. 1992; Müller et al. 1993). Vinyl acetate was not mutagenic in *Escherichia coli* strain PQ37 using the SOS chromotest (Brams et al. 1987).

A statistically significant and concentration-related increase in sister chromatid exchanges was found in both Chinese hamster ovary cells incubated with vinyl acetate at 0.125-1 mM without metabolic activation and after a 4-h pulse treatment with vinyl acetate at 0.3-5 mM with or without metabolic activation (Mäki-Paakkanen et al. 1984; Norppa et al. 1985). Male C57B1/6 mice exhibited a statistically significant increase in micronucleated polychromatic erythrocytes in the bone marrow 30 h after intraperitoneal injection of vinyl acetate at 1,000 or 2,000 mg/kg (1.33 ± 0.29% and 1.57 ± 0.19%, respectively, vs. 0.6 ± 0.10% for olive oil-treated controls), but no increase was seen after injection with 250 or 500 mg/kg (Mäki-Paakkanen and Norppa 1987). Injections of vinyl acetate at 1,000 and 2,000 mg/kg were fatal to 6/14 and 8/14 mice, respectively.

Hepatic DNA adducts were not formed in male or female F344 rats administered ^{14}C-labeled vinyl acetate by oral gavage (1 mCi of radioactivity; rats killed 4 h after administration) or by inhalation (1,200 to 1,800 ppm in static exposure chamber for 4 h) (Simon et al. 1985b). Accumulation of DNA-protein crosslinks followed S-phase kinetics when pUC13 plasmid DNA, calf histones, and rat liver microsomes were incubated with vinyl acetate at 1-100 mM for 3 h at 37°C (Kuykendall and Bogdanffy 1992a,b). DNA-protein crosslink formation was inhibited by the addition of a carboxylesterase inhibitor (bis-[p-nitrophenyl]phosphate, or BNPP) and by the removal of the rat liver microsomes.

To evaluate cytotoxicity in nasal tissues, explants of the maxilloturbinate (lined with pure populations of respiratory epithelia) and endoturbinate-1 (lined with pure populations of olfactory epithelia) from rat nasal cavities were incubated with vinyl acetate at 0, 20, 25, 50, 100, or 200 mM, followed by assaying for acid phosphatase release (Kuykendall et al. 1993a). Vinyl acetate was cytotoxic at 100 and 200 mM after incubation for 20 min and at 50 mM after incubation for at least 1 h, but 25 mM was not cytotoxic after incubation for up to 2 h. Therefore, vinyl acetate at 50 mM for 1 h was chosen to study the effects of a carboxylesterase inhibitor (BNPP) or aldehyde scavenger (semicarbazide) on vinyl acetate - mediated cytotoxicity. To assess the effects of BNPP on vinyl acetate induced cytotoxicity, acetaldehyde production was measured in the nasal tissues first. Acetaldehyde production increased steadily for up to 60 min in respiratory turbinates and up to 40 min in olfactory turbinates, reaching a plateau when acetaldehyde concentrations reached approximately 16 mM. Therefore, BNPP pre-treatment was assessed using a 20-min incubation period with vinyl acetate at 50 mM. Treatment with BNPP for 3 days before tissue collection reduced the cytotoxic effect of vinyl acetate, resulting in only a two-fold increase in acid phosphatase production compared with a three- to four-fold increase without BNPP. BNPP also inhibited the metabolism of vinyl acetate; acetaldehyde release

into the media was reduced by 59% or 37% in respiratory and olfactory turbinates, respectively. When turbinates were incubated with semicarbazide, no effect on cytotoxicity was noted. Further evaluations demonstrated that the vinyl-acetate-induced cytotoxicity was the result of acetic acid production, not acetaldehyde production.

Kuykendall et al. (1993a,b) also assessed the formation of DNA-protein crosslinks in rat nasal epithelial tissues by vinyl acetate and acetaldehyde. Isolated epithelial cells from both olfactory and respiratory turbinates incubated with vinyl aceatate at 0-75 mM generally exhibited a concentration-related increase in DNA-protein crosslink formation. Olfactory and respiratory cells had comparable DNA-protein crosslink formation, as assessed by the absolute difference in DNA accumulation in the protein-bound phases. Epithelial cells were then pre-incubated with increasing concentrations of BNPP for 30 min before the addition of vinyl acetate at 25 mM to assess whether carboxylesterase-dependent metabolism of vinyl acetate to acetaldehyde is necessary for DNA-protein crosslink formation. DNA-protein crosslink formation in respiratory and olfactory cells was 3.9- and 2.9-fold higher, respectively, in cells exposed to vinyl acetate alone compared with untreated cells. When cells were pretreated with BNPP at 1 mM, crosslink formation in respiratory and olfactory cells was reduced by 76% and 78%, respectively. Reduction in crosslink formation was dependent on BNPP concentration.

3.5. Repeated Exposure Data

A 4-week range finding study and a 3-month subchronic study in rats and mice were performed by the same laboratory and are described below. Although repeated-exposure studies are not relevant for derivation of acute exposure values, they do support the premise that exposure to "lower" concentrations of vinyl acetate is compensated for by nasal scrubbing, whereas exposure to concentrations exceeding the scrubbing capacity of the nasal cavity result in lower-respiratory-tract effects.

Groups of five male and five female Sprague-Dawley rats or CD 1 mice were exposed to vinyl acetate at 0, 50, 150, 500, or 1,000 ppm for 6 h/day, 5 days/week for 4 weeks (Owen 1979a,b). The 50-ppm exposure was increased to 1,500 ppm on day 10 (rats) or day 8 (mouse) because marked clinical effects were not observed in the 1,000-ppm groups. Animals were exposed in a stainless steel and glass dynamic inhalation exposure chamber, and chamber concentrations were measured every 15 min by gas chromatography. Mean measured concentrations for the rat and mouse were 51.3, 150.5, 497.6, 1,000.2, and 1,488.5 (rats) or 1,488.7 (mouse) ppm. All animals survived treatment. Although similar effects were found in rats and mice, mice were more sensitive. A concentration-related increase in incidence and severity of respiratory distress and hunched posture was reported in rats exposed to vinyl acetate at 500 ppm or greater and in mice exposed at 150 ppm or greater, but incidence data were not

provided. A concentration-related decrease in overall body weight gain was also noted. Body weight gain in the 150-, 500-, 1,000-, and 50/1,500-ppm groups was 104, 102, 81, and 79% of controls, respectively, for male rats and 95, 92, 80, and 78% of controls, respectively for female rats. In mice, weights were 67, 44, 33, and 33% of controls for male mice, respectively, and 80, 80, 40, and 0% of controls, respectively, for female mice. No gross necropsy findings were reported, and no hematopoietic abnormalities were found in the analysis of bone marrow samples. Spleen weight relative to body weight was decreased at concentrations of 1,000 or 50/1,500 ppm in male rats (85 and 82% of controls, respectively), male mice (80 and 74% of controls, respectively), and female mice (74 and 72% of controls, respectively). The biologic relevance of this finding is unknown. A histopathology report of a 28-day study that appears to be from this study was included a 3-month study by Owen (1980a). Findings in the nasal turbinates, trachea, and bronchi of mice exposed at 50/1,500 ppm were similar to those reported in the 3-month study described below.

In a subchronic study, groups of 10 male and 10 female CD rats or CD-1 mice were exposed to vinyl aceatate at 0, 50, 200, or 1,000 ppm for 6 h/day, 5 days/week for 13 weeks (Owen 1980a,b). Animals were exposed in a stainless steel and glass dynamic inhalation exposure chamber, and chamber concentrations measured every 15 min by gas chromatography. Mean measured concentrations were 0.5, 51, 200, and 999 ppm. A number of effects were noted in rats exposed at 1,000 ppm, including: intermittent respiratory distress, hunched posture, and ruffled fur (incidence data were not provided); decreased overall body weight gain (62% and 56% of controls for males and females, respectively; $p < 0.01$); smaller volume and more concentrated urine compared with controls; and increased lung weight relative to body weight (126% and 130% of controls for males and females, respectively; $p < 0.01$) (Owen 1980b). No effects were noted during ophthalmoscopic examination, hematology or blood chemistry analysis, or gross or microscopic examination (nasal turbinate was included in the microscopic examination).

Mice appeared to be more sensitive to vinyl acetate (Owen 1980a). Intermittent respiratory distress, hunched posture, and ruffled fur were noted in the 200-ppm group over the first 9 days of exposure. The 1,000-ppm group exhibited respiratory distress throughout the exposure and hunched posture and ruffled fur intermittently (incidence data were not provided). Other effects were limited to the 1,000-ppm group. Nine animals in that group died as a consequence of routine blood sampling. It was postulated that vinyl acetate made mice more susceptible to the anesthesia used during the sampling period. Males and females had decreased overall body weight gain (40% and 50% of controls, respectively; $p < 0.01$) and increased lung weight relative to body weight (148% and 155% of controls, respectively; $p < 0.01$). Microscopic examination revealed exposure-related lesions in the upper and lower respiratory tissues of mice exposed at 1,000 ppm. Upper respiratory tract lesions were confined to the nasal cavity and included focal to diffuse rhinitis with associated exudation and transudation into the nasal passages and occasional mucosal

metaplasia. Inflammation was chronic in nature and associated with hyperplasia of epithelial goblet cells. Findings in the laryngeal sections were difficult to assess because of variation in the section (mucosal epithelium undergoes changes from an oral to respiratory epithelium in this section). Non-inflammatory changes were noted in the trachea as well as several areas of suspected metaplasia or hyperplasia. Metaplasia was characterized by a loss of ciliated epithelium and reduction in epithelial size from a columnar to a cuboidal cell. Changes in the pulmonary parenchyma were confined to the bronchial system and manifested as multifocal bronchitis to bronchiolitis, multifocal bronchiectasis, bronchial epithelial metaplasia and hyperplasia, and occasional bronchiolar or bronchial exudation. The investigator commented that these lesions were consistent with changes often observed in mice experimentally or naturally infected with respiratory pathogens. However, the absence of similar changes in control mice precludes an interpretation of infectious pathogenesis. Exposure to vinyl acetate might be synergistic with the induction of microbial pathogens.

3.6. Chronic Toxicity and Carcinogenicity

In a chronic toxicity and oncogenicity study, groups of male and female Crl:CD(SD)BR (Sprague-Dawley) rats and Crl:CD-1(ICR)BR mice were exposed to vinyl acetate at concentrations of 0, 50, 200, or 600 ppm for 6 h/day, 5 days/week for 104 weeks via whole body inhalation (Bogdanffy et al. 1994). Chamber concentrations were measured every 15 min using a gas chromatograph. The main group consisted of groups of 60 mice or rats of each sex that were exposed for 104 weeks; clinical laboratory evaluations were conducted on 10 animals from each group during week 104. In addition, three satellite groups of 10 male and 10 female rats or mice had the following evaluations: clinical laboratory evaluations at week 51 and necropsy at weeks 52-53; clinical laboratory evaluations at week 81 and necropsy at weeks 82-83; and exposure to vinyl acetate for 70 weeks followed by a 15-week recovery period. Clinical signs of rough coat and hunched posture were noted at all concentrations and are believed to be an effect of inhalation exposure.

In rats, exposure to vinyl acetate at 600 ppm resulted in statistically decreased body weight gain and decreased absolute body weight (approximately 10% less than controls at 104 week) (Bogdanffy et al. 1994). Following the recovery period, male rats in the 600-ppm group exhibited a statistically significant increase in body weight gain compared with controls. No effects on body weight gain were observed at 50 or 200 ppm. Clinical pathology evaluation revealed a statistically significant decrease in blood glucose in 600-ppm females at weeks 51, 81, and 104, and a statistically significant decrease in urine volume in all 600-ppm rats at weeks 51 (males only), 81, and 104. Corresponding increases in specific gravity and decreased pH were observed but the differences were not always statistically significant. The investigators attributed effects on blood

glucose and urinary parameters to decreased food and water consumption; however, food and water consumption were not measured. Gross necropsy revealed increases in relative lung weight in the 200- and 600-ppm groups at week 53, the 600-ppm group at week 83, and all treated groups at week 104. Following the 15-week recovery period, no statistically significant differences in terminal body weight or organ weights were observed in any groups of exposed females, whereas body weight gain in male rats remained slightly depressed. Histopathologic examination revealed non-neoplastic changes in the lungs and nose. Findings in the lungs of male and female rats exposed at 600 ppm included bronchial exfoliation, intraluminal fibrous projections, macrophage accumulation, and peribronchiolar/perivascular lymphoid aggregates. Nasal lesions were found in rats exposed at 200 and 600 ppm, and included olfactory epithelial atrophy, squamous metaplasia, regeneration, inflammatory cell infiltrate, and leukocytic exudate; epithelial nest-like folds; basal cell hyperplasia; turbinate leukocyte exudate; and submucosal inflammatory cell infiltrate. Neoplastic changes were confined primarily to the nasal cavity of rats exposed at 600 ppm. Findings in the control, 50-, 200-, and 600-ppm groups included squamous cell carcinoma (males: 0/59, 0/60, 0/59, and 2/59, respectively; females: 0/60, 0/60, 0/60, and 4/59, respectively), carcinoma in situ (males: 0/59, 0/60, 0/59, and 1/59, respectively), and benign lesion of inverted papilloma (males: 0/59, 0/60, 0/59, and 4/59, respectively). Additionally, one female rat exposed at 600 ppm had a squamous cell carcinoma in the larynx.

In mice, body weight gain was statistically decreased in the 200- and 600-ppm groups throughout the study, and in the 50-ppm group through week 52 (Bogdanffy et al. 1994). Absolute body weight in the 600-ppm group at week 104 was approximately 15% less than controls. Following the 15-week recovery period, 600-ppm male mice and all exposed female mice exhibited a statistically significant increase in body weight gain compared with controls. No significant differences were noted in hematology or clinical chemistry parameters. Gross necropsy revealed increases in absolute and relative lung weights in 600-ppm males at weeks 53, 83, and 104, in 600-ppm females at weeks 83 and 104, and 200-ppm males only at week 83. No statistically significant differences in final body weights or organ weights were found after a 15-week recovery period. Histopathologic examination revealed non-neoplastic changes in the lungs, nose, and trachea. Findings in the lungs were present primarily in mice exposed at 600 ppm, and included accumulation of alveolar and brown pigmented macrophages, intra-alveolar eosinophilic material, intraluminal fibroepithelial projections, bronchial gland dilation, bronchial/bronchiolar epithelial flattening and exfoliation, and bronchial/bronchiolar epithelial disorganization. Non-neoplastic nasal lesions were found in the 200- and 600-ppm groups, and included olfactory epithelial atrophy (mainly dorsal meatus or widespread), inflammatory exudate, mucosal inflammatory infiltrate, submucosal gland hyperplasia, squamous metaplasia at the naso/maxilloturbinate region, and replacement of olfactory epithelium by respiratory epithelium. Epithelial hyperplasia of the trachea and bronchi was also evident in 600-ppm group. Neoplastic changes

were confined to a moderately invasive squamous cell carcinoma in a major bronchus of the lung of a 600-ppm male and a single adenocarcinoma in a control male.

The International Agency for Research on Cancer (IARC 1995) has concluded there is inadequate evidence in humans and limited evidence in experimental animals of the carcinogenicity of vinyl acetate . Therefore, IARC states that vinyl acetate is possibly carcinogenic to humans (Group 2B). The weight of the evidence was: (1) vinyl acetate is rapidly transformed into acetaldehyde; (2) sufficient evidence of carcinogenicity of acetaldehyde in experimental animals (both vinyl acetate and acetaldehyde induce nasal cancer in rats after administration by inhalation); and (3) vinyl acetate and acetaldehyde are genotoxic in human cells in vitro and in animals in vivo.

3.7. Summary

Acute toxicity studies of vinyl acetate included a series of studies in dogs, rats, mice, guinea pigs, ands rabbits performed by Smyth and Carpenter (1973); a study in rats by Gage (1970); an RD_{50} value reported in mice (Dudek et al. 1996); and a study investigating the histopathologic lesions in the rat nasal cavity (Bogdanffy et al. 1997). Tables 7-10and 7-11 summarize the lethal and nonlethal effects of vinyl acetate .

The Smyth and Carpenter study provided the best general toxicity data. Nonlethal concentrations produced signs of congested extremities in rats and lacrimation in guinea pigs, but no signs were noted in mice or rabbits. Dogs exhibited lacrimation, nasal froth, and tremors. Lethal concentrations produced signs of irritation (gasping and lacrimation) and central nervous system effects (poor coordination, prostration, and clonic convulsions). Gross necropsy of animals that died indicated that mortality was due to pulmonary irritation (pulmonary congestion, hemorrhages, and excess pleural fluid). Limitations of the Smyth and Carpenter studies include incomplete reporting of study details (no details about exposure chamber, strain and age of animals not specified) and a lack of a control group. Chamber concentrations were not measured, but the nominal concentrations were corrected against a calibration curve.

The Gage (1970) study is of limited utility because the purity of the chemical is unknown, the exposure concentrations were nominal, and clinical signs were reported as a general statement, so it is not known when the clinical signs first occurred. The Dudek et al. (1996) data was published in an abstract, with the RD_{50} being the only toxicity end point investigated.

The Bogdanffy et al. (1997) study primarily focused on histopathologic lesions of the rat nasal epithelium. A single, 6-h exposure to vinyl acetate at 600 or 1,000 ppm resulted in increased cell proliferation in the respiratory and olfactory epithelium, with 200 ppm being a no-observed-adverse-effect level for all histologic effects.

A developmental toxicity study of vinyl acetate in rats reported maternal toxicity at 1,000 ppm, as evidenced by decreased maternal body weight and

body weight gain, and developmental toxicity in the form of delayed fetal growth (Hurtt et al. 1995). Results of genotoxicity testing indicate that vinyl acetate is clastogenic (proposed to result from the metabolite acetaldehdye) and cytotoxic (proposed to be caused by the metabolite acetic acid). A carcinogenicity bioassay reported that rats exposed to vinyl acetate at 600 ppm developed nasal papillomas, squamous cell carcinomas, and carcinoma in situ, but that mice did not develop nasal tumors.

TABLE 7-10 Summary of 4-Hour Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	No. Deaths	Gross Necropsy Findings of Animals That Died
General Mortality Data			
Rat	1,640	0/12	–
	3,280	4/12 (3 died during exposure)	Pulmonary congestion and hemorrhage, froth in trachea, and opaque corneas.
	6,560	12/12 (90 min)	
Mouse	410	0/10	–
	820	1/6 (8 d post-exposure)	Pulmonary congestion, excess pleural fluid.
	1,640	4/6 (during exposure)	
	3,280	5/6 (during exposure)	
	6,560	6/6 (during exposure)	
Guinea pig	1,640	0/6	–
	3,280	1/6 (during exposure)	Pulmonary congestion and emphysema, scattered hemorrhages in the lungs.
	6,560	4/6 (3 during exposure)	
	13,120	6/6 (during exposure)	
Rabbit	1,640	0/4	–
	3,280	3/4	Bloody nostrils, froth in trachea, excess pleural fluid, pulmonary hemorrhages.
	6,560	4/4 (2 during exposure)	
Calculated 4-Hour LC_{50} Data			
Rat	3,680	LC_{50}	–
Mouse	1,460	LC_{50}	–
Guinea pig	5,210	LC_{50}	–
Rabbit	2,760	LC_{50}	–

Source: Smyth and Carpenter 1973.

TABLE 7-11 Summary of Nonlethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Duration	Effect	Reference
Dog	51.25	4	None	Smyth and Carpenter 1973
Dog	102.5	4	None	Smyth and Carpenter 1973
Dog	205	4	Blinking at 1 min, red sclera at 1 h.	Smyth and Carpenter 1973
Dog	820	4	Lacrimation at 2 min, red sclera at 4 h.	Smyth and Carpenter 1973
Dog	1,640	4	Blinking and sneezing at start of exposure; lacrimation at 5 min; inflamed eyelids at 30 min; nasal froth at 4 h.	Smyth and Carpenter 1973
Dog	3,280	4	Rubbing of eyes and nose at start of exposure; tremors at 2.5 h; froth from nostrils at 3.5 h; red eyes.	Smyth and Carpenter 1973
Rat	1,640	4	Extremities congested at 1 h; no effect level for death (0/12).	Smyth and Carpenter 1973
Rat	600	6	Degeneration and necrosis in olfactory epithelium; increase in cell proliferation in nasal respiratory and olfactory epithelium.	Bogdanffy et al. 1997
Rat	1,000	6	Degeneration and necrosis in olfactory and respiratory epithelium; increase in cell proliferation in nasal respiratory and olfactory epithelium.	Bogdanffy et al. 1997
Mouse	410	4	No clinical signs; no effect l evel for death (0/6).	Smyth and Carpenter 1973
Mouse	380	–	RD_{50}	Dudek et al. 1996
Guinea pigs	1,640	4	Lacrimation at 30 min; wet eyes and nose at end of exposure. No effect level for death (0/6).	Smyth and Carpenter 1973
Rabbits	1,640	4	No clinical signs; no effect level for death (0/4).	Smyth and Carpenter 1973

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Groups of male and female Sprague-Dawley rats were exposed for 6 h to ^{14}C-vinyl acetate vapor at 750 ppm by nose-only inhalation to assess excretion,

metabolism, and tissue distribution (Strong et al. 1980). The mean proportion of radioactivity recovered over a 96-h post-exposure period was 4.8% in urine, 3.6% in feces, 74.6% in expired air, and 16.4% in the carcass. The amount recovered in the expired air was almost exclusively $^{14}CO_2$. No radiolabeled carbonates or bicarbonates were recovered in the urine or feces. Tissue distribution measurements of rats killed immediately after exposure revealed that the highest mean concentration of radioactivity (reported as µg equivalents of ^{14}C-vinyl acetate/g) was found in the Harderian gland (2,045 µg equivalents/g), followed by the ileum (393 µg equivalents/g) and submaxillary salivary gland (341 µg equivalents/g). Radioactivity levels in the gastrointestinal tract contents, liver, kidneys, lung, brain, stomach, colon, and ovaries ranged from 150-300 µg equivalents/g. The pattern of distribution was essentially the same but at lower concentrations at 1-, 6-, or 72-h post-exposure, with the highest concentrations at 72 h found in the Harderian gland (193 µg equivalents/g), adrenal gland (112 µg equivalents/g), and ovaries (99 µg equivalents/g). No difference in the pattern of distribution was found between sexes (except for the gonads), or following oral administration. A separate study investigating the metabolic fate of ^{14}C-vinyl acetate at 1,000 ppm administered for 6 h by nose-only inhalation to Sprague-Dawley rats resulted in similar results (Cresswell et al. 1979).

The study by Bogdanffy et al. (1997) provided information on the deposition of inhaled vinyl acetate in the rat nasal cavity. Histopathology results demonstrated a strong anterior to posterior gradient, with the response moving anterior to posterior with increasing concentrations. These findings are indicative of a material in which deposition is metabolically dependent. As vinyl acetate concentration increases, fractional deposition decreases due, in part, to saturation of the metabolism-dependent component of deposition.

The primary metabolic pathway of vinyl acetate is hydrolysis by carboxylesterases to acetic acid and vinyl alcohol, which rearranges to form acetaldehyde (see Figure 7-1 and Table 7-12) (Simon et al. 1985a; Fedtke and Wiegand 1990; Kuykendall et al. 1993a; Bogdanffy and Taylor 1993). Acetaldehyde can be further metabolized to acetate, which can be incorporated into the carbon pool via formation of acetyl coenzyme A and can ultimately result in the formation of CO_2 (Strong et al. 1980). Acetaldehyde can also be oxidized to acetic acid by aldehyde dehydrogenase, a NADH-dependent reaction (Andersen et al. 2002). Monooxygenases do not play a significant role in the metabolism of vinyl acetate, and epoxide formation is not expected to be significant (Simon et al. 1985a; Bogdanffy et al. 1999a). A gas-uptake kinetic study in rats revealed a linear, concentration-dependent decay of vinyl acetate up to a concentration of 650 ppm, indicating the possibility of metabolic saturation (Simon et al. 1985a). At concentrations below saturation, the maximal clearance in rats was 30,000 mg/h/kg, similar to the maximal ventilation rate of 32,000 mg/h/kg. Therefore, the metabolic rate of vinyl acetate is determined by the ventilation rate when metabolic saturation has not been reached.

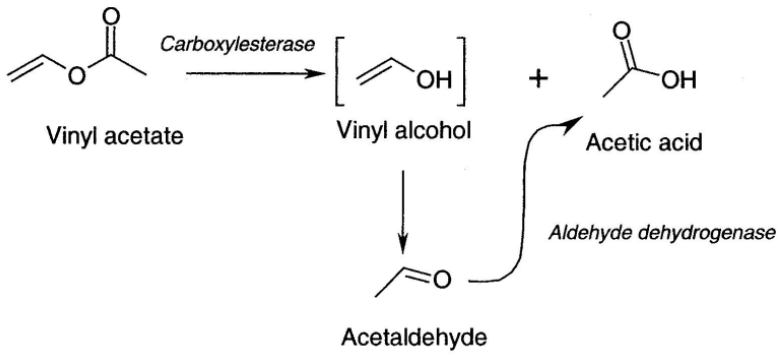

FIGURE 7-1 Pathways of vinyl acetate metabolism. Vinyl alcohol is an unstable intermediate that has not been isolated. Source: Bogdanffy et al. 2001. Permission needed to reprint- appears as Figure 2 in paper. Reprinted with permission; copyright 2001, *Inhalation Toxicology*.

TABLE 7-12 Degradation of Vinyl Acetate and Production of Acetaldehyde with Time

Source (Incubate)	Vinyl Acetate Concentration (ppm)	Time (sec)	Concentration (µmol/mL) Vinyl Acetate	Acetaldehyde	Reference
Human plasma	29	0	0.307	0.025	Strong et al. 1980
		550	0.024	0.292	
	129	0	1.380	0.000	
		720	0.031	1.177	
Human whole blood	129	0	1.380	0.000	Strong et al. 1980
		0	0.074	1.187	
Rat plasma	25	0	0.280	No data	Cresswell et al. 1979
		270	0.011	0.263	
	100	0	1.11	0.052	
		270	0.079	1.05	
Rat whole blood	100	0	1.10	0.014	Cresswell et al. 1979
		565	ND	1.06	
Homogenized rat liver	100	0	0.924	0.064	Cresswell et al. 1979
		260	0.041	0.969	
Homogenized mouse liver		0	0.570	0.050	Cresswell et al. 1979
		320	0.020	0.533	

Information on the kinetics of vinyl acetate hydrolysis is available for whole blood, plasma, erythrocytes, liver microsomes, and nasal tissue. The half-life of vinyl acetate in whole blood and liver homogenates was comparable in rats (60-125 and 50-167 seconds, respectively) and mice (114 and 66 seconds, respectively), with the most active compartment being plasma (57-72 and 36 seconds for rats and mice, respectively) (Creswell et al. 1979; Fedtke and Wiegand 1990). Hydrolysis of vinyl acetate in humans was generally slower than in rats and mice, with a half-life in human whole blood of 210-246 seconds and in human plasma of 150 or 3,720 seconds. However, the half-life of vinyl acetate in erythrocytes was similar in humans (330 seconds) and rats (336 seconds) (Fedtke and Wiegand 1990). Kinetic parameters of enzyme-mediated hydrolysis by rat liver and lung microsomes, rat and human plasma, and purified carboxylesterase are presented in Table 7-13.

Because the nasal cavity was the target organ of toxicity after chronic exposure to vinyl acetate, metabolism of vinyl acetate by nasal tissue was examined. Through the use of a carboxylesterase inhibitor (BNPP) and mono-oxygenase inhibitors (such as diallyl sulfide), metabolism of vinyl acetate by the nose was shown to be carboxylesterase dependent (Plowchalk et al. 1997; Bogdanffy et al. 1999a). Histochemical staining of the rat nasal cavity revealed that a high-affinity carboxylesterase was bound to the luminal plasma membrane (Bogdanffy et al. 1999a). To examine the kinetics of nasal carboxylesterase-mediated metabolism of vinyl acetate, homogenized samples of nasal respiratory and olfactory mucosa from male and female rats and mice were incubated with vinyl acetate (Bogdanffy and Taylor 1993). Few difference in kinetics between male or female rats or mice were observed; however, the olfactory mucosa had higher activity than the respiratory mucosa (see Table 7-13), a result also seen after histochemical staining of the nasal passages of Fischer 344 rats and $B6C3F_1$ mice (Bogdanffy et al. 1987). An in vitro gas technique using whole-tissue samples and physiologically-based pharmacokinetic modeling were used to investigate differences in vinyl acetate metabolism in rat and human nasal tissues (Bogdanffy et al. 1998). Rat respiratory carboxylesterase and aldehyde dehydrogenase activities were approximately three and two times higher than those of humans, respectively, whereas rat olfactory enzyme activities were equivalent to humans (see Table 7-14). K_m values did not differ between species.

As observed in the whole-body gas uptake study (Simon et al. 1985a), substrate inhibition of rat nasal carboxylesterase in vitro was found at high concentrations of vinyl acetate (Bogdanffy and Taylor 1993). This is also evident from studies that demonstrated that in vivo deposition of vinyl acetate in the upper respiratory tract of the rat is concentration dependent (Plowchalk et al. 1997). At low concentrations, removal of vinyl acetate from the airstream is highly efficient; more than 93% was extracted by the rat nose at concentrations of 76 ppm or less. At vinyl acetate concentrations of 76-550 ppm, extraction progressively decreased to about 40% and remained at that level until a vinyl acetate concentration of approximately 2,000 ppm. Acetaldehyde in expired air

increased to an apparent maximum of 227 ppm, which corresponded to a vinyl acetate concentration of 1,000 ppm.

TABLE 7-13 Kinetics of Vinyl Acetate from Various Sources

Source of Enzyme	pH	K_m (mM)	V_{max} (µmol/min/mg protein)	Reference
Rat liver microsomes	8.0	0.73	23	Simon et al. 1985a
Rat lung microsomes	8.0	6.1	6.2	Simon et al. 1985a
Rat plasma	8.0	4.0	0.56	Simon et al. 1985a
Human plasma	8.0	7.1	0.69	Simon et al. 1985a
Respiratory nasal mucosa (mice and rats)	7.4	0.3-0.43	22-46	Bogdanffy and Taylor 1993
Olfactory nasal mucosa (rats and mice)	7.4	0.20-0.52	89-165	Bogdanffy and Taylor 1993
Purified carboxyl esterase	8.0	0.65	238	Simon et al. 1985a

TABLE 7-14 Kinetic Constants for Individual Tissue Specimens Derived from a Mini Vapor Uptake Technique

			V_{max}	
Enzyme	Tissue	K_m (mg/mL)	Activity/Specimen (mg/h)	Activity/Epithelial Cell Volume (mg/h/mm^3)
Rat tissues				
Carboxylesterase	Maxilloturbinate[a]	0.04	2.10	1.89
	3EV[a]	0.05	1.68	1.82
Aldehyde dehydrogenase	Maxilloturbinate	0.80	0.05	0.15
	3EV	0.80	0.10	0.07
Human tissues				
Carboxylesterase	Middle turbinate[a]	0.05	1.50	0.57
	Dorsal meatus[a]	0.05	0.90	1.94
Aldehyde dehydrogenase	Middle turbinate	1.10	0.30	0.08
	Dorsal meatus	1.10	0.05	0.08

[a]Maxilloturbinate (rat) and middle turbinate (human) are lined with respiratory epithelium. 3EV (ventral scroll of the third ethnoturbinate) (rat) and dorsal meatus (human) are lined with olfactory epithelium.
Source: Bogdanffy et al. 1998. Reprinted with permission; copyright 1998, *Toxicological Sciences*.

4.2. Mechanism of Toxicity

Several papers have been written about the mode of action of vinyl acetate (Bogdanffy et al. 1999b, 2001; Andersen et al. 2002; Bogdanffy 2002; Bolt 2003; Bogdanffy and Valentine 2003; Hengstler et al. 2003). Metabolism studies have demonstrated that vinyl acetate is metabolized to acetic acid and vinyl alcohol, which rearranges to form acetaldehyde (Simon et al. 1985a; Bogdanffy and Taylor 1993). Acetaldehyde can be further metabolized to acetic acid. Genotoxicity and cytotoxicity tests demonstrated that clastogenicity and cytotoxicity required the presence of carboxylesterases (Kuykendall and Bogdanffy 1992a,b; Kuykendall et al. 1993a). Production of of acetic acid was shown to be responsible for the observed cytotoxicity, and acetaldehyde was responsible for the DNA-protein crosslinking observed in test systems (Kuykendall et al. 1993a). The proposed mechanism of cytotoxicity is lowering of inter- and intra-cellular pH by the production of acetic acid (Kuykendall et al. 1993a; Plowchalk et al. 1997; Bogdanffy et al. 2001). An in vitro study measuring the pH of individual rat respiratory and olfactory nasal epithelial cells before and during exposure to vinyl acetate confirmed a concentration-related decrease in pH with increasing vinyl acetate concentration, with a maximum decrease in pH of 0.3 pH units (Lantz et al. 2003). The cytotoxic response leads to cellular degeneration followed by cellular proliferation (Kuykendall et al. 1993a; Plowchalk et al. 1997; Bogdanffy et al. 2001). Clastogenic effects include chromosomal aberrations, sister chromatid exchange, and DNA crosslinking in human lymphocytes (Mäki-Paakkanen et al. 1984; He and Lambert 1985; Lambert et al. 1985; Norppa et al. 1985; Jantunen et al. 1986; Mäki-Paakkanen and Norppa 1987); Chinese hamster ovary cells (Mäki-Paakkanen et al. 1984; Norppa et al. 1985); rat liver microsomes (Kuykendall and Bogdanffy 1992a,b); and rat nasal epithelial tissues (Kuyendall et al. 1993a,b). Clastogenic effects appear to be due to the production of acetaldehyde, a weak DNA protein crosslinking agent (Kuykendall et al. 1993a) in combination with a lowering of pH (Morita 1995). Acetaldehyde-induced DNA protein crosslinks are more stable at a pH lower than the physiologic pH (Kuyendall and Bogdanffy 1992a). Therefore, the following continuum of response has been proposed for vinyl acetate (Bogdanffy et al. 2001):

Vinyl acetate metabolism
↓
Reduction of pH
↓
Cytotoxic response - olfactory degeneration
↓
Cellular proliferation
↓
Tumorigenic response

Metabolic saturation of vinyl acetate occurs. Simon et al. (1985a) reported that metabolic saturation is reached around 650 ppm in rats. In the rat nose, removal of vinyl acetate from the airstream is highly efficient at low concentrations (more than 93% was extracted at concentrations of 76 ppm or less), but becomes less efficient with increasing concentrations (extraction progressively decreased to about 40% at 76-550 ppm and remained at that level up to a concentration of about 2,000 ppm) (Plowchalk et al. 1997). Therefore, olfactory degeneration would be the primary end point until metabolic saturation in the nasal cavity is reached. Once metabolic saturation has occurred, vinyl acetate would be able to move further down into the respiratory tract. This is evidenced by the strong anterior to posterior gradient seen in the rat nasal cavity during histopathologic examination after acute exposure to inhaled vinyl acetate (Bogdanffy et al. 1997), by the histopathologic changes noted in the lungs of rats and mice exposed at 600 ppm in a 2-year bioassay (Bogdanffy et al. 1994), and by the pulmonary changes found in rats, mice, guinea pigs, and rabbits exposed to acute, lethal concentrations (Smyth and Carpenter 1973).

4.3. Structure-Activity Relationships

Structure-activity relationships were not used for deriving AEGL values for vinyl acetate .

4.4. Other Relevant Information

4.4.1. Species Variability

Four-hour LC_{50} data varied by a factor of 3.6; the most sensitive species was the mouse, followed by the rabbits, rat, and guinea pig (Smyth and Carpenter 1973). Regardless of species, the cause of death was attributed to pulmonary distress.

Olfactory degeneration is the proposed primary end point of inhaled vinyl acetate until metabolic saturation in the nasal cavity is reached (Bogdanffy et al. 1997). Therefore, much research is available regarding the metabolism of vinyl acetate by the nasal cavity. In general, little difference was observed between male and female mice and rats and humans in the carboxylesterase-mediated metabolism of vinyl acetate, particularly by the olfactory epithelium (Bogdanffy and Taylor 1993; Bogdanffy et al. 1998). Esterase distribution in the nasal respiratory tissue of humans is believed to be similar to that of rats (Andersen et al. 2002). However, considerable variability in olfactory nasal tissue occurs in humans with regard to surface area, composition of epithelial tissue layers (respiratory-type tissue can be interspersed with more characteristic olfactory tissue), and age-related changes (Andersen et al. 2002). Children appear to have histologic organization similar to rodents, in that the olfactory epithelium is well-developed and delineated. Aging humans develop a very heterogenous

mucosa with respiratory-like epithelial cells populating the olfactory region. Glandular structures become sparse and non-esterase-containing tissues fill the submucosa. However, esterase histochemistry of adult olfactory mucosa revealed that sustentacular cells and Bowman's glands do contain significant quantities of carboxylesterase.

4.4.2. Susceptible Populations

Data regarding populations susceptible to vinyl acetate were not available. Although older populations may not be as susceptible to olfactory degeneration as younger ones, they may have increased susceptibility of the respiratory epithelium or even greater pulmonary susceptibility because of decreased removal of vinyl acetate in the nose.

4.4.3. Concentration-Exposure Duration Relationship

The relationship between concentration and duration of exposure as related to lethality was examined by ten Berge et al. (1986) for approximately 20 irritant or systemically-acting vapors and gases. Individual animal data sets were analyzed by probit analysis, with exposure duration and exposure concentration as independent variables. An exponential equation $C^n \times t = k$, where the value of n ranged from 0.8 to 3.5 for different chemicals, was found to be an accurate quantitative descriptor for the chemicals evaluated. Approximately 90% of the values of n range between n = 1 and n = 3. Consequently, these values were selected as the reasonable lower and upper bounds of n. A value of n = 1 is used when extrapolating from shorter to longer durations because the extrapolated values represent the most conservative approach in the absence of other data. Conversely, a value of n = 3 is used when extrapolating from longer to shorter durations because the extrapolated values are more conservative in the absence of other data.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

In a controlled-exposure study, a 2-min exposure of nine subjects to vinyl acetate at 4, 8, or 20 ppm resulted in minimal ocular, nasal, and throat irritation in one or two people (Smyth and Carpenter 1973). For longer durations, one of three individuals reported persistent slight irritation of the throat after being exposed for 4 h at 20 ppm and two of three individuals complained of throat irritation (transient in one and persistent in the other) after being exposed for 2 h at 34 ppm. Exposure at 72 ppm for 30 min resulted in ocular irritation and slight throat irritation for up to 60 min after exposure ended in all four test subjects;

irritation was so severe that subjects expressed unwillingness to work at that concentration for 8 h.

In an occupational health report, Deese and Joyner (1969) reported that ocular irritation from exposure to vinyl acetate at 21.6 ppm would be "intolerable over an extended period"; a slight cough and hoarseness were also reported by three subjects exposed at this concentration. In addition, slight ocular irritation in one of three individuals was reported at 5.7 or 6.8 ppm, and hoarseness in one of three was reported at 4.2 and 5.7 ppm. These findings conflict with those of the human volunteer study by Smyth and Carpenter (1973), in which 20 ppm was tolerated by three subjects for 4 h and findings were limited to olfactory fatigue and slight throat irritation in one individual. The Deese and Joyner (1969) study is of limited use for deriving AEGL values because it was not a controlled-exposure study. As noted earlier, the subjects might have been briefly exposed at a concentration higher than 21.6 ppm. Furthermore, coexposure to other chemicals used in the production facility might have exacerbated or contributed to the ocular irritation. Therefore, this study was not used for deriving AEGL-1 values.

5.2. Animal Data Relevant to AEGL-1

Irritation was noted in a dog exposed to vinyl acetate at 205 ppm for 4 h (blinking was observed after 1 min and the sclera were red after 1 h) (Smyth and Carpenter 1973). In the Bogdanffy et al. (1997) study, no histopathologic effects was found in the olfactory or respiratory epithelium of rats exposed to vinyl acetate at 0, 50, or 200 ppm for 6 h/day, 5 days/week for 1, 5, or 20 days. Thus, 200 ppm is a no-observed-effect level for these end points.

5.3. Derivation of AEGL-1 Values

AEGL-1 values are based on the no-effect level for notable discomfort found in a study of human volunteers (Smyth and Carpenter 1973). This study was selected over the occupational health report (Deese and Joyner 1969) or the rat study (Bogdanffy et al. 1997) because it was a controlled-exposure study in humans. Slight throat irritation was reported by one of three individuals exposed to vinyl acetate at 20 ppm for 4 h; therefore, effects at 20 ppm are considered to be mild and below a notable discomfort threshold. An intraspecies uncertainty factor of 3 was applied because the irritation is caused by a local effect of the chemical and the response is not expected to vary greatly among individuals. Because irritation is considered a threshold effect and should not vary over time, AEGL-1 values were not scaled across time; instead, the same threshold value was adopted for all the exposure durations. The importance of concentration over exposure duration in the irritant response to vinyl acetate is supported by other findings in the Smyth and Carpenter (1973) study. Similar slight irritation was reported in one individual exposed to vinyl acetate at 20 ppm after 2 min

and 4 h. More subjects reported irritation of greater severity when exposed at higher concentrations for shorter durations (e.g., 34 ppm for 2 h or 72 ppm for 30 min). However, the data are limited because of the small number of subjects and varying exposure concentrations. AEGL-1 values for vinyl acetate are presented in Table 7-15.

The AEGL-1 value of 6.7 ppm is similar to the range of concentrations that caused hoarseness and slight ocular irritation in one of three people exposed at 4.2 and 5.7 ppm in a vinyl acetate production facility (Deese and Joyner 1969); however, the data are potentially confounded by variable exposure conditions and concurrent exposure to other chemicals.

A level of distinct odor awareness (LOA) of 0.25 ppm was derived on the basis of the odor detection threshold for vinyl acetate reported by Hellman and Small (1974) (see Appendix C for the derivation). The LOA is the concentration above which more than half of the exposed population is predicted to perceive at least a distinct odor intensity; about 10% of the population will perceive a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of exposure to vinyl acetate from its odor.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

A study by Smyth and Carpenter (1973) reported that controlled exposure to vinyl acetate at 34 ppm for 2 h resulted in persistent throat irritation in one of three individuals, and exposure at 72 ppm for 30 min resulted in ocular irritation and slight throat irritation for up to 60 min after exposure ended in all four subjects. Irritation at 72 ppm was so severe that subjects expressed an unwillingness to work at this concentration for 8 h.

6.2. Animal Data Relevant to AEGL-2

No histopathologic changes or cell proliferation were found in the olfactory or respiratory epithelium of rats exposed to vinyl acteate for 6 h at 0, 50, or 200 ppm. However, concentration-related olfactory epithelium changes (degeneration, necrosis, and exfoliation) and a concentration-related increase in cell proliferation in both the respiratory and olfactory epithelium were found in rats exposed at 600 and 1,000 ppm (Bogdanffy et al. 1997). Whether the lesions were reversible could not be determined because a recovery phase was not included in the study. However, the effects should be completely reversible from both a morphologic and functional standpoint, based on the focal and limited nature of the olfactory lesions, as well as the known regenerative capacity of the olfactory tissue (S.R. Frame, DuPont, Haskell Laboratory, Newark, DE, personal commun., December 1, 2004).

TABLE 7-15 AEGL-1 Values for Vinyl Acetate

10 min	30 min	1 h	4 h	8 h
6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)

6.3. Derivation of AEGL-2 Values

Although human data are preferred over animal data to derive AEGL values, the human study by Smyth and Carpenter was not used because its findings of notable discomfort are not relevant AEGL-2 effects. Therefore, the rat data reported by Bogdanffy et al. (1997) are the basis for the AEGL-2 values. In that study, rats exposed for 6 h to vinyl acetate at 600 and 1,000 ppm had histopathologic changes in the olfactory epithelium; no lesions were observed at 200 or 50 ppm. At 600 ppm, minimal or mild olfactory degeneration and necrosis was observed in 5/5 male rats and moderately severe lesion(s) were found in one nasal segment of 1/5 rats. At 1,000 ppm, 1/5 rats exhibited minimal degeneration and necrosis of the respiratory epithelium, and 2/5 rats had moderately severe lesions of the olfactory epithelium (Bogdanffy et al. 1997). The olfactory lesions are predicted to be reversible (S.R. Frame, DuPont, Haskell Laboratory, Newark, DE, personal commun., December 1, 2004). However, because the study did not include a recovery group, there are no data with which to empirically demonstrate that the effects were reversed. It is plausible that the effects at 600 and 1,000 ppm could be relevant AEGL-2 effects of "other serious, long-lasting adverse health effects" (NRC 2001). In a review of the toxicologic pathology of the nasal epithelium, Harkema et al. (2006) noted that olfactory epithelium damaged by exposure to toxic irritants may recover to near normal morphology, but that recovery may take weeks or months. In addition, some modification of the mucosa may occur during recovery, leading to olfactory epithelium cells that resemble respiratory epithelium. Because the reversibility of the lesions is uncertain, 200 ppm was selected as the point of departure for deriving AEGL-2 values. This concentration is considered a no-effect level for serious, long-lasting histopathologic nasal lesions in rats exposed for 6 h.

A total uncertainty factor of 10 was applied;: 3 for interspecies differences and 3 for intraspecies variability. An interspecies uncertainty factor of 3 was applied because the mechanism of nasal toxicity appears to depend on the metabolism of vinyl acetate to the metabolites acetic acid and acetaldehyde via carboxylesterase and aldehyde dehydrogenase. Studies of the metabolism of vinyl acetate by the nasal cavity reported little difference among male and female mice and rats and humans in the carboxylesterase-mediated metabolism of vinyl acetate, particularly by olfactory epithelium (Bogdanffy and Taylor 1993; Bogdanffy et al. 1998). Esterase distribution in the nasal respiratory tissue of humans is believed to be similar to that of rats (Andersen et al. 2002). An

intraspecies uncertainty factor of 10 would normally be applied because considerable variability in olfactory nasal tissue occurs in humans with regard to surface area, composition of epithelial tissue layers (respiratory-type tissue can be interspersed with more characteristic olfactory tissue), and age-related changes (Andersen et al. 2002). However, a total uncertainty factor of 30 would result in an 8-h AEGL-2 value (5 ppm) lower than the AEGL-1 value of 6.7 ppm. Reduction of an uncertainty factor is appropriate when the weight of evidence indicates that a higher uncertainty factor would result in AEGL values at odds with human data (NRC 2001). Therefore, the intraspecies uncertainty factor was reduced to 3.

The experimentally derived exposure values were scaled to AEGL time frames using the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 0.8 to 3.5 (ten Berge et al. 1986). The value of n was not empirically derived because of insufficient data on vinyl acetate; therefore, default values of n = 1 for extrapolating from shorter to longer durations and n = 3 for extrapolating from longer to shorter durations were used. The 10-min AEGL-2 value was set equal to the 30-min AEGL-2 of 46 ppm because of the uncertainty in extrapolating a 6-h exposure to a 10-min value (NRC 2001).

AEGL-2 values for vinyl acetate are presented in Table 7-16.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human data relevant to AEGL-3 values were available.

7.2. Summary of Animal Data Relevant to AEGL-3

Mortality data on vinyl acetate were available for rats, mice, guinea pigs, and rabbits (Smyth and Carpenter 1973). Chamber concentrations were not measured, but nominal concentrations were corrected against a calibration curve. Lethal concentrations produced signs of irritation (gasping and lacrimation) and central nervous system effects (poor coordination, prostration, and clonic convulsions), and death was attributed to pulmonary irritation (pulmonary congestion, hemorrhages, and excess pleural fluid).

Nonlethal concentrations of vinyl acetate produced signs of congested extremities in rats, lacrimation in guinea pigs, and no signs in mice or rabbits (Smyth and Carpenter 1973). Dogs exhibited lacrimation, nasal froth, and tremors when exposed for 4 h at 3,280 ppm, and irritation but no central nervous system effects at 1,640 ppm (Smyth and Carpenter 1973). Exposure to vinyl acetate at 1,000 ppm for 6 h/day, 5 days/week for 4 weeks was not lethal to male and female rats or mice (Owen 1979a,b; 1980a,b).

TABLE 7-16 AEGL-2 Values for Vinyl Acetate

10 min	30 min	1 h	4 h	8 h
46 ppm (160 mg/m^3)	46 ppm (160 mg/m^3)	36 ppm (130 mg/m^3)	23 ppm (81 mg/m^3)	15 ppm (53 mg/m^3)

As discussed in the context of AEGL-2 values, no histopathologic effects or cell proliferation were noted in the olfactory or respiratory epithelium of rats exposed to vinyl acetate for 6 h at 0, 50, or 200 ppm, but concentration-related olfactory epithelium changes (degeneration, necrosis, and exfoliation) and a concentration-related increase in cell proliferation in both the respiratory and olfactory epithelium were present in animals exposed at 600 and 1,000 ppm (Bogdanffy et al. 1997).

A carcinogenicity assessment was not appropriate for an acute exposure scenario because the proposed mechanism of carcinogenicity suggests a nonlinear mode of action requiring continued exposure to vinyl acetate. Therefore, a one-time exposure at even high concentrations of vinyl acetate would not be expected to result in tumor development.

7.3. Derivation of AEGL-3 Values

The 4-h mortality data for vinyl acetate in five species reported by Smyth and Carpenter (1973) were not suitable for modeling. In studies with rats, mice, and guinea pigs, deaths occurred during exposure at all but the lowest concentration of vinyl acetate. In rabbits, deaths occurred at only the highest concentration. The time of death for each of the rats and mice were not specified, so the data could not be modeled. Times of death for guinea pigs and rabbits were reported, but efforts to model the data were unsuccessful. Only one dog per exposure was tested by Smyth and Carpenter (1973), so those data were also unsuitable for modeling.

In the absence of modeling results to determine a lethality threshold for vinyl acetate, the highest nonlethal concentrations found in different species were considered. Vinyl acetate at 1,640 ppm was nonlethal in rats, guinea pigs, and rabbits exposed for 4 h. In mice, no death occurred in six mice exposed at 410 ppm, and one of six mice died after exposure at 820 ppm (Smyth and Carpenter 1973). In other studies, 1,000 ppm was nonlethal to rats exposed for 6 h (Bogdanffy et al. 1997) or to rats and mice exposed for 6 h/day, 5 days/week for 4 or 13 weeks (Owen 1979a,b; 1980a,b).

Data from the Smyth and Carpenter (1973) study of mice exposed once to vinyl acetate appear to conflict with the results of repeated exposure studies. Smyth and Carpenter (1973) observed one death among six mice exposed for 4 h at 820 ppm; the exposure concentration was calculated as 1,000 ppm and then corrected to 820 ppm on the basis of gas chromatography measurements of calculated concentrations. In contrast, 10 mice (5/sex) survived exposure to vi-

nyl acetate at 1,000 ppm (measured by gas chromatography at 15-min intervals) for 6 h/day, 5/days/week for 4 weeks, and a separate group of 10 mice survived 1,500 ppm for 20 days (initial concentration of 50 ppm was increased to 1,500 ppm on day 8 of the study and continued to the end of the study at 28 days) (Owen 1979a). In a subchronic study, a group of 20 mice (10/sex) survived exposure to vinyl acetate at 1,000 ppm for 6 h/day, 5 days/week for at least 4 weeks (9/20 mice died as a result of routine blood sampling during week 5, 6, or 12) (Owen 1980a). Finally, 104/120 mice survived exposure to vinyl acetate at 600 ppm for 6 h/day, 5 days/week for 104 weeks (Bogdanffy et al. 1994). Among the acute and subchronic studies, the Owen (1979a, 1980a) studies are considered more reliable than those of Smyth and Carpenter (1973) because group sizes were larger, sex and strain of the animals were reported, exposure concentrations were measured by gas chromatography at 15-min intervals, and the study design and findings were reported in more detail.

A point of departure of 1,000 ppm for 6 h was used to derive AEGL-3 values. That concentration was nonlethal in rats exposed for a single 6-h duration (Bogdanffy et al. 1997), as well as in both rats and mice exposed repeatedly for 6 h/day, 5 days/week for 4 weeks (Owen 1979a,b, 1980a,b). A total uncertainty factor of 10 was applied: 3 for interspecies differences and 3 for intraspecies variability. An interspecies uncertainty factor of 3 is applied because the mechanism of nasal toxicity appears to depend on the metabolism of vinyl acetate to the metabolites acetic acid and acetaldehyde via carboxylesterase and aldehyde dehydrogenase. Studies investigating the metabolism of vinyl acetate by the nasal cavity reported little difference among male and female mice, rats, and humans in the carboxylesterase-mediated metabolism of vinyl acetate, particularly by olfactory epithelium (Bogdanffy and Taylor 1993; Bogdanffy et al. 1998). Esterase distribution in the nasal respiratory tissue of humans is believed to be similar to that of rats (Andersen et al. 2002). An intraspecies uncertainty factor of 3 was applied instead of 10. Application of a higher total uncertainty factor of 30 would result in an 8-h AEGL-3 value (25 ppm) lower than concentrations that did not result in serious health effects in a human volunteer study, albeit at shorter exposure durations. No life-threatening effects were found in human volunteers exposed to vinyl acetate at 34 ppm for 2 h or at 72 ppm for 30 min (Smyth and Carpenter 1973). Reduction of an uncertainty factor is appropriate when the weight of evidence indicates that a higher uncertainty factor would result in AEGL values at odds with human data (NRC 2001). Therefore, an intraspecies uncertainty factor of 3 was used.

Time scaling was performed in the same manner described for AEGL-2 values (see Section 6.3). Similarly, the 10-min AEGL-3 value was set equal to the 30-min AEGL-3 of 230 ppm because of the uncertainty in extrapolating a 6-h exposure to a 10-min value (NRC 2001).

AEGL-3 values for vinyl acetate are presented in Table 7-17.

8. SUMMARY OF AEGL VALUES

8.1. AEGL Values and Toxicity End Points

The Smyth and Carpenter (1973) study was used to derive AEGL-1 values for vinyl acetate on the basis of irritation in humans, but there were inadequate data from other human studies of AEGL-1 effects to verify consistency. AEGL-2 values are based on a no-effect level for serious, long-lasting nasal histopathologic lesions in rats. AEGL-3 values are based on the highest nonlethal concentration in rats and mice exposed for 6 h per day for up to 28 days (Owen 1979a,b, 1980a,b; Bogdanffy et al. 1997). AEGL values for vinyl acetate are presented in Table 7-18.

8.2. Comparison with Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures to vinyl acetate are presented in Table 7-19. The emergency response planning guideline 1 (ERPG-1) for vinyl acetate of 5 ppm is similar to the AEGL-1 value of 6.7 ppm. The ERPG-2 of 75 ppm is based on evidence that healthy humans can tolerate irritant effects at 72 ppm for 30 min (Smyth and Carpenter 1973) and that no effects were observed in subchronic studies in animals at concentrations up to 200 ppm (Owen 1980a,b; Bogdanffy et al. 1997). The difference between the ERPG-2 and AEGL-2 values appears to be due to the use of an uncertainty factor for intraspecies differences in deriving the AEGL-2 value, which was not used in determining the ERPG-2 value.

TABLE 7-17 AEGL-3 Values for Vinyl Acetate

10 min	30 min	1 h	4 h	8 h
230 ppm (810 mg/m^3)	230 ppm (810 mg/m^3)	180 ppm (630 mg/m^3)	110 ppm (390 mg/m^3)	75 ppm (260 mg/m^3)

TABLE 7-18 AEGL Values for Vinyl Acetate

	Exposure Duration				
Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)
AEGL-2 (disabling)	46 ppm (160 mg/m^3)	46 ppm (160 mg/m^3)	36 ppm (130 mg/m^3)	23 ppm (81 mg/m^3)	15 ppm (53 mg/m^3)
AEGL-3 (lethal)	230 ppm (810 mg/m^3)	230 ppm (810 mg/m^3)	180 ppm (630 mg/m^3)	110 ppm (390 mg/m^3)	75 ppm (260 mg/m^3)

TABLE 7-19 Standards and Guidelines for Vinyl Acetate

	Exposure Duration					
Guideline	10 min	15 min	30 min	1 h	4 h	8 h
AEGL-1	6.7 ppm		6.7 ppm	6.7 ppm	6.7 ppm	6.7 ppm
AEGL-2	46 ppm		46 ppm	36 ppm	23 ppm	15 ppm
AEGL-3	230 ppm		230 ppm	180 ppm	110 ppm	75 ppm
ERPG-1 (AIHA)[a]				5 ppm		
ERPG-2 (AIHA)				75 ppm		
ERPG-3 (AIHA)				500 ppm		
TLV-TWA (ACGIH®)[b]						10 ppm (A3)
REL-C (NIOSH)[c]		4 ppm				
TLV-STEL (ACGIH®)[d]		15 ppm				
MAC (The Netherlands)[e]						5 ppm

[a]ERPG (emergency response planning guidelines, American Industrial Hygiene Association [AIHA 2004]).
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 protective 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]TLV-TWA (threshold limit value - time weighted average, American Conference of Governmental Industrial Hygienists [ACGIH 2012]) 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. Notation of 3A designates that vinyl acetate is a confirmed animal carcinogen with unknown relevance to humans.
[c]REL-C (recommended exposure limits - ceiling, National Institute for Occupational Safety and Health [NIOSH 2011]) is a ceiling value that must not be exceeded during any part of the workday.
[d]TLV-STEL (threshold limit value - short-term exposure limit, American Conference of Governmental Industrial Hygienists [ACGIH 2012]) is a 15-min time-weighted average exposure that should not be exceeded at any time during a workday, even if the 8-h time-weighted average is within the TLV-TWA. The TLV-STEL is the concentration to which it is believed that workers can be exposed continuously for a short period of time without suffering from: (1) irritation, (2) chronic or irreversible tissue damage, (3) dose-rate-dependent toxic effects, or (4) narcosis of sufficient degree to increase the likelihood of accidental injury, impaired self-rescue, or materially reduced work efficiency.
[e]MAC (maximaal aanvaaarde concentratie [maximal accepted concentration], Dutch Expert Committee for Occupational Standards, , The Netherlands [MSZE 2004]) is defined analogous to the ACGIH TLV-TWA.

AIHA (2004) selected an ERPG-3 of 500 ppm for vinyl acetate on the basis of a study reporting the death of one of six mice exposed at 1,000 ppm (810 ppm after adjustment based on gas chromotograpic calibration) (Smyth and Carpenter 1973) and chronic studies in which rats and mice survived exposure to vinyl acetate at 600 ppm (Bogdanffy et al. 1994). AIHA (2004) reported that mice were the most sensitive species, and that all species exhibited signs consistent with respiratory tract irritation. The organization concluded that "It is believed that nearly all individuals could be exposed to 500 ppm vinyl acetate for up to 1 h without experiencing or developing life-threatening health effects". Thus, the primary difference between the ERPG-3 and AEGL-3 derivations appears to be that the AEGL-3 values incorporate uncertainty factors for interspecies differences and intraspecies variability.

Occupational standards for repeated 8-h exposures to vinyl acetate are 5 ppm (MSZW 2004) and 10 ppm (ACGIH 2012), and 15-min occupational exposure limits are 4 ppm (NIOSH 2011) and 15 ppm (ACGIH 2012). These standards are in the same range as the AEGL-1 of 6.7 ppm for protection against notable irritation.

8.3. Data Adequacy and Research Needs

Although data were considered adequate for derivation of all three AEGL levels, the overall database on vinyl acetate was limited. The volunteer study with controlled exposure to vinyl acetate (Smyth and Carpenter 1973) had inadequate documentation of the study design and findings, and exposure concentrations were calculated rather than measured. In the occupational health study, exposures were variable and subjects were likely exposed to other airborne contaminants concurrently (Deese and Joyner 1969). The animal database for nonlethal effects of vinyl acetate is more robust, and includes single-day, 4-week, 13-week, and chronic exposure studies (Owen 1979a,b, 1980a,b; Bogdanffy et al. 1994, 1997). However, lethality data were only available from the studies by Smyth and Carpenter (1973), which lacked analytic confirmation of exposure concentrations and had results that appear to conflict with those from repeated exposure studies. Thus, well-conducted animal lethality studies would enhance the toxicologic database, as would more rigorous occupational health studies or controlled-exposure experiments in humans.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR VINYL ACETATE

Derivation of AEGL-1 Values

Key study:	Smyth, H.F., and C.P. Carpenter. 1973. Initial Submission: Vinyl Acetate: Single Animal Inhalation and Human Sensory Response with Cover Letter Dated 08/27/92. Special Report 36-52. Carnegie-Mellon Institute, Pittsburgh, PA. Submitted to EPA by Union Carbide Corporation, Danbury. CT. EPA Document. No. 88-920010328. Microfiche No. OTS 0571724.
Toxicity end point:	Human exposure to vinyl acetate at 20 ppm for 4 h resulted in one of three individuals complaining of persistent, slight throat irritation, and exposure at 34 ppm for 2 h resulted in one of three individuals complaining of persistent throat irritation (no longer slight). Therefore, 20 ppm represents a no-effect level for notable discomfort.
Time scaling:	None; because irritation is considered a threshold effect and should not vary over time, the AEGL-1 value is not scaled across time. The threshold is used at the point of departure for all AEGL-1 durations.
Uncertainty factors:	3 for intraspecies variability
Calculations:	
10- and 30-min, 1-, 4-, and 8-h AEGL-1	20 ppm ÷ 3 = 6.7 ppm

Derivation of AEGL-2 Values

Key study:	Bogdanffy, M.S., N.L. Gladnick, T. Kegelman, and S.R. Frame. 1997. Four week inhalation cell proliferation study of the effects of vinyl acetate on rat nasal epithelium. Inhal. Toxicol. 9(1):331-350.

Toxicity end points:	No-observed-effect level of 200 ppm for 6 h for serious, long-lasting histopathologic nasal lesions in rats.
Time scaling	$C^n \times t = k$ (defaults of n = 1 for extrapolating from shorter to longer durations and n = 3 for extrapolating from longer to shorter durations) $(200 \text{ ppm})^1 \times 6 \text{ h} = 1{,}200 \text{ ppm-h}$ $(200 \text{ ppm})^3 \times 6 \text{ h} = 4.8 \times 10^7 \text{ ppm-h}$
Uncertainty factors:	3 for interspecies differences; the mechanism of nasal toxicity appears to depend on the metabolism of vinyl acetate to the metabolites acetic acid and acetaldehyde via carboxylesterase and aldehyde dehydrogenase. Studies investigating the metabolism of vinyl acetate by the nasal cavity found little difference among mice, rats, and humans in the carboxylesterase-mediated metabolism of vinyl acetate, particularly by olfactory epithelium (Bogdanffy and Taylor 1993; Bogdanffy et al. 1998). Esterase distribution in the nasal respiratory tissue of humans is believed to be similar to that of rats (Andersen et al. 2002). 3 for intraspecies variability; the usual factor of 10 would result in an 8-h AEGL-2 value of 5 ppm, a concentration lower than the AEGL-1 value of 6.7 ppm. Reduction of an uncertainty factor is appropriate when the weight of evidence indicates that a higher uncertainty factor would result in AEGL values at odds with human data (NRC 2001).
Modifying factor:	Not applicable
Calculations:	
10-min AEGL-2:	Set equal to the 30-min AEGL-2 value of 46 ppm, because of uncertainty in extrapolating a 6-h exposure to 10-min value (NRC 2001).
30-min AEGL-2:	$C^3 \times 0.5 \text{ h} = 4.8 \times 10^7 \text{ ppm-h}$ $C^3 = 9.6 \times 10^7 \text{ ppm}$ $C = 460 \text{ ppm} \div 10 = 46 \text{ ppm}$

1-h AEGL-2: $C^3 \times 1\ h = 4.8 \times 10^7$ ppm-h
$C^3 = 4.8 \times 10^7$ ppm
C = 360 ppm ÷ 10 = 36 ppm

4-h AEGL-2: $C^3 \times 4\ h = 4.8 \times 10^7$ ppm-h
$C^3 = 1.2 \times 10^7$ ppm
C = 230 ppm ÷ 10 = 23 ppm

8-h AEGL-2: $C^1 \times 8\ h = 1{,}200$ ppm-h
$C^1 = 150$ ppm
C = 150 ppm ÷ 10 = 15 ppm

Derivation of AEGL-3 Values

Key studies:

Bogdanffy, M.S., N.L. Gladnick, T. Kegelman, and S.R. Frame. 1997. Four week inhalation cell proliferation study of the effects of vinyl acetate on rat nasal epithelium. Inhal. Toxicol. 9(1):331-350.

Owen, P.E. 1979a. Vinyl Acetate: 4 Week Inhalation Dose Range Study in the Mouse. Report No. 1884-51/3. Prepared for Society of the Plastics Industry Inc., New York, by Hazleton Laboratories Europe, Ltd., Harrogate, England, August 1979. EPA Document No. FYI-OTS-0184-0278SU. Microfiche No. OTS0278.

Owen, P.E. 1979b. Vinyl Acetate: 4 Week Inhalation Dose Range Study in the Rat. Report No. 1835-51/3. Prepared for Society of the Plastics Industry Inc., New York, by Hazleton Laboratories Europe, Ltd., Harrogate, England, August 1979. EPA Document No. FYI-OTS-0184-0278SU. Microfiche No. OTS0278.

Owen, P.E. 1980a. Vinyl Acetate: 3 Month Inhalation Toxicity Study in the Mouse. Report No. 2303-51/5. Prepared for The Society of the Plastics Industry Inc., New York, by Hazleton Laboratories Europe, Ltd., Harrogate, England, May 1980. EPA Document No. FYI-OTS-0184-0278SU. Microfiche No. OTS0278.

Owen, P.E. 1980b. Vinyl Acetate: 3 Month Inhalation Toxicity Study in the Rat. Report No. 2286-51/5. Prepared for The Society of the Plastics Industry Inc., New York, by Hazleton Laboratories Europe, Ltd., Harrogate, England, May 1980. EPA Document No. FYI-OTS-0184-0278SU. Microfiche No. OTS0278.

Toxicity end points:	1,000 ppm for 6 h was nonlethal in rats and mice.
Time scaling:	$C^n \times t = k$ (defaults of n = 1 for extrapolating from shorter to longer durations and n = 3 for extrapolating from longer to shorter durations) $(1{,}000 \text{ ppm})^1 \times 6 \text{ h} = 6{,}000 \text{ ppm-h}$ $(1{,}000 \text{ ppm})^3 \times 6 \text{ h} = 6.0 \times 10^9 \text{ ppm-h}$
Uncertainty factors:	3 for interspecies differences; the mechanism of nasal toxicity appears to depend on the metabolism of vinyl acetate to the metabolites acetic acid and acetaldehyde via carboxylesterase and aldehyde dehydrogenase. Studies investigating the metabolism of vinyl acetate by the nasal cavity found little difference among mice, rats, and humans in the carboxylesterase-mediated metabolism of vinyl acetate, particularly by olfactory epithelium (Bogdanffy and Taylor 1993; Bogdanffy et al. 1998). Esterase distribution in the nasal respiratory tissue of humans is believed to be similar to that of rats (Andersen et al. 2002). 3 for intraspecies variability; the usual factor of 10 would result in an 8-h AEGL-3 value of 25 ppm, a concentration lower than concentrations that did not result in serious health effects in a human volunteer study. Reduction of an uncertainty factor is appropriate when the weight of the evidence indicates that a higher uncertainty factor would result in AEGL values at odds with human data (NRC 2001).
Modifying factor:	Not applicable
Calculations:	
10-min AEGL-3:	Set equal to the 30-min AEGL-3 value of 230 ppm, because of uncertainty in extrapolating a 6-h exposure to 10-min value (NRC 2001).
30-min AEGL-3:	$C^3 \times 0.5 \text{ h} = 6.0 \times 10^9 \text{ ppm-h}$ $C^3 = 1.2 \times 10^{10} \text{ ppm}$ $C = 2{,}289 \text{ ppm} \div 10 = 230 \text{ ppm}$
1-h AEGL-3:	$C^3 \times 1 \text{ h} = 6.0 \times 10^9 \text{ ppm-h}$ $C^3 = 6.0 \times 10^9 \text{ ppm}$ $C = 1{,}817 \text{ ppm} \div 10 = 180 \text{ ppm}$

4-h AEGL-3: $C^3 \times 4\ h = 6.0 \times 10^9$ ppm-h
$C^3 = 1.5 \times 10^8$ ppm
C = 1,144 ppm ÷ 10 = 110 ppm

8-h AEGL-3: $C^1 \times 8\ h = 6{,}000$ ppm-h
$C^1 = 750$ ppm
C = 750 ppm ÷ 10 = 75 ppm

APPENDIX B

CALCULATION OF LEVEL OF DISTINCT ODOR AWARENESS FOR VINYL ACETATE

The level of distinct odor awareness (LOA) represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, and about 10% of the population will experience strong odor intensity. The LOA should help chemical emergency responders assess the public awareness of the exposure to vinyl acetate on the basis of odor perception. The LOA for vinyl acetate was derived according to the guidance of van Doorn et al. (2002).

For derivation of an odor detection threshold (OT_{50}), a study by Hellman and Small (1974) was used. The study also determined an odor threshold for the reference chemical n-butanol (odor detection threshold 0.04 ppm):

- Odor detection threshold for vinyl acetate : 0.12 ppm
- Odor detection threshold for n-butanol: 0.3 ppm
- Corrected OT_{50} for vinyl acetate : (0.12 ppm × 0.04) ÷ 0.3 = 0.016 ppm

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

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

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

$$3 = 2.33 \times \log (C \div 0.016) + 0.5$$

which can be rearranged to:

$$\log (C \div 0.016) = (3 - 0.5) \div 2.33 = 1.07$$

and results in:

$$C = 10^{1.07} \times 0.016 = 11.8 \times 0.016 = 0.1888 \text{ ppm}$$

The resulting concentration is multiplied by an empirical field correction factor. The factor takes into account that everyday life factors, such as sex, age, sleep, smoking, upper airway infections, allergies, and distractions, increase the odor detection threshold by a factor of 4. In addition, it takes into account that odor perception is very fast (about 5 seconds), which leads to the perception of concentration peaks. On the basis of current knowledge, a factor of 1/3 is

applied to adjust for peak exposure. Adjustment for distraction and peak exposure lead to a correction factor of 1.33 (4 ÷ 3).

$$LOA = C \times 1.33 = 0.189 \text{ ppm} \times 1.33 = 0.25 \text{ ppm}$$

The LOA for vinyl acetate is 0.25 ppm.

APPENDIX C

CATEGORY PLOT FOR VINYL ACETATE

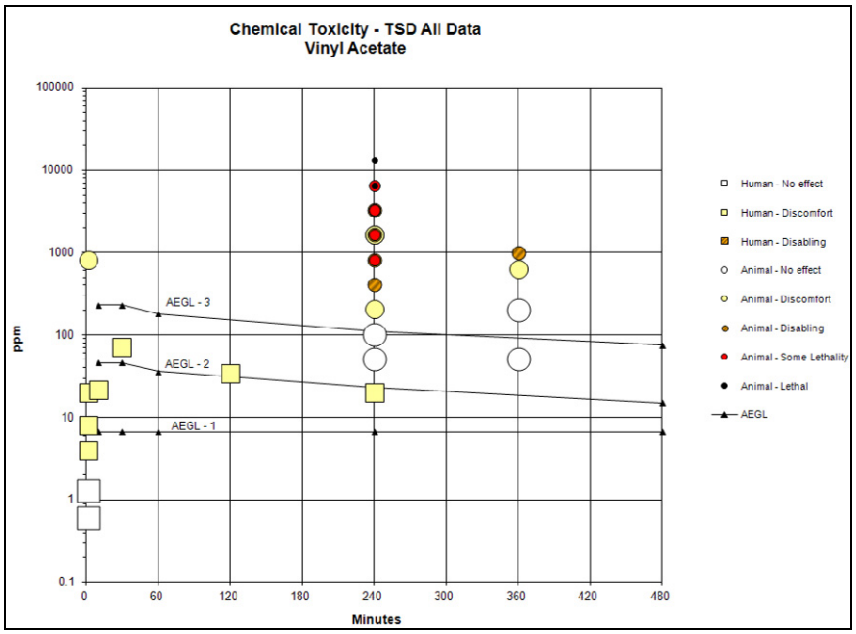

FIGURE C-1 Categoray plot of animal and human toxicity data on vinyl acetate compared with AEGL values.

TABLE C-1 Data Used in Category Plot for Vinyl Acetate

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
NAC/AEGL-1				6.7	10	AEGL	
NAC/AEGL-1				6.7	30	AEGL	
NAC/AEGL-1				6.7	60	AEGL	
NAC/AEGL-1				6.7	240	AEGL	
NAC/AEGL-1				6.7	480	AEGL	
NAC/AEGL-2				46	10	AEGL	
NAC/AEGL-2				46	30	AEGL	
NAC/AEGL-2				36	60	AEGL	
NAC/AEGL-2				23	240	AEGL	
NAC/AEGL-2				15	480	AEGL	
NAC/AEGL-3				230	10	AEGL	
NAC/AEGL-3				230	30	AEGL	
NAC/AEGL-3				180	60	AEGL	
NAC/AEGL-3				110	240	AEGL	
NAC/AEGL-3				75	480	AEGL	
Smyth and Carpenter 1973	Human		1	0.6	2	0	No effects
	Human		1	1.3	2	0	Odor detection
	Human		1	4	2	1	Odor detection; minimal ocular, nasal, throat irritation
	Human		1	8	2	1	Odor detection; minimal ocular, nasal, throat irritation
	Human		1	20	2	1	Odor detection; minimal ocular, nasal, throat irritation

(Continued)

TABLE C-1 Continued

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
	Human		1	20	240	1	Olfactory fatigue; throat irritation
	Human		1	34	120	1	Olfactory fatigue; throat irritation
	Human		1	72	30	1	Olfactory fatigue; throat irritation
Deese and Joyner 1969	Human		1	21.6	10	1	Odor detection, upper respiratory irritation
Smyth and Carpenter 1973	Rat	Both	1	1,640	240	2	Congestion
	Rat	Both	1	3,280	240	SL	Mortality (4/12); gasping, convulsions
	Rat		1	6,560	240	3	Mortality (12/12)
Smyth and Carpenter 1973	Mouse		1	410	240	2	
	Mouse		1	820	240	SL	Mortality (1/6), labored breathing
	Mouse		1	1,640	240	SL	Mortality (4/6), gasping, convulsions
	Mouse		1	3,280	240	SL	Mortality (5/6), gasping, convulsions, ocular effects
	Mouse		1	6,560	240	3	Mortality (6/6)
Smyth and Carpenter 1973	Guinea pig	Male	1	1,640	240	1	Lacrimation
	Guinea pig	Male	1	3,280	240	SL	Mortality (1/6), labored breathing, lacrimation
	Guinea pig	Male	1	6,560	240	SL	Mortality (4/6), gasping, convulsions
	Guinea pig	Male	1	13,120	240	3	Mortality (4/6), gasping, nose rubbing, lacrimation
	Rabbit	Male	1	3,280	240	SL	Mortality (3/4), red nose, cloudy eyes
	Rabbit	Male	1	6,560	240	3	Mortality (4/4); labored breathing, convulsions, cloudy eyes, bloody nose

	Dog	Male	1	51.25	240	0	No effects
	Dog	Male	1	102.5	240	0	No effects
	Dog	Male	1	205	240	1	Blinking, red sclera
	Dog	Male	1	820	240	2	Lacrimation, red sclera
	Dog	Male	1	1,640	240	1	Blinking, sneezing, lacrimation, inflamed eyelids, nasal froth
	Dog	Male	1	3,280	240	2	Ocular and nasal irritation, tremors, froth from nostrils
	Dog		1	820	2	1	Lacrimation
Gage 1970	Rat		1	630	360	1	Low body weight
Bogdanffy et al. 1997	Rat		1	50.8	360	0	No effects
	Rat		1	199.6	360	0	No effects
	Rat		1	1,007.3	360	2	Histopathologic changes (nasal epithelium)

For category: 0 = no effect, 1 = discomfort, 2 = disabling, 3 = lethal; SL = some lethality.

APPENDIX D

ACUTE EXPOSURE GUIDELINE LEVELS FOR VINYL ACETATE

Derivation Summary

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)

Key reference: Smyth, H.F., and C.P. Carpenter. 1973. Initial Submission: Vinyl Acetate: Single Animal Inhalation and Human Sensory Response with Cover Letter Dated 08/27/92. Special Report 36-52. Carnegie-Mellon Institute, Pittsburgh, PA. Submitted to EPA by Union Carbide Corporation, Danbury, CT. EPA Document. No. 88-920010328. Microfiche No. OTS 0571724.

Test species/Strain/Number: Human volunteers, 3-9 subjects (3 volunteers at concentration selected as point of departure)

Exposure route/Concentrations/Durations: 0.6, 1.3, 4, 8, or 20 ppm for 2 min; 20 ppm for 4 h; 34 ppm for 2 h; 72 ppm for 30 min

Effects:

Concentration (ppm)	No. of subjects	Duration (min)	Response
0.6	9	2	None
1.3	9	2	9 immediate odor; 5 no odor at 2 min
4	9	2	9 immediate odor, 3 no odor at 2 min; 1 minimal ocular, nasal, and throat irritation
8	9	2	9 immediate odor; 1 no odor at 2 min; 2 minimal ocular, nasal, and throat irritation
20	9	2	9 immediate odor;1 minimal ocular, nasal, and throat irritation
20	3	240	3 complete olfactory fatigue in 3-116 min; 1 persistent slight throat irritation
34	3	120	1 complete, 2 partial olfactory fatigue; 1 transient, 1 persistent throat irritation
72	4	30	4 strong odor, partial olfactory fatigue; 4 slight throat irritation 20-60 min after exposure; ocular irritation up to 60 min after exposure; subjects expressed unwillingness to work at this concentration for 8 h.

End point/Concentration/Rationale: Exposure to vinyl acetate at 4-20 ppm for 2 min and 20 ppm for 240 min produced slight throat irritation; exposure at 34 ppm for 2 h resulted in one of three individuals complaining of persistent throat irritation; and exposure at 72 ppm for 30 min resulted in irritation severe enough that the exposed subjects expressed unwillingness to work at that concentration for 8 h (Smyth and Carpenter 1973). Therefore, 20 ppm for 4 h represents a no-effect level for notable discomfort.

Uncertainty factors/Rationale:
Total uncertainty factor: 3
Intraspecies: 3, because irritation is caused by a local effect of the chemical and the response is not expected to vary greatly among individuals.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: Because irritation is considered a threshold effect and should not vary over time, AEGL-1 values are not scaled across time. The threshold value was applied to all AEGL durations.

Data adequacy: The key study lacked measured exposure concentrations, but provided adequate basis for AEGL-1 values and is supported to some extent by occupational health data.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
46 ppm (160 mg/m^3)	46 ppm (160 mg/m^3)	36 ppm (130 mg/m^3)	23 ppm (81 mg/m^3)	15 ppm (53 mg/m^3)

Key reference: Bogdanffy, M.S., N.L. Gladnick, T. Kegelman, and S.R. Frame. 1997. Four-week inhalation cell proliferation study of the effects of vinyl acetate on rat nasal epithelium. Inhal. Toxicol. 9(1):331-350.

Test species/Strain/Number: Rat, Sprague-Dawley, 5 males/group

Exposure route/Concentrations/Durations: Inhalation, 0, 50, 200, 600, or 1,000 ppm for 6 h

Effects:
0, 50, 200 ppm: No effects
600 ppm: Degenerative lesions and increased cell proliferation in olfactory epithelium
1,000 ppm: Increased incidence and severity of lesions in olfactory epithelium; some minimal lesions in respiratory epithelium; increased cell proliferation in olfactory epithelium.

End point/Concentration/Rationale: 200 ppm for 6 h is a no-observed-effect level for serious, long-lasting histopathologic nasal lesions

Uncertainty factors/Rationale:
Total uncertainty factor: 10:

(Continued)

AEGL-2 VALUES Continued

Interspecies: 3, because the mechanism of nasal toxicity appears to depend on the metabolism of vinyl acetate to the metabolites acetic acid and acetaldehyde via carboxylesterase and aldehyde dehydrogenase. Studies investigating the metabolism of vinyl acetate by the nasal cavity found little difference among mice, rats and humans in the carboxylesterase-mediated metabolism of vinyl acetate, particularly by olfactory epithelium (Bogdanffy and Taylor 1993; Bogdanffy et al. 1998). Esterase distribution in the nasal respiratory tissue of humans is believed to be similar to that of rats (Andersen et al. 2002).
Intraspecies: 3, because the usual factor of 10 would result in an 8-h AEGL-2 value of 5 ppm, a concentration lower than the AEGL-1 value of 6.7 ppm. Reduction of an uncertainty factor is appropriate when the weight of evidence indicates that a higher uncertainty factor would result in AEGL values at odds with human data (NRC 2001).

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: The experimentally derived exposure values were scaled to AEGL durations using the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 0.8 to 3.5 (ten Berge et al. 1986). The value of n was not empirically derived because of insufficient data on vinyl acetate; therefore, the default values of n = 1 for extrapolating from shorter to longer durations and n = 3 for extrapolating from longer to shorter durations were used. The 10-min AEGL-2 value was set equal to the 30-min value of 46 ppm because of the uncertainty associated with extrapolating a 6-h exposure duration to a 10-min AEGL value (NRC 2001).

Data adequacy: The database for nonlethal effects of vinyl acetate includes single exposure (Bogdanffy et al. 1997), 4-week (Owen 1979a,b), 13-week (Owen 1980a,b), and chronic (Bogdanffy et al. 1994) studies of mice and rats exposed via inhalation, and provides a robust basis for AEGL-2 values.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
230 ppm (810 mg/m^3)	230 ppm (810 mg/m^3)	180 ppm (630 mg/m^3)	110 ppm (390 mg/m^3)	75 ppm (260 mg/m^3)

Key references: Bogdanffy, M.S., N.L. Gladnick, T. Kegelman, and S.R. Frame. 1997. Four-week inhalation cell proliferation study of the effects of vinyl acetate on rat nasal epithelium. Inhal. Toxicol. 9(1):331-350.
Owen, P.E. 1979a. Vinyl Acetate: 4 Week Inhalation Dose Range Study in the Mouse. Report No. 1884-51/3. Prepared for Society of the Plastics Industry Inc., New York, by Hazleton Laboratories Europe, Ltd., Harrogate, England, August 1979. EPA Document No. FYI-OTS-0184-0278SU. Microfiche No. OTS0278.
Owen, P.E. 1979b. Vinyl Acetate: 4 Week Inhalation Dose Range Study in the Rat.

Report No. 1835-51/3. Prepared for Society of the Plastics Industry Inc., New York, by Hazleton Laboratories Europe, Ltd., Harrogate, England, August 1979. EPA Document No. FYI-OTS-0184-0278SU. Microfiche No. OTS0278.
Owen, P.E. 1980a. Vinyl Acetate: 3 Month Inhalation Toxicity Study in the Mouse. Report No. 2303-51/5. Prepared for The Society of the Plastics Industry Inc., New York, by Hazleton Laboratories Europe, Ltd., Harrogate, England, May 1980. EPA Document No. FYI-OTS-0184-0278SU. Microfiche No. OTS0278.
Owen, P.E. 1980b. Vinyl Acetate: 3 Month Inhalation Toxicity Study in the Rat. Report No. 2286-51/5. Prepared for The Society of the Plastics Industry Inc., New York, by Hazleton Laboratories Europe, Ltd., Harrogate, England, May 1980. EPA Document No. FYI-OTS-0184-0278SU. Microfiche No. OTS0278.

Test species/Strain/Number: Rat (Sprague-Dawley and CD) and mouse (CD-1), 5-20 males and females

Exposure route/Concentrations/Durations: 0, 50, 150, 200, 500, 600, or 1,000 ppm for 6 h/day for 1-28 days

Effects: No lethality at 1,000 ppm

End point/Concentration/Rationale: 1,000 ppm for 6 h is considered a threshold for lethality

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, because the mechanism of nasal toxicity appears to depend on the metabolism of vinyl acetate to the metabolites acetic acid and acetaldehyde via carboxylesterase and aldehyde dehydrogenase. Studies investigating the metabolism of vinyl acetate by the nasal cavity found little difference among mice, rats and humans in the carboxylesterase-mediated metabolism of vinyl acetate, particularly by olfactory epithelium (Bogdanffy and Taylor 1993; Bogdanffy et al. 1998). Esterase distribution in the nasal respiratory tissue of humans is believed to be similar to that of rats (Andersen et al. 2002).
Intraspecies: 3, because the usual factor of 10 would result in an 8-h AEGL-3 value of 25 ppm, a concentration lower than experimental concentrations that did not result in serious health effects in a human volunteer study. Reduction of an uncertainty factor is appropriate when the weight of the evidence indicates that a higher uncertainty factor would result in AEGL values at odds with human data (NRC 2001).

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: The experimentally derived exposure values were scaled to AEGL durations using the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 0.8 to 3.5 (ten Berge et al. 1986). The value of n was not empirically derived because of insufficient data on vinyl acetate; therefore, the default values of n = 1 for extrapolating from shorter to longer durations and n = 3 for extrapolating from longer to shorter durations were used.

(Continued)

AEGL-3 VALUES Continued

The 10-min AEGL-3 was set equal to the 30-min value of 230 ppm because of the uncertainty associated with extrapolating a 6-h exposure duration to a 10-min value (NRC 2001).

Data adequacy: The animal database for nonlethal effects of vinyl acetate is robust, and includes single day, 4-week, 13-week, and chronic exposure studies (Owen 1979a,b, 1980a,b; Bogdanffy et al. 1994, 1997). These studies provide a strong basis for identifying a nonlethal point of departure. Lethality data are only available from the poorly documented studies by Smyth and Carpenter (1973), which lacked analytic confirmation of exposure concentrations and provided data that conflict with the results of repeated exposure studies.