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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 10

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

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Preface

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

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

Using the 1993 and 2001 NRC guidelines reports, the NAC—consisting of members from EPA, the Department of Defense (DOD), the Department of Energy (DOE), the Department of Transportation (DOT), other federal and state governments, the chemical industry, academia, and other organizations from the private sector—has developed AEGLs for approximately 200 EHSs.

In 1998, EPA and DOD requested that the NRC independently review the AEGLs developed by NAC. In response to that request, the NRC organized within its Committee on Toxicology (COT) the Committee on Acute Exposure Guideline Levels, which prepared this report. This report is the tenth volume in that series. AEGL documents for *N,N*-dimethylformamide, jet propellant fuels 5

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

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and 8, methyl ethyl ketone, perchloromethyl mercaptan, phosphorus oxychloride, phosphorus trichloride, and sulfuryl chloride are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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

The six 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 six committee interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for *N,N*-dimethylformamide (fourteenth interim report, 2006), jet propellant fuels 5 and 8 (seventeenth interim report, 2010), methyl ethyl ketone (twelfth and fifteenth interim reports, 2005 and 2008, respectively), perchloromethyl mercaptan (fifteenth interim report, 2008), phosphorus oxychloride (eleventh and fifteenth interim reports, 2004 and 2008, respectively), phosphorus trichloride (eleventh and fifteenth interim reports, 2004 and 2008, respectively), and sulfuryl chloride (sixteenth interim report, 2009): Deepak Bhalla (Wayne State University), Harvey Clewell (The Hamner Institutes for Health Sciences), David Gaylor (Gaylor and Associates, LLC), Sidney Green, Jr. (Howard University), A. Wallace Hayes (Harvard School of Public Health), Rogene Henderson (Lovelace Respiratory Research Institute [retired]), Sam Kacew (University of Ottawa), Charles Reinhardt (DuPont Haskell Laboratory [retired]), Kenneth Still (Occupational Toxicology Associates, Inc.), and Bernard M. Wagner (New York University Medical Center [retired]).

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of this volume before its release. The review of the eleventh interim report was overseen by Rakesh Dixit

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(MedImmune/AstraZeneca Biologics), and the twelfth interim report was overseen by David Gaylor (Gaylor and Associates, LLC). The review of the fourteenth, fifteenth, sixteenth, and seventeenth interim reports was overseen by Robert Goyer, University of Western Ontario (retired). Appointed by the NRC, they were responsible for making certain that an independent examination of the interim reports was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The committee gratefully acknowledges the valuable assistance provided by the following persons: Ernest Falke and Iris A. Camacho (both from EPA) and George Rusch (Honeywell, Inc.). The committee also acknowledges Keegan Sawyer, 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), Susan Martel (senior program officer for toxicology), Ruth Crossgrove (senior editor), Radiah Rose (manager of editorial projects), Mirsada Karalic-Loncarevic (manager of the Technical Information Center), Orin Luke (senior program assistant), 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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Dedication

The subcommittee dedicates this series of reports to our late colleague
and co-founder of the Acute Exposure Guideline Levels program,
Dr. Paul Tobin,
whose 31 years of distinguished service with the
U.S. Environmental Protection Agency in the fields of chemistry,
toxicology and health-risk assessment contributed significantly to scientific
knowledge, to the development of the Acute Exposure Guideline Levels
program, and to the protection of public health and safety.

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 10

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

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

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

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

As a first step in assisting the LEPCs, EPA identified approximately 400 EHSs largely on the basis of their immediately dangerous to life and health values, developed by the National Institute for Occupational Safety or Health. Although several public and private groups, such as the Occupational Safety and Health Administration and the American Conference of Governmental Industrial Hygienists, have established exposure limits for some substances and some exposures (e.g., workplace or ambient air quality), these limits are not easily or directly translated into emergency exposure limits for exposures at high levels

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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:

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

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

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upon cessation of exposure.

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

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

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

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

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

For most chemicals, actual human toxicity data are not available or critical information on exposure is lacking, so toxicity data from studies conducted in laboratory animals are extrapolated to estimate the potential toxicity in humans. Such extrapolation requires experienced scientific judgment. The toxicity data

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for animal species most representative of humans in terms of pharmacodynamic and pharmacokinetic properties are used for determining AEGLs. If data are not available on the species that best represents humans, data from the most sensitive animal species are used. Uncertainty factors are commonly used when animal data are used to estimate risk levels for humans. The magnitude of uncertainty factors depends on the quality of the animal data used to determine the no-observed-adverse-effect level (NOAEL) and the mode of action of the substance in question. When available, pharmacokinetic data on tissue doses are considered for interspecies extrapolation.

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

REVIEW OF AEGL REPORTS

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

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

The NRC committee's review of the AEGL reports prepared by NAC and its contractors involves oral and written presentations to the committee by the authors of the reports. The NRC committee provides advice and recommendations for revisions to ensure scientific validity and consistency with the NRC guideline reports (NRC 1993, 2001a). The revised reports are presented at subsequent meetings until the subcommittee is satisfied with the reviews.

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

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AEGL reports. Thus far, the committee has prepared nine reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009, 2010a,b). This report is the tenth volume in that series. AEGL documents for *N,N*-dimethylformamide, jet propellant fuels 5 and 8, methyl ethyl ketone, perchlormethyl mercaptan, phosphorus oxychloride, phosphorus trichloride, and sulfuryl chloride are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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Appendixes

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1

N,N-Dimethylformamide[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 Claudia Troxel (Oak Ridge National Laboratory) and Loren Koller and George Woodall (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee concludes 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).

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effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

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

SUMMARY

N,N-Dimethylformamide (DMF) is a clear-to-slightly yellow liquid with a faint amine (fishy) odor. Odor thresholds have been reported to range from 0.47 to 100 ppm. DMF is a polar compound used as a solvent in the manufacturing of many products. American manufacturers consumed 32 million pounds of DMF in 1993 (TURI 2001). The primary end-users of DMF are manufacturers of pharmaceuticals (12 million pounds), electronic components (10 million pounds), butadiene (3 million pounds), and urethanes (3 million pounds). It is also used as a resin cleanup solvent, reaction solvent, and processing solvent in the manufacture of polyimides, optical brightners, semipermeable membranes, and pesticides.

Human data were limited to controlled inhalation exposures or accidental workplace exposures. Although no adverse effects were reported in the controlled studies, these studies were designed to assess DMF metabolism, and follow-up physical evaluations of the volunteers were not carried out. Reports of both accidental and chronic daily workplace inhalation exposures to DMF describe signs and symptoms, including abdominal pain, nausea, and vomiting, and liver toxicity as indicated by elevated serum enzymes and histologic evaluation. Epidemiologic studies suggest a causal association between DMF exposure and testicular germ cell tumors.

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Single inhalation exposures of mice and rats to high concentrations of DMF (approaching or at saturation of the chemical in air) resulted in mortality (Stasenkova 1961; Shell Oil Company 1982), and inhalation exposure of rats to low and intermediate concentrations resulted only in alterations of liver enzymes (Brondeau et al. 1983; Lundberg et al. 1986; Roure et al. 1996). The cause of death following acute inhalation exposure was not identified. Repeated inhalation exposure of rats, mice, and cats to DMF generally resulted in reduced body weight, and hepatotoxicity indicated by increased liver enzymes and histopathologic changes including degeneration and necrosis. However, repeated inhalation exposure of monkeys to DMF at 500 ppm for 6 h/day, 5 days per week, for up to 13 weeks failed to result in any measurable adverse effects (Hurtt et al. 1991, 1992). Inhalation developmental toxicity studies reported reduced maternal body weight. Developmental effects included reduced fetal weight; increases in the litter incidence of total external, skeletal, and visceral malformations and skeletal variations; and increased number and percentage of dead implants (BASF 1974a,b,c; Kimmerle and Machemer 1975; BASF 1989; Hellwig et al. 1991; Lewis et al. 1992). Genotoxicity testing of DMF has generally been negative (Antoine et al. 1983; NTP 1992). One study found no evidence of carcinogenicity when mice and rats inhaled DMF up to 400 ppm for 2 years (E.I. Dupont de Nemours & Co. 1992); a more recent study found that chronically inhaled DMF produced hepatocellular adenomas and carcinomas in rats at 400 ppm or 800 ppm, respectively, and hepatoblastomas and hepatocellular adenomas and carcinomas in mice at 200 ppm and above (Senoh et al. 2004).

An AEGL-1 value was not recommended because data pertaining to end points relevant to the AEGL-1 definition were not available.

The AEGL-2 derivation was based on the study in which groups of 15 pregnant Himalayan rabbits were exposed to DMF at 0, 50, 150, or 450 ppm for 6 h/day on gestation days (GD) 7-19 (Hellwig et al. 1991). Over GD 7-19, mean maternal body-weight gain was reduced in dams exposed to DMF at 150 ppm compared with controls, while dams in the 450-ppm group lost weight; mean maternal body-weight gain over the entire study period of GD 0-29 was also decreased in dams from the 150- and 450-ppm DMF groups compared with controls. Developmental toxicity was evident at 450 ppm as increases in external malformations and total malformations (external, soft tissue, and skeletal combined). Other effects included a reduction in fetal weight (86% of controls) and statistically significant increases in the litter incidence of skeletal variations, including splitting of skull bones, fused sternebrae, irregular shaped sternebrae, and bipartite sternebrae. An increase in fetal deaths did not occur. No developmental effects were observed at 150 ppm. To protect against irreversible developmental effects (malformations), the rabbit no-observed-adverse-effect level (NOAEL) of 150 ppm for 6 h was used as the point of departure for derivation of AEGL-2 values (Hellwig et al. 1991).

A total uncertainty factor of 3 was applied to the point of departure of 150 ppm for 6 h: 1 for interspecies variability and 3 for intraspecies variability. An interspecies uncertainty factor of 1 was applied because it appears that primates

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are not as sensitive as rodents. Monkeys inhaled DMF at 500 ppm for 6 h/day, 5 days/week, for up to 13 weeks with no measurable adverse effects (parameters examined included clinical signs, body weight, hematology and serum chemistry analyses, urinalysis, semen analysis, and gross necropsy findings). In contrast, subchronic DMF inhalation exposure produced significant hepatic effects in rats at concentrations of 200 ppm (Senoh et al. 2003), 300 ppm (Craig et al. 1984), and 400 ppm (NTP 1992) and in mice at 100 ppm (Senoh et al. 2003), 150 ppm (Craig et al. 1984), and 200 ppm (NTP 1992). Indexes of toxicity after repeated DMF exposure ranged from elevated serum enzymes indicative of liver injury to hepatic degeneration and necrosis. From these exposure data, humans would be expected to be less sensitive than laboratory animals (rodents). Because the mechanism of hepatotoxicity is believed to be related to the metabolism of DMF to a reactive intermediate, fetal toxicity is expected to result from exposure to the parent DMF or metabolites. An oral study assessing the tissue and metabolite distribution of DMF in pregnant rats indicated that DMF and its metabolites were transferred across the placenta by passive diffusion and that maternal plasma, embryo or fetus, placenta, and amniotic fluid belonged to the same compartment (Saillenfait et al. 1997). Therefore, the fetus and placenta will not provide any additional protection or enhancement of DMF toxicity because exposure to DMF and its metabolites will depend on the metabolism by the mother.

An intraspecies uncertainty factor of 10 would normally be applied because a host of interindividual differences could affect the manifestation of DMF toxicity: (1) activity of CYP2E1, an enzyme that plays a pivotal role in the metabolism of DMF to reactive intermediates, can be induced by ethanol consumption, obesity, diabetes, and other lifestyle and genetic factors (Gonzalez 1990; Song et al. 1990; Lucas et al.1998; McCarver et al. 1998), and increased CYP2E1 levels increase the toxic metabolites of DMF; (2) prior consumption of ethanol can exacerbate DMF toxicity in individuals; (3) on the basis of the proposed mechanism of action, detoxification of the reactive intermediate is partly dependent on conjugation with glutathione; therefore, if glutathione levels are depleted for other reasons, the potential exists for greater exposure to the reactive intermediate; and (4) because DMF exposure can result in hepatotoxicity, individuals with chronic liver disease may be at increased risk. However, application of a total uncertainty factor of 10 produces AEGL-2 values that are inconsistent with the available human data. (Values for the 10-min, 30-min and 1-, 4-, and 8-h AEGL-2 using default time-scaling would be 49, 34, 27, 17, and 11 ppm, respectively.) Humans were exposed by inhalation to DMF at 87 ppm for 4 h or at 81 ppm for 2 h to assess the metabolism of DMF (Kimmerle and Eben 1975b; Eben and Kimmerle 1976). These single-exposure studies were conducted to assess DMF metabolism, and no adverse effects were reported; thus, the concentration can be considered an acute exposure concentration unlikely to result in adverse effects in healthy adults. Therefore, the intraspecies uncertainty factor is reduced to 3, resulting in a total uncertainty factor of 3.

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The experimentally derived exposure value is scaled to AEGL time frames using the concentration-time relationship given by the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 1 to 3.5 (ten Berge et al. 1986). The value of n was not empirically derived because of inadequate data; therefore, the default value of n = 1 was used for extrapolating from shorter to longer exposure periods, and a value of n = 3 was used to extrapolate from longer to shorter exposure periods. The 30-min AEGL-2 value was set equal to the 10-min value because of the uncertainty in extrapolating from a 6-h exposure duration to a 10-min duration.

The AEGL-3 derivation was based on the study in which groups of three male and three female rats were exposed to DMF at 3,700 ppm for 1 or 3 h with no mortality, while exposure for 7 h resulted in 83% mortality (Shell Oil Company 1982). Clinical signs were limited to excess grooming in all exposure groups, with lethargy also noted in rats exposed for 7 h. The end point of no mortality in rats exposed at 3,700 ppm for 3 h was chosen for the derivation.

A total uncertainty factor of 10 was applied to the point of departure for the AEGL-3: 1 for interspecies variability and 10 for intraspecies variability. The total uncertainty factor of 10 should protect against all but hypersensitive human hepatotoxic effects. An interspecies uncertainty factor of 1 was applied because it appears that primates are not as sensitive as rodents. Monkeys inhaled DMF at 500 ppm for 6 h/day, 5 days/week, for up to 13 weeks with no measurable adverse effects (parameters examined included clinical signs, body weight, hematology and serum chemistry analyses, urinalysis, semen analysis, and gross necropsy findings). In contrast, subchronic DMF inhalation exposure produced significant hepatic effects in rats at concentrations of 200 ppm (Senoh et al. 2003), 300 ppm (Craig et al. 1984), and 400 ppm (NTP 1992) and in mice at 100 ppm (Senoh et al. 2003), 150 ppm (Craig et al. 1984), and 200 ppm (NTP 1992). Indexes of toxicity after repeated DMF exposure ranged from elevated serum enzymes indicative of liver injury to hepatic degeneration and necrosis. From these exposure data, humans would be expected to be less sensitive than laboratory animals (rodents). An intraspecies uncertainty factor of 10 is applied because a host of interindividual differences could affect the manifestation of DMF toxicity: (1) activity of CYP2E1, an enzyme that plays a pivotal role in the metabolism of DMF, to reactive intermediates, can be induced by ethanol consumption, obesity, diabetes, and other lifestyle and genetic factors (Gonzalez 1990; Song et al. 1990; Lucas et al. 1998; McCarver et al. 1998), and increased CYP2E1 levels increase the toxic metabolites of DMF; (2) prior consumption of ethanol can exacerbate DMF toxicity in individuals; (3) on the basis of the proposed mechanism of action, detoxification of the reactive intermediate is partly dependent on conjugation with glutathione; therefore, if glutathione levels are depleted for other reasons, the potential exists for greater exposure to the reactive intermediate; (4) because DMF exposure can result in hepatotoxicity, individuals with chronic liver disease may be at increased risk. Therefore, a total uncertainty factor of 10 is applied.

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The experimentally derived exposure value is scaled to AEGL time frames using the concentration-time relationship given by the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 1 to 3.5 (ten Berge et al. 1986). The value of n was not empirically derived because of inadequate data; therefore, the default value of n = 1 was used for extrapolating from shorter to longer exposure periods, and a value of n = 3 was used to extrapolate from longer to shorter exposure periods.

There is a high potential for DMF to be absorbed dermally, so this route of exposure should be considered along with inhalation.

The calculated values are listed in Table 1-1 below.

1. INTRODUCTION

DMF is a clear-to-slightly yellow liquid with a faint amine (fishy) odor. It can be synthesized in a one-stage process by reacting dimethylamine in methanol with carbon monoxide in the presence of sodium methylate or with metal carbonyls; it also can be synthesized in a two-stage process from reacting methanol with carbon monoxide in the presence of sodium methylate, followed by reaction with dimethylamine (IARC 1989). DMF is a polar compound used as a solvent in manufacturing acrylic fibers, films, surface coatings, synthetic leather, polyurethane, and wire enamels based on polyimides or polyurethanes (Trochimowicz et al. 1994). It is also used as a solvent for certain epoxy resin curing agents. DMF has applications in hydrocarbon separations (such as recovery or removal of acetylene and extraction of butadiene from hydrocarbon streams) and in selective solvent extractions (such as separating nonparaffinic from paraffinic hydrocarbons in petroleum processing and in the separation of polycarboxylic acids) (IARC 1989; Trochimowicz et al. 1994).

TABLE 1-1 Summary of AEGL Values for DMF[a]

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR[b]	NR	NR	NR	NR	
AEGL-2 (disabling)	110 ppm (330 mg/m^3)	110 ppm (330 mg/m^3)	91 ppm (270 mg/m^3)	57 ppm (170 mg/m^3)	38 ppm (110 mg/m^3)	150 ppm for 6 h in rabbits to protect against irreversible effects (malformations) (Hellwig et al. 1991)
AEGL-3 (lethal)	970 ppm (2,900 mg/m^3)	670 ppm (2,000 mg/m^3)	530 ppm (1,600 mg/m^3)	280 ppm (840 mg/m^3)	140 ppm (420 mg/m^3)	No mortality in 6 rats exposed to 3,700 ppm for 3 h (Shell Oil Company 1982)

[a]There is a high potential for DMF to be absorbed dermally, so this route of exposure should be considered along with inhalation.

[b]NR, not recommended. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

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American manufacturers used 32 million pounds of DMF in 1993 (TURI 2001). The primary end users of DMF are manufacturers of pharmaceuticals (12 million pounds), electronic components (10 million pounds), butadiene (3 million pounds), and urethanes (3 million pounds). DMF is also used as a resin cleanup solvent, reaction solvent, and processing solvent in the manufacture of polyimides, optical brightners, semipermeable membranes, and pesticides.

Human data are available from reports of accidental and controlled inhalation exposures and from epidemiologic studies investigating consequences of chronic exposure. Animal data consisted of acute inhalation studies with mice and rats and studies designed to examine the mode of action responsible for induction of hepatotoxicity. Repeat-exposure studies were available for monkeys, rats, mice, and cats.

The chemical and physical data on DMF are presented in Table 1-2.

TABLE 1-2 Chemical and Physical Data

Parameter	Data	Reference
Synonyms	*N,N*-dimethylformamide, DMF	
CAS registry no.	68-12-2	
Chemical formula	C_3H_7NO	
Molecular weight	73.09	Budavari et al. 1996
Physical state	Liquid	Budavari et al. 1996
Color	Colorless to slightly yellow	Budavari et al. 1996
Melting point	−61°C	Budavari et al. 1996
Boiling point$_{760}$	153°C	Budavari et al. 1996
Solubility in water	Miscible with water and most common organic solvents	Budavari et al. 1996
Vapor pressure	2.6 mmHg (20°C) 3.7 mmHg (25°C)	Trochimowicz et al. 1994 IARC 1989
Saturated vapor pressure	3,755 ppm at 20°C 5,000 ppm at at 25°C	Shell Oil Company 1982 Lundberg et al. 1986
Liquid density (water =1)	0.9445	Budavari et al. 1996
Conversion factors	1 ppm = 2.99 mg/m^3 1 mg/m^3 = 0.33 ppm	NIOSH 2005

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2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No acute lethality data in humans were found in the searched literature.

2.2. Nonlethal Toxicity

2.2.1. Controlled Exposures

DMF has a faint amine odor (Budavari et al. 1996). Odor thresholds range from 0.47 to 100 ppm (EPA 1992). The 0.47-ppm concentration was the threshold for recognition; no data were provided for the 100-ppm concentration. Trochimowicz et al. (1994) reported an odor threshold of 21.4 ppm, and Amoore and Hautala (1983) reported a threshold of 2.2 ppm; they stated that less than 50% of distracted individuals could perceive odor at the Threshold Limit Value (TLV) of 10 ppm.

A number of controlled human inhalation exposures to DMF are available, and these metabolism studies are discussed in Section 4.2. The studies were conducted to assess metabolism, and no adverse effects of inhaled DMF exposure were reported at the concentrations and durations of exposure examined. A summary of the following data is found in Table 1-3: 10 healthy volunteers (five males and five females, ages 25-56 years) were exposed to DMF at 3, 10, or 20 ppm for 8 h (Mraz and Nohova 1992); 10 healthy human volunteers (five males and five females, ages 26-56) were exposed at 20 ppm for 8 h (Mraz et al. 1989); four volunteers (three males and one female, ages 20-50) were exposed to DMF at 53 ± 32 ppm for 2 h (Eben and Kimmerle 1976); and four volunteers were exposed at 26 ± 8 ppm (four males, ages 25-50) or 87 ± 25 ppm for 4 h (three males and one female, ages 20-50) or 21 ± 4 ppm (four males, ages 25-50) for 4 h/day for 5 consecutive days (Kimmerle and Eben 1975b). Alcohol intolerance was not observed when four volunteers (three males and one females; ages 20-50) drank 19 g of ethanol (50 mL of a 38% schnaps or gin) followed by a 2-h exposure to DMF at 82 ± 20 ppm (Eben and Kimmerle 1976). This observation is significant in light of evidence that sufficiently high concomitant DMF and ethanol exposures can result in disulfiram-like symptoms (see Section 4.3).

2.2.2. Case Reports

Potter (1973) described an accidental DMF exposure in a 52-year-old man where DMF splashed on approximately 20% of the victim's body, after which he washed the affected skin, put his clothes back on, and drove home (45 min). The intense odor of DMF was noted in the factory following the accident and in his car. Immediate symptoms were limited to dermal irritation and hyperemia, with anorexia developing 1-2 days later. Sixty-two hours after the accident, he

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developed epigastric pain that spread throughout his abdomen, chest, and thighs, and episodes of vomiting followed. On admission to the hospital, he presented with hypertension, and he complained of weakness and incoordination of his legs, but no objective neurologic changes were apparent. Minimal abdominal tenderness was noted. Increased white blood cells and serum conjugated and total bilirubin, glutamic oxaloacetic transaminase, and glutamic pyruvic transaminase were observed. Urine tested positive for porphobilinogen for the 3 days the patient experienced abdominal pain. Minimal S-T segment and T-wave depressions were noted during electrocardiograms, but the abnormalities returned to normal before discharge. An aspiration biopsy of the liver 11 days after the exposure revealed minimal septal fibrosis and an accumulation of mononuclear cells. Upon discharge from the hospital 15 days postexposure, the patient was free of any symptoms.

A 21-year-old man was hospitalized following accidental exposure to DMF at work (exposure quantity and route not characterized) (Chary 1974). On hospital admission, he experienced upper abdominal pain radiating in his back. Nausea and vomiting, epigastric tenderness, and an erythematous rash on his hands and forearms (possibly suggesting direct skin contact with DMF) developed. Serum amylase levels were increased to 2,400 I.U./liter (L), but a cholecystogram and intravenous cholangiogram were normal. Following the accident, a search of factory records found that a 28-year-old male coworker had previously been admitted to the hospital following accidental exposure to DMF. Again, the exposure route was not characterized, but this patient too had an erythematous rash on his hands and forearms, and suffered from upper abdominal pain, nausea and vomiting, and epigastric tenderness. Serum amylase levels were not measured, but a cholecystogram was normal. Follow-up of the patient revealed continuing complaints of epigastric pain. The three remaining workers in the factory were then questioned about symptoms. All admitted intermittent gastrointestinal symptoms, erythema of exposed parts, and pruritus, particularly after consuming ethanol.

TABLE 1-3 Summary of Controlled Human Exposures to DMF[a]

Number of Subjects	Duration	Concentration (ppm)	Reference
10 (5 males, 5 females)	8 h	3	Mraz and Nahova 1992
		10	
		20	
10 (5 males, 5 females)	8 h	20	Mraz et al. 1989
4 (4 males)	4 h	26	Kimmerle and Eben 1975b
4 (3 males, 1 female)		87	
4 (4 males)	4 h/d for 5 d	21	
4 (3 males, 1 female)	2 h	53	Eben and Kimmerle 1976
		82[b]	

[a]Because these studies were designed only to assess metabolism, clinical signs and symptoms were not evaluated by the study authors.
[b]Exposure occurred following consumption of ethanol.

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2.2.3. Epidemiologic Studies

Fiorito et al. (1997) conducted a cross-sectional study investigating the prevalence of liver function abnormalities in workers exposed to DMF in a synthetic leather factory. The study consisted of 75 exposed workers (average employment 3.8 years) and 75 unexposed individuals matched for age, sex, social status, and place of residence. Although these workers were generally exposed to less than 10 ppm DMF, biologic monitoring revealed that occasional overexposure was possible. Fifty percent of the DMF-exposed workers complained of gastrointestinal symptoms, and 40% of exposed workers also complained of disulfiram-like symptoms (facial flushing [38%], palpitation [30%], headache [22%], dizziness [22%], body flushing [15%], and tremors [14%]) after ethanol consumption. Covariance analysis of clinical chemistry parameters revealed increased alanine aminotransaminase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), and alkaline phosphatase (AP) in DMF-exposed workers compared with the reference group. Twenty-three percent of DMF-exposed workers had abnormal transaminase values, compared with 4% of controls. The study authors concluded that repeated occupational exposure to DMF at levels less than 10 ppm for 8-h TWAs can impair liver function.

In response to a case of suspected toxic hepatitis in a worker from a fabric coating factory, a clinical-epidemiologic investigation and environmental assessment of the patient's workplace was conducted (Redlich et al. 1988). A total of 58 workers participated in the study: All had at least one liver function test; 46 completed a questionnaire addressing demographic background, job history, and symptoms; and 27 underwent an extensive clinical evaluations to assess liver function. Workers were exposed to DMF in the process of coating fabric in poorly ventilated areas, and little effort was made to control direct skin contact with the solvent. Results from the questionnaire and clinic interviews revealed complaints of gastrointestinal problems (31 of 46), headache and dizziness (18 of 46), and alcohol intolerance characterized by facial flushing and palpitations after drinking ethanol (11 of 46; total number consuming ethanol not provided). Clinical chemistry analyses revealed that 36 of 58 workers had increased AST or ALT levels, 19 having elevations greater than twice normal, and 9 of the 19 having increases greater than five times normal. All but one of these employees were production-line workers (35 of 46, vs. 1 of 12 nonproduction-line workers). Histologic examination of liver biopsies from four workers confirmed toxic liver injury. Serologic testing and a ratio of AST to ALT of less than one ruled out infectious hepatitis in all but two workers and alcoholic liver disease in all but one worker, respectively.

The cohort described by Redlich et al. (1988) was re-evaluated by Fleming et al. (1990). In the re-evaluation, the defined exposure population consisted of subjects who were male, Hispanic, and who worked in jobs with DMF exposure. An unexposed population of 111 individuals was chosen from a preemployment population for comparison. A complete liver enzyme profile was determined for each individual. Analysis of the data revealed a statistically sig-

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nificant ($p < 0.0001$) increase in ALT and a decrease in the AST:ALT ratio (ratio of <1.0) in the DMF-exposed group compared with the referent group, but there was no difference in AST levels. Continued surveillance of the workplace over the next 14 months failed to identify any additional cases of liver dysfunction; this observation was coincident with changes in several engineering and industrial hygiene changes and a reduction in the quantity of DMF used in the process. The study authors therefore concluded that the outbreak of liver damage was "almost certainly" causally related to workplace exposure to DMF.

Wrbitzky (1999) measured liver function in workers exposed to DMF alone or after ethanol consumption. The study involved 126 male workers exposed to DMF in their job and 54 comparable unexposed male employees. DMF concentrations measured in workplace air ranged from <0.1 to 37.9 ppm, and the concentrations of the DMF metabolite *N*-methylformamide (NMF)measured in the urine of exposed workers ranged from 0.05 to 22.0 mg/L preshift and 0.9 to 100.0 mg/L post shift. Facial flushing following ethanol consumption was noted by 70% of the DMF-exposed workers compared with 4% of unexposed controls. Exposed workers had significant increases in GGT and ALT activities. Exposed workers were further categorized as having high (0.1-100 ppm) or low exposures (0.1-13.7 ppm) to DMF, and alcohol consumption was assigned using the criteria of consuming no alcohol, consuming <50 g/day, or consuming >50 g/day. A ranking sum value based on GGT, AST, and ALT levels was determined for all groups. The results demonstrated that chronic occupational DMF exposure can impair liver function, and drinking alcohol was synergistic with the hepatotoxicity of DMF.

Catenacci et al. (1984) found no alterations in hepatic function in 54 workers employed for at least 5 years in an acrylic fiber plant and exposed to DMF at <10 ppm for 8-h TWAs. Hepatic parameters included assessment of serum ALT, AST, GGT, and AP.

A cohort study by E.I. Dupont de Nemours & Co. (1973) investigated the association between DMF exposure and adverse health effects. Workers at two DuPont plants (Waynesboro and Camden) were categorized into three groups based on work history: currently exposed to DMF, previously exposed to DMF, or never exposed to DMF. The DMF-exposed workers were compared with the referent group for history of chronic disease, findings at periodic health examinations, and sickness absenteeism over a 5-year period. Although all illnesses were investigated, the liver, gastrointestinal system, and cardiovascular system were of particular focus. Because differences were observed in the distribution of age and race among the DMF-exposed and the referent groups, comparisons were made by age categories and by computing age-adjusted rates. The study authors concluded that there was no significant excess in any of the parameters examined. However, a significant reduction in the prevalence of hypertension was found in workers currently exposed to DMF at the Waynesboro plant, but this finding was not observed in workers previously exposed to DMF. Although it appeared that a similar reduction in the prevalence of hypertension may have

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occurred in employees at the Camden plant, this reduction was not confirmed by the data.

Evaluation of blood pressure in 12 workers exposed to DMF over a 3-month period in 1943 revealed that four individuals had abnormal readings (E.I. Dupont de Nemours & Co. 1944). Three of the four individuals had normal blood pressure readings in the morning but low blood pressure in the afternoon. The fourth individual had a high diastolic reading in the morning and normal blood pressure in the afternoon.

2.3. Developmental and Reproductive Toxicity

Three cases of third-trimester intrauterine death were reported over a period of 3 years (1979-1982) in women (ages 22, 26, and 28) working as quality control analysts in the same pharmaceutical laboratory (Farquharson et al. 1983). DMF was one of a number of unspecified chemicals to which the women were potentially exposed. No workplace air or biologic monitoring data were reported that could be used to document the extent of DMF exposure; therefore, the late deaths could not be attributed to DMF.

2.4. Genotoxicity

DMF failed to induce chromosomal aberrations or sister chromatid exchanges in vitro in lymphocytes from a healthy male donor (Antoine et al. 1983).

2.5. Carcinogenicity

Three cases of testicular germ cell tumors were reported among 153 white male workers employed in a Navy F4 jet airframes repair facility (Ducatman et al. 1986). These three cases prompted investigation of two other aircraft repair facilities: one facility where identical work was being performed and the other where major airframe structural repair of F4 aircraft was never done. A case was defined as "any employee working at an airframe repair facility at least 3 years before the onset of signs or symptoms leading to a documented histopathologic diagnosis of testicular germ-cell cancer." No cases of testicular cancer were identified among 446 workers from the facility that had never performed structural F4 repair work. However, four cases were identified among 680 white male workers at the other facility ($p < 0.01$, Poisson, compared with the expected number of cases based on national incidence rates). One additional worker with testicular cancer was identified at the original facility, but he developed symptoms within 1 year of his employment at the shop and, therefore, his case could not be included. However, he had been employed in another F4 airframe repair shop for over 20 years. An investigation of the work processes occurring in the

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three facilities revealed that all three had similar exposures to various dusts and solvents with one exception: In the repair of F4 airframes, depotting (removal of embedded electrical components in elastomeric materials) was performed on the floor of the airframe repair area using a solvent containing 80% DMF, and this work was performed without the use of ventilators. Although a causal association between chronic occupational DMF exposure and the development of testicular cancer was not established, the authors considered the cluster "highly suspicious."

Levin et al. (1987) reported three cases of testicular cancer in leather tannery workers with DMF inhalation and dermal exposure. The cases included a 32-year-old male exposed for 13 years, a 36-year-old male exposed for 14 years, and a 25-year-old male exposed for 8 years. Histologic analyses of the tumors revealed a metastatic embryonal cell carcinoma, a combined embryonal cell carcinoma and seminoma, and a metastatic embryonal cell carcinoma with foci of choriocarcinoma, respectively.

A case-control study of workers from four DuPont plants investigated whether a significant association existed between DMF exposure and development of cancer of the buccal cavity and pharynx (39 cases), liver (6 cases), prostate (43 cases), testis (11 cases), or malignant melanoma of the skin (39 cases) (Walrath et al. 1989). Cases were identified using the company Cancer Registry, in which cancer cases were reported by male employees active during 1956-1985. Each case was matched to two controls based on sex, salary, birth year, and plant location. Each job with possible DMF exposure was identified, and exposure rankings were assigned based on industrial hygiene monitoring of DMF, monitoring of urinary DMF metabolites, and knowledge of work practices and plant operations. Worker exposure patterns were then classified as ever-vs.-never exposed to DMF or as highest DMF exposure experienced. No significant associations were observed between the identified cancers and having ever been exposed to DMF when considering the summary data of all four plants combined. When considering individual plants, three of four cases of prostate cancer from one plant were associated with DMF exposure. The authors discounted this association as being related to DMF exposure because this association was not observed in any of the other three plants where workers were also exposed to DMF, the DMF exposures were low, and the latency period was short (12-16 years). When evaluating the combination of the highest DMF exposure rank, duration of exposure, and latency, no causal association was observed between DMF exposure and cancer of the buccal cavity and pharynx, liver, malignant melanoma, prostate, or testis. The authors cautioned that this study was limited by the relatively small numbers of cases and the lack of data on workers who were no longer employed by Dupont.

IARC (1989) concluded that there was *limited evidence* for the carcinogenicity of DMF in humans and *inadequate evidence* in experimental animals. Therefore, the overall IARC evaluation was that DMF is possibly carcinogenic to humans (Group 2B).

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2.6. Summary

Reports of accidental exposure described symptoms of DMF exposure, including abdominal pain, nausea, vomiting, and liver toxicity as indicated by increased serum enzymes and histologically confirmed hepatic damage. A local erythematous rash was also described, but it was most likely the result of direct dermal exposure to DMF. Daily exposure to lower concentrations of DMF resulted in gastrointestinal distress, disulfiram-like symptoms following ethanol ingestion, headache, dizziness, changes in blood pressure, and liver injury as indicated by increased liver enzymes and histologic evaluation. One case report suggested a link between DMF exposure and human developmental toxicity, but no data to confirm this association or quantitative measurements of DMF concentrations or descriptions of other chemical exposure in those instances were available. Two reports suggested an association between repeated occupational DMF exposure and testicular germ-cell tumors, but other larger studies in which industrial hygiene and biologic exposure data were collected found no such association. Human data with measured exposure concentrations were generally limited to acute controlled DMF exposures for the purpose of characterizing DMF metabolism. In these metabolism studies, no adverse effects were reported.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Groups of three male or three female Wistar rats were exposed to DMF at approximately 3,700 ppm (3,755 ppm is the saturation concentration at 20°C) for 1, 3, or 7 h followed by an observation period of 14 days (Shell Oil Company 1982). DMF vapors were generated by passing compressed air through a flask by means of a glass frit, on top of which DMF was situated. The portion of the flask containing DMF was immersed in a water bath maintained at 20°C, and the resulting vapor was brought into the exposure chamber. The nominal concentration was estimated by considering the total weight loss of chemical from the flask, the airflow rate, and duration of exposure. In the animals that inhaled DMF for 7 h, all the females died 2 days postexposure, and two of the three males died 3 days postexposure. The remaining male survived to study termination. All rats survived exposure at 3,700 ppm for 1 or 3 h. All exposure groups responded with excessive grooming, and those that inhaled DMF for 7 h exhibited lethargy. The authors stated that “all animals appeared normal shortly after exposure and remained so even if subsequently dying.” Body weight at 0, 7, or 14 days postexposure was comparable in the male and female rats exposed for 1 or 3 h. Necropsy was not performed.

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Ten Crl:CD male rats inhaled DMF at 2,523 ppm for 6 h/day for 5 days (information about exposure chamber not provided) and were observed for 10 days following cessation of exposure (Kennedy and Sherman 1986). Animals were observed and weighed daily. Histopathologic examination was conducted on all rats either upon death or at the termination of the 10-day period. Clinical signs among exposed rats consisted of progressive weakness, discomfort, and body-weight loss. Seven rats died 1 to 3 days after the last exposure with evidence of dehydration and acute liver necrosis. One rat died after the second exposure from acute pulmonary edema and congestion. The two surviving rats improved during the 10-day recovery period, and histopathologic examination of the liver revealed resolution of acute hepatic injury in one of the rats. No adverse effects were noted in the concurrent control group.

3.1.2. Mice

Groups of 20 mice were exposed for 2 h to air containing DMF vapor at concentrations of 0, 670, 1,300, 2,000, 3,100, 4,000, 4,700, 5,700, or 7,700 ppm (reported as 0, 2.0, 4.0, 6.0, 9.4, 12.0, 14.0, 17.0, or 23.0 mg/L) and were then observed for at least 15 days (Stasenkova 1961). Mortality data are summarized in Table 1-4. The LC_{50} (concentration of a substance that is lethal to 50% of the exposed population) as determined by probit analysis was 3,981 ± 187 ppm (calculated by reviewer). Details of experimental protocol, including the method of chamber concentration analysis, were not provided. It appears unlikely that concentrations of ≥ 5,700 ppm could have been attained without generation of DMF aerosols because atmospheric saturation occurs at 3,755 ppm at 20°C (Shell Oil Company 1982) and 5,000 ppm at 25°C (Lundberg et al. 1986).

TABLE 1-4 Mortality of White Mice Exposed for 2 h to Vapor from DMF at Various Concentrations

Concentration (ppm)	Total Death (% mortality)
0	0 (0)
670	0 (0)
1,300	1 (10)
2,000	1 (10)
3,100	10 (50)
4,000	12 (60)
4,700	12 (60)
5,700	16 (80)
7,700	20 (100)

Source: Adapted from Stasenkova 1961.

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3.2. Nonlethal Toxicity

3.2.1. Rats

Groups of 10 female, Sprague-Dawley rats (~200 g) were exposed to DMF by inhalation in a 60-L dynamic exposure chamber for 4 or 8 h (Lundberg et al. 1986). All of the actual DMF concentrations were not provided, but the authors stated that the experimental design involved a geometric concentration series. Solvent concentrations in the chamber were monitored by analysis of a stream of chamber air continuously drawn through an infrared analyzer, and exposure concentrations were adjusted accordingly. Animals were observed for mortality for 24 h after initiation of exposure. All animals survived a 4-h or an 8-h exposure at 5,000 ppm (reported as 13,440 mg/m^3). Because this concentration represented the saturated air concentration at 25°C, an LC_{50} value for the vapor could not be determined.

In an additional study by Lundberg et al. (1986), groups of six rats inhaled air only or DMF for 4 h at approximate concentrations of 140, 280, 560, 1,120, or 2,250 ppm (420, 840, 1,680, 3,360, and 6,720 mg/m^3, respectively; reported as 1/32, 1/16, 1/8, 1/4, or 1/2 of the saturation concentration). Hepatic damage was assessed 20 h later by measuring serum sorbitol dehydrogenase (SDH) in all rats and by histologic analysis of liver from rats exposed at 2,250 ppm (6,720 mg/m^3). SDH concentrations were raised ($p < 0.05$) in rats exposed at 280 or 560 ppm (1/16 or 1/8 of the saturation concentration; exact SDH values not provided) compared with controls, the greatest increase occurring in rats exposed at 560 ppm. SDH concentrations were comparable to control levels in all other exposure groups, including those that inhaled 1,120 or 2,250 ppm. No abnormalities were observed during histologic examination of livers from rats exposed at 2,250 ppm DMF for 4 h.

Groups of 10 male Sprague-Dawley rats inhaled DMF at measured concentrations of 0, 81, 153, 313, 441, or 991 ppm for 4 h in a 200-L dynamic inhalation chamber (with adjustable laminar airflow ranging from 10 to 20 m^3/h) at 23°C (Roure et al. 1996). The concentration of DMF in the chamber was monitored continuously by gas-liquid chromatography, and periodic air samples were also collected with charcoal-packed glass tubes, desorbed with disulfide, and analyzed by gas-liquid chromatography. Serum SDH and glutamate dehydrogenase (GDH) were measured 24, 48, and 72 h postexposure (Table 1-5). Significant concentration-related increases in SDH and GDH were observed in rats exposed at 153-991 ppm, but there were marked variations in the results even among the concurrent controls. SDH and GDH levels were maximally increased by 24 h in rats exposed at 153, 313, or 441 ppm, with SDH levels increased approximately 2-fold in the 153-ppm group, and SDH and GDH levels increased approximately 6-fold and 10.5-fold in the 313- and 441-ppm group, respectively. In contrast, SDH and GDH levels in rats exposed at 991 ppm peaked at 48 h, having increases of 140-fold and 130-fold, respectively and no significant increases at 24 h. At 72-h postexposure, statistically significant increases in en-

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zyme levels were seen only in GDH levels of rats exposed at 441 and 991 ppm (increased 1.5-fold and 20-fold, respectively). Assaying for SDH is generally difficult, and the results often vary (Tietz 1995), a fact reflected in the relatively large standard deviations among the controls (Table 1-5).

Brondeau et al. (1983) exposed groups of eight male Sprague-Dawley rats for 4 h to measured concentrations of DMF at 0, 66, 126, 281, or 314 ppm in a 200-L dynamic inhalation chamber (airflow rate of 10-12 m^3/h). Chamber concentrations were measured at least three times by pumping 5-10 L of chamber air through a glass tube packed with activated charcoal to collect the vapors, desorbing with an appropriate solvent, and analyzing with gas liquid chromatography using internal standards (more specific details not provided because atmosphere sampling and analysis data were not presented specifically for DMF but rather for several test chemicals). Twenty-four hours following termination of DMF exposure, rats were killed and blood was collected to measure serum GDH, AST, and SDH. The minimally active DMF 4-h exposure for hepatotoxicity was 126 ppm based on significant differences ($p < 0.02$) in at least two clinical chemistry parameters. When compared with the concurrent controls, rats that inhaled DMF at 126, 281, or 314 ppm had increased ($p < 0.05$; 0.02) GDH (+38%, +516%, and +260%, respectively); ALT (+37%, +54%, and +50%, respectively); and SDH (+130%, +325%, and +379%, respectively). Rats exposed to DMF at 314 ppm developed increased AST (+38%) compared with controls.

Sherman rats exposed to a saturated vapor concentration of DMF for 4 h survived (no further experimental details provided (Smyth and Carpenter 1948). The concentration used was interpreted as 3,500 ppm (at 20°C) by the National Institute for Occupational Safety and Health (NIOSH 1996) in the original immediately dangerous to life or health (IDLH) derivation as described by Clayton et al. (1963).

TABLE 1-5 Serum SDH and GDH Activities in Rats Following a 4-h Exposure to DMF

Concentration	SDH (U/l)			GDH (U/l)		
(ppm)	24 h	48 h	72 h	24 h	48 h	72 h
0	4.5 ± 1.4	3.8 ± 1.5	4.9 ± 2.6	4.3 ± 0.3	4.6 ± 0.6	4.4 ± 0.6
81	6.4 ± 2.3* [a]	3.9 ± 1.4	4.2 ± 1.5	5.7 ± 1.6**	4.7 ± 0.5	4.6 ± 0.5
0	7.1 ± 1.6	8.4 ± 3.0	11.5 ± 8.6	9.1 ± 14.9	4.9 ± 1.2	5.6 ± 2.2
153	16.1 ± 5.2** [a]	9.2 ± 2.9	13.4 ± 7.4	11.4 ± 5.9	6.0 ± 2.7	8.7 ± 10.8
0	20.7 ± 29.3	7.9 ± 3.8	6.1 ± 1.6	5.8 ± 2.7	5.1 ± 3.3	4.2 ± 1.2
313	120.1 ± 89.7**	12.8 ± 5.5*	8.2 ± 3.6	35.7 ± 12.6**	9.9 ± 3.0**	4.6 ± 1.0
0	8.9 ± 2.7	10.5 ± 2.7	11.6 ± 7.1	3.9 ± 0.6	4.4 ± 0.7	4.6 ± 0.6
444	94.1 ± 57.6**	28.9 ± 31.5	17.2 ± 7.1	41.7 ± 27.9**	16.5 ± 7.3**	7.3 ± 1.8**
0	3.4 ± 0.8	3.0 ± 0.5	3.5 ± 0.9	11.2 ± 20.7	5.1 ± 0.7	4.4 ± 0.6
991	4.5 ± 1.8	422.7 ± 559.6*	30.0 ± 41.3	4.8 ± 0.7	657.3 ± 744.1**	87.5 ± 79.9**

[a]Statistically significant compared with controls: *$p < 0.05$; **$p < 0.01$.
Abbreviations: SDH, serum sorbitol dehydrogenase; GDH, glutamate dehydrogenase.
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3.2.2. Mice

To assess DMF-induced sensory irritation, respiration rates in groups of four male CD-1 mice were measured using whole-body plethysmographs during 10-min head-only inhalation exposures to DMF at 0, 55, 154, 550, 1,658, or 2,110 ppm (Kennedy and Sherman 1986). Sensory irritation as evidenced by reduced respiratory rate was observed at 1,658 and 2,110 ppm (decreases of 12.8% and 28.3% of controls, respectively). An RD_{50} (concentration required to produce a 50% decrease in respiration rate) could not be calculated because the maximum respiratory decrease was only 28%, and the test system could not generate vapor concentrations greater than 2,110 ppm.

3.3. Developmental and Reproductive Toxicity

Groups of 15 artificially inseminated female Himalayan rabbits inhaled air containing DMF at 0, 50, 150, or 450 ppm for 6 h/day on gestation days (GD) 7-19 (BASF 1989; Hellwig et al. 1991). Animals were sham-exposed for 4 days prior to actual exposure to DMF. Chamber concentrations were monitored by gas chromatographic analysis of hourly samples taken from the breathing zone. Animals were killed on GD 29 and laparatomy was performed. Gross necropsy was performed on each dam, and each fetus was examined for external, soft tissue, and skeletal malformations and variations. Selected maternal and fetal effects are summarized in Table 1-6. Over GD 7-19, mean maternal body-weight gain was reduced in dams exposed to DMF at 150 ppm compared with controls, and dams in the 450-ppm group lost weight. Mean maternal body-weight gain over the entire study period of GD 0-29 was also decreased in dams from the 150- and 450-ppm groups compared with controls. Developmental toxicity was evident in the 450-ppm group because of significant reductions in mean fetal body weight compared with weight in the concurrent controls and significant increases in the litter incidence of total external malformations, total skeletal variations, and total malformations (external, soft tissue, and skeletal combined). Significant increases in the litter incidence of skeletal variations included splitting of skull bones, fused sternebrae, irregularly shaped sternebrae, and bipartite sternebrae.

Groups of 17 or 18 impregnated Sprague-Dawley rats were exposed to DMF at 0, 221, or 522 ppm for 6 h/day on GD 4-8 (BASF 1974c). Dams were killed on GD 20 and caesarean section was performed. Dams underwent gross necropsy, and all fetuses were examined externally with two-thirds of the fetuses examined for skeletal abnormalities, and the remaining one-third examined for soft tissue abnormalities. Selected maternal and fetal observations are summarized in Table 1-7. The only treatment-related effect observed in DMF-exposed dams was reduced body-weight gain in those that inhaled 221 ppm over GD 4-11 (−26% compared with controls, respectively; statistical analysis not conducted) and in dams that inhaled 522 ppm over GD 4-11 (−55%), GD 15-20

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(−19%) and GD 4-20 (−23%). Other observations noted among rats exposed to DMF at 522 ppm included an increased absolute number of dead implants and increased percentage of dead implants. The majority of loss occurred early in gestation (prior to GD 13) as evidenced by increases in early resorptions. Mean fetal body weight was reduced ($p < 0.05$) in the 221- and 522-ppm groups. Mean fetal body length and placental weight were reduced ($p < 0.05$) in 221-ppm fetuses, but no such changes were observed in the 522-ppm fetuses. No treatment-related external soft-tissue abnormalities or skeletal malformations and variations were observed.

TABLE 1-6 Selected Results of Pregnant Rabbits Exposed to DMF 6h/day on GD 7-19

	Exposure concentration (ppm)			
Parameter	0	50	150	450
Number of animals	15	15	15	15
Mean maternal body-weight change (g):				
GD 7-19	31.0	42.4	3.1	−34.3
GD 0-29	248.1	202.1	146.4	183.0
Number of litters	12	14	14	15
Number of live fetuses	67	71	72	86
Mean corpora lutea	8.3	8.2	8.2	8.6
Mean implantation sites	6.3	5.9	6.7	6.4
Preimplantation loss (%)	22.8	29.3	16.9	24.3
Postimplantation loss (%)	9.5	11.3	22.6	14.5
Total resorptions	8	12	19	10
Mean fetal weight (g)	43.7	42.1	41.7	37.7** [a]
Number of fetuses (litters) examined	67 (12)	71 (14)	72 (14)	86 (15)
External malformations: total	0 (0)	1 (1)	1 (1)	8* [a] (5)*
Umbilical hernia:	0 (0)	0 (0)	1 (1)	7* (4)
External variation	0 (0)	0 (0)	3 (2)	6* (2)
Pseudoanklosis of for limb	0 (0)	0 (0)	3 (2)	6* (2)
Soft-tissue malformations	2 (2)	2 (2)	3 (3)	7 (5)
Soft-tissue variations	21 (11)	17 (10)	21 (10)	30 (14)
Total skeletal malformations	1 (1)	1 (1)	0 (0)	4 (4)
Total skeletal retardations	33 (11)	30 (10)	29 (14)	23** (10)
Total skeletal variations	10 (6)	8 (7)	16 (10)	73** (15)**
Splitting of skull bones	2 (1)	2 (2)	2 (2)	11* (7)*
Fused sternebrae	5 (4)	2 (2)	13 (8)	51** (13)**
Irregularily shaped sternebrae	2 (2)	3 (3)	1 (1)	34** (13)**
Bipartite sternebrae	0 (0)	0 (0)	0 (0)	12** (8)**
Accessory 13th rib	1 (1)	2 (2)	2 (1)	7 (6)
Total malformations	3 (2)	2 (2)	4 (4)	15* (9)*
Total variations	29 (11)	23 (12)	32 (12)	77** (15)

[a] Statistically significant compared with controls: *$p < 0.05$; **$p < 0.01$.
Abbreviation: GD, gestation day.
Sources: BASF 1989; Hellwig et al. 1991.

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TABLE 1-7 Selected Results of Pregnant Rats Exposed to DMF for 6 h/day on GD 4-8

	Exposure concentration (ppm)		
Parameter	0	221	522
Number of animals	18	18	19
Number of pregnant animals	18	17	18
Mean maternal body-weight change (g):[a]			
GD 4-11[b]	22.6	16.6 (−26)[c]	10.2 (−55)
GD 11-15	19.6	22.1 (+13)	18.9 (−3)
GD 15-20	66.1	67.4 (+2)	53.7 (−19)
GD 4-20	108.2	106.1 (−2)	82.8 (−23)
No. litters	18	17	16
No. live fetuses	201	215	168
Mean number of live fetuses/dam	11.17	12.65	9.33
Total implantation sites	208	224	212
Mean implantation sites/dam	11.56	13.18	11.83
Percent live fetuses related to implantations	96.6	96.0	78.9
Dead implants as percent of total implantations	7	9	45**[e]
	3.37	4.02	21.13
Total Resorptions:			
Early	7	9	45
(number of resorptions/dam)[d]	7 (0.4)	8 (0.5)	44 (2.75)
Middle	0	1	1
Late	0	0	0
Dams with all resorptions	0	0	2
Mean fetal weight, g	3.77	3.55*[e]	3.62*[e]

[a]Calculated by reviewer using mean body-weight values.
[b]Body weights recorded on GD 0, 4, 11, 15, and 20; therefore, body-weight gain over the exposure interval of GD 4-8 could not be calculated.
[c]Percent decrease or increase compared with controls; calculated by reviewer.
[d]Calculated by reviewer: Number of resorptions and number of pregnant dams.
[e]Statistically significant compared with controls: *p <0.05; **p <0.01.
Abbreviation: GD, gestation day.
Source: BASF 1974c.

Groups of 30 impregnated female Sprague-Dawley rats were exposed to air or 287 ppm DMF for 6 h/day (BASF 1974a,b; Hellwig et al. 1991). Two discontinuous exposure regimes were tested: Rats were exposed on GD 0-1, 4-8, 11-15, and 18-19 (Group I) or on GD 0-3, 6-10, and 11-18 (Group II). The DMF concentration was analyzed 12 times during the exposure period (287 ± 50.2

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ppm), and the constancy of the concentration in the chambers was monitored daily using an infrared photometer. Twenty rats/group were killed on GD 20. Gross necropsy and caesarean sections were performed; all fetuses were examined externally, and one-third were fixed and examined for soft tissue abnormalities and two-thirds were fixed and examined for skeletal abnormalities. The remaining 10 dams/group were allowed to deliver, and all dams and pups were killed and examined on day 20 after birth. Effects of exposure in animals from Groups I and II (killed on GD 20) included reduced mean maternal body-weight gain (rats in Groups I and II gained 56% and 39% less than controls, respectively), decreased ($p < 0.05$) mean fetal weight (Group I: 3.34 vs. 3.77 g for controls; Group II: 3.35 vs. 3.70 g for controls), mean fetal length (Group I: 3.55 vs. 3.66 cm for controls; Group II: 3.49 vs. 3.62 cm for controls), and mean placental weight (Group I: 0.49 vs. 0.56 g for controls; Group II: 0.51 vs. 0.59 g for controls). The number of dead implants was statistically increased in dams from Group I (21 vs. 9 for controls; $p < 0.05$). The percentage of total dead implants in Group I was increased after DMF exposure (10.8% vs. 4.43% for controls), but the increase did not attain statistical significance. An increased litter incidence of aplasia of some sternebrae was observed in exposed fetuses from both Groups I and II (Group 1: 12/18 vs. 3/19 for controls; Group II: 11/17 vs. 5/20 for controls). No treatment-related adverse effects were observed in dams or pups that were allowed to deliver their offspring.

Groups of 22 or 23 impregnated Long Evans rats inhaled DMF at measured concentrations of DMF at 0, 18, or 172 ppm dissolved in polyethylene glycol 400 (20 mm^3/L air) for 6 h/day during GD 6-15 (Kimmerle and Machemer 1975). Dams were killed on GD 20, and caesarean sections were performed. All fetuses were examined for external malformations, one-third of the fetuses were examined for visceral malformations, and the remaining two-thirds of the fetuses were examined for skeletal malformations. No clinical signs or body-weight changes were observed in dams. The only effect observed in fetuses was reduced mean fetal body weight in the 172-ppm group (3.78 g vs. 4.07 g for controls; $p < 0.01$), but the reduction in fetal weight was not accompanied by any other signs of growth retardation, such as delays in skeletal ossification.

Groups of 21 impregnated, Crl:CD rats inhaled DMF at 0, 30, or 300 ppm for 6 h/day during GD 6-15 (Lewis et al. 1992). Chamber concentrations were measured by infrared analysis at four intervals during each exposure day (measured concentrations were 0, 31.2 ± 4.6, and 297 ± 22 ppm, respectively). Dams were killed on GD 21 and subjected to gross necropsy. All fetuses were examined externally, two-thirds of the fetuses were examined for skeletal abnormalities, and the remaining one-third of the fetuses were examined for visceral abnormalities. The only effect observed in dams was reduced weight gain over GD 6-15 in those that inhaled 300 ppm (78% of controls; $p < 0.05$). Decreased mean fetal body weight was observed in the 300-ppm group (96% of controls; $p < 0.05$), but the reduced fetal weight was not accompanied by changes in skeletal ossification. No treatment-related malformations were noted.

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3.4. Repeated Exposures

Repeated exposure data are discussed to place the acute toxicity data into perspective.

3.4.1. Nonhuman Primates

Adult male cynomolgus monkeys were exposed to DMF at a nominal concentration of 500 ppm for 6 h/day, 5 days/week, for 2 weeks (Hurtt et al. 1991). One monkey was exposed by whole-body inhalation (4.1 m^3 chamber with airflow of 500 L/min), and a second monkey was exposed head-only (acrylic helmet with airflow rate of 10 L/min). Mean analytic concentrations for the 10-day period were 509 and 385 ppm, respectively. Clinical signs were recorded daily during exposure, and body weight was recorded 1 day before exposure, on study day 8, and after the last exposure. Blood was collected for hematology and clinical chemistry analysis 1 day before exposure at the end of the first exposure day and following the last exposure day. Neither monkey showed clinical signs of toxicity or abnormalities in standard hematology or serum chemistry parameters (included counts of red blood cells, platelets, white blood cells, and white-blood-cell differential; hematocrit; hemoglobin; mean corpuscular volume and hemoglobin concentration; total reticulocytes; SDH; ALT; AP; total bile acids; total bilirubin; urea; nitrogen; creatinine; creatine kinase; total protein; fasting glucose; albumin; cholesterol; isocitrate dehydrogenase; sodium; postassium; chloride; phosphorous; magnesium; and calcium).

In a subsequent study, Hurtt et al. (1992) exposed groups of five male and three female adult cynomolgus monkeys to measured concentrations of DMF at 0, 30, 100, or 500 ppm for 6 h/day, 5 days/week, for 13 weeks using a flow-through exposure chamber (15 air changes/h or 1,025 L/min). No exposure-related changes in clinical signs (assessed once/week; twice daily for morbidity or mortality); body weight (measured prior to first exposure, weekly during the study, and at study termination); hematology or serum chemistry analysis or urinalysis (measured prior to study initiation after first exposure; end of exposure weeks 2, 4, 8, and 12; and at study termination), semen analysis (volume, motility, count, or morphology; measured three times prior to study initiation and once/week during study), or gross necropsy findings were observed.

3.4.2. Rats

Groups of 10 Fischer 344 (F344)/DuCrj male and female rats were exposed to DMF for 6 h/day, 5 days/week at target concentrations of 0, 100, 200, 400, 800, or 1,600 ppm for 2 weeks or at 0, 50, 100, 200, 400, or 800 ppm for 13 weeks (Senoh et al. 2003). In the 2-week exposure group, exposure at 1,600 ppm resulted in the death of three males and seven females, death occurring after the third, fourth, fifth, and tenth exposure. Death was attributed to marked

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centrilobular necrosis of the liver. No clinical signs were noted in any of the other groups. Reduced body-weight gain was observed in male rats exposed to DMF at ≥800 ppm and in female rats exposed at ≥ 400 ppm. Histopathologic examination of rats in the 1,600-ppm exposure group revealed massive hepatic necrosis extending over more than two lobules and centrilobular fibrosis in a more limited area. Centrilobular single-cell necrosis associated with fragmented nucleoli was also seen in male and female rats exposed at 800 ppm. In the 13-week exposure study, body weight was reduced in male and female rats exposed to DMF at 400 and 800 ppm, and feed consumption was reduced in rats exposed at 800 ppm. Relative liver weight was increased in male rats exposed at ≥100 ppm and in female rats exposed at ≥200 ppm. Histopathologic examination revealed increased hepatic single-cell necrosis in male and female rats exposed at ≥200 ppm and in centrilobular hypertrophy in male and female rats exposed at ≥400 ppm. Clinical chemistry analyses revealed increased ALT, AST, lactate dehydrogenase (LDH), GGT, total cholesterol, and phospholipid in male and female rats (generally occurring in males exposed at ≥50 ppm and females exposed at ≥200 ppm). Benchmark dose analysis found a repeat exposure $BMDL_{10}$ (lower confidence limit on the benchmark dose corresponding to a 10% response) of 1.1 and 13.1 ppm for the increased relative liver weight in males and females, respectively, and of 68.5 and 191 ppm for cellular hypertrophy in males and females, respectively.

Groups of 30 male or 30 female F344/N rats were exposed to air containing measured concentrations of DMF at 0, 50, 100, 200, 400, or 800 ppm for 6 h/day, 5 days/week, for 13 weeks (NTP 1992; Lynch et al. 2003). Rats were subdivided into three groups: 10 rats/sex in a base study group, 10 rats/sex in a cardiovascular group, and 10 rats/sex in a renal function group. In the base group, rats were observed twice/day for mortality or moribundity, and body weight and clinical observations were recorded weekly. Blood was drawn for hematologic and clinical chemistry analysis at days 4, 24, and 91 of the study. Necropsy was conducted on all base group rats, and most tissues from the control and high-concentration groups and the livers from rats from all base groups were examined histologically. In the cardiovascular group, blood pressure and electrocardiograms were taken within 24 h of the last DMF exposure, and the hearts of these animals were examined microscopically. In the renal function group, animals were placed in metabolism cages and urine collected for 16 h at the end of the study, and kidneys were collected at necropsy and evaluated histologically. Sperm morphology was evaluated in males at necropsy, and vaginal cytology was investigated in females 2 weeks prior to necropsy by evaluating vaginal lavage fluid. All animals survived to study termination. It was noted that DMF was mildly irritating to rats exposed at 400 or 800 ppm, as indicated by occasional nasal and ocular discharges. Absolute body weight and body-weight gain were decreased in the 400- and 800-ppm males and females. Alterations in liver enzymes (ALT, SDH, and isocitrate dehydrogenase) and bile salts were present at the first analysis on day 4 in the 400- and 800-ppm males and females. Serum cholesterol was increased in all exposed rats; marginal increases in abso-

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lute and relative liver weights were observed. Histologic evaluation revealed minimal-to-moderate necrosis of individual hepatocytes around the central veins and the presence of macrophages containing a golden-brown pigment in the 400- or 800-ppm male and female rats. High-dose female rats had an increased length of estrous cycle compared with controls. No definitive exposure-related effects were observed in renal function, blood pressure, or electrocardiogram readings or in male reproductive parameters.

Groups of F344 rats (number and sex not specified) inhaled DMF at 0, 150, 300, 600, or 1,200 ppm (average measured concentrations of 149, 302, 587, and 1,184 ppm) in a 1.5-m^3 dynamic chamber (airflow approximately 283 L/min) for 6 h/day, 5 days/week, for 12 weeks (Craig et al. 1984). Death occurred before study termination in one male at 300 ppm and in one male and one female at 1,200 ppm; the day of death was not provided. Nasal discharge described as "crusty nose" was observed most frequently at week 2 in all groups exposed to DMF, but this observation was not concentration-related. Body weight was reduced in males at 1,200 ppm beginning at week 4 and in the females at 1,200 ppm beginning at week 2. A concentration-related increase in serum cholesterol was observed in both males and females, the increases being statistically significant at 600 and 1,200 ppm. Females exposed at 1,200 ppm developed hepatocellular collapse near the central veins occasionally extending to the portal zones; fibrosis; accumulation of yellow-brown pigment in Kupffer cells, macrophages, and hepatocytes; variations in nuclear and cell size with the presence of large hepatocytes; and dark staining of the cytoplasm of hepatocytes. Examination of the livers from females exposed at 600 ppm revealed the presence of only a small amount of hepatic pigment and no collapse or fibrosis, but variations in nuclear size and cytoplasmic variations were present to a lesser degree than those at 1,200 ppm. The only hepatic lesions noted in females exposed at 300 ppm were barely discernible variations in nuclear size and cytoplasmic variations. The authors stated that similar hepatic changes were observed in exposed males except for there being little or no collapse and no fibrosis. Histopathologic evaluation of the liver from the one male and one female rat that died early in the 1,200-ppm group revealed widespread collapse, necrosis, and pigment accumulation. One liver also exhibited innumerable mitotic figures (animal affected not identified).

To determine whether age influences the toxicity of inhaled DMF, groups of 10 3-, 4-, 5-, 8-, or 12-week-old female Sprague-Dawley rats were subdivided into two groups of five each: One group at each age was exposed to DMF at 200 ppm in a 1.5 m^3-chamber (ventilation rate of 200 L/min) for 8 h/day, 7 days/week, for 4 weeks, and the other rats served as control groups (Tanaka 1971). At study termination, biochemical tests (protein, AST, ALT, AP, and LDH) and histopathologic evaluations were performed. Significantly increased levels of ALT and AST were observed only in 3-week-old rats. No other biochemical changes were observed. All exposed rats exhibited histopathologic changes in the liver, generally in the central zone of the lobules. The primary alteration was degeneration, as indicated by cloudy swelling of liver cells. In

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some cases, mild fatty change was also noted. It appeared that the younger the rat, the more pronounced the hepatic damage. A correlation was also found between the increase of transaminases and the extent of pathologic change in the liver.

In a second experiment by Tanaka (1971), two groups of 15 3-week-old female Sprague-Dawley rats inhaled DMF at 200 ppm in a 0.6 m^3-gas tight chamber (ventilation rate of 180-200 L/h) for 1 h/day or 8 h/day for 4 weeks. A third group was not exposed and served as the concurrent control. Within each group, five animals were killed at the end of 1, 2, or 4 weeks of exposure, and biochemical and histopathologic evaluations were conducted as in the previous experiment (see previous paragraph). Increased AST and ALT were present in both exposure groups after 1 week of exposure. Histopathologic changes in the liver were the same as those noted in the previous experiment, the changes being more extensive in rats exposed for 8 h daily compared with rats exposed for only 1 h daily. Degeneration was most extensive in rats exposed 8 h daily for 1 week. After 2 and 4 weeks of exposure, hepatic degeneration and marked regeneration were present in both groups of exposed rats.

Groups of 16 rats were exposed to DMF at 100, 230, or 450 ppm in a 0.6-m^3 gas tight chamber (ventilation rate of 180-200 L/h) for 8 h/day, 6 days/week, for up to 120 days (Massmann 1956). During the study, rats were said to have been unaffected by exposure to DMF, and there was no change in body weight. Necropsy revealed liver necrosis. Bronchopneumonic changes were noted in some animals, and hyperemia of the brain, cloudy swelling of renal tubules, and iron deposits in the spleen were observed. However, the report combined experiments on rats and cats, and it was not stated which species (cats or rats) and at what concentration these effects were noted. No other experimental details were provided.

3.4.3. Mice

Groups of 10 Crj:BDF_1 male and female mice inhaled DMF for 6 h/day, 5 days/week, at target concentrations of 0, 100, 200, 400, 800, or 1,600 ppm for 2 weeks or concentrations of 0, 50, 100, 200, 400, or 800 ppm for 13 weeks (Senoh et al. 2003). All mice survived to study termination; no adverse clinical signs were reported. In the 2-week exposure group, reduced body-weight gain was observed in males and females exposed at 1,600 ppm (exact values not provided). Relative liver weights were increased in male mice exposed at ≥400 ppm and in female mice exposed at ≥200 ppm (values not reported). Histopathologic examination of mice exposed at 1,600 ppm revealed focal necrosis structured with small clusters of necrotic hepatocytes and inflammatory cell infiltrate with single-cell necrosis associated with fragmented nucleoli. Centrilobular degeneration was present in male mice exposed at ≥200 ppm and in female mice exposed at ≥800 ppm. In the 13-week study, males exhibited reduced body weight and increased relative liver weight at all DMF concentrations and a reduction in feed

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consumption at 800 ppm, but no significant differences in these parameters were observed in any of the females. Histopathologic examination revealed increased centrilobular hypertrophy in males exposed at ≥50 ppm and in females exposed at 800 ppm. Single-cell necrosis was noted in the males and females exposed at 800 ppm. Focal necrosis was increased in male and female mice exposed at ≥100 ppm, but the increase was not related to concentration. Clinical chemistry analysis revealed increased ALT, LDH, and total cholesterol in male and female mice (at ≥100 ppm).

Groups of 10 male and 10 female $B6C3F_1$ mice were exposed to air containing measured concentrations of DMF at 0, 50, 100, 200, 400, or 800 ppm for 6 h/day, 5 days/week, for 13 weeks (NTP 1992; Lynch et al. 2003). Mice were checked twice per day and body weight, and clinical observations were recorded weekly. Blood was drawn at days 4, 24, and 91 of the study. Sperm morphology was evaluated at necropsy, and vaginal cytology was investigated 2 weeks prior to necropsy by evaluating vaginal lavage fluid. Necropsy was conducted on all mice, and most tissues from the control and high-concentration groups and the livers from mice at all exposure concentrations were examined histologically. No treatment-related deaths were observed (five deaths in exposed male mice were considered incidental). Body-weight gain was decreased in male and female rats exposed at 800 ppm. A concentration-related increase in liver weight was evident in all exposure groups, although the increases were biologically significant only at 200 ppm and higher. Microscopic examination of the liver revealed minimal-to-mild centrilobular hepatocellular hypertrophy in all male exposure groups and in females exposed at 100 ppm or higher. No changes in reproductive tissue parameters were noted in exposed male mice, and female mice showed a significant trend toward an increase in the estrous cycle length.

Groups of 10 male and 10 female $B6C3F_1$ mice were exposed to DMF at 0, 150, 300, 600, or 1,200 ppm (average measured concentrations of 149, 302, 587, or 1,184 ppm) in a 1.5-m^3 dynamic inhalation chamber (airflow approximately 283 L/min) for 6 h/day, 5 days/week, for 12 weeks (Craig et al. 1984). One male at 150 ppm, two males at 600 ppm, and five males at 1,200 ppm were found dead or were killed in moribund condition, and three females at 1,200 ppm were killed in moribund condition (day of death not reported). Other animals that were accidentally killed or withdrawn for other reasons (further details not provided) were evenly distributed among all the groups. Body weight was not affected by exposure, and no clinical toxicity signs or abnormalities in hematology or clinical chemistry parameters were observed. Necropsy of the animals that died or were killed early revealed one male and one female mouse from the 1,200-ppm group with livers exhibiting single-cell necrosis. It is unclear from the study description if the other deaths or early kills were related to exposure. Necropsy of animals surviving to study termination revealed focal areas of discoloration and alterations in the consistency of livers from one male and one female at 600 ppm and from two females at 1,200 ppm. Histologic evaluation was conducted on the livers of nine, nine, nine, six, and five male mice in the 0-, 150-, 300-, 600-, or 1,200-ppm groups, respectively, and on the

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livers of eight, eight, eight, 10, and five female mice in the 0-, 150-, 300-, 600-, or 1,200 ppm groups, respectively. Hepatic changes in males included areas of collapse with the presence of phagocytes containing yellow-brown pigment in three males at 600 ppm and two males at 1,200 ppm. One male at 300 ppm had a large area of coagulative necrosis. In females, liver necrosis was observed in one, one, and two mice from the 150-, 600-, and 1,200-ppm groups, respectively. Kupffer's cells and phagocytes containing pigment were present in only three mice from the 600- and 1,200-ppm groups. Concentration-related hepatic cytomegaly around central veins was found in all groups exposed to DMF.

3.4.4. Cats

Groups of two cats inhaled air containing DMF at 100, 230, or 450 ppm in a 0.6-m^3 gas tight chamber (ventilation rate of 180-200 L/h) for 8-h/day, 6 days/week, for up to 120 days (Massmann 1956). Cats had a poor appetite and lost weight during the course of the study. No other toxicity signs were observed. No changes were observed in hematology, urinalysis, or ECG recordings. Necropsy revealed fatty hepatic degeneration but no necrosis. Bronchopneumonic changes were noted in some animals, and hyperemia of the brain, cloudy swelling of renal tubules, and iron deposits in the spleen were observed. It was not clear in which animals (cats or rats) and at what concentrations and exposure durations these effects were noted. No other details were provided.

3.5. Genotoxicity

In vitro, DMF was not mutagenic in *Salmonella typhimurium* strains TA1535, TA100, TA1537, TA1538, and TA98 with or without metabolic activation (Antoine et al. 1983; NTP 1992) and did not induce sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells with or without metabolic activation (NTP 1992). In vivo, DMF was negative in the micronucleus test on mouse bone-marrow cells and did not cause mouse sperm abnormalities (Antoine et al. 1983). One laboratory found a marginal response in mouse lymphoma L5178Y/T$k^{+/-}$ cells following exposure of DMF, but this response was not seen in two other laboratories (NTP 1992).

3.6. Carcinogenicity

Groups of 87 male and 87 female Crl:CD BR rats and 78 male and 78 female Crl:CD-1 (ICR) BR mice were exposed to DMF at 0, 25, 100, or 400 ppm for 6 h/day, 5 days/week, for up to 2 years (rats) or 18 months (mice) (E.I. Dupont de Nemours & Co. 1992; Malley et al. 1994). Female rats exposed at 400 ppm and male rats exposed at 100 or 400 ppm had decreased absolute body weight, and body-weight gain was reduced in males and females at 100 or 400

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ppm. Males and females exposed at 100 or 400 ppm had exposure-related increases in SDH activity, relative liver weight, centrilobular hepatocellular hypertrophy, and centrilobular lipofuscin and hemosiderin accumulation. Males and females exposed at 400 ppm had an increased incidence of centrilobular single-cell necrosis of hepatocytes, males at 100 or 400 ppm had an increased incidence of hepatic focal cystic degeneration, males at 100 ppm and males and females at 400 ppm had an increased incidence of hepatic clear-cell foci, and females at 400 ppm had an increased incidence of eosinophilic foci. Under the conditions of this study, DMF was not oncogenic in rats, and exposure of up to 400 ppm failed to result in any exposure-related effects on the estrous cycle.

In mice, body weight and body-weight gain were not affected by DMF exposure at up to 400 ppm; males and females at 100 or 400 ppm had increased body weight and body-weight gain compared with controls (E.I. Dupont de Nemours & Co. 1992; Malley et al. 1994). Absolute and relative liver weights were increased in males at 100 ppm and 400 ppm and in females at 400 ppm. Male and female mice from all test groups also exhibited centrilobular hepatocellular hypertrophy, increased incidence of individual hepatocellular necrosis and Kupffer cell hyperplasia with accumulation of lipofuscin and hemosiderin, and a concentration-related increase in eosinophilic and mixed foci of cellular alteration. Under the conditions of this study, DMF was not oncogenic in mice, and exposure of up to 400 ppm failed to result in any exposure-related effects on the estrous cycle.

Groups of 50 male and 50 female F344/DuCrj (SPF) rats and 50 male and 50 female Crj:BDF_1 (SPF) mice were exposed to DMF at 0, 200, 400, or 800 ppm for 6 h/day, 5 days/week, for 104 weeks (Senoh et al. 2004). Three male rats and 13 female rats from the 800-ppm group died by 13 and 21 weeks, respectively. A concentration-related reduction in absolute body weight was observed in DMF-exposed male and female rats, and females exposed at 800 ppm reduced their food consumption. Clinical chemistry revealed a concentration-related increase in AST, ALT, GGT, and AP activity in male and female rats, and males at 800 ppm had increased LDH. Relative liver weight was increased in all DMF-exposed groups. Gross necropsy of the liver of rats that died within the first 21 weeks revealed red zones or accentuated lobular structure, and histopathology revealed centrilobular necrosis in three of the males and all 13 of the females that died. Terminal necropsy of surviving rats revealed white or brown hepatic nodules in males and females exposed at 800 ppm. Histopathology of the males exposed to DMF found increased spongiosis hepatitis at 200 ppm and above, clear-cell foci and eosinophilic-cell foci at 400 ppm and above, and basophilic-cell, mixed-cell, and vacuolated-cell at 800 ppm. Histopathologic examination of the female rats revealed an increase in clear-cell foci at 200 ppm and above, and eosinophilic-cell foci at 400 ppm and above. Neoplastic lesions included an increase in hepatocellular adenomas at 400 ppm and above and hepatocellular carcinomas at 800 ppm. Data are summarized in Table 1-8.

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TABLE 1-8 Incidences of Neoplastic and Non-neoplastic Liver Lesions in Rats and Mice Exposed to DMF for 2 Years

	Males				Females			
Concentration, ppm	0	200	400	800	0	200	400	800
Number of Rats	50	50	50	50	49	50	50	50
Neoplastic lesions								
Hepatocellular adenoma	1	3	13** [a]	20**	1	1	6	16**
Hepatocellular carcinoma	0	1	0	24**	0	0	0	5*[a]
Total hepatocellular tumors	1	4	13**	33**	1	1	6	19**
Pre-neoplastic lesions								
Altered-cell foci						23**		
Clear-cell foci	11	21	35**	40**	3	4	33**	33**
Eosinophilic-cell foci	13	14	34**	40**	0	27	10**	22**
Basophilic-cell foci	24	26	29	42**	23	0	15	29
Mixed-cell foci	0	0	1	6*	0	0	0	1
Vacuolated-cell foci	6	0*	7	16*	0	0	1	3
Spongiosis hepatitis	4	21**	26**	24**	0		0	2
Non-neoplastic lesions								
Necrosis: centrilobular	1	5	0	5	0	3	2	13**
Number of Mice	50	50	49	50	49	50	50	49
Neoplastic lesions								
Hepatocellular adenoma	6	36**	41**	41**	1	42**	47**	48**
Hepatocellular carcinoma	2	12**	16**	16**	3	25**	32**	35**
Hepatoblastoma	0	13**	7**	4	0	0	4	0
Total hepatocellular tumors	8	42**	46**	44**	3	45**	49**	49**
Pre-neoplastic lesions								
Altered-cell foci								
Clear-cell foci	4	21**	13**	17**	3	7	4	2
Eosinophilic-cell foci	1	38**	41**	42**	1	43**	43**	48**
Non-neoplastic lesions								
Centrilobular hypertrophy	0	39**	41**	48**	2	11*	5	16**
Nuclear atypia: centrilobular	0	33**	42**	45**	2	7	3	16**
Necrosis: single cell	12	38**	43**	48**	22	13	6**	19
Inflammatory cell nest	15	37**	42**	48**	24	13*	4**	19

[a]Statistically significant compared with controls: *p <0.05; **p <0.01.
Source: Adapted from Senoh et al. 2004.

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Overall, survival was unaffected in mice that inhaled DMF at up to 800 ppm for 2 years (Senoh et al. 2004). However, two males and 14 females in the 800-ppm group, six males and seven females in the 400-ppm group, and four males and four females from the 200-ppm group died of hepatocellular tumors. Body-weight gain of DMF-exposed mice was suppressed in a concentration-related manner, but food consumption was not affected. Clinical chemistry analyses revealed a concentration-related increase in AST, ALT, LDH, AP, and total cholesterol in male and female mice. Relative and absolute liver weights were increased in all DMF-exposed groups. Gross necropsy revealed multiple occurrences of white, brown, or red nodules in the livers of almost all of the DMF-exposed groups. Histopathology of the livers from male mice revealed an increase in clear-cell and eosinophilic-cell foci, centrilobular hypertrophy, centrilobular nuclear atypia, single-cell necrosis, and inflammatory cell nests at 200 ppm and above. Histopathologic examination of the livers from female mice revealed an increase in eosinophilic-cell foci at 200 ppm and above, and centrilobular hypertrophy at 800 ppm. Neoplastic lesions included an increase in hepatocellular adenomas and hepatocellular carcinomas at 200 ppm and above in both male and female mice. Hepatoblastomas were elevated above historical controls in males at 200 ppm and above and in females at 400 ppm. Data are summarized in Table 1-8.

IARC (1989) concluded that there was *inadequate evidence* for the carcinogenicity of DMF in experimental animals, but that there was *limited evidence* in humans. The overall evaluation was that DMF is *possibly carcinogenic to humans (Group 2B)*. A carcinogenicity assessment was not conducted for DMF in the IRIS database (EPA 1990).

3.7. Summary

A summary of lethal and nonlethal effects of acute DMF exposure can be found in Table 1-9, and a summary of subchronic inhalation exposure is presented in Table 1-10. Acute exposures of mice and rats to high concentrations of DMF resulted in mortality, while low and intermediate concentrations resulted only in alterations of liver enzymes. Repeated exposure of rats, mice, and cats to DMF generally resulted in decreased body weight and hepatotoxicity, as indicated by increases in liver enzymes and histopathologic changes in the liver, including degeneration and necrosis. However, 6-h exposures of monkeys to DMF at 500 ppm did not result in any measurable effects. Developmental toxicity studies reported maternal effects of reduced maternal body weight, and developmental effects included reduced fetal weight; increases in the litter incidence of total external, skeletal, and visceral malformations and skeletal variations; and an increased number and percentage of dead implants. Genotoxicity testing of DMF has generally been negative. One study found no evidence of carcinogenicity when mice and rats inhaled DMF for 2 years; another study

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found that chronically inhaled DMF was associated with hepatocellular adenomas and carcinomas in rats and hepatoblastomas and hepatocellular adenomas and carcinomas in mice.

TABLE 1-9 Summary of Acute Inhalation Data in Laboratory Animals

Concentration (ppm)	Duration	Effect	Reference
		Rat	
3,700	1, 3 h	3/3 males and 3/3 females survived; excessive grooming	Shell Oil Company 1982
	7 h	2/3 males and 3/3 females died; excessive grooming, lethargy	
5,000	4 or 8 h	No mortality (within 24 h)	Lundberg et al. 1986
280, 560	4 h	SDH increased 20 h postexposure (no concentration response)	Lundberg et al. 1986
2,250		SDH not affected; no histologic hepatic changes	
153	4 h	SDH increased (2-fold) 24 h postexposure	Roure et al. 1996
313		SDH and GDH increased (6-fold) 24 h postexposure	
441		SDH and GDH increased (10.5-fold) 24 h postexposure; at 72 h postexposure, only GDH increased 1.5 fold	
991		SDH (140-fold) and GDH increased (130-fold) 48 h postexposure; at 72 h postexposure, only GDH increased 20-fold	
126, 281, 314	4 h	GDH increase: 38%, 516%, and 260%, respectively ALT increase: 37%, 54%, 50%, respectively SDH increase: 130%, 325%, 379%, respectively	Brondeau et al. 1983
		Mouse	
1,628, 2,110	10 min	Respiratory rate decrease of 12.8% and 28.3%, respectively; RD_{50} could not be determined	Kennedy and Sherman 1986
3,981	2 h	LC_{50}	Stasenkova 1961
670		Highest no effect for mortality	

Abbreviations: SDH, sorbitol dehydrogenase; GDH, glutamate dehydrogenase; ALT, alanine aminotransferase; RD_{50}, concentration of a substance that reduces the respiratory rate by 50%; LC_{50}, concentration of a substance that is lethal to 50% of the exposed population.

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TABLE 1-10 Summary of Repeated Exposure Inhalation Data in Laboratory Animals

Concentration (ppm)	Duration	Effect	Reference
		Monkey	
500	6 h/d, 5 d/wk, 2 wk	No adverse effects after first exposure	Hurtt et al. 1991
500	6 h/d, 5 d/wk, 13 wk	No adverse effects	Hurtt et al. 1992
		Rat	
2,523	6 h/d, 5 d	8/10 died (7 of acute liver necrosis; 1 of acute pulmonary edema and congestion); progressive weakness, discomfort, weight loss	Kennedy and Sherman 1986
50, 100, 200 400, 800	6 h/d, 5 d/wk, 13 wk	Increased cholesterol in all exposed groups; mildly irritating (occasional nasal and ocular discharge); increased ALT, SDH, isocitrate dehydrogenase, bile salts on exposure day 4; decreased body weight; hepatocellular necrosis	NTP 1992
150, 300, 600 1,200	6 h/d, 5d/wk, 12 wk	No adverse effect Variations in hepatic nuclear size and cytoplasmic variations at 300 ppm and above; increased cholesterol at 600 ppm and above; 1 male and 1 female died, liver necrosis; surviving rats, decreased body weight, liver necrosis	Craig et al. 1984
100, 200, 400 800, 1,600	6 h/d, 5 d/wk, 2 wk	No clinical signs at any concentration Decreased growth rate at 400 ppm and above Centrilobular single-cell necrosis 3 males and 7 females died within 10 exposures; massive hepatic necrosis	Senoh et al. 2003
50, 100 200, 400, 800	6 h/d, 5 d/wk, 13 wk	Increased liver enzymes at 50 ppm and above Increased relative liver weight at 100 ppm and above Increased hepatic single-cell necrosis at 200 ppm and above Centrilobular hypertrophy at 400 ppm and above, decreased body weight; decreased body weight and food consumption	Senoh et al. 2003
100, 230, 450	8 h/d, 6 d/wk, 120 d	Appeared unaffected by exposure	Massmann 1956

(Continued)

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TABLE 1-10 Continued

Concentration (ppm)	Duration	Effect	Reference
		Mouse	
100, 200, 400, 800, 1,600	6 h/d, 5 d/wk, 2 wk	No clinical signs at any concentration Increased relative liver weight at 200 ppm and above Decreased growth rate, focal hepatic necrosis at 1,600 ppm	Senoh et al. 2003
50, 100, 200, 400, 800	6 h/d, 5 d/wk, 13 wk	Decreased growth rate and increased liver weight in all exposed groups; centrilobular hypertrophy in males at 50 ppm and above Increased liver enzymes at 100 ppm and above Decreased food consumption, single-cell necrosis in liver, centrilobular hypertrophy in females at 800 ppm	Senoh et al. 2003
50, 100, 200, 400, 800	6 h/d, 5 d/wk, 13 wk	Mild centrilobular hepatocellular hypertophy at ≥50 ppm Significant increase in liver weight at ≥200 ppm Decreased growth rate at 800 ppm	NTP 1992
150, 300, 600, 1,200	6 h/d, 5d/wk, 12 wk	1 died; hepatic cytomegaly around central vein at ≥150 ppm Histopathologic hepatic changes at ≥300 ppm 2 died at 600 pm 8 died or killed moribund; single-cell necrosis in 2 mice at 1,200 ppm	Craig et al. 1984
		Cat	
100, 230, 450	8 h/d, 6 d/wk, 120 d	Poor appetite, weight loss; no effects on clinical signs, blood analysis, urinalysis, ECG recordings; necropsy, fatty degeneration and no necrosis	Massmann 1956

4. SPECIAL CONSIDERATIONS

4.1. Absorption and Disposition

Mraz and Nohova (1992) determined that pulmonary retention of DMF was approximately 90% following exposure of groups of male or female volunteers to DMF at 3, 10, or 20 ppm (reported as 10, 30, or 60 mg/m^3) for 8 h. Approximately 20% of excreted metabolites recovered in the urine were from absorption of DMF vapor through the skin.

Hurtt et al. (1991) also observed that dermal absorption accounts for a measurable amount of total DMF absorbed during an inhalation exposure in which one cynomolgus monkey was exposed by whole-body inhalation and another was exposed head only to DMF at 500 ppm for 6 h. Plasma taken 0.5 to

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18 h postexposure revealed that the DMF area under the curve (AUC) value was three times greater in the monkey exposed by whole-body exposure compared with the monkey exposed by head only, indicating that dermal exposure to DMF vapor contributed significantly to the total DMF absorbed dose. The authors also investigated the amount of DMF absorbed by the respiratory tract by measuring the tidal volume and the DMF concentration going into and out of the head-only exposure unit and found that pulmonary absorption was approximately 100%. Lundberg et al. (1983) commented that only negligible amounts of DMF should be found in expired air based on the fact that DMF dissolves in water by hydrogen binding, resulting in a loss of vapor pressure in the respiratory system.

Mraz et al. (1989) reported that the absorbed dose by humans following inhalation exposure to DMF at 20 ppm for 8 h was one-half of that absorbed by male mice, rats, and hamsters after a single intraperitoneal injection of DMF at 0.1, 0.7, or 7 mmol/kg of body weight. However, it must be emphasized here that the rodents were exposed via a parenteral injection route, and the rodents received a much higher bolus dose than humans.

Distribution of DMF and its metabolites was fairly uniform among blood, liver, kidney, brain, and adrenals following a 4-h inhalation exposure of female rats to DMF at 565 or 2,250 ppm, the blood containing slightly higher concentrations (Lundberg et al. 1983). DMF and its metabolites were no longer detected in these tissues by 20 h postexposure to DMF at 565 ppm, or by 48 h postexposure at 2,250 ppm.

Quantitative data on the placental transfer of inhaled DMF were not available. Oral data assessing metabolic tissue profile, time-course disposition, and transfer into milk following a single dose of ^{14}C-DMF at100 mg/kg by gavage were discussed by Saillenfait et al. (1997). Exposure to a single oral 100-mg/kg bolus produced maternal toxicity as evidenced by reductions in maternal body-weight gain, body-weight gain corrected for uterine weight, and feed consumption. Developmental toxicity was indicated by reduced weight. In the time-course disposition portion of the study, pregnant rats were dosed with ^{14}C-DMF on GD 12 or GD 18 and examined over a 48-h period. Similar results were found at both GD 12 and GD 18; the results from GD 12 are described here. The radiolabel reached peak concentration in all tissues within 1 h after dosing, indicating rapid distribution, and remained elevated until 4 h, when the concentration declined. Total radioactivity in the placenta and embryo as a percentage of maternal plasma concentration was 64-70% and 79-93%, respectively, at 0.5-8 h after dosing. After 48 h, the ratio of placental and embryonic tissue radiolabel reached approximately three and four times the concentration in maternal plasma, respectively, suggesting a biphasic rate of distribution and elimination. Excluding the gastrointestinal tract, the highest percentage of the dose was found in the fetus, followed by amniotic fluid, maternal liver, and placenta, the percentages ranging from 6.52% to 2.41% of the administered dose. The metabolic profile of radioactivity and levels of parent DMF, *N*-(hydroxymethyl)-*N*-methylformamide (HMMF) and *N*-methylformamide (NMF) were generally the same in maternal plasma, placenta, amniotic fluid, and fetuses from dams dosed

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on GD 12 or GD 18. DMF levels were highest at 1 h postexposure, and HMMF and NMF were highest at 16 h postexposure. Negligible amounts of *N*-acetyl-*S*(*N*-methylcarbamoyl)cysteine (AMCC) and formamide were recovered. The authors concluded that DMF and its metabolites were transferred across the placenta by passive diffusion and that maternal plasma, embryo or fetus, placenta, and amniotic fluid belonged to the same compartment. Therefore, there is probably only minimal metabolic contribution, if any, of the placenta and fetus to metabolize DMF to HMMF, NMF, formamide, and AMCC. To assess the transfer of DMF into milk, lactating rats were dosed with ^{14}C-DMF on postpartum day 14, and milk was collected up to 24 h after dosing. The concentrations of DMF, HMMF, and NMF in the milk were similar to those measured in maternal plasma.

4.2. Metabolism

DMF is metabolized primarily by hydroxylation of its methyl groups, and hepatic cytochrome P450 2E1 (CYP2E1) is important in the metabolism of DMF in both rats and humans (Mraz et al. 1993; Amato et. al. 2001). The primary urinary metabolite of humans, monkeys, dogs, rats, and mice is HMMF, which can decompose to NMF and formamide (reviewed in Gescher 1993). Many of the early studies report that NMF, a potent rodent hepatotoxicant, was the major DMF metabolite recovered in urine. However, it has since been determined that the conditions used in those early gas-chromatographic analyses resulted in thermolytic degradation of the HMMF metabolite to NMF. Studies measuring plasma concentrations of DMF and its metabolites in monkeys, rats, and mice following acute inhalation exposure reported that both HMMF and NMF are recovered when appropriate methods are used, and the concentrations of each in relation to the other vary; however, HMMF was the primary urinary metabolite recovered (Hundley et al. 1993a,b).

HMFF and NMF can be further metabolized to formamide. Another pathway for metabolism is the oxidation of the formyl group to unidentified reactive intermediates, which appear responsible for hepatotoxicity. The reactive intermediates can be conjugated with glutathione to *S*-(*N*-methylcarbamoyl) glutathione (SMG), ultimately forming the urinary metabolite AMCC (Mraz and Turecek 1987; Mraz et al. 1989).

Metabolism of DMF is a saturable process. The plasma AUC values for DMF and the metabolites NMF and HMMF (combined) were calculated using biologic material taken from groups of two male and two female cynomolgus monkeys inhaling DMF at 30, 100, or 500 ppm for 6 h in the Hurtt et al. (1992) study (Hundley et al. 1993b) or from groups of four male Crl:CD^{7}BR rats and four male mice inhaling DMF at 10, 250, or 500 ppm for 1, 3, or 6 h (Hundley et al. 1993a). The DMF AUC in monkeys, rats, and mice increased disproportionately with exposure concentration; the DMF AUC increased 19- to 37-fold in male and 35- to 54-fold in female monkeys as the inhaled concentration in-

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creased 5-fold (from 100 to 500 ppm), and the plasma AUCs increased 8- and 29-fold in rats and mice, respectively, as exposure concentration doubled (from 250 ppm to 500 ppm). Correspondingly, there was no increase in the NMF and HMMF AUC at the same exposure concentrations in rats or mice, supporting the hypothesis that metabolic saturation occurred. Through in vitro work in rat liver microsomes, Mraz et al. (1993) found that DMF actually inhibits the oxidation of NMF to SMG; the inhibition appears to be primarily competitive.

Mraz et al. (1989) exposed 10 healthy volunteers (five males and five females, age 26-56 years) to air containing a measured concentration of DMF at 20 ppm (reported as 60 mg/m^3) for 8 h, and these investigators also gave male mice, rats, and hamsters DMF at 0.1, 0.7, or 7 mmol/kg of body weight via intraperitoneal injection. The absorbed dose by humans was one-half the lowest dose administered to the animals by injection. The major urinary metabolites recovered in humans over 72 h as a percentage of the administered dose were the following: 16-49% as HMMF, 8-24% as formamide (the precursor of which may be *N*-(hydroxymethyl)formamide (HMF) and 10-23% as AMCC. In rodents, the metabolites recovered in the urine expressed as a percentage of the administered dose were the following: 8-47% as HMMF, 8-38% as formamide, and 1-5% as AMCC. The authors concluded that "this is the first time that a quantitative difference has been observed in the metabolism of DMF between humans and rodents." However, it must be emphasized here that the rodents were exposed via parenteral injection route, and the rodents received a much higher bolus dose than humans.

Excretion of DMF and its metabolites was almost exclusively via the urine. Following a single 4-h exposure of volunteers to DMF at 26 ppm (four men, age 25-50 years) or 87 ppm (three men and one woman, age 20-50 years), Kimmerle and Eben (1975b) found that DMF metabolites (reported as "NMF") were detected in the urine following cessation of exposure, with approximately 50-70% of the metabolites recovered within 4 h postexposure. Formamide elimination was slightly delayed: Elimination occurred primarily 4-20 h postexposure, with significant amounts still detected 20-68 h postexposure. Low concentrations of unchanged DMF were found only in the urine of those exposed at 87 ppm. When volunteers (four men, age 25-50 years) were repeatedly exposed to DMF at 21 ppm for 4 h/day for 5 consecutive days, no accumulation of urinary metabolites was observed. Following each daily exposure, the DMF blood concentration decreased rapidly and was generally no longer detectable 4 h postexposure. Blood and urine analyses demonstrated that repeated exposure did not result in accumulation of the metabolite "NMF."

In a follow-up study, Mraz and Nohova (1992) exposed volunteers (five males and five females, age 25-56) to DMF at 3.3, 10, or 20 ppm for 8 h and measured urinary metabolites over 120 h postexposure. Maximal excretion occurred between 6 and 8 h for DMF and HMMF, between 8 and 14 h for HMF and between 24-34 h for AMCC. The corresponding elimination half-lives were 2, 4, 7, and 23 h, respectively. Urinary metabolites were still present 120 h after exposure at 20 ppm. Mraz et al. (1993) demonstrated that DMF inhibits

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CYP2E1 activity, thereby inhibiting its own metabolism. The authors propose that this inhibition could be the cause of the delayed urinary excretion of AMCC.

In comparing the metabolism of inhaled DMF following acute exposure in dogs and rats, Kimmerle and Eben (1975a) found species-specific differences in the time course of elimination. Groups of six male rats were exposed to DMF at 21, 146, or 2,005 ppm for 3 h or to 29 or 170 ppm for 6 h; two male dogs were exposed at 20 or 170 ppm for 6 h, and two female dogs were exposed at 31 or 134 ppm for 6 h. Although the chemical identity of the metabolites was no different between species, DMF metabolites were present longer in the blood and urine of dogs compared with rats. For example, following exposure at 170 ppm, metabolites were present in dog urine after 6 days, and DMF metabolites were found in rats only up to 24 h postexposure. A similar pattern was observed following exposure to DMF at 20 ppm. These differences in excretion might be related to body mass and metabolism rate: The smaller animals metabolize DMF at a higher rate and eliminated the chemical more quickly than larger animals.

4.2.1. Effect of CYP2E1 Polymorphisms on Metabolism

Nomiyama et al. (2001b) investigated human CYP2E1 *Pst*I/*Rsa*I polymorphism (CYP2E1*5B) in relation to urinary excretion of DMF and its metabolites. A group of 123 male Japanese workers were genotyped for CYP2E1. Of the 123 individuals, 77 were c1 homozygotes; 45 were c2 heterozygotes, and 1 was a c2 homozygote. From these individuals, 7, 5, and 1 of the c1 homozygotes, c2 heterozygotes, and c2 homozygote, respectively, were chosen for the exposure study. Volunteers were asked to refrain from drinking ethanol 24 h before or 72 h after exposure. Subjects were exposed once dermally to a vapor concentration of 6.2 ± 1.0 ppm and once via inhalation to 7.1 ± 1 ppm for a total of 8 h with at least 96 h separating the exposures. For the dermal exposure, 90% of the skin of the volunteers was exposed to vapors of DMF while the subjects sat in the exposure chamber and breathed fresh air through a respirator. During the inhalation exposure, the volunteers sat outside the exposure chamber and inhaled air containing DMF from the exposure chamber. Chamber DMF concentrations were monitored every 10 min using a gas chromatograph. Urine was collected up to 72 h postexposure. The half-lives of urinary NMF were assessed for the c1 homozygotes, c2 heterozygotes, and the c2 homozygote. Following dermal exposure, the urinary half-lives were 3.86 ± 1.90 h, 4.38 ± 1.53 h, and 4.20 h, respectively, and following respiratory exposure were 1.58 ± 0.42 h, 1.84 ± 0.61 h, and 3.20 h, respectively. No significant differences were noted. The authors noted that the urinary NMF half-life for the c2 homozygote following respiratory exposure was greater than the other two genotypes, but no rigorous conclusions could be drawn on the basis of only one data point.

Nomiyama et al. (2001a) investigated the effect of the insertion polymorphism of CYP2E1 (CYP2E1*1C does not have the insertion; CYP2E1*1D has

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the insertion) on the biotransformation of DMF and measured urinary NMF in Japanese workers following DMF exposure. It had been suggested that CYP2E1 polymorphism might be associated with up to a 3-fold increase in activity in obese people or after ethanol consumption (McCarver et al. 1998). The frequency of the insertion polymorphism ranges from 0.011 for the Swedish up to 0.389 in Pigmy populations, with Caucasians having a frequency of 0.02 to 0.034 (summarized by Nomiyama et al. 2001a). In the Nomiyama et al. (2001a) study, 22 subjects had the CYP2E1*1C/*1C genotype, 21 had the *1C/*1D genotype, and 1 had the *1D*/1D genotype, with an overall frequency of the insertion polymorphism of 0.261. The participating subjects wore diffusive passive samplers attached to their collars during the last 8-h work shift to assess breathing zone DMF concentrations, and urine was collected "just after" the work shift (no further details provided). Mean DMF exposure was 4.3, 1.8, and 21.9 ppm for the respective genotypes. The slope of the line correlating DMF exposure levels with NMF levels measured in the urine was comparable across all groups. A multivariate analysis investigating the interaction between the *D1 allele and obesity or ethanol intake failed to reveal any significant contributions to the variability of NMF values in urine. The authors concluded that the *D1 allele had no appreciable influence on the metabolism of inhaled DMF as assessed by measurement of urinary NFM concentrations.

4.3. Mechanism of Toxicity

The exact mechanism of DMF-induced hepatotoxicity is unknown, but the hepatotoxicity observed after repeated DMF exposure is related to its metabolites, as only those formamides and acetamides that undergo oxidation at their formyl moiety are hepatotoxic (Kestell et al. 1987). The identification of AMCC as a urinary metabolite following DMF exposure (Mraz et al. 1989) prompted the hypothesis that DMF is metabolized to a reactive intermediate responsible for the liver damage unless it is conjugated with thiol-containing molecules to form *N*-methylcarbamic acid thioesters (Gescher 1993; Mraz et al. 1993). The unidentified reactive intermediate(s) is (are) postulated to be formed during metabolism of NMF or HMMF to SMG. Because AMCC has also been identified as a metabolite of methyl isocyanate (MIC), it has been speculated that MIC might be a reactive intermediate in the disposition of DMF. Support that MIC might be a metabolite of DMF is found in the studies reporting identical hemoglobin (Hb) adducts (*N*-methylcarbamoylated valine-globin) in workers exposed to DMF and individuals exposed to MIC, as well as those derived from the in situ reaction between Hb and MIC (Angerer et al. 1998; Kafferlein and Angerer 2001). The identical Hb adduct has also been identified at much lower concentrations in blood from the general population, indicating the adduct is not unique to DMF or MIC exposure.

The precise mechanism of the disulfiram-like symptoms that occur with combined ethanol consumption and DMF exposure is not known. Disulfiram

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(Antabuse) has been used in treatment of alcoholism, where it inhibits aldehyde dehydrogenase, resulting in increasing circulating acetaldehyde (Hardman and Limbird 2001). Individuals treated with disulfiram who consume sufficient quantities of ethanol develop facial flushing, a pulsing headache, respiratory difficulties, nausea, vomiting, chest pain, hypotension, weakness, vertigo, and confusion. The facial flushing is then replaced by pallor, and blood pressure may plummet. Subjects exposed to DMF following ethanol consumption report face flushing, palpitation, headache, dizziness, body flushing, and tremors (Redlich et al. 1988; Fiorito et al. 1997; Wrbitzky 1999). Because DMF does not inhibit alcohol or aldehyde dehydrogenase in vitro, a metabolite of DMF might be responsible for the enzyme inactivation (Mraz et al. 1993).

4.4. Other Relevant Information

4.4.1. Species Variability

The mode of DMF-induced hepatotoxicity is thought to be related to the metabolism of DMF to reactive intermediates, and CYP2E1 plays a pivotal role in the metabolism of DMF (Mraz et al. 1993; Amato et al. 2001). Mraz et al. (1993) reported that the in vitro Michaelis constant (K_m) and the maximum rate of metabolism (V_{max}) values for CYP2E1 are comparable between human and rat liver (Table 1-11).

Despite the similar properties of hepatic CYP2E1 in rats and humans, it appears that there are species differences regarding the response to DMF exposure, rodents being more sensitive than primates. Monkeys inhaled DMF at 500 ppm for 6 h/day, 5 days/week, for up to 13 weeks with no measurable adverse effects (parameters examined include clinical signs, body weight, hematology and serum chemistry analyses, urinalysis, semen analysis, and gross necropsy findings) (Hurtt et al. 1991, 1992). In contrast, subchronic DMF inhalation exposure produced significant hepatic effects in rats at concentrations of 200 ppm (Senoh et al. 2003), 300 ppm (Craig et al. 1984), and 400 ppm (NTP 1992) and in mice at 100 ppm (Senoh et al. 2003), 150 ppm (Craig et al. 1984), and 200 ppm (NTP 1992). Indexes of toxicity after repeated DMF exposure ranged from elevated serum enzymes indicative of liver injury to hepatic degeneration and necrosis. Because humans are more similar to primates than to rodents, humans are expected to be less sensitive than laboratory animals (rodents).

4.4.2. Susceptible Subpopulations

Interindividual differences could affect the manifestation of DMF toxicity. First, CYP2E1 activity can be induced by moderate ethanol consumption, obesity, and diabetes (Gonzalez 1990; Song et al. 1990; Lucas et al. 1998; McCarver et al. 1998). Increased CYP2E1 levels could increase generation of

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TABLE 1-11 Rat and Human Liver Microsome Kinetic Parameters for Metabolic Oxidation of Formamides

		Apparent K_m (mM)		Apparent $V_{max,}$ Nmol/(mg of microsomal protein)/min	
Substrate	Product	Rat	Human	Rat	Human
DMF[a]	HMMF	0.20 ± 0.06	0.12 ± 0.06	0.54 ± 0.20	0.57 ± 0.49
NMF[b]	SMG	4.28 ± 1.35	3.92 ± 2.11	0.34 ± 0.08	0.24 ± 0.17
HMMF[b]	SMG	2.52 ± 0.34	1.25	0.016 ± 0.005	0.033

[a]Substrate concentration range: 0.02-5 mM.
[b]Substrate concentration range: 0.4-10 mM.
Abbreviations: DMF, dimethylformamide; HMMF, *N*-(hydroxymethyl)-*N*-methylformamide; NMF, *N*-methylformamide; SMG, *S*-(*N*-methylcarbamoyl)glutathione.
Source: Mraz et al. 1993. Reprinted with permission; copyright 1993, *Chemical Research in Toxicology*.

the metabolites of DMF. Second, ethanol consumption prior to DMF exposure results in disulfiram-type reactions. Third, detoxification of the reactive intermediate is partly dependent on conjugation with glutathione. If glutathione levels are depleted, the potential exists for greater exposure to the reactive intermediates. Last, because repeated DMF exposure has produced hepatotoxicity in exposed workers (Kennedy 1986; Scailteur and Lauwreys 1987), individuals with compromised liver function or prior DMF contact may be at an increased risk.

4.4.3. Concentration–Exposure-Duration Relationship

Experimentally derived exposure values are scaled to AEGL time frames using the concentration-time relationship given by the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 1 to 3.5 (ten Berge et al. 1986). The value of n could not be empirically derived due to inadequate data; therefore, the default value of n = 1 was used for extrapolating from shorter to longer exposure periods, and a value of n = 3 was used to extrapolate from longer to shorter exposure periods.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

The controlled human exposures in which the metabolism of DMF was investigated were not designed to assess the toxicity of DMF exposure (Kimmerle and Eben 1975b; Mraz et al. 1989; Mraz and Nohova 1992). It is not clear whether any symptoms, including irritation, were present.

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5.2. Summary of Animal Data Relevant to AEGL-1

No animal data were found that were relevant to derivation of an AEGL-1.

5.3. Derivation of AEGL-1

An AEGL-1 is not recommended because an appropriate AEGL-1 end point was not noted in any of the available studies (Table 1-12).

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No human data relevant to derivation of an AEGL-2 were available.

6.2. Summary of Animal Data Relevant to AEGL-2

In a developmental toxicity study, groups of 15 pregnant Himalayan rabbits were exposed to DMF at 0, 50, 150, or 450 ppm for 6 h/day on GD 7-19 (Hellwig et al. 1991). Over GD 7-19, mean maternal body-weight gain was reduced in dams exposed at 150 ppm compared with controls, while dams in the 450-ppm group lost weight. Mean maternal body-weight gain over the entire study period of GD 0-29 was also decreased in dams from the 150- and 450-ppm DMF groups compared with controls. Developmental toxicity was evident at 450 ppm as increases in external malformations and total malformations (external, soft tissue, and skeletal combined). Other effects included a reduction in fetal weight (86% of controls), and statistically significant increases in the litter incidence of skeletal variations, including splitting of skull bones, fused sternebrae, irregular shaped sternebrae, and bipartite sternebrae. An increase in fetal deaths did not occur. No developmental effects were observed at 150 ppm.

TABLE 1-12 AEGL-1 Values for DMF[a]

10 min	30 min	1 h	4 h	8 h
NR[b]	NR	NR	NR	NR

[a]There is a high potential for DMF to be absorbed dermally, so this route of exposure should be considered along with inhalation.
[b]Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.
Abbreviation: NR, not recommended.

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6.3. Derivation of AEGL-2

The AEGL-2 derivation was based on the study in which groups of 15 pregnant Himalayan rabbits were exposed to DMF at 0, 50, 150, or 450 ppm for 6 h/day on GD 7-19 (Hellwig et al. 1991). Over GD 7-19, mean maternal body-weight gain was reduced in dams exposed at 150 ppm compared with controls, while dams in the 450-ppm group lost weight; mean maternal body-weight gain over the entire study period of GD 0-29 was also decreased in dams from the 150- and 450-ppm DMF groups compared with controls. Developmental toxicity was evident at 450 ppm as increases in external malformations and total malformations (external, soft tissue, and skeletal combined). Other effects included a reduction in fetal weight (86% of controls), and statistically significant increases in the litter incidence of skeletal variations, including splitting of skull bones, fused sternebrae, irregular shaped sternebrae, and bipartite sternebrae. An increase in fetal deaths did not occur. No developmental effects were observed at 150 ppm. To protect against irreversible developmental effects (malformations), the rabbit NOAEL of 150 ppm for 6 h was used as the point of departure for derivation of AEGL-2 values (Hellwig et al. 1991).

A total uncertainty factor of 3 was applied to the point of departure of 150 ppm for 6 h: 1 for interspecies variability and 3 for intraspecies variability. An interspecies uncertainty factor of 1 was applied because it appears that primates are not as sensitive as rodents. Monkeys inhaled DMF at 500 ppm for 6 h/day, 5 days/week, for up to 13 weeks with no measurable adverse effects (parameters examined included clinical signs, body weight, hematology and serum chemistry analyses, urinalysis, semen analysis, and gross necropsy findings). In contrast, subchronic DMF inhalation exposure produced significant hepatic effects in rats at concentrations of 200 ppm (Senoh et al. 2003), 300 ppm (Craig et al. 1984), and 400 ppm (NTP 1992) and in mice at 100 ppm (Senoh et al. 2003), 150 ppm (Craig et al. 1984), and 200 ppm (NTP 1992). Indexes of toxicity after repeated DMF exposure ranged from elevated serum enzymes indicative of liver injury to hepatic degeneration and necrosis. From these exposure data, humans are expected to be less sensitive than laboratory animals (rodents). Because the mechanism of hepatotoxicity is thought to be related to the metabolism of DMF to a reactive intermediate, fetal toxicity is expected to result from exposure to the parent DMF or metabolites. An oral study assessing the tissue and metabolite distribution of DMF in pregnant rats indicated that DMF and its metabolites were transferred across the placenta by passive diffusion and that maternal plasma, embryo or fetus, placenta, and amniotic fluid belonged to the same compartment (Saillenfait et al. 1997). Therefore, the fetus and placenta will not provide any additional protection or enhancement of DMF toxicity because exposure to DMF and its metabolites will depend on the metabolism by the mother. An intraspecies uncertainty factor of 10 would normally be applied because a host of interindividual differences could affect the manifestation of DMF toxicity: (1) activity of CYP2E1, an enzyme that plays a pivotal role in the metabolism of DMF to reactive intermediates, can be induced by ethanol con-

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sumption, obesity, diabetes, and other lifestyle and genetic factors (Gonzalez 1990; Song et al. 1990; Lucas et al. 1998; McCarver et al. 1998), and increased CYP2E1 levels increase the toxic metabolites of DMF; (2) prior consumption of ethanol can exacerbate DMF toxicity in individuals; (3) on the basis of the proposed mechanism of action, detoxification of the reactive intermediate is partly dependent on conjugation with glutathione; therefore, if glutathione levels are depleted for other reasons, the potential exists for greater exposure to the reactive intermediate; and (4) because DMF exposure can result in hepatotoxicity, those individuals with chronic liver disease may be at increased risk.

Application of a total uncertainty factor of 10 produces AEGL-2 values that are inconsistent with the available human data (values for the 10-min, 30-min, 1-h, 4-h, and 8-h AEGL-2 using default time-scaling would be 49, 34, 27, 17, and 11 ppm, respectively). Humans were exposed by inhalation to DMF at 87 ppm for 4 h or at 81 ppm for 2 h to assess the metabolism of DMF (Kimmerle and Eben 1975b; Eben and Kimmerle 1976). Although these single exposure studies were conducted to assess DMF metabolism, no adverse effects were reported, and the concentration can be considered an acute exposure concentration unlikely to result in adverse effects in healthy adults. Therefore, the intraspecies uncertainty factor is reduced to 3, resulting in a total uncertainty factor of 3.

The experimentally derived exposure value is scaled to AEGL time frames using the concentration-time relationship given by the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 1 to 3.5 (ten Berge et al. 1986). The value of n was not empirically derived because of inadequate data; therefore, the default value of n = 1 was used for extrapolating from shorter to longer exposure periods and a value of n = 3 was used to extrapolate from longer to shorter exposure periods. The 30-min AEGL-2 value was set equal to the 10-min value because of the uncertainty in extrapolating from a 6-h exposure duration to a 10-min duration.

The AEGL-2 values are presented in Table 1-13.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human data relevant to derivation of an AEGL -3 were available.

7.2. Summary of Animal Data Relevant to AEGL-3

Groups of six rats (three male and three female) survived a 1- or 3-h exposure to 3,700 ppm, while exposure for 7 h resulted in mortality in two of three males and three of three females (Shell Oil Company 1982). Mortality occurred 2 or 3 days postexposure. Although no mortality was observed in groups of 10

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TABLE 1-13 AEGL-2 Values for DMF[a]

10 min	30 min	1 h	4 h	8 h
110 ppm (330mg/m^3)	110 ppm (330 mg/m^3)	91 ppm (270 mg/m^3)	57 ppm (170 mg/m^3)	38 ppm (110 mg/m^3)

[a]There is a high potential for DMF to be absorbed dermally, so this route of exposure should be considered along with inhalation.

female rats exposed at 5,000 ppm for 4 or 8 h, animals were observed for only 24 h for mortality (Lundberg et al. 1986). Stasenkova (1961) reported a NOEL for mortality of 670 ppm and a LOEL of 1,300 ppm in mice exposed to DMF for 2 h. A corresponding LC_{50} of 3,981 ppm was calculated by the reviewer. The reported exposure concentrations in the Stasenkova study are not deemed reliable because the highest reported exposure concentration was 7,700 ppm, well above the saturation point for this chemical.

7.3. Derivation of AEGL-3

The AEGL-3 derivation was based on the study in which groups of three male and three female rats were exposed to DMF at 3,700 ppm for 1 or 3 h; no mortality occurred, but exposure for 7 h resulted in 83% mortality (Shell Oil Company 1982). Clinical signs were limited to excess grooming in all exposure groups; lethargy was noted in rats exposed for 7 h. The end point of no mortality in rats exposed at 3,700 ppm for 3 h was chosen for the derivation.

A total uncertainty factor of 10 was applied to the point of departure for the AEGL-3: 1 for interspecies variability and 10 for intraspecies variability. The total uncertainty factor of 10 should protect against all but hypersensitive human hepatotoxic effects. An interspecies uncertainty factor of 1 was applied because it appears that primates are not as sensitive as rodents. Monkeys inhaled DMF at 500 ppm for 6 h/day, 5 days/week, for up to 13 weeks with no measurable adverse effects (parameters examined included clinical signs, body weight, hematology and serum chemistry analyses, urinalysis, semen analysis, and gross necropsy findings). In contrast, subchronic DMF inhalation exposure produced significant hepatic effects in rats at concentrations of 200 ppm (Senoh et al. 2003), 300 ppm (Craig et al. 1984), and 400 ppm (NTP 1992) and in mice at 100 ppm (Senoh et al. 2003), 150 ppm (Craig et al. 1984), and 200 ppm (NTP 1992). Indexes of toxicity after repeated DMF exposure ranged from elevated serum enzymes indicative of liver injury to hepatic degeneration and necrosis. From these exposure data, humans are expected to be less sensitive than laboratory animals (rodents). An intraspecies uncertainty factor of 10 is applied because a host of interindividual differences could affect the manifestation of DMF toxicity: (1) activity of CYP2E1, an enzyme that plays a pivotal role in the metabolism of DMF to reactive intermediates, can be induced by ethanol consumption,

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obesity, diabetes, and other lifestyle and genetic factors (Gonzalez 1990; Song et al. 1990; Lucas et al. 1998; McCarver et al. 1998), and increased CYP2E1 levels increase the toxic metabolites of DMF; (2) prior consumption of ethanol can exacerbate DMF toxicity in individuals; (3) on the basis of the proposed mechanism of action, detoxification of the reactive intermediate is partly dependent upon conjugation with glutathione; therefore, if glutathione levels are depleted for other reasons, the potential exists for greater exposure to the reactive intermediate; and (4) because DMF exposure can result in hepatotoxicity, those individuals with chronic liver disease may be at increased risk. Therefore, a total uncertainty factor of 10 is applied.

The experimentally derived exposure value is scaled to AEGL time frames using the concentration-time relationship given by the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 1 to 3.5 (ten Berge et al. 1986). The value of n was not empirically derived because of inadequate data; therefore, the default value of n = 1 was used for extrapolating from shorter to longer exposure periods, and a value of n = 3 was used to extrapolate from longer to shorter exposure periods.

AEGL-3 values are presented in Table 1-14.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

The AEGL values for DMF are summarized in Table 1-15. An AEGL-1 is not recommended on the basis of inadequate data. The AEGL-2 was based on a NOAEL for irreversible developmental effects (malformations) in rabbits. The AEGL-3 was based on the highest concentration and longest exposure duration causing no mortality in rats.

A useful way to evaluate the AEGL values in context of existing empirical data is presented in Figure 1-1. For this plot, the toxic response was placed into severity categories. The severity categories fit into definitions of the AEGL health effects: no effects, discomfort, disabling, lethal, and partially lethal (an experimental concentration at which some of the animals died and some did not). The effects that place an experimental result into a particular category vary according to the spectrum of data available on a specific chemical and the effects from exposure to that chemical. The doses often span a number of orders of magnitude, especially when human data exist. Therefore, the concentration is placed on a log scale. The graph in Figure 1-1 plots the DMF AEGL values along with the existing acute human and animal toxicity data for DMF in terms of the categories assigned to them. From this plot, it is apparent that the AEGL values are below any exposure concentration in animals resulting in any effects and should therefore be protective of human health.

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TABLE 1-14 AEGL-3 Values for DMF[a]

10 min	30 min	1 h	4 h	8 h
970 ppm (2,900 mg/m^3)	670 ppm (2,000 mg/m^3)	530 ppm (1,600 mg/m^3)	280 ppm (840 mg/m^3)	140 ppm (420mg/m^3)

[a]There is a high potential for DMF to be absorbed dermally, so this route of exposure should be considered along with inhalation.

TABLE 1-15 Summary of AEGL Values for DMF[a]

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR[a]	NR	NR	NR	NR
AEGL-2 (disabling)	110 ppm (330 m^3)	110 ppm (330 m^3)	91 ppm (270m^3)	57 ppm (170 m^3)	38 ppm (110 m^3)
AEGL-3 (lethal)	970 ppm (2,900 m^3)	670 ppm (2,000 m^3)	530 ppm (1,600 m^3)	280 ppm (840 m^3)	140 ppm (420 m^3)

[a]There is a high potential for DMF to be absorbed dermally, so this route of exposure should be considered along with inhalation.
[b]NR, not recommended. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

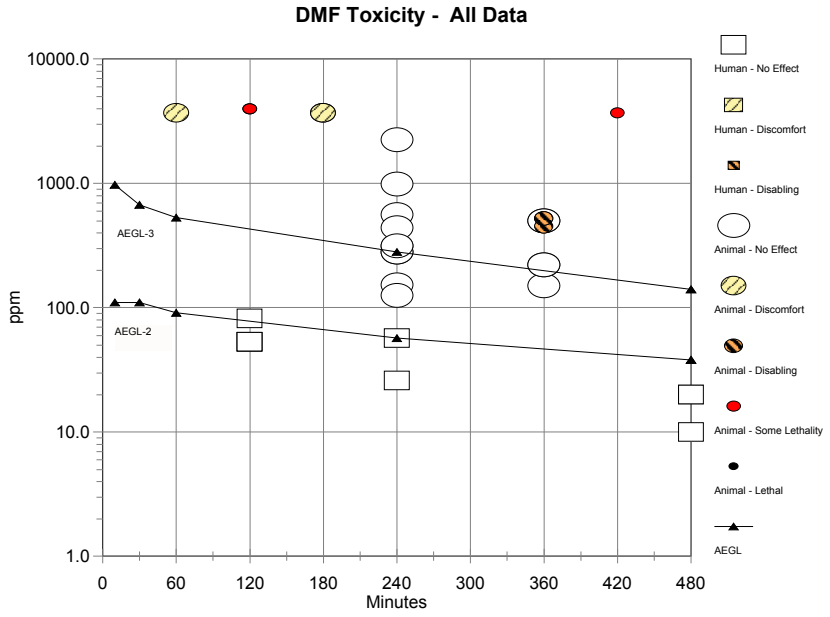

FIGURE 1-1 Category plot of animal toxicity data compared with AEGL values.

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8.2. Comparison with Other Standards and Guidelines

Standards and guidelines for short-term exposures are listed in Table 1-16. The 1-h AEGL-2 values are comparable to the ERPG-2, while the AEGL-3 values are above the ERPG-3. The 30-min AEGL-3 is above the IDLH. Occupational workplace standards lie below the 8-h AEGL-2 levels.

TABLE 1-16 Extant Standards and Guidelines for DMF

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	110 ppm	110 ppm	91 ppm	57 ppm	38 ppm
AEGL-3	970 ppm	670 ppm	530 ppm	280 ppm	140 ppm
ERPG-1 (AIHA)[a]			2 ppm		
ERPG-2 (AIHA)			100 ppm		
ERPG-3 (AIHA)			200 ppm		
IDLH (NIOSH)[b]		500 ppm			
TLV-TWA (ACGIH)[c]					10 ppm
PEL-TWA (OSHA)[d]					10 ppm (30 mg/m^3)
REL-TWA (NIOSH)[e]					10 ppm
MAK (Germany)[f]					10 ppm (30 mg/m^3)
MAC (The Netherlands)[g]					5 ppm (15 mg/m^3)

[a]ERPG (emergency response planning guidelines, American Industrial Hygiene Association, AIHA 2002).
The ERPG-1 is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 h without experiencing effects other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. An ERPG-1 for DMF was based on the approximate geometric mean of the odor threshold data. The ERPG-2 is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action. The ERPG-2 for DMF is based primarily on human experience in which volunteers were exposed to concentrations up to 87 ppm for 4 h with no reported adverse effects (Kimmerle and Eben 1975b). The ERPG-3 is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects. The ERPG-3 for DMF is based on animal data (2-h mouse LC_{50} calculated to be 3,140 ppm) in addition to reports of irritation in workers and of high concentrations and the fact that some members or the community might be more susceptible to DMF.

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[b]IDLH (immediately dangerous to life or health, National Institute for Occupational Safety and Health, NIOSH 1996) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms or any irreversible health effects. The IDLH for DMF is based on acute inhalation toxicity data in animals (Stasenkova 1961).
[c]TLV-TWA (Threshold Limit Value-time-weighted average, American Conference of Governmental Industrial Hygienists, ACGIH 2009) is the TWA concentration for a normal 8-h work day and a 40-h work week to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. DMF has an adopted urinary Biological Exposure Index (*N*-methylformamide at 15 mg/L at end of shift and *N*-acetyl-*S*-(*N*-methylcarbamoyl cysteine) at 40 mg/L prior to last shift of the last work week). DMF is among the chemical substances currently under study for possible revision.
[d]PEL-TWA (permissible exposure limits - time-weighted average, Occupational Health and Safety Administration, OSHA 29 CFR 1910.1000 [1999]) is analogous to the ACGIH TLV-TWA but is for exposures of no more than 10 h/day, 40 h/week.
[e]REL-TWA (recommended exposure limit-time-weighted average, National Institute for Occupational Safety and Health, NIOSH 2005) is analogous to the ACGIH TLV-TWA.
[f]MAK (maximale Arbeitsplatzkonzentration [maximum workplace concentration], Deutsche Forschungsgemeinschaft [German Research Association], DFG 2002) is analogous to the ACGIH TLV-TWA.
[g]MAC (maximaal aanvaarde concentratie [maximum accepted concentration], Dutch Expert Committee for Occupational Standards, The Netherlands, (MSZW 2004) is analogous to the ACGIH TLV-TWA.

8.3. Data Quality and Research Needs

Quality data for derivation of the AEGL values were very limited, and data meeting the definition of AEGL-1 end points were not available. Nonlethal acute inhalation effects in animals were limited to measurements of alterations in liver enzymes; livers from animals subjected to a single exposure were not examined histologically. Histologic analyses of tissues from animals that died following acute DMF exposure were generally not available. Studies addressing the acute lethal and nonlethal toxicity of inhaled DMF over exposure durations of 10 min up to 8 h would be useful to further elucidate the health effects.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR *N,N*-DIMETHYLFORMAMIDE

Derivation of AEGL-1 Values

An AEGL-1 value was not derived because it was not appropriate. No data pertaining to end points relevant to the AEGL-1 definition were available. 10- and 30-min and 1-, 4-, and 8-h AEGL-1: not recommended.

Derivation of AEGL-2 Values

Key studies:	Hellwig et al. 1991; BASF 1989
Toxicity end points:	No developmental effects seen in rabbits exposed to 150 ppm for 6 h; exposure at 450 ppm for 6 h resulted in irreversible developmental effects (malformations)
Time-scaling:	$C^n \times t = k$ (default of n = 3 for longer to shorter exposure periods; n = 1 for shorter to longer exposure periods) $[(150 \text{ ppm})/3]^1 \times 6 \text{ h} = 300 \text{ ppm-h}$ $[(150 \text{ ppm})/3]^3 \times 6 \text{ h} = 750{,}000 \text{ ppm-h}$
Uncertainty factors:	1 for interspecies variability 3 for intraspecies variability Combined uncertainty factor of 3
Modifying factor:	Not applicable
Calculations:	
10-min AEGL-2:	Set equal to 30-min value due to uncertainty in extrapolating from 6 h exposure duration to 10 min
30-min AEGL-2:	$C^3 \times 0.5 \text{ h} = 750{,}000 \text{ ppm-h}$ $C^3 = 1{,}500{,}000 \text{ ppm}$ $C = 114 \text{ ppm} = 110 \text{ ppm}$
1-h AEGL-2:	$C^3 \times 1 \text{ h} = 750{,}000 \text{ ppm-h}$ $C^3 = 91 \text{ ppm}$
4-h AEGL-2:	$C^3 \times 4 \text{ h} = 750{,}000 \text{ ppm-h}$ $C^2 = 187{,}500 \text{ ppm}$ $C = 57 \text{ ppm}$

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8-h AEGL-2: $C^1 \times 8$ h = 300 ppm-h
C^1 = 37.5 ppm
C = 38 ppm

Derivation of AEGL-3 Values

Key studies: Shell Oil Company 1982

Toxicity end points: Goup of three male and three female rats survived a 3-h exposure to DMF at
3,700 ppm

Time-scaling: $C^n \times t = k$ (default of n = 3 for longer to shorter exposure periods; n = 1 for shorter to longer exposure periods)
$[(3{,}700 \text{ ppm})/10]^1 \times 3$ h = 1,110 ppm-h
$[(3{,}700 \text{ ppm})/10]^3 \times 3$ h = 151,959,000 ppm-h

Uncertainty factors: 1 for interspecies variability
10 for intraspecies variability
Combined uncertainty factor of 10

Modifying factor: Not applicable

Calculations:

10-min AEGL-3: $C^3 \times 0.167$ = 151,959,000 ppm-h
C^3 = 909,934,132 ppm
C = 969 ppm = 970 ppm

30-min AEGL-3: $C^3 \times 0.5$ = 151,959,000 ppm-h
C^3 = 303,918,000 ppm
C = 672 ppm = 670 ppm

1-h AEGL-3: $C^3 \times 1$ h = 151,959,000 ppm-h
C^3 = 151,959,000 ppm
C = 534 ppm = 530 ppm

4-h AEGL-3: $C^1 \times 4$ h = 1,110 ppm-h
C^1 = 277.5 ppm
C = 280 ppm

8-h AEGL-3: $C^1 \times 8$ h = 1,110 ppm-h
C^1 = 138.8 ppm
C = 140 ppm

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APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR *N,N*-DIMETHYLFORMAMIDE

Derivation Summary *N,N*-Dimethylformamide

AEGL-1 VALUES

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

Reference: Not applicable

Test species/Strain/Number: Not applicable

Exposure route/Concentrations/Durations: Not applicable

Effects: Not applicable

End point/Concentration/Rationale: Not applicable

Uncertainty factors/Rationale: Not applicable

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time-scaling: Not applicable

Data adequacy: No human or animal data pertaining to end points relevant to the AEGL-1 definition were available. Absence of an AEGL-1 does not imply that exposures below the AEGL-2 values are without adverse effects.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
110 ppm	110 ppm	91 ppm	57 ppm	38 ppm

Key references:
Hellwig, J., J. Merkle, H.J. Klimisch, and R. Jackh. 1991. Studies on the prenatal toxicity of *N,N*-dimethylformamide in mice, rats and rabbits. Food Chem. Toxicol. 29(3):193-201.
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Test species/Strain/Number: 15 Himalayan rabbits per group

Exposure route/Concentrations/Durations: Inhaled DMF at 0, 50, 150, or 450 ppm for 6 h/d over GD 7-19

(Continued)

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AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
110 ppm	110 ppm	91 ppm	57 ppm	38 ppm

Effects: (1) Maternal toxicity evident at 150 and 450 ppm as decreased body-weight gain or weight loss over GD 7-19 and GD 0-29. (2) Developmental toxicity evident at 450 ppm as increase in external malformations and total malformations (external, soft tissue, and skeletal combined), as decrease in fetal weight (86% of controls), and as increase in litter incidence of skeletal variations (splitting of skull bones; fused, irregular shaped, and bipartite sternebrae). No developmental effects were observed at 150 ppm.

End point/Concentration/Rationale: 150 ppm for 6 h to protect against irreversible developmental effects (malformations)

Uncertainty factors/Rationale:
Total uncertainty factor: 3

Interspecies: 1was applied because it appears that primates are not as sensitive as rodents. Monkeys inhaled DMF at 500 ppm for 6 h/d, 5 d/wk, for up to 13 weeks with no measurable adverse effects. In contrast, subchronic DMF inhalation exposure produced significant hepatic effects in rats at concentrations of 200 ppm (Senoh et al. 2003), 300 ppm (Craig et al. 1984) and 400 ppm (NTP 1992) and in mice at 100 ppm (Senoh et al. 2003), 150 ppm (Craig et al. 1984), and 200 ppm (NTP 1992). Indexes of toxicity after repeated DMF exposure ranged from elevated serum enzymes indicative of liver injury to hepatic degeneration and necrosis. From these exposure data, humans are expected to be less sensitive than laboratory animals (rodents). Because the mechanism of hepatotoxicity is thought to be related to the metabolism of DMF to a reactive intermediate, fetal toxicity is expected to result from exposure to the parent DMF or metabolites. An oral study assessing the tissue and metabolite distribution of DMF in pregnant rats indicated that DMF and its metabolites were transferred across the placenta by passive diffusion and that maternal plasma, embryo or fetus, placenta, and amniotic fluid belonged to the same compartment (Saillenfait et al. 1997). Therefore, the fetus and placenta will not provide any additional protection or enhancement of DMF toxicity because exposure to DMF and its metabolites will depend on the metabolism by the mother.

Intraspecies: 3, an intraspecies uncertainty factor of 10 would normally be applied because a host of interindividual differences could affect the manifestation of DMF toxicity: (1) activity of CYP2E1, an enzyme that plays a pivotal role in the metabolism of DMF to reactive intermediates, can be induced by ethanol consumption, obesity, diabetes, and other lifestyle and genetic factors (Gonzalez 1990; Song et al. 1990; Lucas et al. 1998; McCarver et al. 1998), and increased CYP2E1 levels increase the toxic metabolites of DMF;(2) prior consumption of ethanol can exacerbate DMF toxicity in individuals; (3) on the basis of the proposed mechanism of action, detoxification of the reactive intermediate is partly dependent on conjugation with glutathione; therefore, if glutathione levels are depleted for other reasons, the potential exists for greater exposure to the reactive

(Continued)

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AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
110 ppm	110 ppm	91 ppm	57 ppm	38 ppm

intermediate; (4) because DMF exposure can result in hepatotoxicity, individuals with chronic liver disease may be at increased risk. However, application of a total uncertainty factor of 10 produces AEGL-2 values that are inconsistent with the available human data (values for the 10- and 30-min and1-, 4-, and 8-h AEGL-2 using default time-scaling would be 49, 34, 27, 17, and 11 ppm, respectively). Humans were exposed by inhalation of DMF at 87 ppm for 4 h or at 81 ppm for 2 h to assess the metabolism of DMF (Kimmerle and Eben 1975b; Eben and Kimmerle 1976). These single-exposure studies were conducted to assess DMF metabolism, and no adverse effects were reported; the concentration can be considered an acute exposure concentration unlikely to result in adverse effects in healthy adults. Therefore, the intraspecies uncertainty factor is reduced to 3.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time-scaling: Default time-scaling using n = 3, 1. The 30-min AEGL-2 value was set equal to the 10-min value because of the uncertainty in extrapolating from a 6-h exposure duration to a 10-min duration.

Data quality and support for the AEGL values: Data meeting the definition of an AEGL-2 end point were limited to developmental toxicity studies. Other nonlethal acute health effects in animals were limited to alterations in liver enzymes because livers from animals following a single exposure were not examined histologically. Histologic analysis of tissues from animals that died following acute exposure was not available to determine the cause of death.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
970 ppm	670 ppm	530 ppm	280 ppm	140 ppm

Key reference: Shell Oil Company. 1982. Test Standardization: Inhalation Toxicity Testing of 8 Chemicals According to the OECD Inhalation Hazard Test. EPA Document No. 878212113. Microfiche No. OTS0205969. U.S. Environmental Protection Agency, Washington, DC

Test species/Strain/Number: groups of three male and three female Wistar rats

Exposure route/Concentrations/Durations: exposed to 3,700 ppm DMF for 1, 3, or 7 h and observed for mortality for 14 days postexposure

Effects: 1- or 3-h exposure at 3,700 ppm, no mortality; 7-h exposure at 3,700 ppm, killed 2/3 males and 3/3 females

End point/Concentration/Rationale: exposure for 3 h to 3,700 ppm did not result in mortality

(Continued)

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AEGL-3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
970 ppm	670 ppm	530 ppm	280 ppm	140 ppm

Uncertainty factors/Rationale:
Total uncertainty factor: 10

Interspecies: 1 was applied because it appears that primates are not as sensitive as rodents. Monkeys inhaled DMF at 500 ppm for 6 h/d, 5 d/wk, for up to 13 weeks with no measurable adverse effects. In contrast, subchronic DMF inhalation exposure produced significant hepatic effects in rats at concentrations of 200 ppm (Senoh et al. 2003), 300 ppm (Craig et al. 1984), and 400 ppm (NTP 1992) and in mice at 100 ppm (Senoh et al. 2003), 150 ppm (Craig et al. 1984), and 200 ppm (NTP 1992). Indexes of toxicity after repeated DMF exposure ranged from elevated serum enzymes indicative of liver injury to hepatic degeneration and necrosis. From these exposure data, humans are expected to be less sensitive than laboratory animals (rodents). Because the mechanism of hepatotoxicity is thought to be related to the metabolism of DMF to a reactive intermediate, fetal toxicity is expected to result from exposure to the parent DMF or metabolites. An oral study assessing the tissue and metabolite distribution of DMF in pregnant rats indicated that DMF and its metabolites were transferred across the placenta by passive diffusion and that maternal plasma, embryo or fetus, placenta, and amniotic fluid belonged to the same compartment (Saillenfait et al. 1997). Therefore, the fetus and placenta will not provide any additional protection or enhancement of DMF toxicity because exposure to DMF and its metabolites will depend on the metabolism by the mother.

Intraspecies: 10 was applied because a host of interindividual differences could affect the manifestation of DMF toxicity: (1) activity of CYP2E1, an enzyme that plays a pivotal role in the metabolism of DMF to reactive intermediates, can be induced by ethanol consumption, obesity, diabetes, and other lifestyle and genetic factors (Gonzalez 1990; Song et al. 1990; Lucas et al. 1998; McCarver et al. 1998), and increased CYP2E1 levels increase the toxic metabolites of DMF; (2) prior consumption of ethanol can exacerbate DMF toxicity in individuals; (3) on the basis of the proposed mechanism of action, detoxification of the reactive intermediate is partly dependent on conjugation with glutathione; therefore, if glutathione levels are depleted for other reasons, the potential exists for greater exposure to the reactive intermediate; and (4) because DMF exposure can result in hepatotoxicity, individuals with chronic liver disease may be at increased risk.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time-scaling: Default time-scaling using n = 3, 1

Data quality and support for the AEGL values: Quality data for derivation of the AEGL-3 value were sparse. The AEGL-3 level is based on a study in which groups of only 3 rats of each sex were used, as opposed to 10 animals per group. The other studies investigating lethality following acute exposure to DMF did not observe animals for 14 days postexposure and did not report reliable exposure concentrations. However, the lethality data provided in the key study is consistent with the weight of evidence.

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2

Jet Propellant Fuels 5 and 8[1]

Acute Exposure Guideline Levels

PREFACE

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

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory

[1]This document was prepared by the AEGL Development Team composed of Sylvia Talmage (Summitec Corporation) and John Hinz (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances. The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

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effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

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

SUMMARY

Jet propellant (JP) fuels, used in military and civilian aircraft, are complex mixtures of aliphatic and aromatic hydrocarbons made by blending various distillate stocks of petroleum. The primary military fuel for land-based military aircraft is JP-8; this fuel replaces JP-4, which is no longer in use. JP-5 was developed by the U.S. Navy for shipboard service. The composition of JP-8 and JP-5 is basically that of kerosene (with additives), and they have similar chemical and physical characteristics (ATSDR 1998). Worldwide, approximately 60 billion gallons of military JP-8 and the equivalent commercial Jet A and Jet A-1 are consumed on an annual basis. The military jet fuels contain additives that are not found in commercial jet fuels. Civilian and military personnel may be exposed to jet fuels during fuel production, aircraft fueling, aircraft maintenance, and accidental spills or pipeline leaks. The primary hazard associated with release of jet fuels is fire and explosion.

This document focuses on the toxicity of JP-8 with some attention to the chemically similar JP-5. These two fuels have a similar composition and appear to have similar toxicities (ATSDR 1998). Monitoring data indicate that exposures to JP-4, which has a higher vapor pressure than JP-8 and JP-5, were higher than those associated with JP-8 and JP-5. Data were located on acute sensory and systemic effects of JP-8 and JP-5 in mice and rats; subchronic toxicity studies have addressed systemic and pulmonary toxicity. For both fuels, eye irrita-

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tion was observed at concentrations of ≥ 2,500 mg/m^3. Mild skin irritation was observed after direct topical application. Several short-term and repeated exposure studies addressed the toxicity of jet fuel aerosols. Exposure to aerosolized jet fuels was associated with enhanced toxicity compared with equivalent exposure to fuel vapors, the lungs and immune system being the target organs. However, emergency exposures are expected to be in the form of vapor exposures that result from spills, whereas aerosols are relevant only to occupational exposures during aircraft-foam removal operations or aircraft cold starts. Studies that addressed the toxicity of jet fuel only in the aerosolized form were not used to derive AEGL values (Martin et al. 2010; Tremblay et al. 2010). The data collected during aerosol inhalation studies are included in this technical support document (TSD) for completeness. Animal studies also examined potential neurotoxicity, developmental and reproductive toxicity, and carcinogenicity. The JP fuels are not considered genotoxic or carcinogenic and, in a preliminary study, JP-8 failed to cause spermatotoxic effects in humans. A characteristic nephropathy and resulting renal cancer, specific to male rats exposed to jet fuels, is not relevant to humans. Concentrations of jet fuels of ≥ 2,500 mg/m^3 also induce central nervous system (CNS) depression. Many of the components of jet fuels are lipophilic solvents. In general, the lipophilic solvents that induce CNS depression attain steady state in the blood within an hour.

The AEGL-1 was based on the sensory irritation study of Whitman and Hinz (2001) wherein an RD_{50} (the concentration that reduced the respiratory rate of Swiss-Webster mice by 50%) was measured for JP-8 vapor plus aerosol at 2,876 mg/m^3. The RD_{50} test is a standard protocol (ASTM E981-84 [1988]) for estimating sensory irritancy of airborne chemicals. Groups of four male Swiss-Webster mice were exposed for 30 min at 681, 1,090, 1,837, or 3,565 mg/m^3. Reductions in the respiratory rate within 30 min were concentration-dependent, and breathing patterns were characteristic of upper airway sensory irritation. On the basis of a correlation between the RD_{50} and sensory irritancy concentrations for a large number of structurally diverse chemicals, a 10-fold reduction of the RD_{50} results in a concentration that elicits sensory irritation in humans but that can be tolerated for hours to days (Alarie 1981; Schaper 1993). Irritation is concentration-dependent, and there is adaptation to the mild sensory irritation that characterizes the AEGL-1. Using this reasoning, the resulting concentration of 290 mg/m^3 can be tolerated at each AEGL-1 exposure duration. The 290 mg/m^3 value is supported by the lack of adverse health effects in subchronic toxicity animal studies with repeated or continuous exposures to JP-8 vapor at 1,000 mg/m^3 (Mattie et al. 1991; Briggs 2001; Rossi et al. 2001).

The AEGL-2 is based on inhalation studies with rats and mice demonstrating that exposure to JP-8 at 1,100 mg/m^3 failed to elicit signs of intoxication or CNS depression. The shorter-term studies (30 min to 4 h) with exposures to JP-8 or JP-5 in mixed vapor and aerosol forms at 3,430-5,000 mg/m^3 (MacEwen and Vernot 1985; Wolfe et al. 1996; Whitman and Hinz 2001) with support from studies using repeated or continuous vapor exposures at 1,000 mg/m^3 (Mattie et al. 1991; Briggs 2001; Rossi et al. 2001) were used as the basis for the AEGL-2.

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No uncertainty factors were applied to the results of studies at the 1,000 mg/m^3 concentration because no adverse effects were observed, and the exposures were repeated or continuous for up to 90 days. The higher concentrations of JP-8 (3,430, 3,565, and 4,440 mg/m^3) and of JP-5 (5,000 mg/m^3) were divided by an interspecies factor of 1 (compared with humans, systemic uptake is greater in rodents based on higher respiration rate and cardiac output) and by an intraspecies uncertainty factor of 3 to protect potentially sensitive individuals. An intraspecies uncertainty factor of 3 is considered adequate because the thresholds for both sensory irritation and CNS depression for solvents in humans and rodents do not generally differ by more than 3-fold. The lower value, 1,100 mg/mg^3, in the resulting range of values, 1,100-1,700 mg/m^3, is approximately the same concentration as in the no-adverse-effect repeated-exposure studies. CNS depression is a concentration-related effect. For solvents that cause CNS effects, steady state is generally approached within 1 h. In addition, because the exposure duration in the key study was 4 h, the 1,100 mg/m^3 value was used for the 4-h and shorter time periods. Because the exposure of rats and mice at 1,000 mg/m^3 was continuous (24 h/day) for up to 90 days (Mattie et al. 1991), the 1,100-mg/m^3 value can also be used for the 8-h AEGL. The fact that the exposures in most of these studies, especially at the higher concentrations, were to mixed JP-8 vapor and aerosols supports the AEGL-2 values.

Because of their relatively low vapor pressure, the physical properties suggest JP-8 and JP-5 might not attain a sustained vapor concentration high enough to cause death. As reported by Wolfe et al. (1996), the highest vapor concentration of JP-8 that could be attained under an experimental system at 35ºC was 3,430 mg/m^{3,} and the highest vapor and aerosol concentration that could be generated was 4,440 mg/m^3. However, the highest vapor and aerosol attainable under ambient concentrations has been estimated at 700 mg/m^3, and 500 mg/m^3 is the upper bound for a stable JP-8 aerosol. Based on the likelihood that airborne concentrations of JP-8 or JP-5 aerosol and vapor sufficient to cause death cannot be sustained under ambient conditions, an AEGL-3 was not derived.

Although the AEGL values are based on reported mixed aerosol and vapor concentrations of jet fuels, the primary exposure is to the vapor. Exposure to aerosols will probably result in deep lung deposition. Therefore, AEGLs based on mixed aerosol and vapor exposures are more conservative than those based on gas-phase exposures. Aerosol concentrations of 10 mg/m^3 result in a visible cloud. These concentrations and higher will result in liquid deposition on surfaces.

AEGL values are summarized in Table 2-1 below.

I. INTRODUCTION

Jet propellant or jet propulsion (JP) fuels are used in military aviation for turbine engine and jet aircraft. Jet fuels are complex mixtures of aliphatic and

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aromatic hydrocarbons made by blending petroleum distillates, such as naphtha (the low boiling fraction of petroleum), gasoline, and kerosene to meet military or commercial specifications (U.S. Air Force 1989). Jet fuels are composed of aliphatic, monocyclane, aromatic, and alkene hydrocarbons in the C_5 to C_{16} range. Aliphatic alkanes (paraffins) and cycloalkanes (naphthenes) are the major constituents (75-90%) of kerosene (Cavender 1994a,b,c; reviewed in ATSDR 1998). The boiling range for jet fuels is usually well above that of benzene and *n*-hexane. Conversely, the maximum final boiling point of middle distillate fuels tends to exclude the presence of high-boiling polycyclic aromatic hydrocarbons. The composition of jet fuels varies depending on the type of crude oil from which the fuel is derived, the refining process used, and the additives. Additives include antioxidants, metal deactivators, corrosion or icing inhibitors, and electrical conductivity agents (reviewed in ATSDR 1998). The major vapor-phase hydrocarbon components of JP-8 are listed in Appendix A.

TABLE 2-1 Summary of AEGL Values for JP-5 and JP-8[a,b]

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	290 mg/m^3	290 mg/m^3	290 mg/m^3	290 mg/m^3	290 mg/m^3	Slight sensory irritation in humans (extrapolated from mouse RD_{50} test) (Whitman and Hinz 2001)
AEGL-2 (disabling)	1,100 mg/m^3	1,100 mg/m^3	1,100 mg/m^3	1,100 mg/m^3	1,100 mg/m^3	No clinical signs during repeated exposures at 1,000 mg/m^3 to rats and mice (Mattie et al. 1991; Briggs 2001; Rossi et al.. 2001); sensory irritation at >3,430 mg/m^3 in rats and mice (Wolfe et al. 1996; Whitman and Hinz 2001)
AEGL-3 (lethal)	Not determined	Not determined	Not determined	Not determined	Not determined	No data[c]

[a]The values apply to JP-8 vapor or vapor and aerosol and not to the pure aerosol.
[b]The values apply to JP-8 vapor and not to JP-8+100.
[c]A lethal concentration was not attained in the available toxicity studies; the low vapor pressures of JP-8 and JP-5 may preclude attainment of a lethal concentration.
Abbreviation: RD_{50}, concentration that reduces the respiratory rate by 50%.

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The present document focuses on the toxicity of JP-8, the jet fuel used by the U.S. military. Information on JP-5 (used by the Navy for shipboard aircraft) is included in this document because, chemically, JP-5 can be considered a subset of JP-8 (ATSDR 1998; Potter and Simmons 1998). Both JP-8 and JP-5 are middle distillates with boiling ranges of 150-275°C. JP-8 contains alkane carbon ranging from *n*-C_8 through *n*-C_{17}; whereas JP-5 contains carbons ranging from *n*-C_7 through *n*-C_{18} (Potter and Simmons 1998). Prior to 1979, JP-4—a naphtha-based, wide-cut fuel made from straight-run, desulfurized kerosene blended with lower boiling distillates or made by blending refined shale oil distillates (ATSDR 1995)—was used by the Air Force. JP-4 was replaced by JP-8 in 1994, and JP-8 is now the standardized fuel for the U.S. military. Thus, the human monitoring and animal toxicity studies with JP-4 are not discussed in this document. Data on JP-7, a specialized high-altitude fuel restricted to reconnaissance aircraft (MacNaughton and Uddin 1984), are not included since JP-7 is no longer used.

JP-5 is a turbine engine fuel developed by the U.S. Navy for use aboard aircraft carriers because of its lower volatility and lower post-crash fire hazard compared with JP-4 (ATSDR 1998). JP-5 has a specified distillation temperature of 205°C for the 10% recovery point to 290°C for the end point (Military Specification MIL-T-5624K [1976]). The U.S. Naval Service is anticipating transition from the nearly exclusive use of JP-5 to predominant use of JP-8, consistent with the other military services and the militaries of most NATO countries.

Compared with JP-4, the less volatile JP-8 contains alkanes in the C_8 to C_{17} range. In a survey of JP-8 fuels, the average aromatic content was 14.5%, the highest aromatic content reported being 18.8% (Martel 1989). The composition (v/v) of JP-8 consists of approximately 9% C_8 to C_9 aliphatic hydrocarbons, approximately 65% C_{10} to C_{14} aliphatic hydrocarbons, approximately 7% C_{15} to C_{17} aliphatic hydrocarbons, and approximately 18% aromatic hydrocarbons (NRC 1996; Carlton and Smith 2000). Typical aromatic hydrocarbons include benzene, ethylbenzene, toluene, and xylenes, but the distillation fraction of JP-8 minimizes the presence of benzene and related low-boiling aromatic hydrocarbons. Ambient air samples in aircraft fuel tank maintenance areas are dominated by C_9 to C_{12} *n*-alkanes; the primary *n*-alkanes in these samples are nonane (C_9), decane (C_{10}), and undecane (C_{11}) (Pleil et al. 2000). The benzene content is 0.005% by volume (Carlton and Smith 2000). The typical aromatic hydrocarbons in JP-8 are the polycyclic aromatics and not the lighter aromatics, such as benzene, toluene, xylenes, and ethyl benzene found in gasoline (Appendix A).

Only the studies of Carlton and Smith (2000) discuss benzene exposures measured during maintenance operations on military aircraft fuel tanks. The exposures occur inside the fuel tanks or with personnel removing foam from the tanks. The latter operation involves the generation of aerosols as the foam is pulled out of the fuel tank. Benzene is more water soluble than other jet fuel components, and some benzene remains in the small amount of water present after many refuelings. This amount can result in measurable benzene concentra-

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tions during these operations even though the levels of benzene in the bulk fuel are not detectable (see Appendix A). Benzene is not a component of concern for JP-8 AEGLs.

Except for additives included to meet military specifications, JP-8 is similar to international jet fuels A and A-1, the former used in U.S. commercial aircraft. JP-8 contains antioxidants, static inhibitors, corrosion inhibitors, fuel system icing inhibitors, lubrication improvers, biocides, and thermal stability improvers (Military Specification MIL-T-5624P [1992]). According to the Navy Environmental Health Center, additives to JP-8 typically compose <2% of the volume (NEHC 2001). Addition of antioxidants—such as 2,6-di-tert-butyl-4-methylphenol—or metal deactivators—such as *N,N*-disalcylidene-1,2-propanediamine—is optional. Static dissipaters—such as Stadis 450 (50-60% toluene)—organic acid corrosion inhibitors (8Q21), and icing inhibitors—such as diethylene glycol monomethyl ether—are required. JP-5 differs in that an antioxidant is required and a metal deactivator and static dissipater are not used.

To improve the thermal stability of JP-8, a proprietary package of additives including an antioxidant (butylated hydroxytoluene), a metal deactivator *(N,N*-disalicylal-1,2-propane diamine), and a detergent and dispersant (8Q405) are added at concentrations of 100-300 ppm. The resulting fuel is called JP-8+100 (Wolfe et al. 1996; Kornguth 1998). JP-8+100 is not widely used at present.

The chemical identification and chemical and physical properties of JP-8 and JP-5 are summarized in Table 2-2. Many of the physical properties of JP-8, such as autoignition temperature (229ºC), and flammability and explosive limits, both 0.7%-5%, are identical to those of kerosene (ATSDR 1998). The flashpoint is 38ºC, indicating that fire is the major hazard associated with jet fuels. Because of the complex and variable composition of jet fuels, the molecular weight is expressed as an average, and concentrations are expressed in terms of their total hydrocarbon content measured in mass units (mg/m^3).

Worldwide, approximately 60 billion gallons of JP-8 and commercial Jet A and Jet A-1 are consumed each year (Armbrust Aviation Group 1998). Annual use of JP-8 by the U.S. military services and North Atlantic Treaty Organization forces is estimated at 4.5 billion gallons (Zeiger and Smith 1998). The U.S. military utilization of JP-8 and JP-5 exceeds 2.2 billion gallons per year (Henz 1998). In addition to fueling aircraft and tanks, the military uses JP-8 for heating tents and buildings.

Exposure to jet fuels can occur during production and refining, monitoring of storage tanks, aircraft fueling and defueling, spills during handling, and leaks at storage facilities. Under some conditions, aircraft jettison excess fuel into the upper atmosphere (ATSDR 1998; Rossi et al. 2001). Annually, several hundred thousand military personnel are involved in these operations. Thus, exposure to JP-8 represents the largest single source of chemical exposure in the U.S. military (Pleil et al. 2000); civilian exposure is restricted to the chemically similar Jet A used in commercial aircraft.

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TABLE 2-2 Chemical and Physical Data for Jet Fuels 8 and 5

Parameter	Data	Reference
Synonyms		
JP-8	Kerosene, aviation kerosene, fuel oil number 1, jet kerosene, turbo fuel A, straight run kerosene, distillate fuel oil-light, MIL-T-83133D, AVTUR, NATO F-34	ATSDR 1998, NRC 1996, Chevron Phillips 2009a
JP-5	Kerosene, MIL-T-5624N	Chevron Phillips 2008
Molecular formula	Not applicable	
Structure	Not applicable	
Molecular weight (mean)		
JP-8	167, 180	MacNaughton and Uddin 1984
JP-5	168, 170, 185	NIOSH 2005; NRC 1996
CAS Registry Number		
JP-8	8008-20-6[a]/70892-10-3[b]	ATSDR 1998
JP-5	8008-20-6[a]/70892-10-3[b]	ATSDR 1998
Physical state		
JP-8	Clear-to-light amber liquid	ATSDR 1998; Richie et al. 2001a
JP-5	Clear liquid	ATSDR 1998
Solubility in water		
JP-8	5 mg/L (kerosene)	ATSDR 1998
JP-5	5 mg/L (kerosene)	ATSDR 1998
Density (specific gravity)		
JP-8	0.81 g/mL	Potter and Simmons 1998
JP-5	0.82 g/mL	Potter and Simmons 1998
Vapor pressure		
JP-8	1.8 mmHg (28°C) 0.4-3.3 mmHg (20°C)	NRC 1996 SwRI 2001
JP-5	5.9-26.4 mmHg (kerosene) 1.8 mmHg (28°C)	ATSDR 1998 NRC 1996
Vapor density, JP-8 (air = 1)	4.5-5	Ritchie et al. 2001a
Explosive limits, JP-8		
Lower explosive limit	0.7-0.9%	Ritchie et al. 2001a
Upper explosive limit	5-6%	
Flash point		
JP-8	37.8°C	Chevron Phillips 2010
JP-5	60°C	Chevron Phillips 2009b

(Continued)

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TABLE 2-2 Continued

Parameter	Data	Reference
Liquid density (water = 1)		
JP-8	0.788-0.845 kg/L	ATSDR 1998
JP-5	0.788-0.845 kg/L	ATSDR 1998
Melting point		
JP-8	−52ºC	ATSDR 1998
JP-5	−46ºC	ATSDR 1998
Boiling range		
JP-8	150-275ºC	Potter and Simmons 1998
JP-5	150-275ºC	Potter and Simmons 1998
Conversion factors (STP)[c]		
JP-8	1 ppm ≈ 8 mg/m^3 1 mg/m^3 ≈ 0.12 ppm	NRC 1996
JP-5	1 ppm ≈ 8.3 mg/m^3 1 mg/m^3 ≈ 0.12 ppm	NRC 1996

[a]The CAS Reg. No. is that of kerosene.
[b]The CAS Reg. No. is that of fuel oil no. 1.
[c]Conversion factors at standard temperature and pressure (STP) are based on the average molecular weight.

2. HUMAN TOXICITY DATA

At sufficiently high exposures, liquid and vapor JP-8 may be irritating to the eyes and skin. Dermal exposure may cause defatting, drying, and irritation of the skin (U.S. Air Force 1989). Topical exposure can induce skin inflammation, which has been documented by morphologic and ultrastructural changes (ATSDR 1998; McDougal and Rogers 2004; Monteiro-Rivere et al. 2004). Workers exposed to jet fuels have complained of dizziness, headache, nausea, and fatigue (NRC 1996; ATSDR 1995, 1998). Aspiration of the liquid fuel into the lungs can give rise to chemical pneumonitis.

The toxicity data of various jet fuels have been summarized and reviewed in IARC (1989), ATSDR (1995, 1998), Bruckner and Warren (2001), Ritchie et al. (2001a, 2003), and NRC (2003). Past exposures to concentrations as high as 3,000 mg/m^3 were to the more volatile JP-4 and equivalents (Knave et al. 1978; Martone 1981). Increased complaints of dizziness and fatigue have been associated with these concentrations. The low vapor pressure of JP-8 and JP-5 and the moderately high average molecular weights indicate that their relatively low volatility is such that a systemic health risk from vapor inhalation is unlikely (ACGIH 2009). In its toxicologic assessment of JP-8, the NRC (2003, pp. 4-5) noted: “No relevant adverse effects were observed for hepatotoxicity, renal toxicity, and cardiovascular toxicity, although the exposure concentrations did not

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exceed 1,000 mg/m^3. Adequate studies have not been conducted to assess the potential toxicity of inhaled JP-8 for reproductive toxicity, developmental toxicity, and genotoxicity".

2.1. Acute Lethality

No reports of humans fatalities associated with JP-8 or JP-5 exposure were located in the available literature.

2.2. Nonlethal Toxicity

The odor thresholds of JP-8 and JP-5 have been reported at 1 ppm and 0.082 ppm, respectively. The odor is described as similar to that of kerosene (ATSDR 1998).

Olsen (1998) compared liver function, kidney and hematopoietic system function, serum proteins, neurocognitive function, and general physical health of 18 Air Force personnel exposed to jet fuels with 18 nonexposed subjects. The exposed subjects were evaluated while exposed to JP-4 and at 3, 6, and 18 months after JP-8 replaced JP-4. Exposure to naphthas was <3 ppm. Benzene concentrations were 0.05 ppm during exposure to JP-4 and nondetectable during exposure to JP-8. No significant differences were found between exposed and nonexposed subjects with regard to liver and kidney function, frequency of symptoms, or general physical health. Two of the subjects exposed to JP-8 developed a rash on their hands. After 18 months of exposure to JP-8, several hematopoietic parameters were affected in that exposed workers had lower mean corpuscular volume and mean corpuscular hemoglobin and higher mean corpuscular hemoglobin concentration (smaller cells with a higher concentration of hemoglobin) than the nonexposed subjects.

Norseth et al. (1998) measured circulating serum alanine aminotransferase (formerly called serum glutamic pyruvic transaminase) and serum aspartate amino transferase (formerly called serum glutamic oxaloacetic transaminase), and glutathione transferase liver enzyme activities as an indicator of liver damage in Norwegian crew chiefs exposed to JP-8. Exposures were to C_5-C_9 aliphatic hydrocarbons at 0.13 ppm and to C_9-C_{13} at 3.11 ppm. Compared with controls, there were no meaningful differences between the two groups.

2.2.1. Clinical Studies

Because JP-8 is a kerosene-based fuel, the results of human exposures to kerosene offer useful comparisons. When six volunteers (age range 23-49 years) inhaled several different concentrations of deodorized kerosene, the odor threshold was 0.6 mg/m^3 (0.09 ppm) (Carpenter et al. 1976). The kerosene consisted

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of 55.2% paraffins, 40.9% naphthenes, and 3.9% aromatics and had a boiling range of 208-272°C. There were no complaints of irritation or discomfort when six volunteers (age range 20-63 years) were exposed to a measured concentration of 140 mg/m^3 (20 ppm) for 15 min. Three of the volunteers experienced slight olfactory fatigue. The authors reported that 14,000 mg/m^3 is the highest obtainable vapor concentration of deodorized kerosene at 25°C.

2.2.2. Accidental Exposures

Two individuals were exposed for 1 h to an unknown concentration of JP-5 in the cockpit of an unpressurized aircraft (Porter 1990). The odor was described as "overwhelming", and the individuals experienced burning eyes and euphoria (one individual) during exposure and complaints of headache, nausea, coordination difficulties, and transient memory defects after exposures were made. The effects subsided within 24 h in one individual and within 4 days in the other.

2.2.3. Monitoring Data

Because of its wide use in the past, most published monitoring data involve JP-4. Because of its higher volatility than JP-8, ambient air concentrations of JP-4 at military installations were higher than the currently measured concentrations of JP-8. Measured concentrations of JP-4 jet fuel inside aircraft shelters at bases ranged from 33 to 3,090 mg/m^3 and were dependent on temperature and shelter size. Concentrations of the less volatile JP-8 averaged <20 mg/m^3 at three shelters. Refueling normally took 3-5 min, although in one case, aircraft refueling associated with a measured exposure concentration of JP-4 at 620 mg/m^3 took 30 min (Martone 1981). At Swedish and Danish military bases where aviation fuel was equivalent to JP-4, maximum 5-min workplace concentrations ranged up to 3,226 mg/m^3 (Knave et al. 1978), and 8-h time-weighted averages (TWAs) ranged up to 3,000 mg/m^3 (Knave et al. 1978; Thomas and Richardson 1981; Holm et al. 1987; Døssing et al. 1985; Selden and Ahlborg 1986, 1987). Vapor concentrations often exceeded 350 mg/m^3 (a specific exposure duration was not given) (Selden and Ahlborg 1986, 1987); exposure durations to unspecified concentrations ranged up to 31 years (Døssing et al. 1985).

Workplace air concentration data for JP-8 and JP-5 are summarized in Table 2-3. The highest concentrations of JP-8 were measured inside empty aircraft fuel tanks during maintenance and foam removal. Workers who enter the fuel tanks wear a supplied air respirator or a self-contained breathing apparatus, whereas the outside attendants do not. Therefore, information on potential adverse health effects (from JP-8 and JP-5 inhalation) could not be derived from these studies.

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TABLE 2-3 Monitoring Data for JP-8 and JP-5

Fuel Type	Concentration	Exposure Duration	Reference
JP-8	<20 mg/m^3	Min (fueling time)	Martone 1981
JP-8	1.83 ppm (naphthas)[a]	Ambient concentrations over work shift	Puhala et al. 1997
JP-8	<3 ppm (naphthas)	18 mon	Olsen 1998
JP-8	0.13 ppm (C_5-C_9) 3.11 ppm (C_9-C_{13})	Routine exposures	Norseth et al. 1998
JP-8	Inside fuel tanks:[b] 0.12-2,308 mg/m^3 17-10,295 mg/m^3	 8-h TWA 15-min samples	Smith and Zelnick 1998
JP-8	Inside fuel tanks; tanks with no foam: 52 mg/m^3 (range, 4-954 mg/m^3) 14 mg/m^3 Fuel tanks with foam: 431 mg/m^3 (range, 7-10,295 mg/m^3) 183 mg/m^3	 15-min TWA 8-h TWA 15-min TWA 8-h TWA	Carlton and Smith 2000
JP-8	Outside fuel tank: 2.7 ppm (C_8-C_{12}) Inside fuel tank: 104 ppm (C_8-C_{12})	Routine aircraft maintenance	Pleil et al. 2000
JP-8	0.54 ppm (naphtha)	8-h TWA	Smith et al. 1997
JP-8 (mist)	10->200 mg/m^3	Dissipated in <1 min	Leith et al. 1998
JP-8 (aerosol)	16-119 mg/m^3	Min to h	Robledo and Witten 1998
JP-5	<0.48-153 mg/m^3 (range) 4.4 mg/m^3 (mean)	TWA	NRC 1996

[a]Defined as all vapor phase hydrocarbons expected form JP-8.
[b]Samples were taken inside aircraft fuel tanks during maintenance operations; workers wear supplied air respirators during tank entry.
Abbreviation: time-weighted average.

Data from the U.S. Navy Occupational Safety and Health Program were reported by the National Research Council (NRC 1996). TWA personal-exposure measurements of JP-5 vapor, taken from November 1984 to February 1993, ranged from <0.48 to 153 mg/m^3. The geometric mean was 4.4 mg/m^3.

Smith and Zelnick (1998) reported the results of JP-8 and benzene monitoring taken during aircraft fuel tank entry during maintenance at U.S. Air Force

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bases. Samples were collected on charcoal tubes and analyzed by gas chromatography with a flame ionizing detector. A total of 250 15-min short-term exposure limit (STEL) samples were taken; concentrations ranged from 17-10,295 mg/m^3 for JP-8 and 0.06-41 mg/m^3 for benzene. Calculated 8-h TWA concentrations ranged from 0.12-2,308 mg/m^3 for JP-8 and 0.002-3.3 mg/m^3 for benzene. As noted, these maintenance workers wear respirators during fuel tank entry, and inhalation exposure was precluded.

Pleil et al. (2000) reported personal monitoring data for JP-8 at various Air Force bases during routine operations. A number of marker compounds, more specific to JP-8 exposure than other fuels or solvents, were measured. These marker compounds were also monitored in exhaled breath of service personnel. Concentrations of individual fuel components in indoor air and in the vicinity of exhaust from aircraft cold-starts were all <0.02 ppm. Of the marker compounds, nonane, decane, *o*-xylene, undecane, and *m,p*-xylene were present in the highest concentrations in and around fuel tanks during maintenance operations. During fuel tank maintenance and foam removal, workers stationed outside the fuel tanks were exposed to mean nonane and decane concentrations at 1.8 and 0.6 ppm, respectively. Except for some aromatics such as *o*-xylene present at 0.2 ppm, most other components including benzene were present at ≈0.02 ppm. Inside the fuel tanks, mean concentrations of nonane, decane and decane were each 31-34 ppm. Summed concentrations of C_8 through C_{12} (hexane through dodecane), outside and inside the tanks were 2.7 ppm and 104 ppm, respectively. Workers that entered the fuel tanks wore respirators, whereas the outside attendants did not. Analysis of breath samples from the latter two groups of workers showed nearly identical results. Therefore, the authors concluded that workers who entered the tanks had considerable dermal exposure (as well as inhalation exposure upon exiting the tanks).

At three U.S. Air Force bases in the United States, mean concentrations of individual components of jet fuels (JP-4, JP-5, and JP-8) ranged up to 0.009 ppm for benzene and 1.83 ppm for naphthas (Puhala et al., 1997). Maximum values at one of the bases were 4.04 ppm for naphtha and 0.03 ppm for benzene. Historical data indicated that exposures were to much higher concentrations when JP-4 was the primary fuel; at that time, the maximum TWA value for naphthas was 586 ppm, and the maximum TWA value for benzene was 13.2 ppm. Exposure concentrations were highest for aircraft maintenance workers.

Carlton and Smith (2000) measured exposures of personnel during aircraft fuel tank entry and repair at 12 U.S. Air Force bases. Different types of aircraft and fuel tank types (containing explosion suppression foam or no foam) were surveyed. The tanks were purged with air prior to worker entry. Workers who entered the tanks wore supplied air respirators during initial tank entry and foam removal; the assistant attendant and monitor who remained outside the tank but in close proximity did not wear a respirator. A total of 500 breathing zone samples involving 77 workers were taken. Nearly half of the samples were 15-min short-term samples. The partial period and short-term samples were used to calculate 8-h TWAs. The mean 15-min TWAs were 52 mg/m^3 (range, 0.1 to 1,304

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mg/m^3) in tanks containing no foam to 430 mg/m^3 (range, 4 to 10,295 mg/m^3) in tanks containing foam. Respective mean 8-h TWA exposures were 14 mg/m^3 and 183 mg/m^3. Benzene concentrations in grab samples taken in the fuel tanks were also measured, and although in one case ranged up to 49 mg/m^3, short-term and 8-h TWA values were 4.6 and 0.74 mg/m^3, respectively.

Aerosols of JP-8 have been observed when ambient temperatures are low. At Eilson Air Force Base in Alaska, mist concentrations of 10 to >200 mg/m^3 were present, but generally lasted less than 1 min (Leith et al. 1998). During refueling and preflight operations at Davis-Monthan Air Force Base (Tucson, Arizona) and Montana Air National Guard Base (Great Falls, Montana), time-weighted aerosol concentrations of JP-8 were measured at 16 to 119 mg/m^3 (2- to 6-h exposures) (Robledo and Witten 1998). The 119-mg/m^3 concentration composed a single sample during a 3.5-min refueling (Pfaff et al. 1995).

Additional JP-8 occupational exposure data taken in conjunction with complaints of symptoms are discussed in Section 2.3 (Neurotoxicity).

2.3. Neurotoxicity

The neurotoxicity of selected hydrocarbon fuels was reviewed by Ritchie et al. (2001b) who addressed exposure to low levels of certain volatile organic chemical constituents of hydrocarbon fuels.

Smith (1998) enumerated the anecdotal health complaints from ground crews handling JP-8. The complaints included headaches and dizziness, offensive odor, and local damage resulting from direct skin contact. Concentrations were not reported. Results of tests of neurocognitive function found no significant differences between personnel exposed to JP-8 compared with 18 nonexposed subjects (Olsen 1998). Details of the latter study were not reported in the available abstract.

Smith et al. (1997) measured the effect of chronic low-level JP-8 exposure on postural balance of a group of representative U.S. Air Force personnel; 27 workers employed in jet-fuel-related occupations at two bases for an average of 12 years (range, 0.8 to 30 years; average exposure to JP-8, 4.56 years) were compared with a matched control group of 25 workers. The mean age at time of evaluation was 37.5 years (range 23.6 to 57.4 years); there were 20 males and 7 females. Thirty-seven percent of the group had worked only with JP-8. Monitoring data for benzene; toluene; *m*-, *o*-, and *p*-xylenes; and naphthas were taken on two separate 8-h work periods for each worker. Postural sway movements while standing on a platform were measured electronically. Statistically significant associations between exposure and increased postural sway, particularly for benzene, toluene, and xylene, were found. The strongest association was between sway length and benzene concentration, and this association was strongest when tests were conducted under the most difficult condition—eyes closed and standing on 4 inches of foam. According to the authors, this association indicated a subtle influence on vestibular and proprioception function. To measure

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the effect of acute exposures, the time of day of the test administration was compared with the sway results. There was no difference between exposed subjects tested early in the working day and subjects tested later in the day. The effects were not adjusted for concomitant exposure to other chemicals. Eight-hour TWA exposures to components of all fuels for all job categories were: benzene, 0.006 ppm; toluene, 0.01 ppm; xylenes, 0.008 ppm; and naphthas, 0.54 ppm. Exposures to all JP-8 components in milligrams per cubic meter could not be calculated from the published data.

An eye-blink conditioning test was used to evaluate potential neurologic changes in military personnel exposed chronically to JP-8 (McInturf et al. 2001). Workers with JP-8 exposure were matched with a control group of military personnel. Subjects learned a classically conditioned response between an auditory stimulus and a corneal air puff, the conditioned response. Subjects were tested for capacity to learn the response after a rest period from occupational exposure and for recall of the response following 4 h of occupational exposure to JP-8. Compared with matched controls, the JP-8 exposed workers were slow to learn the response and had an increase in mean time from onset of the stimulus to the eye-blink response. No further details were given in the available abstract.

2.4. Immunotoxicity

Rhodes et al. (2001) reported increased white blood cell counts in military personnel exposed to JP-8, compared with a low-exposure group, but these changes were within normal clinical ranges. Olsen (1998) found no difference in total white blood cell count and differential counts among Air Force personnel before and 18 months after the Air Force converted to JP-8.

2.5. Developmental and Reproductive Effects

No studies regarding human exposure and aspects of developmental toxicity were located in the published literature. In a study that examined sperm quality (concentration, motility, viability, morphology, morphometry, and stability of sperm chromatin) in 50 aircraft maintenance workers at an Air Force installation at 15 and 30 weeks after exposure to both JP-8 and solvents began, there was no significant association between sperm quality of maintenance workers and jet fuel exposure (primarily JP-4) (LeMasters et al. 1999). Exposures were low, as all measured fuel components—naphthas, benzene, xylenes, toluene, and so forth—and a solvent—1,1,1-trichloroethane—were below 6 ppm.

2.6. Genotoxicity

Addition of petroleum-derived JP-5 failed to interfere with sarcoma virus transformation of cultured human fibroblasts (ATSDR 1998). Incubation of cul-

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tured human lymphocytes with JP-8 at dilutions of 1:75 to 1:500 resulted in increasing DNA damage with increasing dose, as measured using the Comet assay (Jackman et al. 2001).

2.7. Carcinogenicity

Following a review of available human data on occupational exposure to military fuel vapors, the NRC (2003) concluded that the available data are insufficient to draw a conclusion regarding the carcinogenicity of inhaled JP-8. Based on inadequate evidence for the carcinogenicity of jet fuels in humans and animals and the limited evidence of carcinogenicity in experimental animals of straight-run kerosene and of hydrotreated kerosene, IARC (1989) concluded that jet fuel is not classifiable as to its carcinogenic potential in human beings. According to ATSDR (1998), there are limited epidemiologic data regarding carcinogenicity in humans following chronic inhalation exposure to kerosene.

2.8. Summary

At sufficiently high exposures, JP-8 liquids and vapors may be irritating to the eyes and skin. Dermal exposure to neat JP-8 can cause skin irritation and skin damage (Olsen 1998; Smith 1998). The primary effect of acute inhalation exposure to JP-8 vapor is on the CNS where high concentrations result in dizziness, headache, nausea, and fatigue (Davies 1964; Porter 1990).

Workplace monitoring data indicate that in the past exposures to vapors of JP-4 were relatively high, whereas exposures to the currently used JP-8 are comparatively low. Measured concentrations of JP-4 ranged up to 3,090 mg/m^3 at U.S. air bases (Martone 1981) and 3,226 mg/m^3 at a Swedish jet motor factory (Knave et al. 1978). In the later study, the overall mean TWA was 300 mg/m^3, and the highest average was 974 mg/m^3. TWA exposures to JP-5 at Navy sites ranged up to 153 mg/m^3 (NRC 1996). Although the Swedish study did not correlate symptoms with exposure, some of the acute exposures may have been associated with headache and dizziness. Most occupational monitoring studies reported total hydrocarbon vapor concentrations, but later reports indicated that aerosols may be present during aircraft fueling operations. More recently, aerosols of JP-8 of up to 119 mg/m^3 have been measured in the vicinity of aircraft refueling operations (Pfaff et al. 1995). Particles are most commonly generated during start-up of cold jet engines. Emergency exposures are expected to be to spills resulting in vapor exposures, while aerosols are relevant only to occupational exposures during aircraft foam removal operations or aircraft cold starts. Exposures to high concentrations of JP-8 have occurred during jet aircraft fuel tank maintenance, but personnel wear respirators when entering the fuel tanks, thus minimizing inhalation exposure.

Occupational exposures may have had some influence on the hematopoietic system (Olsen 1998) and liver enzymes (Norseth et al. 1998). Increased

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postural sway correlated with occupational exposure to routine concentrations of benzene, toluene, and xylene and was associated with cumulative exposure (Smith et al. 1997). On the basis of the results of the epidemiologic studies (primarily JP-4), including Selden and Ahlborg (1986, 1987, 1991), the NRC (1996, p. 5) concluded that the studies of "Swedish military personnel exposed to jet-fuel vapors at concentrations greater than 350 mg/m^3 for several years did not show increased evidence of cancer." No studies that addressed potential developmental effects in humans were located.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

During attempts to generate a vapor concentration of JP-5 of 1,500 mg/m^3 (the highest stable concentration attainable), a respirable aerosol was produced that resulted in 50% mortality of C57BL/6 mice by the end of 6 days continuous exposure (Gaworski et al. 1984; MacEwen and Vernot 1985). Oily deposits were observed on the animals and on the chamber windows. Aerosol counts indicated 3.6×10^5 respirable particles per cubic foot (ft^3) (0.5-1.4 μm diameter) at this concentration. Young adult beagles were lethargic during exposures to this same concentration of vapor and aerosol.

3.2. Nonlethal Toxicity

3.2.1. Eye and Dermal Irritation

JP-8 was tested for eye and skin irritation in rats and rabbits and skin sensitization in mice and guinea pigs (MacEwen and Vernot 1984; Clark et al. 1989; Kinkead et al. 1992a,b; Kanikkannan et al. 2000). The undiluted test material (0.1 mL) was not irritating when instilled into the eyes of rabbits. The undiluted test material, placed on the intact or abraded skin and covered with an occluded patch for 24 h, produced a slight to moderate amount of reddening (MacEwen and Vernot 1984). Neat JP-8 showed a weak-to-mild sensitization reaction in guinea pigs and mice (MacEwen and Vernot 1984; Kinkead et al. 1992b; Kanikkannan et al. 2000).

JP-5 was nonirritating to the eyes and skin of New Zealand white rabbits, but it was a mild-to-moderate dermal sensitizer (Cowan and Jenkins 1981; Cowan et al. 1981; Kinkead et al. 1992a). In a more recent study, neat JP-8 applied to rabbit skin failed to elicit irritation, and repeated application to the skin of guinea pigs failed to elicit a sensitization reaction (Wolfe et al. 1996). In vitro studies with porcine or human skin showed that JP-8 penetrates the skin (Riviere et al. 1999; Kanikkannan et al. 2001), albeit not at concentrations sufficient to cause systemic toxicity (McDougal et al. 2000; McDougal and Robinson 2002).

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Permeation of individual chemical components was chemical-specific. In vivo, neat JP-8 was more irritating to pig skin than an equal volume of neat toluene or neat nonane (Kanikkannan et al. 2001). When equal volumes were applied dermally, JP-8 was more irritating to rat skin than JP-4 (Baker et al. 1999). Dermal application of 25 μL of Jet A, JP-8, or JP-8+100 to pig skin in vivo under occluded or nonoccluded conditions for 5 or 24 h or 5 days continuous contact resulted in no erythema and very slight edema for all fuels only after 5 days and only under occluded conditions (Monteiro-Rivere et al. 2001). Fabric soaked with 335 μL of the fuels (to mimic worker exposure) and applied every day for 4 days under occluded conditions had the greatest effect, resulting in slight erythema and edema on day 5. Under this latter condition, epidermal thickening occurred and epidermal rete peg depth increased. The epidermal proliferative response was greatest with JP-8+100. Although irritation and dermal absorption may occur with exposure to the liquid fuel, the dermal absorption route was not considered significant for exposure to the vapor.

3.2.2. Inhalation Toxicity Studies

Several acute vapor inhalation studies with JP-8 and JP-5 and utilizing the rat and mouse were located (Table 2-4). Longer-term studies of 6 weeks to 3 months, the latter with continuous exposure of mice, rats, and dogs (JP-5) or mice and rats (JP-8) are included to compare with values derived from acute exposures. These studies addressed sensory irritation as well as systemic effects. Generation of high concentrations of vapor in laboratory chamber studies requires introduction of a mixture of vapor and aerosol (NRC 2003). Several studies with JP-8 aerosol alone, usually with repeated exposures, also used rats and mice. "The animal data show toxicity from aerosol inhalation. However, these publications do not provide adequate information to permit a judgment of aerosol size and stability nor do they speak to the extent to which the sampling systems distinguished between aerosol and vapor" (Dietzel et al. 2005; ACGIH 2009). The NRC (2003, p. 3) reviewed the methods used to generate the exposure atmospheres in the aerosol studies and "suspects that the total JP-8 concentrations in the atmosphere may have been underreported." The data collected during aerosol inhalation studies are included in this TSD for completeness. A distinction is made in Table 2-4 between exposure to the vapor and exposure to aerosols. Where available, data on the source of the jet fuel (that is, petroleum or shale derived) is specified in the first column of Table 2-4 (although the available data indicate no substantial differences in toxicity between petroleum and shale-derived JP fuels).

Many of the reported studies were performed in the same laboratory and used the same methodology. The inhalation studies conducted at Wright-Patterson Air Force Base used 23.4 m^3 Thomas domes, and all animals were exposed in groups, which were continuously monitored for toxicity during the

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TABLE 2-4 Summaries of Studies on the Toxicity of Jet Fuels to Mammalian Species

Fuel Type	Species	Exposure Concentration[a]	Exposure Duration	Effects	Reference
JP-8 vapor and aerosol	Swiss-Webster mice (M)	681, 1,090, 1,837, 3,565 mg/m^3	30 min	No clinical signs RD_{50} of 2,876 mg/m^3	Whitman and Hinz. 2001
JP-8 vapor and aerosol	F344 rat (M, F) F344 rat (M, F)	3,430 mg/m^3 4,440 mg/m^3	4 h 4 h	No deaths; eye/upper respiratory track irritation No deaths	Wolfe et al. 1996; Feldmann et al. 1997
JP-8 aerosol	C57BL/ 6 mice (M)	5.0, 11.7, 27.8, 50.0, 112.5 mg/m^3	1 h	No changes in pulmonary function parameters; 27.8 mg/m^3: increase in BALF parameters; 50 mg/m: increased alveolar permeability; 112.5 mg/m^3: microscopic/ultrastructural lung changes	Robledo and Witten 1998
JP-8 aerosol	B6.A.D. mice	7, 12, 26, 48, 118 mg/m^3	7 d, 1 h/d	No changes in pulmonary function parameters, 48 and 118 mg/m^3: changes in BALF components; bronchiolar edema, cellular necrosis, and increased permeability	Robledo et al. 2000
JP-8 aerosol	C57BL/6 mice (M, F)	0, 100, 250, 500, 1,000, 2,500 mg/m^3	1 h/d, 7 d	Immediately postexposure: ≥500 mg/m^3 : decreases in wet weight of spleen and thymus; decrease in viable cells of spleen; ≥100 mg/m^3: decrease in viable cells of thymus; changes in numbers of immune cells of bone marrow, lymph nodes, and peripheral blood and in types of immune cells in all immune organs and tissues; alterations in immune function; many effects; and reversible at 28 days postexposure	Harris et al. 1997a,b
JP-8 aerosol	Swiss-Webster mice (M)	0, 1,000, 2,500 mg/m^3	1 h/d, 5 or 7 d	Lungs: changes in protein abundance; kidneys: changes in protein abundance	Witzmann et al. 1999; 2000b
JP-8 aerosol	F344 rat (M)[e]	495 mg/m^3 (7 d) 520 mg/m^3 (28 d)	1 h/d, 7 or 28 d	Increased lung dynamic compliance (7 d); increased pulmonary resistance Lower chemical mediator in BALF;[f] Increased alveolar permeability[g] No pathologic lung changes Lower body-weight gain Increased organ weights (liver, spleen, kidney); no liver lesions, ALT normal; kidney, spleen changes	Pfaff et al. 1995, Chen et al. 1992, Pfaff et al. 1992, Witten et al. 1992, Parton et al. 1993 Pfaff et al. 1993

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JP-8 aerosol	F344 rat (M)[e]	495-520 mg/m^3 813-1,094 mg/m^3	7, 28, 56 d, 1 h/d 5 d/wk	Changes in lung permeability: 28 d, both concentrations, 56 d, high concentration; partial recovery at 56 d Lung histopathology (all groups): interstitial edema, epithelial thickening, vacuolization of type II cells	Witten 1994 Hays et al. 1995
JP-8 vapor and aerosol	F344 Brown Norway rats (M)	2,490 mg/m^3	1 h/d, 5 d/wk, 4 wk	FOB: greater arousal and activity than controls; Morris swim task: no learning or memory deficits	Baldwin et al. 2001
JP-8 vapor	Rat (M)	0, 250, 500, or 1,000 mg/m^3	6 wk, 6 h/d, 5 d/wk	No clinical signs; no effects on male fertility; no microscopic lesions in the testes; some biochemical changes in testes	Briggs 2001
JP-8 vapor	Sprague-Dawley rat (M)	1,000 mg/m^3	6 wk, 6 h/d, 5 d/wk	No clinical signs; no effects in 9 of 10 neurobehavioral tests; significant decrease in response time in 1 of 10 tests, but no decrease in overall activity; some changes in brain neurotransmitter activities	Rossi et al. 2001
JP-8 Vapor	Sprague-Dawley rat (M)	500, 1,000	6 wk 6 h/d, 5 d/wk	No clinical signs, no change in body weights; 62 days postexposure: 500 mg/m^3: no effect and superior performance in operant behavior tests compared with controls; 1,000 mg/m^3: threshold for operant task deficit; changes in brain neurotransmitters	Ritchie et al. 2001c
JP-8 vapor	F344 rat (M, F) C57BL/ 6 mouse (M, F)	500 mg/m^3 1,000 mg/m^3	90 d, continuous; killed at 0 wk to 21 mon	No clinical signs in either species; No or minor hematologic, clinical chemistry changes No lung lesions (rats, electron microscopy) No tumors Male rats: decreased body-weight gain accelerated chronic progressive nephrosis reversible kidney hyaline droplet formation liver basophilic foci, nondefinitive liver effects Mice: no treatment-related lesions	MacEwen and Vernot 1985; Mattie et al. 1991

(Continued)

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TABLE 2-4 Continued

Fuel Type	Species	Exposure Concentration[a]	Exposure Duration	Effects	Reference
JP-8+100 vapor and aerosol	Swiss-Webster mice (M)	777, 1,519, 2,356 mg/m^3	30 min	No clinical signs RD_{50} of 1,629 mg/m^3	Whitman and Hinz. 2001
JP-5 Aerosol	F344 rat (M) C57BL/ 6 mouse (M)	2,500, 5,000 mg/m^3[d]	1 h	Eye irritation (both concentrations) and CNS depression in both species (5,000 mg/m^3); renal hyaline droplet formation with some urinary biochemical changes in male rats at 5,000 mg/m^3; no other histopathologic effects	MacEwen and Vernot 1985
JP-5 (P) JP-5 (S)	Sprague-Dawley rat (M)	1,125 mg/m^3 (P) 1,636 mg/m^3 (S)	6 wk, 6 h/d, 5 d/w	Increased water consumption; no neuropathies (no changes in SEP); no liver enzyme changes; no histopathologic effects	Bogo et al. 1983, 1984
JP-5 vapor	Sprague-Dawley rat (M)	1,200 mg/m^3	6 wk, 6 h/d, 5 d/wk	No clinical signs; no effect on 9 of 10 neurobehavioral tests; increased forelimb grip strength; some changes in blood and brain neurotransmitter activities	Rossi et al. 2001
JP-5 (P) JP-5 (S)	F344 rat (M, F) C57BL/ 6 mouse (F) Beagle dog (M, F)	150 mg/m^3 (P, S) 750 mg/m^3 (P, S)[d]	90 d, continuous; killed at 0 wk and 19-24 mon postexposure	Necrosis of renal tubular epithelial cells and subnormal weight gain in male rats exposed to JP-5 (P,S) at both concentrations; mild hepatocellular vacuolization in rats exposed to 750 mg/m^3 JP-5/(S); minor hematology changes, liver glycogen accumulation in dogs exposed to JP-5 (P,S) at both concentrations; mild reversible liver cell changes and mild nasal inflammation in female mice exposed to JP-5 (S)	Cowan and Jenkins 1981; Cowan et al. 1981; Gaworski et al. 1984, 1985; MacNaughton and Uddin 1984; MacEwen and Vernot 1985

[a]All exposures are to vapors except as otherwise noted; aerosol studies involve primarily vapor with some aerosol present.
[b]Saturated vapor (concentration estimated).
[c]The 5,000 mg/m^3 concentration was chosen to produce a benzene concentration of 80 mg/m^3 (25 ppm).
[d]An aerosol may have been present at this concentration.
[e]Nose-only exposure.
[f]Refers to Substance P; no differences for cell counts or the stable metabolite of prostacyclin.
[g]Lung epithelial permeability measured by clearance of technetium-labeled diethylenetriamine pentaacetate.
Abbreviations: P, petroleum-derived jet fuel; S, shale-derived jet fuel; ALT, alanine aminotransferase; BALF, bronchoalveolar lavage fluid.
FOB = functional observational battery (a series of tests designed to measure neurotoxicity); SEP = somatosensory evoked potential.

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studies. Jet fuel vapors were generated by passing fuel through dual constant temperature evaporator towers operated at 50-57ºC and mixed with air to establish the desired atmospheric concentrations. Vapor concentrations were measured continuously using a Beckman model 400 hydrocarbon analyzer. The absence of aerosols was documented with a Royco aerosol particle counter. Chamber atmospheres were verified using gas chromatography and mass spectrometry (MacNaughton and Uddin 1984). Sufficient numbers of animals were used to provide statistical verification of the observations.

In a 6-week study with adult Sprague-Dawley rats (Bogo et al. 1983, 1984), petroleum- and shale-derived JP-5 was first aerosolized in an aerosol generator and then, following removal of particles >0.5 um, was vaporized and mixed with air; vapor generation was maintained with a heated liquid and air countercurrent flow system. The vapor concentration was calculated from the net loss of liquid fuel and the total volume of airflow through the system. A computer-controlled gas-sampling and chromatographic analysis system monitored the total hydrocarbons, oxygen, and carbon dioxide in the chambers. Rats were exposed in groups of six in 30-L Leach chambers.

The majority of studies with combined vapor and aerosol of JP-8 were conducted by staff at the University of Arizona: Pfaff et al. (1995), Hays et al. (1995), and Robledo and Witten (1998). Jet fuel was aerosolized by placing 3 mL of JP-8 in an Ultra-Neb 99 nebulizer (DeVILBISS). Rats were exposed nose-only in groups of 12 in a 0.5-m^3 IN-TOX exposure chamber. Exposure concentrations were determined from changes in plate weights of a seven-stage cascade impactor after each exposure. Analysis was by gas chromatography. In the Pfaff et al. (1995) study, the aerosol to vapor mass ratio was 1.5. Particle size averaged 1.7 ± 2.2 µm (MMAD [mass mean aerodynamic diameter] ± GSD [geometric standard deviation]). In the Robledo and Witten (1998) study, particle MMADs for the different concentrations ranged from 2.0 ± 1.7 to 3.4 ± 2.3 µm. However, the actual aerosol and vapor concentrations in these studies are unclear (Dietzel et al. 2005). The JP-8 fuel used in many of the more recent studies was supplied by the Propulsion Directorate, Fuel Division, at Wright-Patterson Air Force Base. The fuel was prepared by blending approximately 250 fuel samples obtained from fuel manufacturers worldwide (Witzmann et al. 2000a) and is therefore considered a representative sample.

Studies addressing irritation and systemic toxicity of JP-5 and JP-8 are discussed in more detail below. Neurotoxicity, immunotoxicity, and developmental and reproductive toxicity studies are discussed in Sections 3.3, 3.4, and 3.5, respectively.

3.2.2.1. Dogs

Groups of three male and three female beagle dogs were exposed continuously to concentrations of 0, 150, or 750 mg/m^3 of JP-5 petroleum or shale-oil derived vapor for 90 days (Gaworski et al. 1984; 1985). Density of aerosol par-

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ticles (0.5 to 1.4 µm) was measured prior to the exposures and was found to be 1,100 and 6,200 particles/ft^3, respectively, in the 150- and 750-mg/m^3 exposure chambers; the particle count in laboratory air was 1,530 particles/ft^3. The benzene concentrations averaged 0.1 and 0.5 ppm at the 150- and 750-mg/m^3 exposures, respectively. All data for males and females were combined for analyses. These concentrations did not affect body-weight gain. Clinical chemistry parameters were within normal limits. Red-blood-cell osmotic fragility was increased in the petroleum-derived 750-mg/m^3 group, and erythrocyte counts and hematocrit and hemoglobin levels were lowered in both the petroleum and shale-derived 750-mg/m^3 groups, but the differences were not statistically significant compared with the control group. Dogs exposed to shale-derived JP-5 at 750 mg/m^3 developed increased liver weights, and dogs exposed to petroleum-derived JP-5 (both concentrations) had glycogen accumulation in their livers. There were no other lesions.

3.2.2.2. Rats

JP-8. Wolfe et al. (1996; see also Feldman et al. [1977] for published abstract) exposed groups of five male and five female Fischer 344 (F344) rats to a target concentration of 5,000 mg/m^3 of vaporized or aerosolized JP-8 for 4 h. The generation system consisted of two flasks (one for vapor and one for vapor and aerosol generation) containing a six-jet compressed air nebulizer. The flasks were kept in a 34ºC water bath. For the vapor study, an industrial HEPA filter was used to prevent aerosol from entering the exposure system. Under this system, the highest vapor concentration obtainable in the vapor-only exposure was 3,430 mg/m^3. No deaths occurred, but animals exhibited signs of eye or upper respiratory irritation during exposure. Exposed animals lost weight on the first 1-2 days postexposure but gained weight during the remainder of the 14-day observation period. No control data for body weights were provided. No gross exposure-related lesions were observed. The vapor and aerosol concentrations during exposure to aerosolized JP-8 were 2,630 and 1,810 mg/m^3, respectively for a combined exposure of 4,440 mg/m^3. The particle MMD was 1.79 ± 1.60 µm. No deaths occurred, and exposed animals gained weight during the 14-day observation period. These tests were also performed with JP-8 containing several additive packages (JP-8+100) designed to increase thermal stability and decrease fuel fouling. Test results with the vaporized and aerosolized fuel plus additives were similar to those of the vaporized and aerosolized fuel alone. It should be noted that, under this experimental system, the vapor and vapor and aerosol atmospheres contained a higher percentage of the lower molecular weight hydrocarbons (C_9-C_{11}) than the neat fuel.

Groups of 95 male and 75 female F344 rats were exposed to JP-8 vapor at concentrations of 0, 500, or 1,000 mg/m^3 continuously for 90 days (MacEwen and Vernot 1985; Mattie et al. 1991). Animals were killed immediately after cessation of exposure and up to 21 months postexposure. Clinical signs, body-

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weight, and hematologic and clinical chemistry parameters were monitored during the exposures. No clinical signs of toxicity or biologically significant changes in hematologic and clinical chemistry were observed. Body weight of exposed males was significantly depressed during the exposures and postexposure (both concentrations), but there was no dose-response relationship. Twenty-one months after exposure, relative liver and kidney weights of male rats were increased and SGPT of female rats was reduced in the 1,000-mg/m^3 group. Hyaline droplet formation in the kidneys of males was reversible by 2 months postexposure, and linear mineralization in the kidneys was reversible by 9 months postexposure. However, the incidence of chronic progressive nephrosis increased in males postexposure. A dose-dependent increased incidence of basophilic foci was observed in the livers of exposed males, but this effect is of uncertain biologic significance. The increased incidence of splenic hematopoiesis in female rats at 21 months was not accompanied by changes in hematologic parameters and thus was attributed to biologic variation. Scanning electron microscopy of the lungs of male rats revealed no differences between exposed and control groups.

In contrast to vapor-only studies, single and repeated exposures to JP-8 aerosol resulted in severe consequences. F344 rats were exposed nose-only to an aerosol and vapor mix of JP-8 for 1 h/day, 5 days/week for 7, 28, or 56 days to study pulmonary changes. Exposure concentrations ranged from 495 to 1094 mg/m^3, and particle size for both exposures averaged 1.1 ± 2.2 μm MMAD. This study was reported in a series of articles and abstracts, the most recent being Pfaff et al. (1995) and Hays et al. (1995) (Table 2-4). Following 7 days of exposure at 495 mg/m^3 or 28 days at 520 mg/m^3, pulmonary resistance was significantly increased in both groups compared with their concurrent control groups, but resistance was not increased compared with baseline values (Pfaff et al. 1995). However, when corrected for body weight, resistance was significantly increased in the exposed groups compared with the control and baseline groups. Dynamic compliance was increased after the 7-day exposure but not after 28 days, indicating an adaptive response. The ratio of lung wet weights to body weights was also increased after the 7-day exposure but not after 28 days of exposure. Analysis of bronchoalveolar lavage fluid (BALF) revealed no differences in cell counts or 6-keto $PGF_{1\alpha}$, a measure of endothelial cell function; pulmonary alveolar clearance (as measured by ^{99m}technetium-labeled diethylenetriamine pentaacetate) was increased as was substance P, a neuropeptide associated with airway reactivity. Light microscopic examination of the lungs found no differences between the exposed and control groups. Compared with the control groups, both exposed groups gained significantly less body weight during the exposures.

Following 56 days of exposure at 813-1,094 mg/m^3, lung epithelial permeability was significantly increased; this effect was no longer present in the combined lower-dose group (average concentration reported at 500 mg/m^3) (Hays et al. 1995). Electron microscopy revealed pulmonary inflammation with degeneration of Type II epithelial cells after 7 days of exposure at the high con-

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centration and after 28 and 56 days of exposure at both 495 and 1094 mg/m^3, the changes partially resolving in the low-dose group at 56 days. In general, the lungs had a normal appearance at 56 days. No liver pathology or liver enzyme changes were reported after 7 or 28-day exposures to aerosolized JP-8 at 5,000 or 1,000 mg/m^3 (Parton et al. 1993).

Male Sprague-Dawley rats were exposed whole-body to 1,000 mg/m^3 JP-8 vapor for 6 h/day, 5 days/week for 6 weeks (Witzmann et al. 2000a). During and following the exposures, there were no exposure-related deaths or visible signs of irritancy or distress. The mean body weight of the exposed group was slightly lower than that of the controls during exposure, but was similar to that of controls by 14 days postexposure (data not provided). At 82 days postexposure, liver and kidney were examined for changes in protein abundance and protein charge modification. Proteomic analysis revealed nonsignificant quantitative and qualitative alterations in the expression of lamin A in the liver and of 10-formyltetrahydrofolate dehydrogenase and glutathione-*S*-transferase in the kidneys of the exposed rats. Protein charge modification index analysis indicated significant alterations in the expression of lamin A and 10-formyltetrahydrofolate.

JP-5. Groups of 20 male F344 rats inhaled JP-5 vapor at 2,500 or 5,000 mg/m^3 for 1 h (MacEwen and Vernot 1985). Generation of the 5,000 mg/m^3 concentration resulted in development of an aerosol, which coated the fur of the animals. Ocular irritation as evidenced by mild lacrimation, eye closure, and pawing at the eyelids was observed during exposure at 5,000 mg/m^3. Eye irritation (undefined) also occurred in animals exposed at 2,500 mg/m^3. Lethargy and delayed righting reflex, which continued 2 h postexposure, were present at 5,000 mg/m^3 but not at 2,500 mg/m^3. During the postexposure period, there were some urinary biochemical changes, and at death, the animals exhibited hyaline droplet formation in the kidneys (see Sections 4.2 and 4.4.1 for a discussion of this nephropathy). There were no effects on body-weight gain or on liver or kidney weights in rats killed at 24 h or 28 days postexposure.

Groups of 75 male and 75 female F344 rats were exposed continuously to JP-5 petroleum or shale-derived vapor at 0, 150, or 750 mg/m^3 for 90 days (Cowan and Jenkins 1981; Cowan et al. 1981; Gaworski et al. 1984; 1985). In addition to the vapor concentration, an aerosol may have been present in the chamber at the higher concentration. Male rats exposed to both concentrations of fuels from both sources developed renal tubular epithelial necrosis. Reduced body-weight gain, increased kidney/body-weight ratios, and slightly elevated blood urea nitrogen and creatinine levels were consistent with that effect. Those effects were absent in female rats, although exposure to the higher concentration of shale JP-5 resulted in a slight reduction in body-weight gain. Mild liver changes and mild nasal inflammation also occurred in rats exposed to shale JP-5, but these changes were not dose-related.

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3.2.2.3. Mice

JP-8. The sensory irritation associated with JP-8 as well as that of JP-4 and JP-8+100 were evaluated by Whitman and Hinz (2001) using the standard RD_{50} test (ASTM E981-84 [1988]). Groups of four young male Swiss-Webster mice were administered the test compounds separately for a 30-min period via a head-only exposure system. The test atmospheres were administered as either vapor only (JP-4) or combined vapor and aerosols (JP-8 and JP-8+100). As noted, achieving high concentrations of JP-8 in laboratory chamber studies requires introduction of a mixture of vapor and aerosol (NRC 2003). Group mean vapor concentrations were 685, 956, 1,888, and 11,430 mg/m^3 for JP-4 vapor; 681, 1,090, 1,837, and 3,565 mg/m^3 for JP-8 vapor and aerosol; and 777, 1,519, and 2,356 mg/m^3 for JP-8+100 vapor and aerosol. The proportion of aerosol in the JP-8 exposures ranged from 3% at 681 mg/m^3 to 35% at 3,613 mg/m^3. An additional group of four mice was exposed to JP-8 at 708 mg/m^3 in the vapor-only phase. The test atmospheres were generated using a syringe pump to deliver the fuel to the inside surface of a heated glass countercurrent generator. The heated vapors were drawn into the exposure chamber with the air supply. Aerosol atmospheres were generated with a nebulizer. Atmospheres were collected on charcoal sorbant tubes, and exposure concentrations were determined as total hydrocarbon concentration via gas chromatography. These analyses showed that the lower molecular weight hydrocarbons were more abundant in the vapor samples than in the vapor and aerosol samples.

Exposure to JP-4, JP-8, and JP-8+100 evoked breathing patterns characteristic of upper airway sensory irritation. There was no indication of pulmonary irritation or narcosis at any of the concentrations examined. For JP-4, group mean respiratory rates decreased from baseline values by 11, 28, 51, and 59% at mean exposure concentrations of 685, 956, 1,888, and 11,430 mg/m^3, respectively. The calculated RD_{50} for JP-4 was 4,842 mg/m^3. For JP-8, group mean respiratory rates were decreased from baseline by 22, 38, 46, and 50% at mean exposure concentrations of 681, 1,090, 1,837, and 3,565 mg/m^3, respectively (Table 2-5). The RD_{50} for JP-8 was 2,876 mg/m^3. At the vapor-only exposure of 708 mg/m^3, the respiratory rate was decreased by 28%, which is similar to the decrease of 22% observed with the vapor and aerosol concentration of 681 mg/m^3. It should be noted that the irritant response tapered off at the highest exposure, that is, reductions in respiratory rate were similar at 1,837 mg/m^3 (46%) and 3,565 mg/m^3 (50%). For JP-8+100, group mean respiratory rates were reduced by 18, 53, and 63% at mean exposure concentrations of 777, 1,519, and 2,356 mg/m^3, respectively. The RD_{50} for JP-8+100 was 1,629 mg/m^3. Mice in all JP-8 groups and mice in the higher exposure groups of JP-4 and JP-8+100 exhibited a concentration-dependent delay in recovery of respiratory rate in the 10 min following the exposures. However, all mice appeared normal at clinical observations prior to, during, and immediately after the exposures. For

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TABLE 2-5 RD_{50} Test of JP-8 with Swiss-Webster Mice

Concentration (mg/m^3)	Decrease in Respiratory Rate (%)
681	22
1,090	38
1,837	46
3,565	50
2,876	Calculated RD_{50}

Source: Adapted from Whitman and Hinz 2001.
Abbreviation: RD_{50}, concentration that reduces the respiratory rate by 50%.

these jet fuels, particularly JP-8, the slope of the respiratory rate vs concentration flattened at the highest exposure, that is, the highest concentration, 3,565 mg/m^3 elicited a 50% response, which is similar to the RD_{50}. This flattening of the response at high concentrations occurs with hydrocarbon solvents and may reflect coverage of all of the nasal tissue with the vapor and liquid.

It is interesting to note that the RD_{50} of *n*-nonane (*n*-C_9), the primary component in the airborne volatile fraction of JP-8 in aircraft maintenance areas could not be measured at concentrations between 1,000 and 1,500 ppm (5,246-7,869 mg/m^3). These concentrations failed to reduce the respiratory rate by 50% in CF-1 male mice (Kristiansen and Nielsen 1988). The same was true for decane and undecane. However, reduced respiratory rates were measured for heptane (*n*-C_7). The RD_{50} for heptane was between 15,600 and 17,400 ppm, and the RD_{50} for octane was greater than 10,000 ppm. The authors noted that the concentrations tested for the respective chemicals were higher than 50% saturation at room temperature. In another study, an 8-h exposure of male Sprague-Dawley rats to *n*-nonane at 2,414 ppm failed to cause death (Nilsen et al. 1988), but 8-h exposures at $\geq$ 3,560 ppm resulted in lethality.

Several studies in mice that delivered JP-8 in the form of an aerosol, identified changes in protein expression in different organs. The toxicologic significance of these changes and their relationship to human health is unknown. Following a 1-h/day, 7-day, nose-only exposure of aerosolized JP-8 to male Swiss-Webster mice at 0, 1,000, or 2,500 mg/m^3, molecular biomarkers in terms of protein changes in the lungs were analyzed by gel electrophoresis (Witzmann et al. 1999). Of 796 proteins resolved by electrophoresis, 42 were significantly increased or decreased by exposure to 2,500 mg/m^3. The affected proteins were identified as related to protein synthetic machinery; toxic and metabolic stress and detoxification systems; ultrastructural damage; and functional responses to carbon dioxide handling, acid-base homeostasis, and fluid secretion. The study authors described the results as a significant but comparatively moderate effect of JP-8 aerosol on protein expression. In a similar study, protein expression in the cytosol fraction of kidneys was analyzed following exposure of male Swiss-Webster mice to aerosolized JP-8 at 1,000 mg/m^3 for 1 h/day for 5 days (Witzmann et al. 2000b). The roles of the quantitatively altered proteins (6% of the

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974 proteins resolved by electrophoresis) were identified as the same as those altered in the lung. The study authors again concluded that the changes in protein expression were moderate. (Compared with results in the control group, no change in abundance was greater than 34%.)

Groups of 25 male B6.A.D. mice (genetically identical to C57BL/6 except that they are double congenic for nonresponsiveness to aryl hydrocarbon hydroxylase induction and slow *N*-acetylation) were exposed nose-only to air or aerosolized JP-8 at 7, 12, 26, 48, or 118 mg/m^3 for 1 h/day over 7 days (Robledo et al. 2000). Pulmonary function and respiratory permeability measurements and BALF analysis were performed followed by histologic evaluation of the lungs. At 24 to 30 h after the exposures, there were no changes in dynamic compliance or airway resistance in any of the mice. Compared with the control value, respiratory clearance of ^{99m}technetium-labeled-diethylenetriaminepentaacetic acid was approximately doubled in the 7-, 48-, and 118-mg/m^3 dose groups, and there was no increase in the 12- and 26-mg/m^3 groups. bronchoalveolar fluid (BALF) analysis revealed increases in total protein and lactic dehydrogenase and reductions in *N*-acetyl-β-D-glucosaminidase and alveolar macrophages at 48 and 119 mg/m^3. Light microscopic examination revealed minimal and infrequent deterioration of the alveolar-capillary barrier with sporadic areas of erythrocyte accumulation within alveolar spaces at the two higher exposures. Ultrastructural evaluation of the lungs revealed increases in lamellar bodies and vacuolation of alveolar type II epithelial cells and bronchiolar alterations characterized by perivascular edema, Clara cell vacuolization, and necrosis at the two higher doses. Ciliated epithelial cells appeared mostly unaffected except for changes to intercellular spaces. These changes were reversible following a single exposure.

Groups of 100 male and 100 female C57Bl/6 mice were exposed to vapor concentrations of JP-8 of 0, 500, or 1,000 mg/m^3 continuously for 90 days (MacEwen and Vernot 1985; Mattie et al. 1991). Animals were killed immediately after exposure and up to 20 months postexposure. Clinical signs, body weights, and hematologic and clinical chemistry parameters were monitored during exposure. No clinical signs of toxicity or biologically significant changes in hematologic and clinical chemistry parameters were observed. During the 2-week to 20-month recovery period, an increase in mortality of male mice due to necrotizing dermatitis associated with fighting occurred. The incidence (47/100) was the same in both exposure groups. The incidence of fighting-induced dermatitis was also increased in exposed female mice.

JP-5. Groups of 20 male C5BL/6 mice were exposed to JP-5 vapor concentrations of 2,500 or 5,000 mg/m^3 for 1 h (MacEwen and Vernot 1985). Generation of the 5,000 mg/m^3 concentration resulted in production of an aerosol that coated the fur of the animals. Eye irritation was present at both exposure concentrations, but resolved at 2,500 mg/m^3 after termination of exposure. There was no effect on subsequent body-weight gain. One mouse exposed at 5,000 mg/m^3 exhibited hind limb paralysis upon removal from exposure. The paralysis continued with some recovery until scheduled animals were killed at 28 days postexposure. Because none of the other mice or rats in this study exhibited hind

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limb paralysis, the study was repeated with 40 mice exposed at 5,000 mg/m^3. None of the mice in the followup study demonstrated a loss of mobility, indicating the observation made in the first study was not exposure related.

Groups of more than 100 female C57BL/6 mice were exposed continuously to concentrations of JP-5 petroleum- or JP-5 shale-derived vapor at 0, 150, or 750 mg/m^3 for 90 days (Gaworski et al. 1984, 1985). In addition to the vapor concentration, an aerosol may have been present in the chamber at the highest concentration. These exposures had no effect on body-weight gain. Non-dose-related (but statistically significantly increased) incidences of hepatocellular fatty infiltration with vacuolization were observed in the mice exposed to JP-5 from either shale or crude oil sources.

3.2.2.4. Rabbits

An increased concentration of substance P (a selective neurokinin receptor agonist) was present in the lungs of rabbits following chronic exposure to JP-5 (Witten et al. 1990). Substance P may exert a protective effect against toxicity.

3.3. Neurotoxicity

In a series of neurobehavioral studies with adult male Sprague-Dawley rats, Bogo et al. (1983, 1984) dosed groups of 6-10 rats orally (via gavage) with either petroleum- or shale-derived JP-5. Doses ranged from 1 to 24 mL/kg. The control groups received an equivalent amount of water by gavage. Rats were observed for general behavior, overnight activity, food and water consumption, and body-weight changes. Because results were similar among the separate substudies, the general results are summarized here. Food and water consumption and body weight were reduced for 2-3 days after dosing. Overnight home-cage activity increased in rats dosed with 3, 5, or 8 mL/kg, but the hyperactivity was not dose related. Activity was greater in a separate study when rats were dosed with 24 mL/kg. Also in a separate study, home-cage daytime activity increased between 2.5 and 6 h after dosing with 3 or 5 mL/kg; the increase was not observed in control rats or rats given 1 mL/kg. Although rats appeared hypersensitive to touch after dosing, two tests of motor function (the accelerod, which is a shock-motivated skilled test of motor function and a test of aggression) failed to reveal any differences between the control and the JP-5 exposed groups. The authors attributed the hyperactivity at 6 h after dosing to gastric irritation and the rat inability to regurgitate.

In the same study (Bogo et al. 1983), male Sprague-Dawley rats inhaled petroleum- or shale-oil derived JP-5 at concentrations below those resulting in anesthesia. Concentrations of 1,125 mg/m^3 of petroleum-derived JP-5 (reported as decane) or 1,636 mg/m^3 shale-derived JP-5 were administered 6 h/day, 5 days/week, for 35 days. Aside from an increase in drinking-water intake, there were no alterations in behavior or motor function and no changes in neurophysi-

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ologic function (measured as electrical potential over the somatosensory area of the brain) or serum liver enzymes (SGPT and SGOT). There were no histopathologic effects on any organs examined, including the liver.

Groups of 32 adult male Sprague-Dawley rats inhaled either JP-5 at 1,200 mg/m^3 or JP-8 at 1,000 mg/m^3 for 6 h/day, 5 days/week, for 6 consecutive weeks (Rossi et al. 2001). Two groups of 16 rats each exposed to filtered, conditioned air served as controls. Atmospheres were monitored using an infrared spectrophotometer. No aerosol was detected. There were no exposure-related clinical signs, and there were no significant differences in body weight or rate of weight gain between the exposed groups and respective control groups. Sixty-five days after the last exposure, the rats were subjected to 10 neurobehavioral tests consisting of startle response (two tests), appetitive reinforcer approach sensitization, forelimb grip strength, total locomotor activity, tail flick response, social interaction with conspecifics, passive avoidance, forced swim test, and a water maze. Significant differences in response between exposed and control groups were observed in 2 of the 10 tests: the number of seconds for approach to the novel appetitive stimulus was increased over those of the respective control for both exposed groups, but the difference was significant only for the group exposed to JP-8. Times spent within different parts of the test system did not differ among exposed and control groups, indicating similar spontaneous locomotor activity. The appetitive stimulus approach sensitization test is hypothesized to quantify dopamine system sensitization. JP-5-exposed rats exhibited significantly increased forelimb grip strength compared with their control group. The forelimb grip strength test evaluated muscle strength and inhibition of motor response activity. The increase in grip strength was not observed in rats exposed to JP-8.

Following the above neurobehavioral tests (85 days postexposure), all rats were killed and the blood and five different regions of the brain were analyzed for norepinephrine, dopamine, 3,4-hydroxyphenylacetic acid, homovanillic acid, serotonin, and 5-hydroxyindoleacetic acid (Rossi et al. 2001). A single control value was used for comparison. The only significant differences in blood neurotransmitters were in the levels of 5-hydroxyindoleacetic acid, a metabolite of serotonin. Compared with the control values, 5-hydroxyindoleacetic acid was significantly increased in JP-5-exposed rats and significantly reduced in JP-8-exposed rats. However, circulating concentrations of serotonin did not differ among control and exposed groups. Compared with control rats, JP-5-exposed rats exhibited increased ($p < 0.05$) dopamine in the hippocampus, level 3,4-dihydroxyphenylacetic acid in the cerebral cortex, and significantly reduced homovanillic acid in the hippocampus. Compared with the control rats, JP-8-exposed rats had decreases of 3,4-dihydroxyphenylacetic acid in both the cerebellum and brainstem. The relationship between the increased approach to a novel appetite stimulus and the changes in blood and brain neurotransmitters and their metabolites is not understood. The authors concluded that exposure to JP-5 or JP-8 did not alter basic sensory, motor, or inhibitory functions and did not modulate the capacity of rats to lean and recall tasks of minimal complexity.

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In a continuation of the above study, groups of 16 adult male Sprague-Dawley rats were exposed (whole body) to JP-8 vapor at 0 (room air), 500, or 1,000 mg/m^3 for 6 h/day, 5 days/week, for 6 weeks (Ritchie et al. 2001c). The 1,000 mg/m^3 concentration was the highest vapor concentration that could be generated without formation of an aerosol. Chamber atmospheres were quantified by measuring hexane with infrared spectrometry. Mean body weight of the exposed and control groups did not differ during exposure or during the 7-day postexposure observation period. Clinical observations found no changes in health status or neurobehavioral activity during this time. Following exposure, the rats were rested for 65 days and then tested for ability to acquire and perform operant tasks of increasing difficulty from simple lever pressing to the learning of 3-lever, 4-response operant chains. Rats were slightly food-deprived in order to facilitate the food-reward tests. In the first three measurements (lever acquisition, fixed ratio, and lever spatial reversal), there was no significant difference between the control group and the groups previously exposed at 500 mg/m^3 or 1,000 mg/m^3 for any measured parameter. In the stimulus reversal and the incremental repeated acquisition task, significant differences between the 500- and 1,000-mg/m^3 groups were observed on some days. Although there were more incorrect responses in the 1,000-mg/m^3 group compared with the control group, these differences were not statistically significant. The attainment of significance for the high-dose group compared with the low-dose group (but not with the control) was due to the superior performance of the low-dose group on operant tasks of moderate or greater difficulty.

Following the operant training, four rats from each exposure group were killed, and five regional areas of the brain were analyzed for concentrations of norepinephrine, dopamine, 3,4-dihydroxyphenylacetic acid, serotonin, homovanillic acid, and 5-hydroxyindoleacetic acid (Ritchie et al. 2001c). Compared with the control results, there was significantly more dopamine in the cerebral cortex and 3,4-dihydroxyphenlyacetic acid (a metabolite of dopamine) in the brainstem of samples from the 500- and 1,000-mg/m^3 groups. Dopamine concentrations were similar in the 500- and 1,000-mg/m^3 groups, and 3,4-dihydroxyphenylacetic acid was higher in the 500-mg/m^3 group than in the 1,000-mg/m^3 group. There were no significant differences compared with the control results for neurotransmitters or neurotransmitter metabolites in any other regions of the brain.

Baldwin et al. (2001) reported on behavioral and memory alterations of rats exposed to aerosolized JP-8. Five F344 Brown Norway rats was exposed (nose-only) to 1,059 mg/m^3 for 1 h/day for 25 days followed by exposure at 2,491 mg/m^3 for 1 h/day for 3 days (overall mean exposure 1,237 mg/m^3). An additional group was administered aerosolized substance P for 15 min following JP-8 exposure; a control group inhaled air only. Potential alterations in behavior were tested with the EPA functional observational battery (FOB) and two versions of the Morris swim task to address spatial and visual discrimination. Substance P was tested to determine if potential deleterious effects of JP-8 exposure on behavior and spatial learning could be ameliorated. During exposure, tran-

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sient body-weight loss was observed in the two exposed groups compared with the control; the weight loss resolved by day 19. The two exposed groups showed similar behaviors during the FOB and so were compared as a group to the concurrent control. JP-8 exposed rats, tested on days 4, 9, 14, 19, and 24, showed more rearing activity (day 24), greater arousal (days 9 and 24), and less grooming behavior (day 19) than controls. Although gait and limb strength were unaffected, hind claw contracture was observed in several JP-8 exposed rats over the 28-day period compared with only a single observation in the control group. In the Morris swim test, JP-8 exposed rats swam significantly faster than controls during testing, but there were no significant differences between the exposed and control performance in either the visual discrimination or spatial version of the Morris swim tank task.

3.4. Immunotoxicity

Although emergency exposures are expected to be to spills resulting in primarily vapor exposures, many of the following studies addressed the immunotoxicity of jet fuel aerosols. Aerosols are not generated during aircraft refueling operations. Aerosols will only be developed during aircraft foam removal operations (occupational exposure) or aircraft engine cold starts (occupational exposure). Nevertheless, these studies are summarized here for complete coverage of the database. It should be noted that the lung has an innate immune system that responds to inhaled microbes and particles (University of California 2006). Lung epithelial cells rapidly release antimicrobial polypeptides in response to microbe or particle inhalation, including aerosols. The innate immune response also recruits a secondary adaptive immune response. The immunosuppression response of the thymus and spleen are not fully understood.

Groups of 12 male C57BL/6 mice were exposed (nose-only) to aerosolized JP-8 for 1 h (Robledo and Witten 1998) at concentrations of 0, 5.0, 11.7, 27.8, 50.0, and 112.5 mg/m^3. At 24 to 30 h after exposure, alveolar permeability, BALF markers, pulmonary function, and histopathology were evaluated. Pulmonary function (dynamic compliance, static compliance, and total resistance; measured with a pneumotachograph) in anesthetized, tracheostomized mice did not differ between control mice and those exposed to jet fuel. Alveolar permeability (as indicated by the clearance of ^{99m}technetium-labeled diethylenetriamine pentaacetate) increased in a dose-dependent manner, with increases of 128% and 173% at the 50.0 and 112.5 mg/m^3 concentrations, respectively. The following BALF parameters were significantly increased in a concentration-dependent manner beginning with the stated concentration: total protein, 112.5 mg/m^3; lactate dehydrogenase, 27.8 mg/m^3; *N*-acetyl-β-D-glucosaminidase, 27.8 mg/m^3. Total cell counts were increased significantly and alveolar macrophages were reduced significantly at 112.5 mg/m^3. Light microscopy revealed alveolar-septal thickening, monocytic infiltration, and scattered areas of interstitial edema, which became consistent at 112.5 mg/m^3. At this concentration, ultra-

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structural evaluation revealed an increase in the size and number of surfactant-secreting lamellar bodies of alveolar type II cells and moderate to severe vacuolization of smooth endoplasmic reticulum with normal-appearing mitochondria in nonciliated bronchiolar (Clara) cells. Sporadic edema in terminal bronchioles and areas of goblet cell hyperplasia in small bronchioles were also evident. Adjacent ciliated epithelial cells were not affected.

Male and female C57BL/6 mice exposed under the same protocol as that of Robledo and Witten (1998) above but exposed for 7 days were examined for changes in the immune system 24 h after the last exposure (Harris et al., 1997a). Exposure concentrations of JP-8 were 0, 100, 250, 500, 1,000, or 2,500 mg/m^3. Exposure to ≥ 500 mg/m^3 resulted in significant reductions in wet weights of the spleen and thymus. Counts of total viable cells from these organs indicated similar effects with cell counts lower in the spleen at exposure concentrations of ≥ 500 mg/m^3 and in the thymus at ≥ 100 mg/m^3. Changes in the numbers of immune cells in the lymph nodes, bone marrow, and peripheral blood also occurred, with a general reduction at the lowest exposure concentration (with the exception of bone marrow), increases at the next three higher concentrations, and reductions at the highest concentration. Flow cytometric analyses revealed loss of different immune cell subpopulations in different organs. In general, a concentration of 2,500 mg/m^3 appeared to be immunotoxic, and mitogenesis assays with splenic cells revealed decreased immune function.

In a followup to the above study, the recovery of mice exposed to JP-8 at 1,000 or 2,500 mg/m^3 was studied at 1, 7, 14, 21, and 28 days postexposure (Harris et al. 1997b). Spleen and thymus weights generally recovered by 7 days postexposure (both concentrations) with significantly increased spleen and thymus weights (over the control) for some intervals. Viable splenic immune cell numbers remained significantly lower than control values, but viable thymic immune cells recovered by 21 days postexposure. Immune cell numbers of lymph nodes, bone marrow, and peripheral blood had generally recovered by 7 days postexposure. Immunosuppression as measured by mitogenesis assays indicated recovery at 28 days postexposure for the 1,000-mg/m^3 group but not for those exposed at 2,500 mg/m^3. In reporting preliminary results of a study with C57BL6 mice, Harris et al. (2000) found that transient immune cell loss followed a single 1-h exposure at 1,000 mg/m^3, but partial to full recovery was observed in most organs (spleen, thymus, and bone marrow) at 24 h postexposure.

Harris et al. (2001) reported preliminary results of a study in which timed-pregnant C57BL/6 mice were exposed to JP-8 to 1,000 mg/m^3 for 1 h/day either early or late in gestation (days of exposure were not reported in the available abstract). Dams were allowed to deliver and numbers of offspring by sex were tallied. When the offspring were 6-8 weeks old, dams and surviving offspring were killed, and immunologic assays were performed. Fewer pups were born to JP-8-exposed dams as compared with air-exposed controls, and significantly fewer male offspring were born after the dams inhaled jet fuel. At 8 weeks post-in-utero exposure, pups of JP-8-exposed dams had lower immune organ weights,

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decreased immune organ cell numbers, and suppressed immune function. This observation was particularly true for male offspring.

Male Swiss-Webster mice were exposed nose-only to aerosolized JP-8+100 at concentrations of 1,000 or 2,500 ppm for 1 h/day for 7 days to study effects on glutathione S-transferase activity in the eye and brain and effects on tissue proteins. Immunohistochemical assays showed increases of this conjugating enzyme in the radial glia of the cerebellum and retina and a reduction in the inner layers of the retina (Kornguth 1998). Electrophoresis of the proteins of the cytosolic fractions of kidney, liver, and lung tissues and serum of the exposed mice showed moderate quantitative changes in the proteins of these tissues (Witzmann et al. 1999, 2000a,b).

Keil et al. (2003) reported that repeated prenatal exposure to JP-8 at very large oral bolus doses (1,000 or 2,000 mg/kg/day on gestation days 6-15) can target the developing murine fetus and result in impaired immune function and altered T_4 levels in adulthood. At weaning, these doses had no effect on body or organ weight, splenic and thymic cellularity, splenic lymphocyte subpopulations, or T-cell subpopulations.

In addition to the inhalation and oral studies cited above, dermal application of JP-8 to mice and rats has also produced a systemic immunosuppressive effect (Ullrich 1999; Ullrich and Lyons 2000; Kabbur et al. 2001). Although the steps in the immune response are not fully understood, it appears to be mediated via an increase in cytokines, such as interleukin-10.

3.5. Developmental and Reproductive Effects

A total of 150 time-mated female Crl:CD7 rats were administered JP-8 fuel on days 6-15 of pregnancy by gavage at doses of 0, 500, 1,000, 1,500, or 2,000 mg/kg/day (Cooper and Mattie 1996). Rats were killed on day 28 of pregnancy and fetuses were examined for malformations. The average body weight of dams as well as of male and female fetuses was significantly reduced at the two highest concentrations. The number of pregnant females, number of corpora lutea per female, number of fetuses per female, and post-implantation loss were all within normal limits. There was no significant difference in the number of malformations between the control and any treated group.

Mattie et al. (2000) reported on the reproductive toxicity of JP-8 in both male and female Sprague-Dawley rats treated by gavage. In the first part of the study, young male Sprague Dawley rats, weighing 180-220 g were administered 0, 750, 1,500, or 3,000 mg/kg daily for 70 days. Treatment continued during mating to untreated females (days 70-90) after which the males were killed. General toxicity, fertility (pregnancy rate and gestation duration for females) and sperm parameters of the males were evaluated. Beginning with days 26-42 of treatment, mean body weights of the groups were lower in a dose-dependent manner with males in the 3,000 mg/kg group losing weight over the treatment period. Pregnancy rates were low in all groups with percent of females pregnant

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in the 0, 750, 1,500, and 3,000 mg/kg groups of 47, 39, 57, and 53%, respectively. Mean gestation lengths were similar among groups. Epididymal sperm analyses revealed no differences among groups in sperm concentration or motility parameters. Results of microscopic examinations of male rats were reported in Matttie et al. (1995). Male rat-specific α2u-microglobulin nephropathy was observed. Gastritis and a perianal dermatitis were also observed. Although several liver enzymes were increased in the treated groups (aspartate aminotransferase and alanine aminotransferase), the increases were not dose-dependent and liver weights were not increased.

Mattie et al. (2000) also administered JP-8 by gavage to groups of 35 young female Sprague-Dawley rats (180-200 g) at daily doses of 0, 750, or 1,500 mg/kg for 21 weeks. The 21-week period included 90 days of treatment followed by treatment during cohabitation, gestation, delivery, and lactation. Males were not exposed. Females were killed one day after weaning (day 22 of lactation). Litters were standardized to 4 males and 4 females. Pregnancy rate and gestation duration were recorded for the dams. Litter size, number born dead and pup weights (by sex) on various days through postnatal day 90 were recorded. On the day prior to killing, urine was collected for urinalysis; at death, blood was collected from 10 dams/group for hematology and clinical chemistry evaluation, and organs were collected, weighed, and subjected to gross and microscopic examination.

Beginning with week 7, body weights of exposed groups were slightly lower than the control group weight. By week 8 and continuing to week 20, the difference in body weight compared with the control weight was significant in the 1,500-mg/kg/day group. Mean terminal body weights (week 21) were similar among all groups. Pregnancy rates, gestation length, litter size, and percent live pups were similar among control and exposed groups. On postnatal day 1, group mean pup weights of all exposed groups were within 95% of the control pup weight. On postnatal days 4, 14, and 21, there was a trend for decreased pup weight with increasing dose; the difference was statistically significantly lower on those days that correlated with lower maternal body weights. This difference in pup groups was no longer evident by postnatal day 90.

There were no exposure-related clinical signs in dams throughout the second part of the study, and there were no effects on mortality. As noted, body weights of dams were reduced, the lowered weight attaining significance primarily in the 1,500-mg/kg/day group. At study termination, absolute liver weights and liver weights relative to both body and brain weights were significantly increased in the 750- and 1,500-mg/kg/day groups. Kidney weight relative to brain weight was also increased in the two higher dose groups. Changes in urine and hematology and clinical chemistry parameters were observed but were not dose related. Hyperplasia of the stomach and perianal dermatitis were observed microscopically. Incidences were dose-dependent, attaining statistical significance in the 750-mg/kg/day (hyperplasia of the stomach) and 1,500-mg/kg/day groups (anal dermatitis and hyperplasia of the stomach).

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Briggs (2001) exposed male Sprague-Dawley rats (whole body) to JP-8 at 0, 250, 500, or 1,000 mg/m^3 for 6 h/day, 5 days/week, for 6 weeks to assess the potential for JP-8 to produce reproductive toxicity. No signs of toxicity were observed during the exposure period. After an 87-day recovery period, there were no exposure-related differences in sperm concentration or motility among control and exposure groups. Microscopically, no lesions were observed in the testes. Although biochemical studies revealed some differences in protein expression in the testes (Witzmann et al. 2003), these changes did not interfere with normal sperm maturation or function.

3.6. Genotoxicity

Inhalation of JP-5 failed to increase sister chromatid exchanges or micronuclei in peripheral lymphocytes of beagle dogs. JP-5 was not mutagenic in *Salmonella typhimurium* standard preincubation tests, with or without metabolic activation (ATSDR 1998).

JP-8 was not mutagenic in *Salmonella* tester strains TA1535, TA1537, TA1538, TA98, and TA100 either with or without metabolic activation by S9; mouse lymphoma assay; or dominant lethal assays (Brusick and Matheson 1978b; ATSDR 1998). JP-8 was cytotoxic at the higher concentrations tested.

3.7. Chronic Toxicity and Carcinogenicity

No tumors were formed in rats or mice exposed at 500 or 1,000 mg/m^3 continuously for 90 days and killed up to 21 months later (Mattie et al. 1991). With the exception of an increased incidence of liver adenomas in female mice exposed to shale-derived JP-5 at 150 or 750 mg/m^3 for 90 days and killed 19 or 24 months later, JP-5 was negative for tumors (Gaworski et al. 1985). Tumor data in laboratory animals exposed to hydrocarbon fuels were further evaluated by Bruner (1984). No renal tumors were observed in rats following the 90-day continuous exposure to 750 mg/m^3 and observed for a lifetime. Liver adenomas were not increased in female mice exposed to petroleum-derived JP-5 or in male mice or male or female rats exposed to JP-5 from either source.

JP-5 was not carcinogenic to male or female B6C3F$_1$ mice when applied dermally for 2 years at doses of 0, 250, or 500 mg/kg in acetone (NTP 1986). There were increased incidences of chronic dermatitis, judged as mild and moderate in severity in the low- and high-dose groups, respectively, at the site of application. Skin tumors were found in C3H mice exposed dermally with neat Jet A twice a week for 2 years on an intermittent schedule (Freeman et al. 1993) and in C3H mice exposed dermally three times a week (25 mg/dose) for up to 105 weeks (Clark et al. 1988).

Following a review of skin painting studies with a variety of petroleum distillates, NRC (1996; 2003) and Nessel (1999) concluded that there is only tenuous evidence that these fuels pose a carcinogenic hazard after topical appli-

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cation, and the induction of tumors at the site of (excessive) application depends on skin irritation and subsequent cell proliferation.

3.8. Summary

Jet fuels in the vapor form exhibit low acute and chronic toxicity in animal studies. Regardless of the source of the fuel or the differences in distillation temperatures, the toxicities appear to be similar in all tested species.

No deaths occurred in rats and mice exposed for 1 h to JP-5 aerosol at a concentration of 5,000 mg/m^3 (MacEwen and Vernot 1985), in rats exposed to JP-8 for 4 h at either a vapor concentration of 3,430 mg/m^3 or a vapor plus aerosol concentration of 4,440 mg/m^3 (Wolfe et al. 1996). Furthermore, no deaths and no effects applicable to humans occurred during a 90-day continuous exposure of rats or mice to vapor of JP-8 at 1,000 mg/m^3; there were no effects on the lungs (Mattie et al. 1991).

Reproductive parameters in male rats were not affected, either immediately following oral intubation (Mattie et al. 2000) or following JP-8 inhalation for 6 weeks with a recovery period (Briggs 2001).

Long-term exposures (90 days) to JP-8 and other jet fuels resulted in lower body-weight gain and produced nephropathy specific to male rats. The nephropathy, characterized by hyaline droplet formation and necrosis is exclusive to male rats (Bruner and Pitts 1983). The male rat nephropathy and resulting kidney cancer associated with exposure to jet fuels is not relevant to humans (see Section 4.2. Mechanism of Toxicity). The jet fuels discussed here (JP-5 and JP-8) are not carcinogenic or genotoxic and are not reproductive or developmental toxicants.

Aerosols present along with the vapors of the jet fuels are more toxic than vapors alone as determined by histopathologic effects on the lungs. A 1-h exposure of mice to a concentration of 112.5 mg/m^3 resulted in no changes in several pulmonary function parameters, but several reversible biochemical and ultrastructural changes were observed in the lungs (Robledo and Witten 1998). The implication of these changes is unknown.

JP-8 when delivered in the aerosol phase in nose-only exposures induces more severe effects than exposures to the vapor or vapor and aerosol phase formed under most conditions. Under this exposure condition, repeated exposures of rats and mice resulted in pulmonary responses characterized by increased respiratory permeability, peribronchiolar edema, and cellular necrosis at concentrations as low as 48 mg/m^3 for 1 h daily (Robledo and Witten 1998, Robledo et al. 2000). The immune system is a target of JP-8 in aerosol form (see Bruckner and Warren 2001). Daily repeated 1 h exposures at concentrations of 1,000 or 2,500 mg/m^3 resulted in decreases in immune organ weights and viable immune cell numbers with a decrease in immune system function; these effects were only partially reversible after 1 month (Harris et al. 1997a,b). Aerosolized

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JP-8 at a concentration of 4,440 mg/m^3 for 4 h caused no gross exposure-related lesions; histopathologic examinations were not performed (Wolfe et al. 1996).

Rodent studies with repeated exposures show JP-8 can induce changes in protein expression in the liver, kidney, lungs, and testes (Witzmann et al. 1999, 2000a,b, 2003) and significant changes in pulmonary (Pfaff et al. 1995; Robledo et al. 2000) or immune system function (Harris et al. 1997a,b) (all from Rossi et al. 2001. The altered protein responses are indicative of possible repair and regeneration and detoxification mechanisms and are present long after exposure has ceased. These health effects or biomarkers of aerosol exposure have not been reported in fuel-exposed humans.

The jet fuels discussed here (JP-5 and JP-8) are not carcinogenic or genotoxic and are not reproductive or developmental toxicants.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No information was located that specifically addressed the absorption, distribution, or metabolism of JP fuels following oral, dermal, or inhalation exposures. Effects following human and animal exposures lend indirect evidence to the fact that absorption occurs by these routes. Because jet fuel is a mixture of chemicals, the toxicokinetics are complex. Many aliphatic, alicyclic, and aromatic hydrocarbons are hydroxylated, conjugated with sulfate or glucuronic acid, and eliminated in the urine (Cavender 1994a,b,c). See NRC (1996; 2003) for a review of the toxicokinetics of components of jet fuels: benzene, alkylbenzenes (toluene and xylenes), and C9-C13 aliphatic and aromatic hydrocarbons. Most JP-8 components are metabolized or oxidized primarily in the liver by cytochrome P-450/CYP2E1. Pharmacokinetic modeling of *n*-nonane, based on blood and tissue partition coefficients from a series of inhalation studies with F344 rats at 100, 500, and 1,000 ppm, predicts that human brain concentration during a 4-h exposure at 1.8 ppb would be 0.1 mg/L (Robinson 2000). *n*-Nonane is a lipophilic compound (log K_{ow} of 5.65) that preferentially concentrates in brain tissue (Zahlsen et al. 1990; 1992). PBPK models of uptake and clearance of individual components, such as *n*-decane, have been developed, but the authors reported that the model needs refining before predictions of tissue and blood concentrations at low concentrations of decane vapor can be made (Perleberg et al. 2004).

There have been investigations of the pharmacokinetics of combinations of $\geq$ 3 aromatics and/or long-chain aliphatics (Pedersen et al. 1984; Zahlsen et al. 1990, 1992; Lof et al. 1999). There have also been efforts to develop physiologically based pharmacokinetic (PBPK) models for complex mixtures (Tardif et al. 1997; Haddad et al. 2001). Dennison et al. (2003) developed a chemical lumping approach to analyze the effects of gasoline on the kinetics of individual aromatic components from gas uptake studies. Gasoline contains many of the

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same hydrocarbons as JP-8. The model assumes that essentially all of the components of gasoline serve as competitive inhibitors of oxidation of the other components. Campbell and Fisher (2007) developed a PBPK model to assess the effect of JP-8 vapor on individual component kinetics of the selected hydrocarbons *m*-xylene and ethylbenzene. At concentrations of JP-8 vapor at 390, 1,100, or 2,700 mg/m^3, clearance of hydrocarbons was rapid, concentrations of monitored components decreasing in concentration from 30% to 70% by 0.5 h post-exposure. The model described the kinetic binary interaction between *m*-xylene and ethylbenzene and adequately described the impact of the remaining aromatic fraction of the JP-8 exposure on the kinetics of *m*-xylene and ethylbenzene.

4.2. Mechanism of Toxicity

Aliphatic and alicyclic hydrocarbons cause CNS depression (narcosis) and asphyxia following acute exposures to high concentrations (Cavender 1994a,b, c; Bruckner and Warren 2001). Exposure to high concentrations may cause excitement, loss of equilibrium, stupor, and coma. The effectiveness of the individual components of jet fuels as CNS depressants is related to their volatilization, potency, and blood/air partition coefficients (NRC 1996). Recovery from CNS effects is rapid and complete in the majority of cases.

Because hydrocarbons are lipophilic, they partition into and accumulate in neuronal membranes and myelin. The more lipophilic the hydrocarbon is (that is, the higher its neuronal tissue:blood partition coefficient), the more potent a CNS depressant it is. The mere presence of hydrocarbons has generally been thought to disrupt the ability of the neuron to propagate an action potential and repolarize. Recent research has revealed that hydrocarbons might act by more specific mechanisms and might affect specific neurotransmitters and membrane receptors (that is, by enhancing gamma-aminobutyric acid[A]) receptor function or by activating dopaminergic systems). Hypotheses and pertinent experimental results have been published by a number of researchers, including Mihic et al. (1994), Engelke et al. (1996), Cruz et al. (1998), and Balster (1998).

In rodents, exposure to JP-8 vapor at 500 mg/m^3 increases activity, whereas exposure to higher concentrations (1,000 mg/m^3) may result in modulation of the capacity to learn or perform difficult tasks. These exposures have also been shown to affect the concentrations of the neurotransmitter dopamine and its metabolite 3,4-dihydroxyphenylacetic acid in different regions of the brain (Ritchie et al. 2001c). In another study, rats inhaling JP-8 at 1,000 mg/m^3 exhibited a significant increase in approach to a novel appetitive stimulus and significantly decreased levels of 3,4-dihydroxyphenylacetic acid in both the cerebellum and brainstem regions (Rossi et al. 2001). The relationship of changes in levels of neurotransmitters in the brain to activity level and task performance is unknown.

Many volatile hydrocarbons are of low acute toxicity. Concentrations that cause CNS depression are generally not injurious to the lung. CNS depression in

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rats and mice was observed with JP-5 at 5,000 mg/m^3 (MacEwen and Vernot 1985) but not in mice inhaling JP-8 at 3,565 mg/m^3 for 30 min (Whitman and Hinz 2001). The aromatic hydrocarbons are more toxic than the aliphatic and alicyclic hydrocarbons but, due to their lower boiling point, are present to a much smaller extent in jet fuels. The interactions of the individual components were not predictable with current information. These volatile hydrocarbons can be used as biomarkers of exposure in jet fuel exposed workers. For example, acute increases in benzene and toluene have been measured in the blood, urine, and exhaled breath of chronically exposed workers (Smith et al. 1997; Pleil et al. 2000). Some hydrocarbons are also primary skin irritants.

Long-term exposure to some hydrocarbons results in α_{2u}-globulin nephropathy and associated carcinogenicity specific to male rats (Bruner and Pitts 1983; Swenberg 1993; Bruckner and Warren 2001). The nephropathy is characterized by hyaline droplet formation and necrosis of kidney cells. The toxic effect is attributed to the α_{2u}-microglobulin protein, which is specific to the male rat. The α_{2u}-microglobulin protein is synthesized in the liver of male rats and is readily excreted in the glomerular filtrate (Bruner et al. 1993; Swenberg 1993). The mechanism leading to nephropathy, necrosis, cell proliferation, and neoplasms involves the ability of select hydrocarbons to combine with the protein to form poorly digestible complexes and prevent efficient catabolism of the protein following resorption from the glomerular filtrate. The tubular epithelial cells become engorged with the protein, resulting in metabolic disturbances followed by cell death and exfoliation. Exfoliated necrotic cells form tubular casts that plug the nephron near the corticomedullary junction. The casts become mineralized and may be flushed into the medullary segments where they may remain. α_{2u}-Microglobulin nephropathy is also specific to male rats. The protein is not synthesized in humans (EPA 1991). Therefore, this adverse effect is not relevant to human exposure to jet fuels. The incidence of renal tumors in male rats induced by chemicals causing α_{2u}-globulin nephropathy is low, 0 to 26% (Swenberg 1993). Consistent with the low incidence of neoplasms are the 90-day studies of MacEwen and Vernot (1985) in which findings of nephropathy were reported in male rats exposed to either JP-5 or JP-8, but no kidney tumors were reported at the 24-month killing.

4.3. Structure-Activity Relationships

Many of the hydrocarbons in jet fuels affect the CNS. Experimental data showed that saturated hydrocarbons are absorbed to a lesser extent than unsaturated hydrocarbons in the rat (Dahl et al. 1988) and that aliphatic hydrocarbons are less efficiently absorbed by human blood than aromatic hydrocarbons (Astrand et al. 1975). Compared with aromatic hydrocarbons, aliphatic hydrocarbons are thought to have lower acute narcotic effects, lesser mucous membrane irritation, lower vapor pressure, and lower blood:air partition coefficients (Lof et al. 1999). Furthermore, in rats, uptake of several aliphatic hydrocarbons, as

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measured by blood:air partition coefficients, is lower than that of the aromatic hydrocarbons (Perbellini et al. 1985).

4.4. Other Relevant Information

4.4.1. Species Differences

Except for nephropathy in the male rat, no species differences in toxicity were observed among rodents in the several studies with jet fuels. Studies with hydrocarbon vapors, including jet fuels, showed a pattern of nephropathy in several strains of male rats, including Sprague-Dawley, Wistar, and F344 (MacEwen and Vernot 1984, 1985). These lesions consist of renal tubular degeneration along with mineral deposits in the renal papillae (see Section 4.2. Mechanism of Toxicity).

Jet fuel is a complex mixture of hundreds of aliphatic and aromatic hydrocarbons. When exposed to single hydrocarbons, uptake, as measured by blood concentrations and blood:air partition coefficients, is greater in rodents than humans (Benignus et al. 1981; Gargas et al. 1989). Greater chemical uptake is also due to the more rapid respiration rate and greater cardiac output in rodents compared with humans (Witschi and Last 2001; Kale et al. 2002). For the specific chemical, *n*-hexane, affinity of red blood cells of rats was greater (92% uptake) than that of human blood cells (66% uptake) (Lam et al. 1990).

The extent of CNS depression caused by each chemical is dependent on the concentration of the parent chemical present in the brain (reflected in the blood concentration). Therefore, at a constant concentration, rodents may be more sensitive to the effects of specific hydrocarbons than humans. For lipophilic compounds, elimination may be faster in rodents than in humans.

4.4.2. Susceptible Populations

Although the hydrocarbons that constitute jet fuels are not primary irritants, high concentrations of JP-8 ($\geq$ 681 mg/m^3) elicit a classic respiratory depression response (Whitman and Hinz 2001). The threshold for response to irritants is expected to differ by no more than a 3-fold factor in the general population.

Robledo and Witten (1998) exposed C57BL/6 mice deficient in aryl hydrocarbon hydroxylase and *N*-acetyltransferase enzymes to aerosols of JP-8 ranging from 0 to 112.5 mg/m^3 for 1 h. Aryl hydrocarbon hydroxylase is responsible for biotransformation of aromatic hydrocarbons, such as benzo(*a*)pyrene, which are present in JP-8. Aromatic amines, the substrate for *N*-acetyltransferases, are not major constituents of JP-8. Exposure conditions and pulmonary function tests were the same as those for congenic mice that were not deficient in these enzymes (Section 3.2.3). Pulmonary responses were similar in both strains of mice. No differences in immune function changes were found in these

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two strains of mice or between males and females when exposed to aerosolized JP-8 at concentrations up to 2,500 mg/m^3 (Harris et al. 1997a).

Young and Witten (2000) found that aged mice (12-14 months old) exhibited more changes in pulmonary parameters, including lung permeability, dynamic compliance, and pulmonary resistance, following exposure of aerosolized JP-8+100 to 1,000 mg/m^3 than young mice (3-4 months old).

No susceptible human populations were identified from monitoring studies. No information on children was located. Children and the elderly may be more or less sensitive to the toxic effects of solvents and vapors, but age-dependent susceptibilities to acute effects usually differ by no more than 2- to 3-fold (Bruckner and Warren 2001). Although humans differ in the rate at which they metabolize chemicals, the susceptibility of the general population to CNS depressants varies by no more than 2- to 3-fold as indicated by the minimum alveolar concentration, the concentration of an anesthetic that produces immobility in 50% of patients (Kennedy and Longnecker 1996; Marshall and Longnecker 1996).

4.4.3. Concentration-Exposure Duration Relationship

For the end points of both sensory irritation and depression of the CNS by solvents, there is generally a concentration threshold. All the jet fuels administered in the phase of vapor or combined vapor and aerosol exhibited low toxicity during acute, repeated, and chronic exposures. Time to steady state for individual components depends on lipophilicity as well as chemical interactions. Once steady state is attained, the CNS effect observed with exposures to high concentrations is most likely a concentration-dependent effect with exposure duration of lesser importance. For *n*-nonane, inhaled by F344 rats at 100, 500, or 1,000 ppm for 4 h, steady state was approached in the blood within 2 h at the two higher concentrations (Robinson 2000). The blood:air partition coefficient was 5.13.

For many hydrocarbons administered singly, CNS depression occurs at "high" concentrations. For example, *n*-heptane at 15,513 ppm (63,575 mg/m^3) failed to induce anesthesia in mice when administered over a 30-min period (Kristiansen and Nielsen 1988). CNS depression was observed within 20 and 8 min when exposures were at 15,668-21,746 and 24,801 ppm, respectively. The blood:air partition coefficient for *n*-heptane is 1.9 (Perbellini et al. 1985).

Fifteen young adult males inhaled 1,250 or 2,500 mg/m^3 of white spirit (Stoddard Solvent) for 30 min during rest or exercise (Astrand et al. 1975). White spirit (boiling range 150-200°C) contains 83% aliphatic and alicyclic hydrocarbons and 17% aromatic hydrocarbons. Pulmonary absorption of the aliphatics ranged from 46% to 59% and that of the aromatics from 58% to 70%. Blood concentration of *n*-decane, used as a marker of aliphatic hydrocarbons, increased at the start of each exposure but tended to level off toward the end of the exposure. Aromatics continued to rise during the exposure period. In con-

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trast, Stokholm and Cohr (1979) found that the aromatic fraction of white spirit reached steady state in alveolar air of 21 human subjects earlier than the aliphatic fraction. Steady state in alveolar air was reached after 20 min of exposure at rest and after 1 h during work. Exposures were at 204, 600, 1,200, and 2,400 mg/m^3.

Several animal studies that addressed mixtures used exposure durations of 1 to several weeks, and blood and brain concentrations of the chemicals were not measured prior to a 1-week exposure. In rats exposed to dearomatized white spirit at 0, 400, or 800 ppm for 3 weeks, blood and brain concentrations of *n*-nonane, *n*-decane, and *n*-undecane did not increase after 1 week; whereas fat concentrations were still increasing (Lof et al. 1999). After 1 week of exposure to white spirit at 400 ppm, blood concentrations of *n*-nonane, *n*-decane, and *n*-undecane were 0.10, 0.70, and 0.16 mg/kg, respectively. Following exposure to white spirit at 800 ppm, blood concentrations were 0.26, 2.09, and 1.06, respectively.

4.4.4. Concurrent Exposure Issues

In past studies with JP-4, exposure to benzene has been an area of concern. The typical benzene content of jet fuels, such as JP-4 and JP-8, is less than 0.5% by weight or volume (Martone 1981; ATSDR 1995). In a study of Air Force personnel engaged in aircraft maintenance, the highest TWA exposure to benzene was 0.034 ppm (Smith et al. 1997). ATSDR (1998) noted that the boiling point range of kerosene and the resulting jet fuels is well above the boiling point of benzene and many polycyclic aromatic hydrocarbons (PAHs); therefore, the benzene content of jet fuels in normally below 0.02%, and the PAH content is virtually zero.

Although emergency exposures are expected to be to spills resulting in vapor exposures, exposure to respirable aerosols during aircraft fueling and maintenance is of concern because several studies have shown that aerosols are more toxic than vapors. Highly visible aerosol emissions have been observed during jet aircraft cold starts, resulting in some crew members working behind the aircraft becoming drenched in fuel (Bruckner and Warren 2001). Toxicity studies that specifically utilized aerosols rather than vapor alone have identified JP-8-induced effects on the lung and immune system (see Table 2-4; Chen et al. 1992; Pfaff et al. 1992; 1993; 1995; Witten et al. 1992; Parton et al. 1993; Witten 1994; Hays et al. 1995; Harris et al. 1997a,b). The mechanism of lung injury appears to involve reduction of substance P, which participates in the maintenance of airway epithelial cell competency in the lung (Pfaff et al. 1996). In mice, JP-8 aerosols decreased immune organ weights and cellularities, altered the number of viable immune cells of several immune tissues, and resulted in the loss of different immune cell subpopulations in immune organs. Some of these changes were present up to 1 month postexposure. Treatment with aerosolized

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substance P protected against the JP-8-induced lung and immune system effects (Harris et al. 1997c). Microscopic changes in the lungs and other organs were not observed in mice and rats exposed to JP-8 vapor at 1,000 mg/m^3 for 90 days (MacEwen and Vernot 1985; Mattie et al. 1991). The inhalation of JP-8 aerosol may be relevant to military personnel in close proximity to aircraft fueling, cold start, or maintenance operations, but the relevance to the civilian population, that is, community exposure, where vapor is a more likely mode of exposure is not clear.

Inhalation is the primary route of exposure for most populations. Dermal exposure is relevant for military personnel and maintenance workers. Following dermal contact, individual volatile components may evaporate (low-molecular-weight volatile components) or penetrate the skin (less volatile, longer chain [hydrophobic] hydrocarbons) and pass into the blood for distribution throughout the body (NRC 2003). The NRC concluded that the exposure via the dermal route can be substantial for military personnel.

5. DATA ANALYSIS FOR AEGL-1

The proposed AEGLs were based on jet fuels as mixtures of hydrocarbons rather than individual components because both occupational and experimental animal exposures have been to the partial to total vaporization products of the fuels. Although vapor compositions may differ in different situations and with different fuels, the large database encompassing many jet fuels and the chronic nature of the exposures allows derivation of short-term values with considerable confidence.

Although early toxicity studies with jet fuel vapors found few toxic effects, even following chronic exposures, aerosols that are more toxic may be formed under certain conditions. However, emergency exposures are expected to be in the form of vapor exposures that result from spills, whereas aerosols are relevant only to occupational exposures during aircraft-foam removal operations or aircraft cold starts. Studies that addressed the toxicity of jet fuel only in the aerosolized form were not used to derive AEGL values (Martin et al. 2010; Tremblay et al. 2010).

5.1. Summary of Human Data Relevant to AEGL-1

There are no useful acute data involving human exposures. Monitoring data compose the primary exposure data for JP-8. Specific symptoms or complaints could not be related to exposure concentrations. Furthermore, the chronic nature of occupational exposures must be taken into consideration. Highest exposures occurred during fuel tank entry during which time the workers wore respirators.

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5.2. Summary of Animal Data Relevant to AEGL-1

Although jet fuels are not primary irritants, they elicit a characteristic irritant response at high concentrations. Whitman and Hinz (2001) reported results of the standard RD_{50} test using several jet fuels. Exposure to JP-8 vapor and aerosol at 681, 1,090 1,837, and 3,565 mg/m^3 for 30 min decreased the respiratory rate of male Swiss-Webster mice by 22%, 38%, 46%, and 50%, respectively. The RD_{50} was 2,876 mg/m^3. The respiratory rate decrease of 22% at 681 mg/m^3 is considered a slight to moderate response.

Repeated exposures (6 weeks to 90 days) of rats and mice to JP-8 vapor at a concentration of 1,000 mg/m^3 failed to induce clinical signs (MacEwen and Vernot 1985; Mattie et al. 1991; Briggs 2001; Rossi et al. 2001) or effects on the male reproductive system (Briggs 2001), but this concentration may be the threshold for neurobehavioral changes (Rossi et al. 2001).

5.3. Derivation of AEGL-1

The AEGL-1 is based on the sensory irritation study of Whitman and Hinz (2001), specifically the RD_{50} for JP-8 of 2,876 mg/m^3. This is a robust study based on aerosol and vapor atmospheres in accordance with the ASTM E981-84 method. According to Alarie (1981), reducing the RD_{50} by 10-fold results in an exposure concentration of the JP-8 mixture that produces some sensory irritation to humans that is tolerable for hours to days. This effect is consistent with an AEGL-1 effect. The resulting value is 290 mg/m^3. Because primary irritation is a concentration effect independent of time, the 290 mg/m^3 value was applied to all AEGL-1 exposure durations (Table 2-6).

The primary volatile components of JP-8 present in the vapor phase, the *n*-alkane solvents in the C9 to C12 range, are not primary irritants. As indicated in Table 2-4, there were no other adverse clinical effects in animal studies with repeated exposure to JP-8 vapor at 1,000 mg/m^3 (MacEwen and Vernot 1985; Mattie et al. 1991; Briggs 2001; Rossi et al. 2001). Rossi et al. (2001) reported some changes in brain neurotransmitter activities. Applying an interspecies uncertainty factor of 1 (chosen because the uptake of these chemicals is higher in rodents than in humans [Gargas et al. 1989]) and an intraspecies uncertainty factor of 3 (chosen to account for potential differences in human susceptibility to sensory irritation) results in a value of 330 mg/m^3. This value supports the value of 290 mg/m^3 determined using the RD_{50} study of Whitman and Hinz (2001). Appendix B contains a category plot of animal toxicity data and AEGL values.

TABLE 2-6 AEGL-1 Values for JP-5 and JP-8

0 min	30 min	1 h	4 h1	8 h
290 mg/m^3	290 mg/m^3	290 mg/m^3	290 mg/m^3	290 mg/m^3

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6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

The available monitoring data indicate that exposures to jet fuels at threshold concentrations for CNS depression have occurred, but actual concentrations are unavailable. At this time, aircraft maintenance workers wear respirators when entering fuel tanks where exposures are potentially quite high. Thus, no information on adverse health effects could be derived from these studies. Past exposures to concentrations as high as 3,000 mg/m^3 were to the more volatile JP-4 or an equivalent fuel (Knave et al. 1978; Martone 1981). Such symptoms as dizziness and fatigue may have been associated with these concentrations.

6.2. Summary of Animal Data Relevant to AEGL-2

A 30-min exposure to JP-8 vapor and aerosol at 3,565 mg/m^3 failed to induce obvious clinical signs in mice but decreased the respiratory rate by 50% (Whitman and Hinz 2001). Four-hour exposures of rats to JP-8 vapor at 3,430 mg/m^3 or aerosol and vapor at 4,440 mg/m^3 induced eye and upper respiratory irritation (Wolfe et al. 1996). Conversely, as noted for the AEGL-1, repeated exposures to of JP-8 vapor at 1,000 mg/m^3 generally failed to elicit adverse effects in animal studies. Finally, exposure of rats and mice to JP-5, considered a subset of JP-8, at 5,000 mg/m^3 for 1 h resulted in eye irritation and signs of CNS depression (MacEwen and Vernot 1985; Mattie et al. 1991); these effects were not observed during repeated exposures to JP-5 at 1,200 mg/m^3 (Rossi et al. 2001) or during repeated exposures to JP-5 at 1,636 mg/m^3 (Bogo et al. 1983, 1984).

6.3. Derivation of AEGL-2

The AEGL-2 is based on several animal studies that indicate that exposure at 1,100 mg/m^3 would not elicit adverse health effects or CNS depression but may be the threshold for such effects. As noted, repeated exposures of rats and mice to JP-5 or JP-8 in the vapor phase at 1,000 mg/m^3 or to a single exposure of JP-5 vapor and aerosol at 5,000 mg/m^3 is without adverse effects other than sensory irritation and some CNS depression at 5,000 mg/m^3.

The studies using repeated exposures to 1,000 mg/m^3 (MacEwen and Vernot 1985; Mattie et al. 1991; Briggs 2001; Rossi et al. 2001) and the shorter term studies (30 min to 4 h) with exposures at 3,430-5,000 mg/m^3 (MacEwen and Vernot 1985; Mattie et al. 1991; Wolfe et al. 1996; Whitman and Hinz 2001) were used as the basis for the AEGL-2. No uncertainty factors were applied to the 1,000 mg/m^3 concentration because there were no effects and the exposures were repeated for up to 90 days. The higher concentrations of JP-8, 3,430 and

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4,440 mg/m^3, and of JP-5, 5,000 mg/m^3, were divided by an interspecies factor of 1 (there were no species differences in susceptibility in numerous studies) and by an intraspecies uncertainty factor of 3 to protect potentially sensitive adults. Doses of volatile organic hydrocarbons (VOCs) absorbed systemically are considerably greater in mice and rats than in humans subjected to equivalent inhalation exposures. This response is attributable to rodent's relatively high respiratory rates, cardiac outputs, and blood:air partition coefficients. Therefore, no-effect levels for CNS depression in rodents are quite protective for humans. An intraspecies uncertainty factor of 3 is considered adequate because the thresholds for both sensory irritation and CNS depression to solvents do not generally differ by more than 3-fold (Bruckner and Warren 2001). The lower value, 1,100 mg/mg^3, in the resulting range of values, 1,100-1,700 mg/m^3, is approximately the same concentration as that in the no-adverse-effect repeated exposure studies.

No information was available on time to steady-state blood levels for many of the components of jet fuel. Therefore, no information was available for time-scaling. CNS depression is a concentration-related effect. Because the exposure duration in the key study was for 4 h, the 1,100-mg/m^3 value was used for the 4-h and shorter time periods. Because the exposure of rats and mice at 1,000 mg/m^3 was continuous (24 h/day) for up to 90 days (Mattie et al. 1991), the 1,100-mg/m^3 value can also be used for the longest AEGL exposure duration of 8 h (Table 2-7). The fact that the exposures in most of these studies, especially at the higher concentrations, were to both the vapor and aerosol supports AEGL-2 values. A category graph of AEGL values in relation to toxicity data is in Appendix B.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human data relevant to calculation of AEGL-3 values were located. In humans and animals, the primary effect associated with inhalation exposure to aliphatic and aromatic hydrocarbons is CNS depression. Due to the low vapor pressure of JP-8 (1.8 mmHg at 28°C), it is unlikely that atmospheric concentrations would reach lethal concentrations during community exposures. The saturated vapor concentration of JP-8 under "ambient conditions" is approximately 700 mg/m^3 (F. Whitman, ExxonMobil Biomedical Science, Inc., personal commun., Oct.31, 2001). It is possible that lethal concentrations of JP-8 cannot be attained or sustained.

TABLE 2-7 AEGL-2 Values for JP-5 and JP-8

10 min	30 min	1 h	4 h	8 h
1,100 mg/m^3	1,100 mg/m^3	1,100 mg/m^3	1,100 mg/m^3	1,100 mg/m^3

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7.2. Summary of Animal Data Relevant to AEGL-3

None of the acute studies with jet fuel vapor resulted in lethality. The only reported effects of 4-h exposures to JP-8 at a vapor concentration of 3,430 mg/m^3 or JP-8 at a vapor and aerosol concentration of 4,440 mg/m^3 were eye and upper respiratory irritation (Wolfe et al. 1996), symptoms consistent with the definition of the AEGL-2. Those values were the highest vapor and vapor and aerosol concentrations, respectively, attained under laboratory exposure conditions.

7.3. Derivation of AEGL-3

In the study reported by Wolfe et al. (1996), the highest vapor concentration of JP-8 that could be attained was 3,430 mg/m^3. The highest vapor and aerosol concentration that could be attained was 4,440 mg/m^3. It is not apparent that concentrations high enough to cause death can be attained. A concentration of 500 mg/m^3 is assumed to be the upper bound for a stable cloud of inhalable dust (and aerosols) (Craig and Lux 1998). On the basis of the likelihood that lethal concentrations of JP-8 cannot be attained and sustained under ambient conditions, an AEGL-3 was not determined.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

The AEGL values for various exposure durations are listed in Table 2-8. Derivation summaries are in Appendix C.

TABLE 2-8 Summary of AEGL Values

Classification	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	290 mg/m^3	290 mg/m^3	290 mg/m^3	290 mg/m^3	290 mg/m^3
AEGL-2 (Disabling)	1,100 mg/m^3	1,100 mg/m^3	1,100 mg/m^3	1,100 mg/m^3	1,100 mg/m^3
AEGL-3 (Lethal)	Not determined[a]	Not determined	Not determined	Not determined	Not determined

[a]There are no data on lethal concentrations.

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8.2. Comparison with Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures are listed in Table 2-9. The U.S. Navy's 8-h TWA-PEL and 15-min STEL for shipboard exposures of Navy personnel are 200 and 1,000 mg/m^3. The previous PEL and STEL of 350 and 1,800 mg/m^3 (NAVOSH 1992, NEHC 1993), respectively, were based on the Navy's review of manufacturers' technical documentation and the NIOSH recommendations for maximum exposure to refined petroleum solvents. The values are for exposure to JP-5 and JP-8. The NRC (1996; Bakshi and Henderson 1998) reviewed the U.S. Navy's standards and recommended that the NAVOSH STEL be lowered from 1,800 mg/m^3 to 1,000 mg/m^3. The U.S. Air Force's values for JP-8 for the respective exposure durations are the same as the U.S. Navy's. The U.S. Air Force requested that the NRC review the available toxicologic, epidemiologic, exposure, and other relevant data on JP-8; independently re-evaluate the scientific basis of the PEL of 350 mg/m^3; identify data gaps; and make recommendations for future research relevant to deriving the PEL (NRC 2003). The NRC Subcommittee on Jet-Propulsion Fuel 8 concluded that the interim PEL of 350 mg/m^3 might be too high to be protective of human health but did not propose a specific PEL for JP-8.

The military TWAs are for healthy adults. The 8-h 200-mg/m^3 value is slightly lower than the AEGL-1, which is for the general population but is for acute exposures. Most agencies have not derived guidelines specific to jet fuels, but instead use the more general category of petroleum distillates. The Swedish TWA occupational exposure limit of 350 mg/m^3 for an 8-h day (and 500 mg/m^3 for a TWA over 15 min) is for aviation fuels.

TABLE 2-9 Extant Standards and Guidelines for Jet Fuels, Gasoline, and Kerosene

	Exposure Durations for JP-5 and JP-8				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	290 mg/m^3	290 mg/m^3	290 mg/m^3	290 mg/m^3	290 mg/m^3
AEGL-2	1,100 mg/m^3	1,100 mg/m^3	1,100 mg/m^3	1,100 mg/m^3	1,100 mg/m^3
AEGL-3	Not determined	Not determined	Not determined	Not determined	Not determined
PEL-TWA (NAVOSH)[a]					200 mg/m^3
PEL-TWA (AFOSH)[b]					200 mg/m^3
STEL (NAVOSH)[c]					1,000 mg/m^3
STEL (AFOSH)[d]					1,000 mg/m^3

(Continued)

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TABLE 2-9 Continued

	Exposure Durations for JP-5 and JP-8				
Guideline	10 min	30 min	1 h	4 h	8 h
	Exposure Durations for Related Chemicals				
	Short Term		8 h		
IDLH (NIOSH)[e]	1,100 ppm (4,500 mg/m^3) (petroleum distillates [naphtha])				
TLV-TWA (ACGIH)[f]			200 mg/m^3 (kerosene/jet fuels)		
PEL-TWA (OSHA)[g]			Naphtha[h] (coal tar) – 100 ppm (400 mg/m^3)		
REL-TWA (NIOSH)[i]			Kerosene – 100 mg/m^3 Petroleum distillates (naphtha) – 350 mg/m^3		
REL-Ceiling (NIOSH)[j]	Petroleum distillates (naphtha) – 1,800 mg/m^3				
TLV-STEL (ACGIH)[k]	None established				
PEL-STEL (OSHA)[l]	Petroleum distillates (naphtha) (rubber solvent) – 500 ppm (2,000 mg/m^3)				

[a]PEL-TWA (permissible exposure limit-time-weighted average, Navy Occupational Safety and Health [NAVOSH] Standard). (NAVOSH 1992).
[b]PEL-TWA (permissible exposure limit-time-weighted average, Air Force Occupational Safety and Health [AFOSH] Standard) (U.S. Air Force 2005).
[c]STEL (short-term exposure limit, NAVOSH Standard) (NAVOSH 1992).
[d]STEL (short-term exposure limit, AFOSH Standard) (U.S. Air Force 2005).
[e]IDLH (immediately dangerous to life or health concentrations, National Institute for Occupational Safety and Health [NIOSH]) (NIOSH 1996) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms or any irreversible health effects. The IDLH for petroleum distillates (naphtha) is based strictly on safety considerations, being 10% of the lower explosive limit of 1.1%.
[f]TLV-TWA (Threshold Limit Value-time-weighted average, American Conference of Governmental Industrial Hygienists [ACGIH]) (ACGIH 2009) is the TWA concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.
[g]PEL-TWA (permissible exposure limit–time-weighted average, Occupational Safety and Health Administration [OSHA]) (29 CFR 1910.1000 [2005]) is analogous to the ACGIH TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week.
[h]Naphtha is the low-boiling fraction of petroleum and is composed chiefly of pentanes and hexanes.
[i]REL-TWA (recommended exposure limit-time-weighted-average, NIOSH) (NIOSH 2005) is analogous to the ACGIH TLV-TWA.
[j]REL-Ceiling (recommended exposure limit-ceiling, NIOSH) (NIOSH 1996) is the concentration of the chemical in air that should not be exceeded.
[k]TLV-STEL (Threshold Limit Value-short-term exposure limit, ACGIH) (ACGIH 2009) is defined as a 15-min TWA exposure that should not be exceeded at any time during the workday even if the 8-h TWA is within the TLV-TWA. Exposures above the TLV-TWA

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up to the STEL should not be longer than 15 min and should not occur more than 4 times per day. There should be at least 60 min between successive exposures in this range.
[f]PEL-STEL (permissible exposure limit–short-term exposure limit, OSHA) (29 CFR 1910.1000 [2005]) is analogous to the ACGIH TLV-STEL.

The NIOSH IDLH is defined comparable to an AEGL-2. The IDLH for petroleum distillates (naphtha) was originally 4,000 ppm based on a study with gasoline (Drinker et al. 1943). In the Drinker (1943) study, subjects inhaling 0.26% (9,150 mg/m^3) for 1 h reported mild exhilaration and muscular incoordination; at 1.1% (38,000 mg/m^3), the subjects appeared intoxicated, most within 5 min. The present IDLH value of 1,100 ppm is based strictly on safety considerations, being 10% of the lower explosive limit of 1.1% (NIOSH 1996).

Because benzene, a component of JP-8, is a known human carcinogen (EPA 2003), the benzene concentration in JP-8 at the AEGL-2 value was compared with standards and guidelines. The benzene content of neat fuel is <0.005% by volume (Carlton and Smith 2000). Ratios of benzene to total JP-8 concentrations in instantaneous samples taken during aircraft fuel tank maintenance monitoring studies ranged from 0.0004 to 0.001, that is, up to 1 mg/m^3 of benzene in 1,000 mg/m^3 of JP-8 vapor (Carlton and Smith 2000). Therefore, under ambient conditions of evaporation of JP-8, the atmospheric concentration of benzene in 1,100 mg/mg^3 of JP-8 vapor would be 1.1 mg/m^3 (0.34 ppm). This value is above the NIOSH REL of 0.3 mg/m^3 for benzene, but below the OSHA PEL of 3.2 mg/m^3. It is below the NRC 1-h EEGL of 160 mg/m^3, the NIOSH IDLH of 1500 mg/m^3, and the 8-h AEGL-2 for benzene of 200 ppm.

8.3. Data Adequacy and Research Needs

Although data on human exposures to JP-5 and JP-8 were located, most of the concentrations were too low to be of value in developing AEGLs. Exposure to higher concentration during aircraft fuel tank entry occurred only when personnel were wearing respirators, thus health effects could not be derived from these studies. Animal studies used several species (rat, mouse, and dog) and addressed sensory irritation, neurotoxicity, and male fertility, as well as other systemic effects. Studies with aerosols addressed direct lung effects and effects on the immune system. The data were sufficient for deriving AEGL-1 and AEGL-2 values. Animal studies with repeated exposures support the safety of values derived for acute exposure durations.

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APPENDIX A

INDIVIDUAL HYDROCARBON DATA—NEAT JET FUELS,[a] PERCENT BY VOLUME

TABLE A-1 Hydrocarbon Data for Jet Fuels 4, 8, and 8+100

Hydrocarbon	JP-4	JP-8	JP-8+100
Isopentane	0.1437	ND	ND
n-Pentane	0.3237	ND	ND
2-Methylpentane	0.7302	ND	ND
3-Methylpentane	0.4139	ND	ND
n-Hexane	1.5403	0.0011	0.0023
Methylcyclopentane	1.3913	0.0006	0.0014
Benzene	0.3551	ND	ND
Cyclohexane	1.7803	0.0033	0.0030
3-Methylhexane	1.5065	0.0119	0.0078
Isooctane	2.4941	0.0256	0.0112
n-Heptane	3.3458	0.0481	0.0357
Toluene	2.0009	0.0721	0.0664
3-Methylheptane	0.9567	0.0604	0.0524
n-Octane	3.8056	0.2609	0.2506
Ethylbenzene	0.6458	0.1414	0.1322
p-, *m*-Xylene	3.3541	0.6610	0.6319
n-Nonane	1.5714	0.9103	0.8886
Cumene	0.1870	0.1756	0.1672
Propylbenzene	0.1830	0.2846	0.2698
p-, *m*-Ethyltoluene	0.5318	0.6921	0.6801
1,3,5-Trimethylbenzene	0.5948	1.0785	1.0677
o-Ethyltoluene	0.4586	0.8522	0.8416
1,2,4-Trimethylbenzene	0.8171	1.2355	1.2192
n-Decane	1.2687	2.8907	2.8641
n-Undecane	1.7350	5.5171	5.5065
n-Dodecane	1.8808	5.3191	5.3032
n-Tetradecane	1.4537	3.0523	3.0658
n-Hexadecane	0.3169	0.7690	0.7602
Total analytes[b]	35.7868	24.0634	23.8289

[a]Source: Whitman and Hinz 2001, p. 46.
[b]Percent of test substance analyzed; other hydrocarbons unidentified.

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APPENDIX B

CATEGORY GRAPH OF TOXICITY DATA AND AEGL VALUES

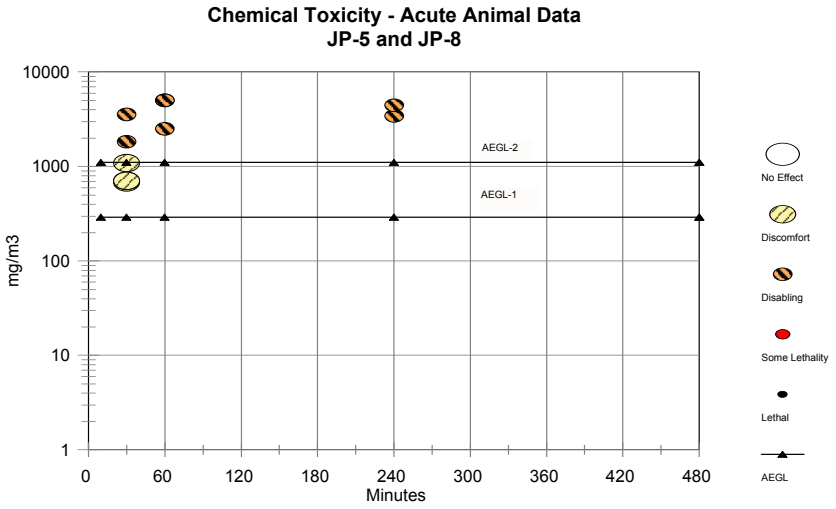

FIGURE 2-1 Category graph for JP-5 and JP-8. Note: Only acute studies are graphed.

TABLE B-2 Data Used in Category Graph

Source	Species	mg/m^3	Minutes	Category[a]
NAC/AEGL-1		290	10	AEGL
NAC/AEGL-1		290	30	AEGL
NAC/AEGL-1		290	60	AEGL
NAC/AEGL-1		290	240	AEGL
NAC/AEGL-1		290	480	AEGL
NAC/AEGL-2		1,100	10	AEGL
NAC/AEGL-2		1,100	30	AEGL
NAC/AEGL-2		1,100	60	AEGL
NAC/AEGL-2		1,100	240	AEGL
NAC/AEGL-2		1,100	480	AEGL

(Continued)

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TABLE B-2 Continued

Source	Species	mg/m^3	Minutes	Category[a]
NAC/AEGL-3		ND	10	AEGL
NAC/AEGL-3		ND	30	AEGL
NAC/AEGL-3		ND	60	AEGL
NAC/AEGL-3		ND	240	AEGL
NAC/AEGL-3		ND	480	AEGL
Whitman and Hinz 2001	Mouse	681	30	1: 22% depression, respiratory rate
Whitman and Hinz 2001	Mouse	1,090	30	1: 38% depression, respiratory rate
Whitman and Hinz 2001	Mouse	1,837	30	2: 46% depression, respiratory rate
Whitman and Hinz 2001	Mouse	3,565	30	2: 50% depression, respiratory rate
Whitman and Hinz 2001	Mouse	708 (vapor)	30	1: 28% depression, respiratory rate
Wolfe et al. 1996	Rat	3,430 (vapor)	240	2: Eye, upper respiratory tract irritation
Wolfe et al. 1996	Rat	4,440 (2,630 vapor + 1,810 aerosol)	240	2: No deaths
MacEwen and Vernot 1985	Rat	2,500	60	2: Eye irritation
MacEwen and Vernot 1985	Rat	5,000	60	2: CNS depression

[a]Categories: 0, no effect; 1, discomfort; 2, disabling; and 3, lethal.
Abbreviations: ND, not determined; CNS, central nervous system.

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APPENDIX C

ACUTE EXPOSURE GUIDELINE LEVELS FOR JP-5 AND JP-8

Derivation Summary for JP-5 AND JP-8

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
290 mg/m^3	290 mg/m^3	290 mg/m^3	290 mg/m^3	290 mg/m^3

Key reference: Whitman, F.T., and J.P. Hinz. 2001. Sensory Irritation Study in Mice: JP-4, JP-8, JP-8+100. Report No. IERA RS-BR-SR-2001-0005. ADA398112. Air Force Institute for Environment, Safety and Occupational Health Risk Analysis, Brooks Air Force Base TX.
Supporting reference: MacEwen, J.D., and E.H. Vernot. 1985. Investigation of the 1-h emergency exposure limit of JP-5. Pp. 137-144 in Toxic Hazards Research Unit Annual Report: 1985. AAMRL-TR-85-058. AD-A161558. Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH.

Test species/Strain/Number: Mouse/Swiss-Webster/4 per group

Exposure route/Concentrations/Durations: Inhalation concentrations at 681, 1,090, 1,837, 3,565 mg/m^3 (vapor + aerosol), and 708 mg/m^3 (vapor only) for 30 min

Effects:
681 mg/m^3: 22% decrease in respiratory rate
1,090 mg/m^3: 38% decrease in respiratory rate
1,837 mg/m^3: 46% decrease in respiratory rate
3,565 mg/m^3: 50% decrease in respiratory rate
708 mg/m^3: 28% decrease in respiratory rate (vapor-only exposure)
2,876 mg/m^3: calculated RD_{50}

End point/Concentration/Rationale: 290 mg/m^3 across all AEGL-1 exposure durations (0.1 times the calculated mouse RD_{50} of 2,876 mg/m^3 [slight irritation withstood for hours,according to Alarie 1981])

Uncertainty factors/Rationale:
Total uncertainty factor: Not applicable. (The mouse RD_{50} was reduced by a factor of 10, which reduces the sensory irritation to a concentration tolerated for hours to days by most individuals.) The factor of 10 is the same as applying interspecies and intraspecies uncertainty factors of 3 each.
Interspecies: Not applicable
Intraspecies: Not applicable

Modifying factor: Not applied

Animal-to-human dosimetric adjustment: Not applied

Time-scaling: Not applied; the repeated nature of many of the studies ensures the safety of a single exposure.

(Continued)

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AEGL-1 VALUES Continued

10 min	30 min	1 h	4 h	8 h
290 mg/m^3	290 mg/m^3	290 mg/m^3	290 mg/m^3	290 mg/m^3

Data adequacy: The database of inhalation and oral studies in rodents is robust. Studies addressed irritation, neurotoxicity, immunotoxicity, developmental and reproductive effects, genotoxicity, and carcinogenicity. Human exposures to JP-8 were limited to occupational exposures; monitoring studies with other aviation fuels showed few effects. The value is supported by animal studies in which repeated and continuous exposures at 1,000 mg/m^3 for up to 90 days failed to elicit clinical signs or adverse health effects. Interspecies and intraspecies uncertainty factors of 1 and 3, respectively would result in a similar value, 330 mg/m^3.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
1,100 mg/m^3	1,100 mg/m^3	1,100 mg/m^3	1,100 mg/m^3	1,100 mg/m^3

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Test species/Strain/Number: Rat/F344/groups of 5 to 95
Mouse/Swiss-Webster/4 per group

(Continued)

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AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
1,100 mg/m^3	1,100 mg/m^3	1,100 mg/m^3	1,100 mg/m^3	1,100 mg/m^3

Exposure route/Concentrations/Durations: 3,430-5,000 mg/m^3 for 30 min to 4 h (vapor + aerosol); 1,000 mg/m^3 for up to 90 days. The exposure at 5,000 mg/m^3 involved JP-5, which is similar in composition to JP-8.

Effects:
3,430 mg/m^3: eye and upper respiratory irritation (Wolfe et al. 1996)
3,565 mg/m^3: no clinical signs; respiratory rate depression of 50% (Whitman et al. 2001)
4,440 mg/m^3: eye and upper respiratory irritation (Wolfe et al. 1996)
5,000 mg/m^3: eye irritation and signs of CNS depression (MacEwen and Vernot 1985; Mattie et al. 1991)
1,000 mg/m^3: no severely adverse effects (Briggs 2001; Rossi et al. 2001; and others)

End point/Concentration/Rationale: Weight of evidence from all studies; escape might be impeded at the highest concentration of 5,000 mg/m^3.

Uncertainty factors/Rationale:
Total uncertainty factor: 3 applied to concentrations of 3,430-5,000 mg/m^3; 1 applied to 1,000 mg/m^3
Interspecies: 1 applied to all concentrations; rodent uptake is greater than human uptake based on higher respiratory rate and cardiac output and higher blood:air partition coefficients.
Intraspecies: 3 applied to 3,430-5,000 mg/m^3 (1,100 mg/m^3); no susceptible populations identified; upper respiratory sensory irritation and threshold for CNS effects do not differ by more than 3-fold in the general population; 1 applied to repeated exposures of 1,000 mg/m^3 because no adverse health effects identified.

Modifying factor: Not applied

Animal-to-human dosimetric adjustment: Not applied

Time-scaling: Not applied; CNS depression is a concentration threshold effect. The repeated nature of many of the studies ensures the safety of a single exposure.

Data adequacy: Robust database of inhalation and oral studies in rodents that addressed irritation, neurotoxicity, immunotoxicity, developmental and reproductive effects, genotoxicity, and carcinogenicity. Human exposures to JP-8 were limited to occupational exposures; monitoring studies with other aviation fuels showed few effects.

AEGL-3 VALUES

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

Data adequacy: There are no data on lethal concentrations.

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3

Methyl Ethyl Ketone[1]

Acute Exposure Guideline Levels

PREFACE

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

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory

[1]This document was prepared by the AEGL Development Team composed of Sylvia Talmage (Summitec Corporation) and Jim Holler and William Bress (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee 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).

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effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

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

SUMMARY

Methyl ethyl ketone (MEK) is a volatile solvent with a sweet and sharp acetone-like odor. MEK is widely used as a solvent in common household products, such as inks, paints, cleaning fluids, varnishes, and glues. In most industrial applications, it is used as a component of a mixture of organic solvents. It has also been detected in a wide variety of natural products and may be a minor product of normal mammalian metabolism. In 1999, U.S. production capacity was 675 million pounds.

The inhalation toxicity of MEK is low. In clinical studies, a constant concentration of 200 ppm and short exposures at 380 ppm were judged nonirritating. At high concentrations of several thousand parts per million, MEK causes reversible central nervous system (CNS) depression as evidenced by neurobehavioral effects in animals. Data on human exposures were available from clinical studies and workplace monitoring. Animal studies with a variety of species (baboon, rat, mouse, and guinea pig) addressed irritation, neurotoxicity, developmental toxicity, and lethality. Exposure durations ranged from acute to chronic. MEK is not teratogenic, but at high concentrations, it is mildly fetotoxic to rats and mice. Genotoxicity was also addressed. No information on a concentration-exposure duration relationship for a defined end point was found. In clinical studies of 4-h duration, uptake was rapid during the first hour of expo-

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sure at 200 ppm, approaching steady state in the blood by the end of the exposure (Liira et al. 1988a,b).

Four well-conducted clinical studies indicated that MEK is not a sensory irritant, nor does it induce neurobehavioral changes at concentrations up to 200 ppm for 2 or 4 h (Dick et al 1992; Muttray et al 2002; Shibata et al. 2002) or at variable concentrations ranging from 10 to 380 ppm over 4 h (five 8-min peaks to 380 ppm) (Seeber et al. 2002). Seeber et al. (2002) tested healthy subjects as well as subjects with self-reported multiple chemical sensitivity (sMCS). Subjects with sMCS reported no adverse symptoms during the 8-min exposures to 380 ppm. Additional metabolism studies were conducted at concentrations of 25 to 400 ppm for 4 h, but these studies did not address sensory irritation or neurotoxic effects. In a clinical study with 24 male and female subjects, a concentration of 200 ppm was judged unobjectionable for an 8-h exposure (Dick et al. 1992). Therefore, 200 ppm was selected as the threshold for sensory irritation and was used to derive the AEGL-1. The selection of this value is supported by numerous clinical studies in which volunteers were routinely exposed to MEK at 200-400 ppm for up to 4 h and by the exposure of sMCS subjects to it at 380 ppm for short periods of time. Because effects were not different in sensitive subjects at the higher concentration of 380 ppm, an intraspecies uncertainty factor of 1 was applied. Because steady-state would be approached within 4 h at the 200-ppm concentration (Liira et al. 1988a,b) and because MEK is rapidly metabolized, the 200-ppm concentration was used across all AEGL-1 exposure durations.

The AEGL-2 was based on an exposure concentration that did not result in neurobehavioral effects on the first day of the subchronic study by Cavendar et al. (1983). Rats were exposed to MEK at 5,000 ppm for 6 h/day, 5 days/week, for 90 days. No lesions were reported in this study (specific neuropathologic studies were conducted on the medulla and peripheral nerves), and there were no neurofunctional deficits. Narcosis was not observed on the first day of exposure or on subsequent days. The concentration may be close to the threshold for narcosis, as evidenced by mild somnolence in a repeated exposure study in which rats were exposed at 6,000 ppm for several weeks (Altenkirch et al. 1978). Because uptake is dependent on the ventilatory rate and cardiac output, which are higher in rodents than in humans, an interspecies uncertainty factor of 1 was applied (at similar exposure concentrations, blood levels of MEK are higher in rats than in humans [Liira et al. 1990a]). Because the threshold for narcosis differs by no more than 2- to 3-fold among the general population (see Section 4.4.2), an intraspecies uncertainty factor of 3 was applied to protect sensitive individuals. At the 5,000-ppm concentration, steady-state in the blood is predicted to occur sometime after 4 h. Therefore, the 4- and 8-h AEGL-2 values were set equal to 1,700 ppm. The data show that for a common end point, higher concentrations can be tolerated at the shorter exposure durations. Therefore, the values for the shorter exposure durations were time-scaled from the 4-h time using the default n value of 3.

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The AEGL-3 values were derived using different studies. The 10- and 30-min time periods were derived using the studies by Klimisch (1988) and Zakhari et al. (1977) with support from Hansen et al. (1992). The 1-, 4-, and 8-h values were derived from the study by Fowles et al. (1999) using data from La Belle and Brieger (1955). No deaths occurred in rats after a 30-min exposure to MEK at 92,239 ppm (Klimisch 1988), and no deaths occurred in mice after a 45-min exposure at 50,000 ppm (Zakhari et al. 1977). A projected value of 32 or 145 ppm for 30 min would decrease the respiratory rate of mice by 50% (Hansen et al. 1992). The highest tested concentration in the Hansen et al. (1992) study was 26,000 ppm. On the basis of these data it is thought that nearly all individuals could be exposed at 10,000 ppm for up to 30 min without developing life-threatening effects. Inter- and intraspecies uncertainty factors of 1 and 3, respectively, were applied for the AEGL-2. Additional studies support the 10,000-ppm value as being nonlethal: 10,000 ppm for 10 or 30 min was narcotic to mice in one study (Glowa and Dews 1987) but not in another (Hansen et al. 1992), 10,000 ppm was tolerated by rats for 8 h/day for several days (Altenkirch et al. 1978), and no deaths occurred in guinea pigs inhaling 10,000 ppm for 13.5 h (Patty et al. 1935).

The longer-term AEGL-3 values were based on a maximum likelihood estimate, with a 1% response (MLE_{01}), of 7,500 ppm calculated by Fowles et al. (1999) from a 4-h study with rats exposed at several concentrations for 4 h (La Belle and Brieger 1955). In this study, the 4-h LC_{50} (concentration lethal to 50% of the exposed population) was 11,700 ppm, and the highest concentration resulting in no deaths was 7,850 ppm for 4 h. The 7,500-ppm MLE_{01} concentration was divided by an interspecies uncertainty factor of 1 and an intraspecies uncertainty factor of 3, using the same rationale as that for AEGL-1. The resulting value of 2,500 ppm was used for both the 4-h and 8-h AEGL-3 values. MEK may approach steady state in the blood by the end of 8 h. The 4-h 2,500 ppm value was time-scaled to the 1-h time using the default n value of 3 for scaling to shorter time intervals. The 8-h AEGL-3 of 2,500 ppm is low compared with 8-h nonlethal concentrations in animal studies cited above.

The calculated values are listed in Table 3-1 below.

1. INTRODUCTION

MEK is a volatile solvent with a sweet and sharp acetone-like odor. It is commercially manufactured from *n*-butenes in a metal-catalyzed hydrogenation reaction that proceeds through the intermediate formation of 2-butanol. MEK is widely used as a solvent in industrial settings and common household products, such as protective coatings, adhesives, inks, paints, cleaning fluids, and dewaxing agents. It is a common ingredient in consumer products, such as varnishes and glues. In most applications, it is used as a component of a mixture of organic solvents. It has also been detected in a wide variety of natural

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products and may be a minor product of normal mammalian metabolism (WHO 1993; Morgott et al. 2001). In 1999, U.S. production capacity was 675 million pounds (ChemExpo 2001). Global capacity in 2002 was about 1.3 million metric tons (Greiner and Funada 2009). Chemical and physical properties are listed in Table 3-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

The relative toxicity of ketones is low (Morgott et al. 2001), and no studies were located regarding deaths of humans following inhalation, oral, or dermal exposure to MEK (ATSDR 1992; WHO 1993).

TABLE 3-1 Summary of AEGL Values for Methyl Ethyl Ketone

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	200 ppm (586 mg/m^3)	200 ppm (586 mg/m^3)	200 ppm (586 mg/m^3)	200 ppm (586 mg/m^3)	200 ppm (586 mg/m^3)	NOAEL for subjective symptoms in humans (Dick et al. 1992; Muttray et al. 2002; Seeber et al. 2002 Shibata et al. 2002)
AEGL-2 (disabling)	4,900 ppm[a] (14,357 mg/m^3)	3,400 ppm[a] (9,962 mg/m^3)	2,700 ppm[a] (7,911 mg/m^3)	1,700 ppm (4,980 mg/m^3)	1,700 ppm (4,980 mg/m^3)	Threshold for narcosis in rats (Cavender et al. 1983)
AEGL-3 (lethal)	[b]	[b]	4,000 ppm[a] (11,720 mg/m^3)	2,500 ppm[a] (7,325 mg/m^3)	2,500 ppm[a] (7,325 mg/m^3)	Threshold for lethality, mouse, rat (La Belle and Brieger 1955; Zakhari et al. 1977; Klimisch 1988; Hansen et al. 1992)

[a]The 10- and 30-min and the 1-h AEGL-2 values and the 1-, 4-, and 8-h AEGL-3 values are higher than one-tenth of the lower explosive limit (LEL) of methyl ethyl ketone in air (LEL = 18,000 ppm). Therefore, safety considerations against the hazard of explosion must be taken into account.
[b]The 10- and 30-min AEGL-3 value of 10,000 ppm (29,300 mg/m^3) is higher than 50% of the LEL of methyl ethyl ketone in air (LEL = 18,000 ppm). Therefore, extreme safety considerations against the hazard of explosion must be taken into account.
Abbreviation: NOAEL, no-observed-adverse-effect level.

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TABLE 3-2 Chemical and Physical Data for Methyl Ethyl Ketone

Parameter	Data	Reference
Synonyms	MEK, 2-butanone, ethyl methyl ketone, methyl acetone, 2-oxobutane	ATSDR 1992; O'Neil et al. 2001
CAS registry no.	78-93-3	ATSDR 1992
Chemical formula	$CH_3COCH_2CH_3$	O'Neil et al. 2001
Molecular weight	72.10	O'Neil et al. 2001
Physical state	Liquid	O'Neil et al. 2001
Boiling point	79.6°C	O'Neil et al. 2001
Melting point	−86°C	O'Neil et al. 2001
Solubility in water	275,000 mg/L 353,000 mg/L	O'Neil et al. 2001 HSDB 2008
Vapor pressure	90.6 mmHg at 25°C	ATSDR 1992
Vapor density (air =1)	1.3814 2.41	O'Neil et al. 2001 HSDB 2008
Liquid density (water =1)	0.805	O'Neil et al. 2001
Flash point	6°C (closed cup)	O'Neil et al. 2001
Explosive limits Upper Lower	 12% by volume 1.8% by volume	ACGIH 2006
Conversion factors	1 ppm = 2.93 mg/m^3 1 mg/m^3 = 0.341 ppm	ATSDR 1992

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold

The odor of MEK has been described as sweet and sharp with the hedonic tone described as neutral to unpleasant (Leonardos et al. 1969; Hellman and Small 1974). The odor threshold has variously been reported as 0.25 to 147 ppm (Billings and Jonas 1981; Amoore and Hautala 1983; Ruth 1986); following standardization of results from different threshold studies, an odor detection threshold of 7.8 ppm was reported (Devos et al. 1990). In the Devos et al. (1990) study, odor thresholds were similar for male and female control subjects, 8.2 and 8.1 ppm, and for male and female subjects with multiple chemical sensitivities, 5.7 and 7.6 ppm. The odor recognition thresholds for trained panels of experts were similar, 6 ppm (Hellman and Small 1974) and 10 ppm (Leonardos et al. 1969). The threshold for irritation as reported by Ruth (1986) was 200 ppm. No data were provided for this value.

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2.2.2. Clinical Studies

Five clinical studies addressed subjective symptoms during MEK exposure. These studies are summarized in Table 3-3 and discussed in the text below. Clinical studies that addressed neurotoxic end points are discussed in Section 2.3 (neurotoxicity) and are also summarized in Table 3-3. During metabolism studies, groups of healthy subjects were exposed to MEK at 200 ppm (Liira et al. 1988a,b; 1990a,b; Shibata et al. 2002), 300 ppm (Tada et al. 1972; van Engelen et al. 1997), or 400 ppm (Liira et al. 1990a) for 2-4 h. A series of studies by Dick et al. (1984; 1988; 1989; 1992) and a study by Shibata et al. (2002) addressed sensory irritation and neurotoxicity as well as metabolism. Two studies involved coexposures to MEK and *n*-hexane (van Engelen et al. 1997; Shibata et al. 2002). No adverse symptoms were reported in these studies. In some cases exercise was incorporated into the study protocol.

Nelson et al. (1943) exposed 10 male and female volunteers to several concentrations of MEK for 3 to 5 min to determine a concentration that would be satisfactory for industrial exposures and a concentration that would be "unpleasant" or objectionable. Atmospheres were generated by adding a known quantity of vapor saturated air to the measured flow of air being forced into the chamber; there were no analytic measurements. The volunteers found that nose and throat irritation were slight at 100 ppm. Mild eye irritation was reported by some subjects at 200 ppm, and 350 ppm was considered objectionable for an 8-h exposure. The majority of subjects considered 200 ppm satisfactory for an 8-h exposure.

In a combined metabolism and sensory irritation study, four healthy male subjects with no prior exposure to organic solvents inhaled MEK at 100 or 200 ppm for 2 h, both in combination with hexane at 50 ppm (Shibata et al. 2002). The subjects exercised on a ergometer bicycle at a constant workload of 50 watts. The subjects rated the severity of the following symptoms: discomfort in eye, running nose, discomfort in throat or airways, headache, fatigue, nausea, dizziness, feeling of intoxication, difficulty in breathing, and odor of solvents. The rating system ranged from "no effect at all" to "almost unbearable." Except for odor, all symptoms were rated between "not at all" and "hardly at all" by the subjects. Solvent odor ratings increased with increasing exposure to MEK (rating not stated). Combined exposure to MEK and *n*-hexane depressed the metabolism of *n*-hexane. There were no differences in heart rate or performed workload among the different exposure conditions. Metabolism results are summarized in Section 4.1.2.

In a double-blind study, Dick et al. (1992) exposed 13 male and 11 female subjects, ages 18-32, to 200 ppm for 4 h in a test of neurobehavioral performance (summarized in Section 2.3) and sensory and irritant effects. The 4-h exposure session was composed of two 2-h periods. Additional subjects were exposed to methyl isobutyl ketone, a combination of MEK and methyl isobutyl

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TABLE 3-3 Summary of Human Studies for Methyl Ethyl Ketone

Concentration (ppm)	Exposure Duration	Effect and Type of Study	Reference
90-270 (average 150)	4 h	Concentrations not held constant; underestimation of times of 5 to 30 s by men and expansion of variation of time estimation in women; questionable results	Nakaaki 1974
100	3-5 min	Slight nose and throat irritation	Nelson et al. 1943
200	3-5 min	Mild eye irritation in some subjects; judged satisfactory for 8-h exposure	
350	3-5 min	Judged objectionable for 8-h exposure	
100, 200	2 h	Metabolism study; exposures in combination with *n*-hexane; constant workload of 50 watts; odor noticeable; no irritation and no subjective symptoms	Shibata et al. 2002
200	4 h	No significant difference in choice reaction time, visual vigilance, or pattern recognition tests	Dick et al. 1984
200	4 h	No significant difference in psychomotor tests of choice reaction time, visual vigilance, dual task of auditory tone discrimination and tracking, memory scanning, postural sway, profile of moods states	Dick et al. 1988; 1989
200	4 h	Noticeable strong, unobjectionable odor; subjective symptoms similar to control responses	Dick et al. 1992
200	4 h	No irritation; no subjective symptoms; strong odor; increase in mucociliary transport time; nonsignificant changes in proinflammatory cytokines	Muttray et al. 2002
10	4 h	No effect	Seeber et al. 2002; van Thriel et al. 2003a
10-380 (five 8-min peaks to 380 ppm; time-weighted average ≈188)	4 h	Intense odor; irritation rated “hardly at all”; subjects with self-reported multiple chemical sensitivity included in the study	
25, 200, 400	4 h	Metabolism studies; exercise incorporated into some protocols	Liira et al. 1988a,b; 1990a,b
300	2-4 h	Metabolism study; sensory and neurobehavioral effects not addressed	Tada et al. 1972
300-600	Occupational	Central-nervous-system effects, possibly attributable to concurrent dermal exposure	Smith and Mayers 1944
33,000, 100,000	Few breaths	Intolerable, irritation to eyes and nose	Patty et al. 1935
10,000	Few breaths	Almost intolerable, irritation to eyes and nose	
3,300	Not given	Strong odor, moderately irritating to eyes and nose	

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ketone, or an alcoholic drink, which served as a positive control for the neurobehavioral tests. Two control groups were also used: a chemical-control group and an alcohol-control group. The chemical control group was exposed to a combination of MEK and methyl isobutyl ketone at 25 ppm for 5 min at the beginning of the control session. For the subjective part of the study, two questionnaires were used. The "Subjective I" questionnaire consisted of a yes/no format in response to the following items: (1) presence of odor, (2) strong odor, (3) objectionable odor, (4) headache, (5) nausea, (6) throat dryness or coughing, (7) tearing, and (8) unpleasant exposure. The "Subjective II" questionnaire also required yes/no responses to indicate whether the subjects had been exposed to a chemical or to the control atmosphere. The percentages of exposed subjects reporting yes to the eight items above involving odor and irritation were 96%, 48%, 48%, 7%, 19%, 50%, 17%, and 44%, respectively. Except for strong odor, similar numbers of positive responses were recorded for the chemical-control group: 94%, 22%, 40%, 12%, 6%, 34%, 24%, and 34%. As noted, 48% of subjects exposed to MEK reported a strong odor and 22% of the subjects in the chemical-control group reported a strong odor ($p < 0.05$). The authors, in comparing the headache response between the chemical-control and chemically exposed groups, suggested that test-taking for 4 h accounted for the headache effect. In response to the Subjective II questionnaire, 96% of the subjects exposed to MEK correctly reported that they had been exposed to a chemical.

Muttray et al. (2002) exposed 19 healthy nonsmoking males, ages 22-41, to MEK at 0 or 200 ppm for 4 h. The study was not blind in that subjects were aware of a chemical odor during the exposure to MEK. A questionnaire of 17 items relating to irritation of the mucous membranes, difficulties in breathing, and prenarcotic symptoms was administered before, after 2 h, and after 4 h of exposure. The nasal mucosa was examined. There was no subjective irritation of nasal mucosa. On a scale of 0 to 5, all median scores were 0 (no symptoms). Mucociliary transport time was statistically significantly higher, 660 vs. 600 s. Some cytokines were slightly, nonsignificantly increased, whereas others were unaffected. The authors considered any changes subclinical.

Seeber et al. (2002, see also van Thriel et al. 2002, 2003b) evaluated psychologicl reactions related to chemosensory irritation. Specifically, the authors focused on relationships between irritation, odor, and annoyance in response to acute solvent exposure. They conducted 14 inhalation studies with 4-h exposures to each of eight chemicals. The subjects rated odor (scale of 0 ["not at all"] to 5 ["very strong"]), annoyance or well-being (scale of 1 ["not annoying"] to 7 ["very annoying"]), and eye and nose irritation (same scale as for odor) every half hour. For MEK, 24 paid naive subjects were exposed at a constant concentration of 10 ppm (near the odor threshold) or at five peaks of 380 ppm (initial exposure) with decreases to 10 ppm. The low and high concentrations were held for 8 min; they were linked by periods of increasing or decreasing concentrations for 22 min. The time-weighted average (TWA) in a similar study reported by van Thriel et al. (2003a) was 188 ppm. Rating surveys were taken during the maximum and minimum exposures and during the control exposure, and muco-

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sal swelling as measured by anterior active rhinomenometry was measured. The study was single blind because the subjects were unaware of the exposures, but the staff had little interaction with the subjects. The exposure chamber was 28 m^3, and concentrations were measured. Irritation, odor, and annoyance scores during exposure to clean air were 0.1, 0.1, and 1.3, respectively. The eye irritation score was 0.4 for the constant 10-ppm MEK concentration. For the changing conditions, odor ratings followed the peaks and valleys of the exposure concentrations, ratings of ≥ 3 ranging from 0-9% of respondents at 10 ppm to 55-91% of respondents at 380 ppm. The averaged ratings for eye and nose irritation were similar and were verbally scored "hardly at all." Statistically, odor had the strongest effect, followed by annoyance and irritation. The authors (Seeber et al. 2002) concluded that there was no evidence of sensory irritation on a subjective level.

When subjects in the Seeber et al. (2002) study were divided into those with "self-reported multiple chemical sensitivity" (sMCS), measured by response to items on a questionnaire, and subjects who were not sensitive to chemicals (controls), the scores for the sMCS increased with time, whereas those for the controls did not. Each of the nine ratings for the sMCS subjects, taken during the 4-h exposure, was ≤ 1 ("hardly at all") for nose and eye irritation, and the scores for the controls were all ≤ 0.25 (close to "not at all"). The 95% confidence interval for nose and eye irritation never rose above a score of 1.5. Inflammatory biomarkers—eosinophil cationic protein, myeloperoxidase, interleukin 1β, substance P, and neurokinin—were not affected by either exposure in either the control or the sMCS groups (van Thriel et al. 2003a). A weak dose-response increase in nasal symptoms was reported by the sMCS group; however, mean scores for nasal and eye irritation were never greater than 1 on a scale of 0-5; controls scored 0.2. There was no effect on nasal flow. (Compared with the controls, sMCS subjects had a significant decrease in the flow value in anterior rhinomanometry independent of dose [Wiesmuller et al. 2002]). Breathing rate and heart rate of the two groups of subjects reported in another paper (Haumann et al. 2003) were not changed appreciably by the exposures.

Patty et al. (1935) stated that 33,000 and 100,000 ppm were intolerable to humans because of irritation of the eyes and nasal passages. A concentration of 10,000 ppm was intolerable after a few inhalations because of irritation to the eyes and nose, and 3300 ppm had a moderate-to-strong odor and was moderately irritating to the eyes and nose (no exposure durations given). The raw data or the source of the data were not provided, but the exposures presumably took place during the authors' exposure of guinea pigs to the same concentrations.

2.2.3. Monitoring Studies

Monitoring studies indicated that workers were routinely exposed to MEK at ≤ 100 ppm, as taken by instantaneous and 4-h passive samplers (Miyasaka et al. 1982; Brugnone et al. 1983; Perbellini et al. 1984), and to TWA exposures up

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to 224 ppm (Yoshikawa et al. 1995) and 270 ppm (median value, 26 ppm) (Imbriani et al. 1989); in one case, 4-h TWA exposures ranged up to 950 ppm (Ghittori et al. 1987). Samples were taken by several methods, including instantaneous samples via glass tubes and 2- and 4-h passive samplers. In some cases, workers were exposed to a mixture of solvents. Health effects were not addressed in these studies.

2.2.4. Case Reports

In occupational settings, the primary routes of exposure are inhalation and skin contact. Symptoms incurred by workers during occupational exposures have been described. MEK is a strong degreasing agent, and contact with the skin might result in dermatitis. Workers handling MEK while manufacturing raincoat water-proofing material developed severe dermatosis with a complete lack of sensation in the digits and limbs (Smith and Mayers 1944). Workroom concentrations ranged from 300 to 600 ppm. Dermal contact with liquid MEK during the processes was highly likely because it was reported that workers tended to wash their hands in the solvent. Two workers in a similar plant where exposures were at 1,000 ppm measured as ketone vapors (acetone at 330-495 ppm plus MEK at 398-561 ppm) suffered episodes of CNS depression, and loss of consciousness (Smith and Mayers 1944).

2.2.5. Epidemiologic Studies

Available epidemiology studies involved a mixture of solvents and generally addressed neurotoxicity (Arlien-Soberg 1991). Adverse effects could not clearly be related to exposure to MEK alone and therefore are not discussed in this report. Epidemiology studies that addressed the potential carcinogenicity of MEK are discussed in Section 2.6 (Carcinogenicity).

2.3. Neurotoxicity

During 4-h exposures of male and female human subjects to MEK at 90 to 270 ppm, the subjects participated in time-estimation tests (Nakaaki 1974). The concentration increased over the 4-h periods; the average concentration for each exposure was 150 ppm. There were nine morning and nine afternoon sessions, and two males and two females participated in each session. Males tended to underestimate times of 5 to 30 s, and females showed more variable results compared with control estimates of time. The time-estimation values from this study were highly variable, and no statistical differences were presented between or among the exposure groups. The subjects reported a strong odor at 90 ppm. This study differs from recent well-conducted clinical studies in that symptoms of tears and sneezes were reported (see Table 3-3 for results of recent stud-

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ies). Furthermore, when testing solvents, such as acetone, with similar mechanisms of action, time-estimation changes in males and females differed from those of MEK.

Dick et al. (1984) exposed groups of paid volunteers to MEK at 0 or 200 ppm for 4 h in a study of psychomotor performance. A group of 20 male and female volunteers were exposed at 200 ppm for 4 h. The control group consisted of 20 volunteers. The MEK concentration was continuously monitored with infrared analyzers and confirmed by gas chromatography. The average concentration over the 4-h period was 190 ppm. Two performance tests, reaction time and visual vigilance, were administered throughout the pre-exposure, exposure, and postexposure periods; a third test, pattern discrimination, was run only during the pre-exposure and exposure period. There were no statistically significant differences between the treated and the control groups on any test.

In a double-blind study, groups of 9-12 male and 10-13 female volunteers ranging in age from 18 to 32 years were exposed to MEK at 0 or 200 ppm or to 95% ethanol (0.84 mL/kg as a positive control) for 4 h (Dick et al. 1988, 1989). The computerized testing regimen consisted of 2-h sessions on each of 3 days: a practice session on day 1; tests prior to exposure, during exposure (two testing sessions) and postexposure on day 2; and tests postexposure on day 3. During each 2-h test session, four psychomotor tests (choice reaction time, visual vigilance, dual task, and short-term memory scanning); a neurophysiologic test (eye blink reflex); and one sensorimotor test (postural sway) were administered to the test subjects. A profile-of-mood states psychologic test was administered following exposure and on the following day. Exposure to MEK produced no statistically significant interpretable results. Exposure to MEK at 100 ppm and to either acetone at 125 ppm or toluene at 50 ppm (Dick et al. 1984) had no significant effect on behavioral tests. Ethanol, at a measured blood alcohol content of 0.07-0.08%, produced pronounced performance decrements in several tests.

In a third double-blind study, Dick et al. (1992) exposed 13 male and 11 female volunteers, ages 18-32, to 200 ppm for 4 h while they performed five psychomotor tests—choice reaction time, simple reaction time, visual vigilance, dual task, and memory scanning—and one sensorimotor test—postural sway. The 4-h exposure session was composed of two 2-h periods. Sensory effects for this study are summarized in Section 2.2. As in the earlier study (Dick et al. 1988), ethanol (0.84 mL/kg) was used as a positive control substance. According to the authors, the exposure to MEK did not produce any conclusive, consistently interpretable effect of chemical treatment. In contrast, ethanol ingestion produced significant decrements on every performance test except memory scanning.

In contrast to acute exposures, chronic exposures may be neurotoxic. Workers in a cable factory exposed at 50-120 ppm over an 8-h work shift for an average of 14 years had increased mood disorders and reported more headaches, memory difficulties, and sensory irritation than controls. Although tested, decrements in neurobehavioral tests were not reported for MEK (Mitran et al. 1997).

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2.4. Developmental and Reproductive Toxicity

No information was found specific to the developmental and reproductive toxicity of MEK in humans.

2.5. Genotoxicity

No studies regarding the genotoxicity of MEK in humans via the inhalation route were located in the available literature. In an in vitro study, MEK at concentrations of 10^{-2}, 10^{-3}, or 10^{-4} M was neither cytotoxic nor increased tritiated thymidine uptake in human lymphocytes (Perocco et al. 1983).

2.6. Carcinogenicity

In an early unpublished study of 306 male employees who had been employed in the lubricants dewaxing unit (a petroleum refining process) of a refinery, the overall mortality was less than expected, and there was no evidence of an excess of deaths from cancer (Enterline 1978). Five deaths from cancer occurred, and six were expected. Two of the deaths were from prostate cancer.

A retrospective epidemiology study was undertaken of 446 men who had worked at two MEK dewaxing plants for a period of at least 1 continuous year (Alderson and Rattan 1980). The solvent exposure consisted of MEK and benzene prior to 1971, after which benzene was replaced with toluene. There was a slight reduction in overall mortality: observed deaths, 46; expected deaths, 55.5; and a slight deficiency of deaths from neoplasms: observed, 13; expected, 14.4. There were more deaths than expected from buccal cavity and pharyngeal cancers: observed, 2; expected, 0.13; and fewer deaths than expected from lung cancer: observed, 1; expected, 6.0. From the results, the authors concluded that there was no clear evidence of a cancer hazard.

Wen et al. (1985) conducted a retrospective cohort mortality study of 1,008 men employed in solvent dewaxing units of a refinery between 1935 and 1978. Exposure was to benzene and MEK prior to 1945 and to MEK and toluene thereafter. Personal samples indicated that the 8-h TWA for MEK was approximately 1 ppm. Less than 5% of the samples were more than 5 ppm. The TWA toluene concentration was also approximately 1 ppm. Measurements of other solvents, including benzene, hexane, xylene, and methyl isobutyl ketone, were < 0.1 ppm. The standardized mortality ratio (SMR) (compared with the U.S. population) for all causes was 0.70, and the SMR for cancer was 0.86. Prostate cancers were nonsignificantly increased among maintenance workers but not among workers specifically assigned to the MEK units.

2.7. Summary

The relative toxicity of most ketones is low, and no information on deaths

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attributable to exposure to MEK was located. The odor recognition threshold for MEK ranges from 6 to 10 ppm (Leonardos et al. 1969; Hellman and Small 1974). Volunteers exposed to MEK for 3-5 min judged 200 ppm as acceptable for an 8-h exposure and 350 ppm as objectionable for an 8-h exposure (Nelson et al. 1943). In a more recent 4-h study, 200 ppm was also judged as unobjectionable by healthy volunteers (Dick et al. 1992). Additional behavioral and metabolism studies with human volunteers conducted at 200 and 400 ppm for 4 h did not reveal either irritant or neurotoxic effects. The Dick et al. studies (1984, 1988, 1989, 1992) with exposures at 200 ppm for 4 h found no exposure-related changes in performance on psychomotor and mood tests or incidences of irritation. A 4-h exposure at 90-270 ppm caused minor disturbances in the conception of time (Nakaaki 1974). Several recent clinical studies (Dick et al 1992; Muttray et al. 2002; Seeber et al. 2002; Shibata et al. 2002) reported that MEK was associated with strong odor rather than irritation. This finding shows that odor rather that irritation was probably responsible for symptom complaints in earlier studies, such as Nelson et al. (1943). Subjects with sMCS found repeated 8-min exposures at a concentration of 380 ppm practically nonirritating (Seeber et al. 2002). Some workers exposed at higher concentrations, up to 1,000 ppm total ketones for unknown exposure durations, suffered CNS depression (Smith and Mayers 1944), but dermal exposure to the liquid in addition to inhalation exposure most likely contributed to the effects.

No studies regarding genotoxicity in humans were located. No information was found specific to the developmental and reproductive toxicity of MEK in humans. Two retrospective epidemiology studies of workers chronically exposed to MEK at petroleum refining plants reported that deaths due to cancers were fewer than expected (Alderson and Rattan 1980; Wen et al. 1985).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Data on acute lethality were available for the rat, mouse, and guinea pig. Data are summarized in Table 3-4.

3.1.1. Rats

Carpenter et al. (1949) reported that a 4-h exposure of Sherman rats to MEK at 2,000 ppm killed two to four of six rats (exact number not stated). However, in a later study, this same group (Pozzani et al. 1959; Smyth et al. 1962) reported that rats exposed at 2,000 ppm for 2 h showed no toxicity, an 8-h exposure at 8,000 ppm killed half of the rats, and an exposure at 16,000 ppm caused the deaths of all of the rats in the exposure group. All concentrations were nominal.

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TABLE 3-4 Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Duration	Effect	Reference
Rat	92,239	3 h	LT_{50}	Klimisch 1988
	92,239	30 min	No deaths	
Rat	8,000	8 h	LC_{50}	Pozzani et al. 1959;
	2,000	2 h	No signs of toxicity	Smyth et al. 1962
Rat	20,200	4 h	100% mortality	La Belle and
	18,100	4 h	100% mortality	Brieger 1955
	13,750	4 h	87.5% mortality	
	12,200	4 h	50% mortality	
	9,260	4 h	12.5% mortality	
	9,090	4 h	12.5% mortality	
	7,850	4 h	No deaths	
	11,700	4 h	LC_{50}	
Mouse	103,000	43 min	Mean survival time	La Belle and Brieger 1955
Mouse	100,000	45 min	100% mortality	Zakhari et al. 1977
	90,000	45 min	80% mortality	
	80,000	45 min	50% mortality	
	70,000	45 min	20% mortality	
	60,000	45 min	No deaths	
	50,000	45 min	No deaths	
	69,500	45 min	LC_{50}	
Guinea pig	100,000	45 min	Lethal	Patty et al. 1935
	33,000	200 min	Lethal	
	10,000	2-4 min	Irritation of eyes and nose	
		40 min		
		90 min	Lacrimation	
		4-4.7 h	Incoordination	
		13.5 h	Narcosis	
	3,300	13.5 h	No deaths No overt signs of toxicity	

Groups of eight adult male albino rats inhaled concentrations of 7,850, 9,090, 9,260, 12,200, 13,750, 18,100, or 20,200 ppm for 4 h (La Belle and Brieger 1955). Atmospheres were measured spectrophotometrically. Respective mortalities were 0%, 12.5%, 12.5%, 50%, 87.5%, 100%, and 100%. The calculated LC_{50} was 11,700 ± 2,400 ppm. Most deaths were "immediate", narcosis having preceded death.

Klimisch (1988) exposed three male and three female rats (strain unspecified) to the saturated vapor of MEK at 20°C to determine the time to 50% mortality (LT_{50}). The postexposure observation period was 14 days. The concentration that corresponded to a nominal LT_{50} of 3 h was 272 mg/L (approximately 92,239 ppm). No deaths occurred after a 30-min exposure at 92,239 ppm.

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3.1.2. Mice

Adult white mice (strain not identified) exposed to a saturated vapor concentration of MEK, estimated at 103,000 ppm, had a mean survival time of 43 min (La Belle and Brieger 1955). Six groups of 10 male CF-1 mice were exposed at concentrations of 50,000, 60,000, 70,000, 80,000, 90,000, or 100,000 ppm for 45 min (Zakhari et al. 1977). Survivals, observed immediately after exposure, were 100%, 80%, 50%, 20%, 0%, and 0% at the respective exposure concentrations (see Table 3-4). The 45-min LC_{50} was 69,500 ppm. According to Zakhari et al. (1977), the progression of toxic signs was incoordination, narcosis, and respiratory depression followed by death.

3.1.3. Guinea Pigs

Patty et al. (1935) exposed groups of six guinea pigs to MEK at 3,300, 10,000, 33,000, or 100,000 ppm (the latter concentration was the air saturation concentration) for periods up to 13.5 h. The acute effects advanced through several distinct stages as the exposure proceeded: nose irritation (manifested by rubbing of the nose with the forepaws), eye irritation (squinting), lacrimation, incoordination, narcosis, labored breathing, and death. Vapor concentrations of 33,000 and 100,000 ppm produced death by 200 and 45 min, respectively. Gross pathology revealed slight congestion in the brain and marked congestion of the lung, liver, and kidneys of those animals that succumbed during the exposure or were killed immediately after exposure. These signs were absent in most animals that were killed 4 to 8 days later. Animals that survived exposure at 100,000 ppm for 30 min showed severe corneal opacity that regressed by 8 days postexposure. Although the authors could not clearly attribute the cause of death to either irritation of the lungs or a state of narcosis that terminated in death, the complete reversal of effects in all animals that survived the exposures indicated that the primary mode of action was narcosis. No abnormal signs were observed during a 13.5-h exposure at 3,300 ppm. At 10,000 ppm, progressive signs included irritation of the nose and eyes in 2 and 4 min, respectively, lacrimation in 40 min, incoordination in 90 min, and unconsciousness in 4-4.7 h. No gasping respiration or deaths occurred during a 13.5-h exposure at 10,000 ppm.

3.2. Nonlethal Toxicity

Studies with acute exposure durations are summarized in Table 3-5 and discussed below. Studies with neurotoxic end points are listed in Table 3-5 and discussed in Section 3.3. Studies with intermediate exposure durations are also discussed in the following sections.

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TABLE 3-5 Summary of Nonlethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Duration	Effect	Reference
Baboon	100	24 h, 7 days	No effect on match-to-sample task during first day	Geller et al. 1979
Rat	10,000	8 h/day several days	Severe irritation, respiratory tract	Altenkirch et al. 1978
	6,000	8 h/day for weeks	Mildly somnolent, but arousable	
Mouse	31,426	30 min	Calculated 50% decreased respiration	Hansen et al. 1992
	26,000	30 min	Decrease in body movements	
	10,000	30 min	Not anesthetic	
Mouse	10,745	5 min	RD_{50}	De Ceaurriz et al. 1981
Mouse	5,000	10 min	15% decrease in respiratory rate	Stone et al. 1981
	9,000	10 min	RD_{50}	
Mouse	2,891	9.5 min	EC_{50}, schedule-controlled behavior	Glowa and Dews 1987
	10,000	9.5 min	Mice unresponsive	
	5,600	9.5 min	No response in most mice	
	3,000	9.5 min	Response decreased by 75%	
	1,000	9.5 min	Response slightly decreased	
	300	9.5 min	No effect on response	
Mouse	2,065	4 h	50% decrease in immobility in behavioral-despair swimming test	De Ceaurriz et al. 1983

3.2.1. Rats

Altenkirch et al. (1978) exposed a group of five male Wistar rats to MEK for 8 h/day, 7 days/week, for 7 weeks (a control group was not reported). Other groups were exposed to MEK and *n*-hexane or *n*-hexane alone. The initial exposure to MEK alone was at 10,000 ppm but had to be lowered to 6,000 ppm within a few days because of severe irritation of the respiratory tract. The rats exposed to MEK at 1,000 ppm and to *n*-hexane at 9,000 ppm became "somnolent within 5 to 10 min after a short excitation stage but remained arousable during the whole period of exposure." This effect was "less marked" in rats exposed to MEK alone. The authors did not state the day on which this effect was first noted. Transient signs of ataxia and gait disturbances, primarily during the last weeks of exposure, were noted for 10-20 min after exposure. None of the MEK-exposed rats developed motor impairment, and neurohistologic examinations showed no treatment-related lesions. The exposure duration was planned for 15 weeks, but all rats died of bronchopneumonia during the seventh week of exposure.

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In a 90-day study, groups of 15 male and 15 female Fischer 344 rats were exposed to MEK at 0, 1,250, 2,500, or 5,000 ppm for 6 h/day, 5 days/week, for 90 days (ToxiGenics 1981; Cavender et al. 1983). Analytically determined TWA concentrations were 0, 1,254, 2,518, or 5,041 ppm. No animals died during the study, and there were no adverse effects on the clinical health or growth of the rats, although body weights were transiently depressed early in the study for both sexes in the 5,000-ppm group. Daily observations and weekly clinical examinations revealed no nasal or eye irritation. Absolute and relative liver weights were significantly increased in both sexes in the 5,000-ppm group, and some serum hematology and clinical chemistry parameters were increased in females in the 5,000-ppm group. Evaluations of neurologic function (posture, gait, facial muscular tone, and neuromuscular reflexes) revealed no abnormalities. Special neuropathy studies of the medulla and peripheral nerves revealed no lesions attributable to MEK exposure. The U.S. Environmental Protection Agency (EPA 2003) noted the presence of chronic respiratory disease in both control and MEK-exposed rats.

In additional studies of intermediate duration, no clinical signs or deaths were reported during or following exposures of rats at 200 ppm, 12 h/day, for 24 weeks (Takeuchi et al. 1983) or at 1,125 ppm, 24 h/day, for 5 months (Saida et al. 1976).

3.2.2. Mice

Several studies addressed the sensory irritation of MEK. The concentration that depressed the respiratory rate by 50% (RD_{50}) after 5 min for six male OF_1 mice was 10,745 ppm (De Ceaurriz et al. 1981). Atmospheres were measured with gas chromatography. Stone et al. (1981) reported a similar value, 9,000 ppm, using male Swiss-Webster mice with a 10-min exposure period (exposure system not described), whereas Hansen et al. (1992) reported a much higher value, 31,426 ppm during 30-min exposures of male CF_1 mice. The concentration of 31,426 ppm was projected from the data because test concentrations ranged only up to 26,416 ppm (range, 3,809-26,416 ppm). The differences among the studies may be due to the fact that for nonprimary irritants, the concentrations causing decreased respiration plateau at high concentrations. In this study (Hansen et al. 1992), atmospheres were monitored continuously by infrared spectroscopy. The threshold for respiratory rate depression was 3,589 ppm at the beginning of an exposure. Tidal volume was also decreased in this study; this response is not mediated by the trigeminal nerve (which mediates the irritant response). Body movements were unaffected at 10,000 ppm, slightly decreased at 15,000-20,000 ppm, and strongly depressed at 26,416 ppm. Tracheally cannulated mice were also tested at these concentrations and none died. No histopathologic examinations were conducted.

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3.3. Neurotoxicity

Geller et al. (1979) exposed four baboons to MEK at 100 ppm continuously for 7 days. Operant conditioning behavior, a match-to-sample discrimination task, conducted during exposure was compared with pre-exposure test scores for each baboon. There was no significant effect on accuracy, but there was a decrease in mean response time and response during delay beginning on the second day. There was no effect during the first day of exposure. The same animals were used for several chemical tests, and MEK was tested second. At least 1 month elapsed between tests.

During exposure of five adult male Wistar rats to MEK at 10,000 or 6,000 ppm for 8 h/day, the animals were excitable for 5-10 min at the beginning of each exposure and then became mildly somnolent but arousable (Altenkirch et al. 1978). Exposure at 6,000 ppm continued for several weeks. Exposure of guinea pigs at 10,000 ppm caused incoordination in 90 min and narcosis in 4-4.7 h (Patty et al. 1935). Continuous exposure of young male Wistar rats at 750 ppm for 7 days reduced subsequent hexabarbital sleep times (16 min vs. 26 min for controls), (Couri et al. 1977). This effect is most likely due to induction of cytochrome P-450-2B and -2E, which would enhance metabolic clearance and reduce the hypnotic action.

In a schedule-controlled-response experiment that used milk as an incentive, a group of 12 mice was exposed at increasing concentrations of MEK (300, 1,000, 3,000, 5,600, or 10,000 ppm) for a series of eight food presentations or 9.5 min, whichever occurred first (Glowa and Dews 1987). There was a 30-min break between each exposure. There was no effect on behavior at 300 ppm. At 1,000 and 3,000 ppm, responses were decreased by approximately 25% and 75%, respectively. At 5,600 ppm, response in most mice ceased, and at 10,000 ppm, all response ceased. The EC_{50} (concentration that causes an effect in 50% of the exposed population) was 2,891 ppm. Responding completely recovered 30 min after exposure.

Exposure of male Swiss OF1 mice to 1,602, 1,848, 2,050, or 2,438 ppm for 4 h caused a dose-related reduction of immobility in a behavioral-despair swimming test (De Ceaurriz et al. 1983). The concentration associated with a 50% decrease in immobility during the 3-min test was 2,065 ppm. The authors did not interpret the meaning of the increase in swimming time (antidepressive effect of solvents).

During sensory irritation tests with mice that lasted 30 min, Hansen et al. (1992) observed body movements at 26,416 ppm and noted that this concentration did not cause “serious” depression of the CNS, that is, anesthesia or asphyxia.

Exposure of six male Sprague-Dawley rats to MEK at 500 ppm for 22 h/day, 7 days/week, for 6 months did not result in any significant clinical or histopathologic evidence of neurologic dysfunction (Egan et al. 1980). Exposure

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of Fischer 344 rats at up to 5,000 ppm for 90 days did not result in any signs of neurotoxicity or lesions of the nervous system (ToxiGenics 1981; Cavender et al.1983). In the latter study, neurohistopathologic examination of the medulla and the sciatic and tibial nerves revealed no lesions that could be attributed to MEK exposure.

3.4. Developmental and Reproductive Toxicity

Groups of 21-23 pregnant Sprague-Dawley rats were exposed to MEK at nominal concentrations of 1,000 or 30,00 ppm for 7 h/day during gestation days 6 through 15 (Schwetz et al. 1974). Experimental exposures at 1,000 or 3,000 ppm were conducted separately, each with a control group. Analytically determined concentrations (infrared analysis) were 1,126 and 2,618 ppm. These concentrations were stated as being subanesthetic by the study authors. Neither concentration had an effect on the incidence of fetal resorptions. Fetal body measurements were reduced in the group exposed at 1,000 ppm but not in fetuses of rats exposed at 3,000 ppm. For the group exposed at 3,000 ppm, compared with the control group, there was an increase in the total number of litters containing fetuses with delayed ossification of the sternebrae and in the total number of litters containing fetuses with soft tissue anomalies (both, $p < 0.05$), although no soft-tissue anomaly occurred at a significantly increased incidence compared with the control group. (There were more litters with soft-tissue anomalies than were in the control group, but there were no more anomalies per litter.) There was no maternal toxicity as observed by clinical signs, food consumption, weight gain, conception rate, number of implantations or litter size, serum glutamic-pyruvic transaminase activity, or absolute or relative liver weights.

To confirm the fetotoxic effects observed in the Schwetz et al. (1974) study, Deacon et al. (1981) repeated the study by exposing groups of 25 pregnant Sprague-Dawley rats to MEK at 1,000 or 3,000 ppm for 7 h/day on gestation days 6 through 15. In addition to 35 controls, a group of 25 rats was also exposed at 400 ppm. Analytically determined concentrations were 412, 1,002, and 3,005 ppm, respectively. Slight maternal toxicity was observed in dams exposed at 3,000 ppm as evidenced by decreased weight gain and increased water consumption. In this study, there was no adverse effect on fetal body weight or crown-rump length among litters. No external or soft-tissue alterations were observed among fetuses at any exposure concentration. Slight fetotoxicity was observed among litters of rats exposed at 3,000 ppm as evidenced by an increased incidence of minor skeletal variants—delayed ossification of the skull, extra ribs, and delayed ossification of the cervical centra (all $p < 0.05$). According to the authors, there was no evidence of an embryotoxic or teratogenic response in any exposure group.

Groups of 10 virgin and 33 pregnant Swiss mice (Crl:CD-1) were exposed at 0 (filtered air), 400, 1,000, or 3,000 ppm for 7 h/day on gestation days 6-15

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(Mast et al. 1989; Schwetz et al. 1991). Virgin females were included to assess the state of pregnancy on maternal toxicity. Analytically determined concentrations were 398, 1,010, and 3,020 ppm, respectively. Chamber atmospheres were monitored with a gas chromatograph. Body weights were obtained throughout the study, and uterine and fetal body weights were obtained at death on day 18. Uterine implants were enumerated, and live fetuses were sexed and examined for gross defects. There were no deaths or overt signs of toxicity in virgin or pregnant females during the exposures. Body weights and uterine weights were not affected by exposure, but the liver-to-body-weight ratio was significantly increased in pregnant females in the 3,000-ppm group. Compared with the controls, there was no effect of exposure on number and percentage of pregnant females, implantations/dam, live fetuses/litter, resorptions/litter, dead fetuses/litter, or litters with resorptions. Fetal weights of both males and females of dams exposed at 3,000 ppm were lower than control weights, the difference attaining significance in males (5%) and males and females combined (4%) (both, $p < 0.05$). The number of fetuses with malformations was slightly increased in the 3,000-ppm group, 323 vs. 310 in the control group, but the difference was not statistically significant on the basis of number of fetuses, litters affected, or number of fetuses per litter. However, several types of malformations observed in the exposed group were not present in the control group: cleft palate, fused ribs, missing vertebrae, and syndactyly. There was a significant trend for misaligned sternebrae in fetuses ($p < 0.05$) but not on the basis of litters. No significant signs of maternal or developmental toxicity were observed at 1,000 ppm. The authors considered 1,000 ppm to be a no-effect concentration for maternal and developmental toxicity and 3,000 ppm to be a concentration that caused mild developmental toxicity.

Exposure of pregnant female Wistar rats for 23 h/day, 7 days/week, at 800 or 1,000-1,500 ppm prenatally (21 days) or pre- and postnatally (52 days) resulted in concentration-related decreases in pregnancy and resorption rates (Stoltenburg-Didinger et al. 1990).

Decreased fetal body weight was also reported in pregnant rats administered 2-butanol (a metabolite of MEK) by the oral route in a multigeneration and developmental study (Cox et al. 1975). The no-observed-adverse-effect level (NOAEL) and the lowest-observed-adverse-effect level (LOAEL) in this study were 1,771 and 3,122 mg/kg/day.

No studies were located that specifically addressed reproductive toxicity. However, histologic examination of the reproductive organs of male and female rats exposed at 5,000 ppm for 90 days revealed no exposure-related lesions (Cavender et al. 1983).

3.5. Genotoxicity

Genotoxicity studies were reviewed in ATSDR (1992). In in vivo studies, no induction of micronuclei was found in erythrocytes of mice or hamsters in-

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jected intraperitoneally with MEK. MEK was not mutagenic in several strains of *Salmonella typhimurium* or in *Escherichia coli* and *Saccharomyces cerevisiae*, but it induced aneuploidy and chromosome loss in *S. cerevisiae*. In mammalian cells, test results were negative for chromosomal aberrations and unscheduled DNA synthesis in rat liver cells, morphologic transformation in BALB/3T3 cells, and gene mutation in mouse lymphoma cells.

3.6. Chronic Toxicity and Carcinogenicity

No studies that addressed the carcinogenicity of MEK via the inhalation route were located in the available literature. No tumors were observed on the skin of mice exposed with dermal applications of MEK of 50 mg/application, 2 days/week for 1 year (Horton et al. 1965).

3.7. Summary

Data on lethality were available for the rat, mouse, and guinea pig. Lethal values ranged from a 45-min LC_{50} of 69,500 ppm for the mouse (Zakhari et al. 1977) to an 8-h LC_{50} of 8,000 ppm for the rat (Pozzani et al. 1959). However, data were conflicting because Altenkirch et al. (1978) reported no deaths (but severe irritation of the respiratory tract) in rats following exposure at 10,000 for 8 h/day, for several days. Slight narcosis was reported at 6,000 (rat) to 10,000 ppm (mouse) in some studies (Altenkirch et al. 1978; Glowa and Dews 1987) but not at 10,000 ppm in another study with the mouse (Hansen et al. 1992) or at 3,300 ppm for 13.5 h in the guinea pig (Patty et al. 1935). Subtle neurobehavioral changes were observed in the mouse at 2,438 and 2,891 ppm (De Ceaurriz et al. 1983; Glowa and Dews 1987). In a 90-day study, 5,000 ppm for 6 h/day was a no-effect level for neurobehavioral deficits and neurologic lesions in rats (Cavender et al. 1983). EPA (2003) stated that "animal studies provide no convincing evidence that exposure to MEK alone causes persistent neurotoxic effects." Severe respiratory irritation as measured by the RD_{50} in the mouse ranged from 9,000 ppm (Stone et al. 1981) to 31,426 ppm (Hansen et al. 1992).

Results of a series of developmental studies with the mouse and rat determined that 3,000 ppm was toxic to the fetus as indicated by reduced fetal body weight and bone abnormalities; 1,000 ppm was a NOAEL (Deacon et al. 1981; Mast et al. 1989; Schwetz et al. 1991). In the Deacon et al. (1981) study, the developmental toxicity may be related to the concomitant overt maternal toxicity as evidenced by reduced body weights of the dams.

MEK was not genotoxic in a series of tests with *S. typhimurium* and mammalian cells. Although not mutagenic in *S. cerevisiae*, MEK caused mitotic chromosome loss and aneuploidy in this species. No animal studies involving chronic toxicity and carcinogenicity via the inhalation route were located in the available literature.

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4. SPECIAL CONSIDERATIONS

4.1. Metabolism, Disposition, and Kinetics

4.1.1. Metabolism and Disposition

Following a single intraperitoneal injection of 450 mg/kg, male guinea pigs metabolized MEK to 3-hydroxy-2-butanone, 2,3-butanediol, and 2-butanol, the latter a minor metabolite (DiVincenzo et al. 1976). On the basis of these metabolites, the study authors concluded that the metabolism of MEK follows both oxidative and reductive pathways. Reversible reduction of the ketone group yields 2-butanol; microsomal ω-oxidation yields 3-hydroxy-2-butanone, which is reduced to the diol. In this study, the serum half-life of MEK was 270 min, and the clearance time was 12 h. Dietz et al. (1981) detected the same three metabolites in the blood of male Sprague-Dawley rats exposed orally with 1.69 g/kg.

2-Butanol and 2,3-butanediol were measured in the serum or whole blood (Liira et al. 1990b), and 3-hydroxy-2-butanone and 2,3-butanediol (but not 2-butanol) were identified in the urine (Perbellini et al. 1984; Liira et al. 1988a,b) of human subjects exposed to MEK, indicating that the metabolism in humans is similar to that in animals. As excretion of 2,3-butanediol accounted for less than 3% of the inhaled dose and only 5% was exhaled by the lungs as unmetabolized MEK, most of the absorbed MEK apparently enters intermediary metabolism pathways (Liira et al. 1990a; Liira et al. 1991). Urinary excretion of 2,3-butanediol showed great individual variation. Although metabolism is fairly rapid, having an estimated half-life in the blood of 20 to 49 min (Fiserova-Bergerova 1985; Brown et al. 1987), Di Vincenzo et al. (1976) stated that the metabolism of MEK is relatively slow compared with other ketones.

4.1.2. Pharmacokinetic Data

Using human tissues from autopsies, Fiserova-Bergerova and Diaz (1986) determined the tissue-gas partition coefficients of MEK. The fat:gas and blood:gas partition coefficients were 162 and 125, respectively. The gas:tissue partition coefficients for muscle, kidney, lung, and brain ranged from 96 to 107, indicating nearly equal solubility in all tissues. Similar tissue:blood partition coefficients of 0.95 to 1.18 were found by Poulin and Krishnan (1995). Their algorithm utilized information on chemical water solubility and lipid and water content of tissues. Experimentally determined blood:air partition coefficients for an oil and water matrix and rat blood were 159 and 136, respectively (Beliveau and Krishnan 2000). Blood:atmospheric air and blood:alveolar air partition coefficients obtained by Perbellini et al. (1984) were 183 and 104, respectively. A slightly higher value for blood:air of 202 was reported by Sato and Nakajima (1979). At 37°C and using blood from Wistar rats, partition coefficients for wa-

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ter and air and olive oil and air were 134 and 131, respectively; during actual exposures of rats to MEK, the thermodynamic partition concentration was calculated to be 103 (Kessler et al. 1989). The capacity of the tissues to hold MEK was considered to be large due to the high blood and tissue solubility of MEK (Liira et al. 1988a). In all of these studies, the solubility of MEK in tissues was similar to that in blood because tissue-to-blood-concentration ratios were all approximately 1.

The kinetics of MEK were studied with human volunteers (Liira et al. 1988a; see also Liira et al. 1988b, 1990a,b). The subjects were nine healthy male volunteers ranging in age from 18 to 34 years. Exposures were at 200 ppm for 4 h; some exposures encompassed several 10-min exercise periods at a level of 100 watts. The same group was exposed to both the sedentary and exercise conditions with a 1-week break between sessions. Concentrations were monitored with an infrared analyzer. Retention by the lungs was 53% and was not influenced by exercise. The estimated pulmonary uptake was 11.38 and 14.30 millimoles (mmol) for sedentary volunteers and volunteers undergoing exercise periods, respectively. Pulmonary excretion of MEK was 0.26 (sedentary) and 0.41 (exercise) mmol. Apparent MEK clearance was 0.44 (sedentary) and 0.33 L/min/kg (exercise). In a similar study, the area under the curve was 23,400 μmol × min/L (Liira et al. 1990b). The blood concentration rose rapidly during the first hour and then steadily during the following 3 h—reaching approximately 95 μmol/L (6.9 μg/mL) in sedentary subjects and 150 μmol/L (10.9 μg/mL) in exercising subjects (Liira et al. 1988a)—and approached steady state. (Blood concentrations in this study and the following studies are summarized in Table 3-6.) Two elimination phases of MEK from blood were observed, having half-lives of 30 and 81 min. Only 2-3% of the absorbed dose was eliminated by exhalation from the lungs. Blood concentrations during and following a 4-h exposure of eight subjects at 200 ppm (Liira et al. 1988b) are graphed in the Figure 3-1.

In a follow-up study, MEK exposures were at 25, 200, or 400 ppm for 4 h (Liira et al. 1990a). The concentrations in venous blood rose rapidly during the first hour and then more slowly during the subsequent 3 h. At the end of 4 h, the concentrations were 5, 93-100, and 229-309 μM, respectively. Using the data from these exposures and a physiologically based simulation model, Liira et al. (1990a) suggested dose-dependent kinetics of MEK during sedentary exposures exceeding 100 ppm. Earlier, using the physiologically based pharmacokinetics model of Johanson and Naslund (1988), Liira et al. (1988a) suggested that saturation kinetics are reached for MEK at a concentration of 200 ppm for 4 h. In a later study conducted at both 200 and 400 ppm in humans, Liira et al. (1990a) suggest that kinetic saturation is reached at blood concentrations above 100 μM (7 μg/mL) in both humans and rats. Pulmonary ventilation is the rate-limiting step of MEK uptake (Liira et al. 1988a).

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TABLE 3-6 Blood Concentrations of Methyl Ethyl Ketone[a]

Exposure Concentration (ppm)	Blood Concentration (µg/mL)	Exposure Conditions	Reference
		Human Subjects	
Background	0.007	Nonoccupational exposures	Ashley et al. 1994
25	0.36	4 h, sedentary subjects	Liira et al. 1988a;
200	6.9	4 h, sedentary subjects	Liira et al. 1990a
200	10.9	4, h, exercising subjects	Liira et al. 1990a
400	19.4	4 h, sedentary subjects	Liira et al. 1990a
48	0.71	Occupational exposures; simultaneous exposure to other chemicals	Yoshikawa et al. 1995
≤100	2.6 (range, 0.8-9.6)	Occupational exposures	Brugnone et al. 1980; Perbellini et al. 1984
120	0.37[b]	2 h at rest	Imbriani et al. 1989
	0.66	4 h at rest	
	1.4	2 h with exercise	
100	4.3	2 h; exercising subjects (50 watts)	Shibata et al. 2002
200	12.3	Simultaneous exposure to *n*-hexane	
100[c]	2.0	4 h, sedentary subjects	Brown et al. 1987; Dick et al. 1988, 1992
200	3.5, 3.7	4 h, sedentary subjects	
		Rat[d]	
25	1.0	6 h	Liira et al. 1990a;
100	4.8		Liira et al. 1991
300	25		
600	75		

[a]Blood samples were venous blood except for the study of Shibata et al. (2002) in which case the samples were arterial capillary blood.
[b]Blood samples were collected following exposure, which may be responsible for the low values compared with blood collected during the exposures in the other studies.
[c]Coexposure to 125 ppm acetone.
[d]Rat whole blood (Liira et al. 1991) was also collected following exposures.

Imbriani et al. (1989) exposed 15 male subjects, ages 25 to 44 years, to various concentrations ranging from 4 to 212 ppm. Individual subjects were exposed to a constant concentration in the following manner: 4, 59, 103, 123, or 212 ppm for 2 h at rest; 15, 36, 54, 91, or 120 ppm for 4 h at rest; or 10, 43, 61, 118, or 168 ppm for 2 h with light physical exercise, 50 watts for 20 min, three times during the 2 h. Uptake averaged 54% regardless of workload. Although findings are based on single subjects, the venous blood concentrations at the end of exposure at approximately 120 ppm increased from 374 µg/L at 2 h to 657 µg at 4 h. Exercise during the 2-h exposure doubled and tripled the values (1,392 µg/L) of the 4- and 2-h exposures at rest.

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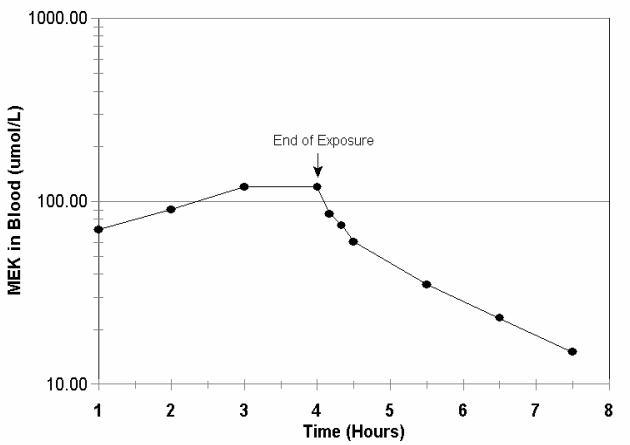

FIGURE 3-1 Methyl ethyl ketone (MEK) concentration (μmol/L) in venous blood during and after a 4-h inhalation exposure of eight subjects at 200 ppm. Source: Adapted from Liira et al. 1988b.

In another kinetics study, a group of 26 healthy males and females (ages 18-32) was exposed to MEK at 200 ppm for 4 h while venous blood and breath concentrations were monitored (Brown et al. 1987; Dick et al. 1988). Blood concentrations reached 3.1 μg/mL at 2 h and 3.5 μg/mL at 4 h. Although the concentration was higher in males (approximately 3.9 μg/mL at 4 h) than females (approximately 3.2 μg/mL at 4 h), the difference did not attain statistical significance. The mean blood concentration was 1.0 μg/mL at 1.5 h postexposure. Exhaled breath concentrations reached equilibrium at 2 h into the exposure, at which time they averaged 11.4 ppm. The exhaled concentration was 0.7 ppm at 1.5 h postexposure and not detectable at 20 h postexposure. MEK was not detected in any pre-exposure blood or breath sample. Results were similar when this study was repeated in 13 males and 11 females (Dick et al. 1992). At 4 h into the exposure, the mean venous blood concentration of MEK was 3.7 ± 1.1 μg/mL (males, 4.0 μg/mL; females, 3.3 μg/mL). At 1.5 h postexposure, the venous blood concentration averaged 1.0 μg/mL. The estimated half-life in this study was 49 min (Brown et al. 1987).

MEK concentrations in arterial capillary blood of four human subjects inhaling 100 or 200 ppm for 2 h, both in combination with *n*-hexane at 50 ppm, were 60 and 170 μmol/L, respectively, at the end of exposure (Shibata et al. 2002). The subjects performed a workload of 50 watts during the exposures. Neither of the MEK exposures influenced the concentration of *n*-hexane in the blood compared with the concentration during exposure to *n*-hexane alone at 50 ppm. However, combined exposure to MEK and *n*-hexane depressed the metabolism of *n*-hexane. The effect of *n*-hexane exposure on MEK metabolism was not reported.

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Tada et al. (1972) exposed four subjects to MEK at 300 ppm for 2 h/day for several successive days. Some exposures were for 2 h in the morning and 2 h in the afternoon. Expired air contained MEK at 23 ppm immediately after a 2-h exposure at 300 ppm.

Brugnone et al. (1980; 1983) and Perbellini et al. (1984) studied the uptake and kinetics of MEK during occupational exposures at several factories in Italy. They compared the alveolar concentrations and urinary excretion of MEK to concentrations found in the workplace atmosphere; alveolar concentrations were also compared with blood concentrations. Alveolar and atmospheric concentrations were highly correlated ($r = 0.7793$). At worker exposures of ≤ 300 µg/L (≤ 100 ppm), the alveolar concentration was 30% of the air concentration (≤ 90 µg/L), indicating an uptake of 70%. The venous blood concentration (842 to 9,573 µg/L; mean, 2,630 µg/L) was 104-116 times the alveolar concentration and 31-35 times the atmospheric concentration. The ratio between blood and alveolar MEK concentration was 104. The correlation between urine 3-hydroxy-2-butanone and atmospheric MEK was good ($r = 0.8179$). Perbellini et al. (1984) calculated the uptake of MEK in workers exposed at 100 µg/L (33 ppm). They used the following formula: uptake = the environmental concentration (100 µg/L) × alveolar ventilation (15 L/min) × alveolar retention (70%). Using these parameters, lung uptake would be 1.05 mg/min. Brugnone (1985) calculated tissue:blood distribution coefficients in vessel-rich tissue, muscle, and fat of 1.0, 1.2, and 0.88, respectively. Biologic half-lives in vessel-rich tissue, muscle, and fat were 0.8, 21.8, and 23.3 min, respectively. Distribution volumes in the three tissue groups were 6.0, 39.6, and 12.8 L, respectively.

Another monitoring study addressed the relationship between occupational exposure and concentrations in the blood and urine of workers. Yoshikawa et al. (1995) studied a group of 72 workers in a printing factory in Japan. Exposures were to a mixture of solvents including toluene, xylene, isopropyl alcohol, and ethyl acetate. Workers wore personal samplers, and urine and blood samples were taken at the end of the work shift. At atmospheric TWA concentrations of 1.3 to 223.7 ppm (mean, 47.6 ppm), urinary MEK ranged from 0.20 to 8.08 mg/L (mean, 1.19 mg/L), and blood concentrations ranged from 0.01 to 6.68 mg/L (mean, 0.71 mg/L). Correlation coefficients between air and blood, air and urine, and blood and urine were all > 0.8. The correlation coefficient for air and urine concentrations did not improve with correction of urinary values for creatinine. Using the regression equation that described the relationship between air and urinary concentrations, Yoshikawa et al. (1995) calculated the urinary value corresponding to the ACGIH occupational exposure TWA of 200 ppm. This value, referred to as the Biological Exposure Index (BEI), was 5.1 mg/L. The authors then calculated the BEI from other occupational monitoring studies. At mean exposure concentrations of 22.8 ppm (Miyasaka et al. 1982), 34.2 ppm (Perbellini et al. 1984), 200 ppm (Ong et al. 1991), and 137.2 ppm (Jang et al. 1993), the BEIs were 5.3, 2.1, 3.6, and 1.4 mg/L, respectively. Possible reasons for the differing values among the studies and for the deviation from the ACGIH's recommendation of 2 mg/L (ACGIH 2006) were discussed.

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Following accidental ingestion of an unknown amount of MEK, a woman was brought to the hospital with metabolic acidosis (Kopelman and Kalfayan 1983). She became unconscious and was hyperventilating. The blood (plasma) concentration of MEK was 13.2 mmol/L (950 µg/mL). Following treatment of the acidosis, she made a complete recovery.

Following 6 h of exposure to MEK at 25, 100, or 300 ppm, concentrations in the blood of rats were 14, 66, and 348 µM, respectively (Liira et al. 1990a). Rats exposed at 600 ppm for 6 h for 1 day or for 6-10 h/day for 8 days had similar blood concentrations of MEK: 1,041 µmol/L after a single exposure and 1,138 µmol/L after repeated exposure (Liira et al. 1991). MEK caused only marginal effects on microsomal cytochrome P-450 activities of the liver. A comparison of uptake by rats with that by humans indicates that, at similar concentrations, uptake is greater in rats than in humans (Liira et al. 1990a).

Walter et al. (1986) and Kessler et al. (1989) investigated the toxicokinetics of MEK in male Wistar rats. In the first study, saturation kinetics were displayed above 150 ppm, with the maximum rate of metabolism (V_{max}) being 600 µmol/h/kg. Below 150 ppm, kinetics were linear. In the second study, metabolism below 180 ppm was not limited by metabolic capacity but by transport to the enzymes. Pulmonary uptake was 40%, and clearance was 53 mL/min.

4.2. Mechanism of Toxicity

MEK is a hydrophilic solvent with actions of CNS depression and irritancy of the nose and eyes, both at relatively high concentrations. Because of its high tissue solubility, low concentrations may be effectively scrubbed by the nasal passages. The mechanism of action of its CNS and anesthetic action is not well understood, although it may involve interaction with cell membranes or changes in membrane-bound receptors (Arlien-Soberg 1991). It is generally accepted that volatile organic chemicals partition into the lipids of myelin sheaths and neuronal membranes and inhibit propagation of action potentials because of their physical presence.

4.3. Structure Activity Relationships

Ketones, such as acetone, MEK, methyl isobutyl ketone, and cyclohexanone, are generally of low acute oral and inhalation toxicity (Morgott et al. 2001). As discussed in Section 4.4.4, ketones metabolized to 2,5-hexanedione cause peripheral neuropathies, generally following repeated exposures. MEK is not metabolized to 2,5-hexanedione by mammalian cells.

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4.4. Other Relevant Information

4.4.1. Species Variability

Data on both lethal concentrations and concentrations involving irritancy and signs of toxicity and neurotoxicity for the rat, mouse, and guinea pig were occasionally variable but generally did not indicate great species differences.

The two primary determinants of systemic uptake of volatile chemicals are respiratory rate and cardiac output. Relative to body weight, rodents have a much higher respiratory rate and cardiac output than humans. (The respiratory rate of the mouse may be up to 10 times that of the human [Witschi and Last 2001; Kale et al. 2002].) As a result of the greater respiratory rate and cardiac output, rodents generally receive a greater overall dose than humans. Although exposure durations varied, the concentrations of MEK in blood were higher in rats than in humans when inhaling similar concentrations (Table 3-6). Humans inhaling 25, 100, or 400 ppm for 4 h had venous blood concentrations of 5, 93-100, and 229-309 µM; whereas concentrations in the blood of rats inhaling 25, 100, or 300 ppm were 14, 66, and 348 µM, respectively (Liira et al. 1990a). The human blood samples were taken during exposures, whereas the rat blood samples were taken following exposures, a procedure that may have allowed for some clearance by the rat.

Pharmacodynamic differences between rodents and humans are unknown but presumably would not differ by more than 3-fold. As mentioned, rodents receive greater systemic doses of volatile organic chemicals than humans upon equivalent exposure, and mice are expected to receive the greatest systemic dose. In absorbed dose, rats are expected to be between mice and humans exposed at the same administered air concentration. As a result, the pharmacokinetic component of the interspecies uncertainty factor would actually range from 0.3- to 0.7-fold. In practice, this would offset a potential 3-fold pharmacodynamic interspecies difference.

4.4.2. Susceptible Populations

No studies were located that identified populations that are unusually susceptible to adverse health effects from exposure to MEK. Although individuals may develop a hypersensitivity to particular solvents, results of monitoring studies did not identify a susceptible population. Individuals with sMCS did not appear more sensitive to the odor or potential irritancy of MEK during exposures up to 380 ppm than did individuals who did not report chemical sensitivity (Seeber et al. 2002). These individuals would not necessarily be more susceptible to CNS effects. The very young, the very old, and individuals with existing liver or other diseases may be more susceptible to chemical toxicity (ATSDR 1992).

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There is concern that exposure to organic solvents may increase the incidence of children born with CNS defects. According to EPA (2003), there is no evidence from animal studies that MEK induces CNS defects. Developmental studies with rodents identified reduced fetal body weight and delayed ossification as developmental effects.

The primary mechanism of action for "high" concentrations of solvents is CNS depression. Although humans differ in the rate at which they metabolize chemicals, the susceptibility of the general population to CNS anesthetics varies by no more than 2- to 3-fold, as indicated by the minimum alveolar concentration (MAC) (the concentration of an anesthetic that produces immobility in 50% of patients) (Kennedy and Longnecker 1996, p.302; Marshall and Longnecker 1996, p. 307). MEK has anesthetic properties. Studies indicate that children, and particularly infants, are more resistant than adults to the effects of various volatile anesthetics (Gregory et al. 1969; Stevens et al. 1975; Lerman et al. 1983; LeDez and Lerman 1987; Chan et al. 1996; Katoh and Ikeda 1992). The susceptibility of individuals of different ages has been extensively studied in the anesthesia literature, where the concentrations of various anesthetic gases in the lung that produce "anesthesia" (that is, lack of movement) have been measured. MACs for several anesthetic gases have been measured as a function of age. The results consistently show a pattern, there being maximal sensitivity (lowest MAC) in newborns, particularly premature newborns, pregnant women, and the elderly. The least sensitive (highest MAC values) occur in older infants, toddlers, and children compared with normal adults. The total range of sensitivity is 2-3 fold. On the basis of this knowledge, it is not unreasonable to assume that the same 2-3 fold difference in sensitivity among individuals would apply for MEK.

4.4.3. Concentration-Exposure-Duration Relationship

No data were located that provided information on the concentration-exposure-duration relationship for the effect of MEK on the CNS. For the end points of both sensory irritation and depression of the CNS by solvents, there is generally a concentration threshold. During clinical studies involving 200 ppm, uptake was rapid during the first hour, and steady state in the blood was approached by 4 h.

For the end point of death, both concentration and exposure duration may be applicable. However, there are no data relevant to the determination of that relationship. For the end point of death, the concentration-exposure-duration relationship for many irritants 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). Where chemical-specific empirical data are lacking, a conservative approach is to use n = 3 when extrapolating from longer to shorter time points and to use n = 1 when extrapolating from shorter to longer time periods (NRC 2001).

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4.4.4. Concurrent Exposure Issues

Solvent exposure in the workplace generally involves mixtures of chemicals. The combined effect of chemicals may be additive, antagonistic, or potentiating. Non-neurotoxic ketones (those that do not induce neuropathies), such as MEK, may potentiate the neurotoxicity and hepatotoxicity of other solvents, including other ketones that are metabolized by the P-450 metabolizing system of the liver (Morgott et al. 2001). Several ketones and related chemicals have been shown to produce a toxic polyneuropathy characterized by multifocal axonal swelling and myelin damage. In humans, symptoms include bilateral symmetrical paresthesia ("pins and needles" feeling) and muscle weakness, primarily in the legs. The neurotoxic agent is thought to be 2,5-hexanedione, a metabolite of several ketones. MEK is not metabolized to 2,5-hexanedione (DiVincenzo et al. 1977).

Data from experimental studies with animals and from clinical data on humans indicate that MEK does not cause neuropathies but potentiates the neurotoxic action of structurally related solvents, such as *n*-hexane and methyl-*n*-butyl ketone. Altenkirch et al. (1982a) reported on neuropathies in solvent-sniffing juveniles. Juveniles who chronically inhaled hexane-containing solvents as narcotics suffered a variety of polyneuropathy syndromes and neuromyelopathies. Addition of MEK to the solvents as a denaturant for a period of time resulted in an outbreak of more severe neuropathies. In clinical studies, combined exposure to *n*-hexane and MEK (200 ppm) did not influence the concentration of *n*-hexane in the blood (Shibata et al. 2002) but decreased the rate of metabolism of *n*-hexane to 2,5-hexanedione. Similar results were reported when co-exposures were to *n*-hexane at 60 ppm and MEK at 200 or 300 ppm (van Engelen et al. 1997).

The potentiation of the neurotoxicity of *n*-hexane, methyl-*n*-butyl ketone, ethyl *n*-butyl ketone, and 2,5-hexanedione by MEK was documented in animal studies (Saida et al. 1976; Altenkirch et al. 1978, 1982a,b; Takeuchi et al. 1983; O'Donoghue et al. 1984; Ralston et al. 1985; Ichihara et al. 1998). In one such study (Altenkirch et al. 1978), male Wistar rats were exposed to MEK at 6,000-10,000 ppm for 8 h/day, 7 days/week, for 15 weeks. These rats did not have neurologic lesions, but rats exposed to *n*-hexane at 10,000 ppm or MEK plus *n*-hexane at 10,000 ppm (MEK at 1,100 ppm and *n*-hexane at 8,900 ppm) developed motor neuropathy with swelling of axons in the peripheral and CNS. MEK in the combined exposure shortened the onset and increased the severity of paresis compared with exposure to *n*-hexane alone.

Exposure to other chemicals may interfere with the metabolism of MEK. Co-exposure to xylene slowed the metabolism of xylene but did not interfere with the metabolism of MEK (Liira et al. 1988b). Blood concentrations of MEK were higher following ethanol ingestion, indicating reduced metabolism, than those following MEK exposure alone (Liira et al. 1990b). In an oral study with rats, exposure to MEK potentiated carbon tetrachloride hepatotoxicity (Traiger and Bruckner 1976).

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Exposure of pregnant Wistar rats for 23 h/day, 7 days/week, to a combination of *n*-hexane at 1,200 ppm and MEK at 300 ppm throughout gestation or during the postnatal period increased the effect of *n*-hexane alone on birth weight and postnatal weight gain, both of which were reduced (Stoltenburg-Didinger et al. 1990). This combination was neurotoxic to the dams but had no effect on the brain development of the pups.

Liquid MEK applied to the skin of the forearms of human volunteers is rapidly absorbed (Munies and Wurster 1965; Wurster and Munies 1965). Uptake by dermal absorption was evidenced by MEK in expired air. Therefore, unprotected dermal contact may represent a significant exposure route.

5. DATA ANALYSIS FOR AEGL-1

The AEGL-1 concentration may cause notable discomfort or irritation in the general population as well as in susceptible individuals.

5.1. Summary of Human Data Relevant to AEGL-1

MEK is not a respiratory irritant at concentrations less than several thousand parts per million. The clinical studies of Dick et al. (1984; 1988; 1992), Muttray et al. (2002), Seeber et al. (2002), and Shibata et al. (2002) did not report sensory irritation or neurobehavioral deficits at a constant concentration of 200 ppm for 2 or 4 h or at concentrations that ranged between 10 and 380 ppm (average 188 ppm) over 4 h. Twenty-four subjects exposed at 200 ppm for 4 h found the concentration unobjectionable (Dick et al. 1992). In a series of neurobehavioral studies, a 4-h exposure of human subjects at 200 ppm had no significant effect on a variety of behavioral tests (Dick et al. 1984, 1988, 1989). No irritation or subjective symptoms of sensory irritation were reported in four male subjects inhaling MEK at 200 ppm for 2 h (Shibata et al. 2002). The same absence of sensory irritation and neurobehavioral deficits was reported by 19 male subjects inhaling MEK at 00 ppm for 4 h (Muttray et al. 2002). During variable concentrations ranging from 10 ppm to 8-min peaks at 380 ppm, five times over 4 h, subjects rated annoyance and irritation either “hardly at all” or “not at all” (Seeber et al. 2002). Both healthy subjects and subjects with sMCS were tested by Seeber et al. (2002). The primary subjective comment in these studies was a noticeable odor. In the study of Nelson et al. (1943), 10 male and female volunteers exposed to MEK for 3-5 min judged 200 ppm as acceptable for an 8-h exposure and 350 ppm as objectionable for an 8-h exposure. There were no analytic measurements in this early study. Sensory irritation was reported in the Nakaaki (1974) study, but this study used variable concentrations, and neurobehavioral results were difficult to interpret. Additional metabolism studies were conducted at concentrations of 25 to 400 ppm for 4 h, but these studies did not address sensory irritation or neurotoxic effects. Although sensory irritation was not specifically addressed in the metabolism studies of Liira et al (1988a,b,

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1990a,b) and Tada et al. (1972), volunteers were routinely exposed to concentrations of 200-400 ppm for 2-4 h without apparent adverse effects.

5.2. Summary of Animal Data Relevant to AEGL-1

No signs of toxicity were observed in rats exposed to MEK at 2,000 ppm for 2 h (Pozzani et al. 1959; Smyth et al. 1962) and guinea pigs exposed at 3,300 for 13.5 h (Patty et al. 1935), although approximately 2,900 ppm was the EC_{50} for a deficit in schedule-controlled behavior in the mouse (Glowa and Dews 1987).

5.3. Derivation of AEGL-1

Four well-conducted clinical studies indicate that MEK is neither a sensory irritant nor does it induce neurobehavioral changes at a concentration of 200 ppm for 4 h or at concentrations ranging between 10 and 380 ppm (average 188 ppm) over 4 h (Dick et al 1992; Muttray et al 2002; Seeber et al. 2002; Shibata et al. 2002; van Thriel et al. 2003a). Additional metabolism studies were conducted at concentrations of 25 to 400 ppm for 4 h, but these studies did not address sensory irritation or neurotoxic effects. A concentration of 200 ppm was judged unobjectionable for an 8-h exposure (Dick et al. 1992). Subjects with sMCS found concentrations ranging between 10 and 380 ppm over 4 h unobjectionable. Therefore, 200 ppm was selected as a NOAEL for sensory irritation and neurobehavioral deficits. The selection of this value is supported by numerous clinical studies in which volunteers were routinely exposed at 200-400 ppm for up to 4 h (Tada et al. 1972; Dick et al. 1984, 1988, 1989, 1992; Liira et al. 1988a,b, 1990a,b). Because the Dick et al. studies reported no sensory irritation or neurotoxicity at 200 ppm and because metabolism was also addressed by the authors at this concentration, it is unlikely that sensory irritation was experienced in other metabolism studies at similar concentrations. Because effects were not greater at the higher concentration of 380 ppm and because subjects with sMCS, a hypersensitive population, did not report enhanced sensory effects compared with control subjects (Seeber et al. 2002), an intraspecies uncertainty factor of 1 was applied. Because steady-state would be approached within 4 h at this low concentration (Liira et al. 1988a,b; 1990a) and because MEK is rapidly metabolized, the 200 ppm concentration was used across all AEGL-1 exposure durations (Table 3-7). Calculations are in Appendix A. Appendix B contains a category graph of the toxicity data in relation to AEGL values.

TABLE 3-7 AEGL-1 Values for Methyl Ethyl Ketone

10 min	30 min	1 h	4 h	8 h
200 ppm (586 mg/m^3)	200 ppm (586 mg/m^3)	200 ppm (586 mg/m^3)	200 ppm (586 mg/m^3)	200 ppm (586 mg/m^3)

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6. DATA ANALYSIS FOR AEGL-2

Concentrations above the AEGL-2 may cause irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

6.1. Summary of Human Data Relevant to AEGL-2

Data on human exposures to concentrations that may cause adverse health effects or an impaired ability to escape are sparse. A concentration of 350 ppm was judged objectionable because it was unpleasant (Nelson et al. 1943), but this concentration would not impair the ability to escape. The lowest concentration reported in the study by Patty et al. (1935), 3,300 ppm, had a moderate-to-strong odor and was moderately irritating to the eyes and nose, but no exposure duration was provided.

6.2. Summary of Animal Data Relevant to AEGL-2

The mean RD_{50}, a concentration that is considered intolerable to humans, was approximately 10,000 ppm in two of three studies with the mouse (De Ceaurriz et al. 1981; Stone et al. 1981). According to Alarie et al (1981), humans would experience "some" sensory irritation during several hours of exposure to MEK at 0.1 × the RD_{50}. This value would be 1,000 ppm. The RD_{50} could not be attained in a study by Hansen et al. (1992), even when exposures were > 20,000 ppm.

Although MEK is of low inhalation toxicity in animal studies, it has been shown to be slightly fetotoxic in laboratory animals when dams are exposed for half of their gestational period (days 6-15). Results of a series of developmental studies with the rat (Deacon et al. 1981) and the mouse (Mast et al. 1989; Schwetz et al. 1991) determined that 3,000 ppm was toxic to the fetus, as indicated by delayed ossification in rats and reduced fetal body weight in mice. A concentration of 1,000 ppm was a NOAEL. Exposures were for 7 h/day. Maternal toxicity, however, indicated that the fetus is not more sensitive than the dam. The relevance of exposure duration of one-half of the rodent gestational period to a short-term exposure for humans is unknown.

In a repeat-exposure inhalation study (Altenkirch et al. 1978) and a subchronic exposure study (Cavender et al. 1983) of MEK, it was shown that 6,000 and 5,000 ppm, respectively, had little effect on rodents. Only five rats were used in the Altenkirch et al. (1978) study, and the use of controls was not mentioned. The Cavender et al. (1983) study used 15 rats of each sex/group and several exposure concentrations, including a control exposure. In this study, 5000 ppm for 6 h/day for 90 days was a no-effect concentration for neurobehavioral deficits and neuropathy. The absence of CNS effects was reported on the first

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day of the study. At 6,000 ppm, mild somnolence was reported in rats, but it was not clear that this effect occurred on the first day of exposure (Altenkirch et al. 1978).

6.3. Derivation of AEGL-2

The sensitive end point of fetotoxicity was not used to derive AEGL-2 values for MEK because the relevance of an exposure of half of the gestational period of a rodent to an acute exposure as short as 10 min for a human is difficult to assess. The end points in the developmental studies of Deacon et al. (1981), Mast et al. (1989), and Schwetz et al. (1991) appear to be related to maternal stress rather than to a direct toxic effect of the chemical.

The AEGL-2 was based on an exposure concentration of MEK that did not result in neurobehavioral effects on the first day of the subchronic exposure study of Cavender et al. (1983). In this study, rats were exposed at 5,000 ppm for 5 days/week for 90 days. No exposure-related lesions were observed. The 5,000-ppm concentration is close to the threshold for neurotoxicity, as evidenced by mild somnolence in another repeat-exposure study in which rats were exposed at 6,000 ppm, 8 h/day, for several weeks (Altenkirch et al. 1978). The Altenkirch et al. (1978) study was not used as the basis of the AEGL-2 because of the small number of animals tested and the apparent failure to include a concurrent control group. Because rodents have a higher respiratory rate and cardiac output than humans, resulting in more rapid and higher uptake of chemicals, an interspecies uncertainty factor of 1 was applied (see discussion in Section 4.4.1 and data of Liira et al. 1990a). Because the threshold for narcosis differs by no more than 2- to 3-fold among the general population (see Section 4.4.2), an intraspecies uncertainty factor of 3 was applied to protect sensitive individuals. Because the threshold for narcosis is concentration-dependent, the resulting 1,700-ppm concentration was applied to the 4- and 8-h exposure durations. The data show that higher exposures can be tolerated for shorter durations (for example, see Hansen et al. 1992). Therefore, the 10- and 30-min and the 1-h values were time-scaled from the 4-h exposure duration with the default n value of 3. AEGL-2 values are listed in Table 3-8. A summary of the calculations can be found in Appendix A. Appendix B is a category graph of toxicity data in relation to AEGL values.

TABLE 3-8 AEGL-2 Values for Methyl Ethyl Ketone

10 min	30 min	1 h	4 h	8 h
4,900 ppm[a] (14,357 mg/m^3)	3,400 ppm[a] (9,962 mg/m^3)	2,700 ppm[a] (7,911 mg/m^3)	1,700 ppm (4,980 mg/m^3)	1,700 ppm (4,980 mg/m^3)

[a]The 10- and 30-min and the 1-h AEGL-2 values are higher than one-tenth of the lower explosive limit (LEL) of methyl ethyl ketone in air (LEL = 18,000 ppm). Therefore, safety considerations against the hazard of explosion must be taken into account.

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The values and end point are supported by the study of Altenkirch et al. (1978), in which rats exposed to MEK 10,000 ppm suffered severe irritation; when the concentration was lowered to 6,000 ppm for 8 h/day, the rats were mildly somnolent but arousable.

7. DATA ANALYSIS FOR AEGL-3

At concentrations above the AEGL-3, the general population, including susceptible individuals, could experience life-threatening health effects or death.

7.1. Summary of Human Data Relevant to AEGL-3

No human data relevant to development of AEGL-3 values were located in the available literature. Patty et al. (1935) reported that concentrations >10,000 for an exposure duration of several breaths were almost intolerable to humans due to eye and nose irritation.

7.2. Summary of Animal Data Relevant to AEGL-3

Two of three early studies with rodents reported LC_{50} values of 11,700 and 8,000 ppm for 4 and 8 h, respectively (La Belle and Brieger 1955; Pozanni et al. 1959), whereas a third study (Patty et al. 1935) reported no deaths of guinea pigs during a 13.5-h exposure at 10,000 ppm. The highest concentration resulting in no deaths of rats during the 4-h exposure period in the La Belle and Brieger (1955) study was 7,850 ppm. No deaths of rodents occurred during short-term exposures, 30 and 45 min, at 92,239 and 50,000 ppm, respectively (Zakhari et al. 1977; Klimisch 1988). Likewise, no deaths occurred in mice exposed at 26,416 ppm for 30 min (Hansen et al. 1992). In the Hansen et al. (1992) study, the concentration that was severely irritating, that is, reduced the respiratory rate by 50%, was projected to be 31,426 ppm.

Fowles et al. (1999) applied the benchmark dose approach to the La Belle and Brieger (1955) rat lethality data to estimate the threshold for lethality. The benchmark dose approach uses several curve fitting models that are applied to data sets. In this case, the log-normal probit and quantal Weibull models were used to estimate the 95% lower confidence limits on the doses producing 1%, 5%, and 10% responses. The results of the models were similar. For the probit model, the benchmark doses corresponding to 1% extra risk (MLE_{01}) and the 95% lower bound on those doses were 7,546 and 5,790 ppm, respectively. The respective values for the Weibull model were 6,579 and 4,193 ppm. The benchmark doses for both models are slightly below the highest exposure concentration of 7,850 ppm, which caused no deaths of rats in the La Belle and Brieger (1955) study.

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7.3. Derivation of AEGL-3

The AEGL-3 values for MEK were derived using different studies. The 10- and 30-min time periods were derived using the studies by Klimisch (1988) and Zakhari et al. (1977) with support from Hansen et al. (1992). The 1-, 4-, and 8-h values were derived from the studies by Fowles (1999) using data from La Belle and Brieger (1955). No deaths occurred in rats after a 30-min exposure at 92,239 ppm (Klimisch 1988), and no deaths occurred in mice after a 45-min exposure at 50,000 ppm (Zakhari et al. 1977); a projected value of 32,145 ppm for 30 min would decrease the respiratory rate of mice by 50% (Hansen et al. 1992). The highest tested concentration in the Hansen et al. (1992) study was 26,000 ppm. On the basis of these data, nearly all individuals could be exposed at 10,000 ppm for up to 30 min without developing life-threatening effects. Application of inter- and intraspecies uncertainty factors of 1 and 3 were applied as done for the AEGL-2. Additional studies support the 10,000-ppm value as being nonlethal: 10,000 ppm for 10 or 30 min was narcotic to mice in one study (Glowa and Dews 1987) but not in another (Hansen et al. 1992); 10,000 ppm was tolerated by rats for 8 h/day for several days (Altenkirch et al. 1978), and no deaths occurred in guinea pigs at 10,000 ppm for 13.5 h (Patty et al. 1935).

The longer-term AEGL-3 values were based on the MLE_{01} of 7,500 ppm calculated by Fowles et al. (1999) from a 4-h study with rats exposed at several concentrations for 4 h (La Belle and Brieger 1955). In this study, the 4-h LC_{50} was 11,700 ppm, and the highest concentration resulting in no deaths was 7,850 ppm for 4 h. The 7,500-ppm MLE_{01} concentration was divided by an interspecies uncertainty factor of 1 and an intraspecies uncertainty factor of 3. The resulting value of 2,500 ppm was used for both the 4-h and 8-h AEGL-3 values. The 4-h 2,500 ppm value was time-scaled to the 1-h time, using the default n value of 3 for scaling to shorter time intervals. Calculations are in Appendix A, and values are listed in Table 3-9. Appendix B contains a category graph of toxicity data in relation to AEGL values.

8. SUMMARY OF AEGL VALUES

8.1. AEGL Values and Toxicity End Points

The AEGL values and toxicity end points are listed in Table 3-10. Appendix C contains development summaries for the AEGL values. Information was available on toxicity end points that met the definitions of the three AEGL values. The AEGL-1 was based on four studies with human subjects that were specifically designed to address objectionable odor or irritancy (Dick et al. 1992; Muttray et al. 2002; Seeber et al. 2002; Shibata et al. 2002) and supported by numerous behavioral and metabolism studies in which volunteers were routinely exposed at 200-400 ppm for various periods of time (Tada et al. 1972; Nakaaki 1974; Dick et al. 1984, 1988, 1989; Liira et al. 1988a,b, 1990a,b). Subjects with

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sMCS were tested in the study of Seeber et al. (2002) (van Thriel et al. 2003a), and exposures ranged between 10 and 380 ppm (average 188 ppm) over the 4 h. Therefore, 200 ppm was considered safe for the general population, and no uncertainty factor was applied.

TABLE 3-9 AEGL-3 Values for Methyl Ethyl Ketone

10 min	30 min	1 h	4 h	8 h
[a]	[a]	4,000 ppm[b] (11,720 mg/m^3)	2,500 ppm[b] (7,325 mg/m^3)	2,500 ppm[b] (7,325 mg/m^3)

[a]The 10- and 30-min AEGL-3 value of 10,000 ppm (29,300 mg/m^3) is higher than 50% of the LEL of methyl ethyl ketone in air (LEL = 18,000 ppm). Therefore, extreme safety considerations against the hazard of explosion must be taken into account.
[b]The 1-, 4-, and 8-h AEGL-3 values are higher than 1/10 of the lower explosive limit (LEL) of methyl ethyl ketone in air (LEL = 18,000 ppm). Therefore, safety considerations against the hazard of explosion must be taken into account.

TABLE 3-10 Summary of AEGL Values for Methyl Ethyl Ketone

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (Nondisabling)	200 ppm (586 mg/m^3)	200 ppm (586 mg/m^3)	200 ppm (586 mg/m^3)	200 ppm (586 mg/m^3)	200 ppm (586 mg/m^3)	NOAEL for subjective symptoms in humans (Dick et al. 1992; Muttray et al. 2002; Seeber et al. 2002; Shibata et al. 2002)
AEGL-2 (Disabling)	4,900 ppm[a] (14,357 mg/m^3)	3,400 ppm[a] (9,962 mg/m^3)	2,700 ppm[a] (7,911 mg/m^3)	1,700 ppm (4,980 mg/m^3)	1,700 ppm (4,980 mg/m^3)	Threshold for narcosis in rats (Cavender et al. 1983)
AEGL-3 (Lethal)	[b]	[b]	4,000 ppm[a] (11,720 mg/m^3)	2,500 ppm[a] (7,325 mg/m^3)	2,500 ppm[a] (7,325 mg/m^3)	Threshold for lethality, mouse, rat (La Belle and Brieger 1955; Zakhari et al. 1977; Klimisch 1988; Hansen et al. 1992)

[a]The 10- and 30-min and the 1-h AEGL-2 values and the 1-, 4-, and 8-h AEGL-3 values are higher than one-tenth of the lower explosive limit (LEL) of methyl ethyl ketone in air (LEL = 18,000 ppm). Therefore, safety considerations against the hazard of explosion must be taken into account.
[b]The 10- and 30-min AEGL-3 value of 10,000 ppm (29,300 mg/m^3) is higher than 50% of the LEL of methyl ethyl ketone in air (LEL = 18,000 ppm). Therefore, extreme safety considerations against the hazard of explosion must be taken into account.
Abbreviation: NOAEL, no-observed-adverse-effect level.

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The AEGL-2 was based on an exposure concentration that did not result in neurobehavioral deficits on the first day of a subchronic exposure study with rats (Cavender et al. 1983). This concentration of 5,000 ppm is supported by a repeated exposure inhalation study (Altenkirch et al. 1978). A 6,000 ppm concentration was the threshold for narcosis in the rat (Altenkirch et al. 1978). The clinical sign of mild somnolence in this study is consistent with the known effect of solvents on the CNS. The 5,000-ppm NOAEL for CNS depression of the Cavender et al. (1983) study was divided by interspecies and intraspecies uncertainty factors of 1 and 3, respectively. Although CNS depression is concentration-related rather than time-dependent, higher exposures can be tolerated for short durations. Therefore, the 1,700-ppm value was applied to the 4- and 8-h durations and the shorter time values were time-scaled from the 4-h duration.

The AEGL-3 was based on several animal studies. The 10- and 30-min AEGL-3 values were based on several nonlethal rodent values: 92,239 ppm for 30 min (Klimisch 1988), 60,000 ppm for 45 min (Zakhari et al. 1977), and 26,000 ppm for 30 min (Hansen et al. 1992). On the basis of these data, nearly all individuals could be exposed at 10,000 ppm for up to 30 min without developing life-threatening effects. The 10,000 ppm value was applied to both the 10 and 30-min AEGL-3 exposure durations. Values for the longer-term exposure durations were based on the MLE_{01} of 7,500 ppm calculated from the 4-h rat study of La Belle and Brieger (1955) by Fowles et al. (1999). The resulting 2,500 ppm value was used for both the 4- and 8-h exposure durations, as MEK may approach steady state in the blood during a 4-h exposure. In the absence of empirical data on the relationship between the concentration causing effects and exposure duration, temporal scaling to the 1-h time period was performed using the conservative value of $n = 3$.

8.2. Comparison with Other Standards and Guidelines

Primarily workplace guidelines have been derived for MEK (Table 3-11). Workplace standards are protective of any adverse health effect during chronic exposures and are most comparable to the AEGL-1. The AEGL-1 is the same as the American Conference of Governmental Industrial Hygienists (ACGIH), Occupational Safety and Health Administration (OSHA), and National Institute for Occupational Safety and Health (NIOSH) recommended workplace exposure limits, as well as the workplace exposure limits derived in Germany and The Netherlands. It is below the NIOSH short-term exposure limit of 300 ppm. The ACGIH based their value on a review of the literature. The NIOSH IDLH is comparable and similar to the 30-min AEGL-2. The IDLH is below the 30-min AEGL-3 of 10,000 ppm. The IDLH of 3,000 ppm is based on early data, which stated that a 2-h exposure of rats to 2,000 ppm caused no deaths, but four of six rats exposed at 4,000 ppm for a 2-h period died (Smyth 1956). NIOSH adjusted the values for a 30-min exposure.

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TABLE 3-11 Extant Standards and Guidelines for Methyl Ethyl Ketone

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	200 ppm	200 ppm	200 ppm	200 ppm	200 ppm
AEGL-2	4,900 ppm[a]	3,400 ppm[a]	2,700 ppm[a]	1,700 ppm	1,700 ppm
AEGL-3	[b]	[b]	4,000 ppm[a]	2,500 ppm[a]	2,500 ppm[a]
IDLH (NIOSH)[c]		3,000 ppm			
TLV-TWA (ACGIH)[d]					200 ppm
PEL-TWA (OSHA)[e]					200 ppm
REL-TWA (NIOSH)[f]					200 ppm
TLV-STEL (ACGIH)[g]					300 ppm
REL-STEL (NIOSH)[h]					300 ppm
MAK (Germany)[i,j]					200 ppm
MAC (The Netherlands)[k]					200 ppm, skin[l]

[a]The 10- and 30-min and 1-h AEGL-2 values and the 1-, 4-, and 8-h AEGL-3 values are higher than 1/10 of the lower explosive limit (LEL) of methyl ethyl ketone in air (LEL = 18,000 ppm). Therefore, safety considerations against the hazard of explosion must be taken into account.

[b]The 10- and 30-min AEGL-3 value of 10,000 ppm (29,300 mg/m^3) is higher than 50% of the LEL of methyl ethyl ketone in air (LEL = 18,000 ppm). Therefore, extreme safety considerations against the hazard of explosion must be taken into account.

[c]IDLH (immediately dangerous to life or health, National Institute for Occupational Safety and Health) (NIOSH 1996) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms, or any irreversible health effects.

[d]TLV-TWA (Threshold Limit Value–time-weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 2006) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[e]PEL-TWA **(**permissible exposure limits–time-weighted average, Occupational Health and Safety Administration) (OSHA) (29 CFR 1910.1000 [1996]) is analogous to the ACGIH TLV-TWA but is for exposures of no more than 10 h/day, 40 h/week.

[f]REL-TWA **(**recommended exposure limits–time-weighted average, National Institute for Occupational Safety and Health) (NIOSH 2005) is analogous to the ACGIH TLV-TWA.

[g]TLV-STEL **(**Threshold Limit Value–short-term exposure limit, American Conference of Governmental Industrial Hygienists **)** (ACGIH 2006) is defined as a 15-min TWA exposure that should not be exceeded at any time during the workday even if the 8-h TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be

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longer than 15 min and should not occur more than 4 times per day. There should be at least 60 min between successive exposures in this range.

[h]REL-STEL **(**recommended exposure limits–short-term exposure limit, National Institute for Occupational Safety and Health**)** (NIOSH 2005) is analogous to the ACGIH TLV-TWA.

[i]MAK (maximale Arbeitsplatzkonzentration [maximum workplace concentration]) (Deutsche Forschungsgemeinschaft [German Research Association] (DFG 2003) is analogous to the ACGIH-TLV-TWA.

[j]MAK Spitzenbegrenzung (Peak Limit I) (Deutsche Forschungsgemeinschaft [German Research Association] (DFG 2003) is the same as the 8-h MAK.

[k]MAC (maximaal aanvaarde concentratie [maximum accepted concentration], Dutch Expert Committee for Occupational Standards, The Netherlands) (MSZW 2004) is analogous to the ACGIH-TLV-TWA.

[l]Skin notation: MEK may be absorbed through the skin.

8.3. Data Adequacy and Research Needs

The database on human studies is extensive and includes controlled clinical and workplace monitoring studies. Human exposures were generally to relatively low concentrations and showed that MEK is not irritating to the eyes and mucous membranes of the upper respiratory tract. Only with unmeasured, presumably higher exposures in association with dermal contact was the CNS involved. Several human studies addressed neurobehavioral effects and metabolism. Animal studies with a variety of species (baboon, rat, mouse, and guinea pig) addressed irritation, neurotoxicity, developmental toxicity, subchronic toxicity, and lethality. Exposure durations ranged from acute to subchronic. Genotoxicity was also addressed. The most notable data deficiency is the lack of a well-defined exposure-response relationship for the AEGL-2 and AEGL-3 end points. However, for many solvents that act as anesthetics, a threshold concentration rather than duration of exposure defines whether an effect will occur.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR METHYL ETHYL KETONE

Derivation of AEGL-1 Values

Key studies:	Dick et al. (1992); Muttray et al. 2002; Seeber et al. 2002; Shibata et al. 2002
Toxicity end points:	200 for 4 h and 380 ppm for several 8-min exposure durations were NOAELs for sensory irritation and CNS effects; the lower number was chosen as the basis for the AEGL-1.
Time-scaling:	Not applied
Uncertainty factors:	1 for intraspecies variability
Modifying factor:	Not applied
Calculations: durations.	The 200-ppm concentration was used for all exposure
10-min AEGL-1:	200 ppm
30-min AEGL-1:	200 ppm
1-h AEGL-1:	200 ppm
4-h AEGL-1:	200 ppm
8-h AEGL-1:	200 ppm

Derivation of AEGL-2 Values

Key studies:	Altenkirch et al. (1978); Cavender et al. (1983)
Toxicity end points:	5,000 ppm was a NOAEL for neurobehavioral effects (narcosis) on the first and subsequent days of a sub-chronic study with rats; exposures were for 6 h/day, 5 days/week, for 90 days.
Time-scaling:	Default value of n = 3 applied to shorter exposure durations

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Uncertainty factors:	1 for interspecies; rodents have higher respiratory rates and cardiac output than humans; metabolism differences will not be significant at high, acute exposures. 3 for intraspecies; differences among humans for CNS effects of anesthetics are not expected to vary greatly.
Modifying factor:	Not applied
Calculations:	5,000 ppm/3 = 1,700 ppm $C^3 \times 240$ min = k $(1{,}700)^3 \times 240$ min = 1.179×10^{12} ppm^3-min
10-min AEGL-2:	$[(1.179 \times 10^{12}$ ppm^3-min)/10 min$]^{1/3}$ C = 4,900 ppm
30-min AEGL-2:	$[(1.179 \times 10^{12}$ ppm^3-min)/10 min$]^{1/3}$ C = 3400 ppm
1-h AEGL-2:	$[(1.179 \times 10^{12}$ ppm^3-min)/60 min$]^{1/3}$ C = 2700 ppm
4-h AEGL-2:	1,700 ppm
8-h AEGL-2:	1,700 ppm

Derivation of AEGL-3 Values

Key studies:	10 and 30 min: Zakhari et al. 1977; Klimisch 1988; Hansen et al. 1992; 1, 4, and 8 h: La Belle and Brieger 1955
Toxicity end points:	(1) Threshold for lethality—mouse, rat 30-min exposure of rats at 92,239 ppm (Klimisch 1988) 45-min exposure of mice at 50,000 ppm (Zakhari et al. 1977) Calculated 30-min RD_{50} of 31,246 ppm—mice (Hansen et al. 1992) (2) 4-h MLE_{01} of 7,500 ppm for rat calculated by Fowles et al. (1999) from data of La Belle and Brieger (1955)

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Time-scaling	None for 10- and 30-min values None for 4- and 8-h values 1-h value time-scaled from 4-h value using n = 3 ($C^n \times t = k$)
Uncertainty factors:	1 for interspecies; rodents have higher respiratory rates and cardiac output than humans; metabolism differences will not be significant at high, acute exposures. 3 for intraspecies; differences among humans for irritancy and CNS effects are not expected to vary greatly.
Modifying factor:	Not applied
Calculations:	(1) values adjusted to 10,000 ppm (2) 7,500 ppm/3 = 2,500 ppm 4-h value: $(2{,}500\ \text{ppm})^3 \times 240\ \text{min} = 3.75 \times 10^{12}$ ppm^3-min
10-min AEGL-3:	10,000 ppm
30-min AEGL-3:	10,000 ppm
1-h AEGL-3:	$C^3 \times 60\ \text{min} = 3.75 \times 10^{12}$ ppm^3-min C = 4,000 ppm
4-h AEGL-3:	2,500 ppm
8-h AEGL-3:	2,500 ppm

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APPENDIX B

CATEGORY GRAPH OF TOXICITY DATA AND AEGL VALUES

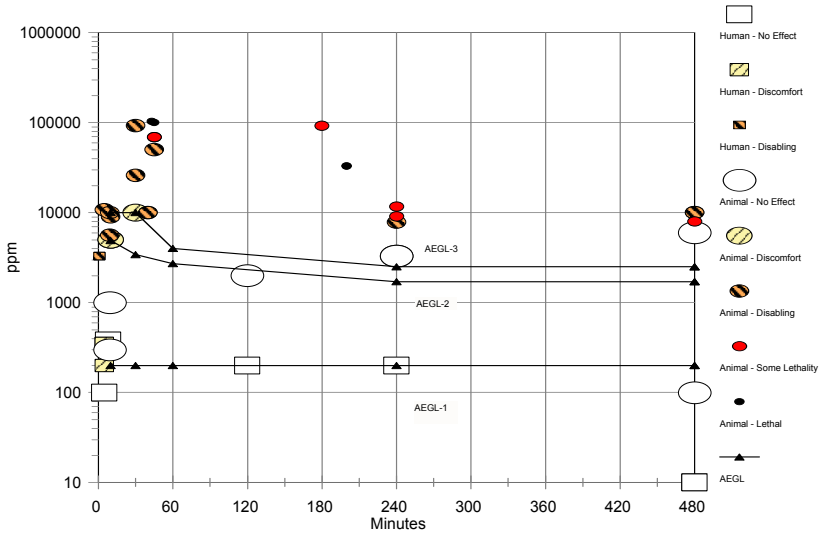

FIGURE 3-2 Category graph of toxicity data and AEGL values.

TABLE B-1 Data Used in Category Graph

Source	Species	ppm	Minutes	Category[a]
NAC/AEGL-1		200	10	AEGL
NAC/AEGL-1		200	30	AEGL
NAC/AEGL-1		200	60	AEGL
NAC/AEGL-1		200	240	AEGL
NAC/AEGL-1		200	480	AEGL
NAC/AEGL-2		4,900	10	AEGL
NAC/AEGL-2		3,400	30	AEGL
NAC/AEGL-2		2,700	60	AEGL
NAC/AEGL-2		1,700	240	AEGL
NAC/AEGL-2		1,700	480	AEGL
NAC/AEGL-3		10,000	10	AEGL
NAC/AEGL-3		10,000	30	AEGL
NAC/AEGL-3		4,000	60	AEGL

(Continued)

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TABLE B-1 Continued

Source	Species	ppm	Minutes	Category[a]
NAC/AEGL-3		2,500	240	AEGL
NAC/AEGL-3		2,500	480	AEGL
Nelson et al. 1943	Human	100	5	0
	Human	200	5	1
	Human	350	5	1
Shibata et al. 2002 and others	Human	200	120	0
Dick et al. 1992 and others	Human	200	240	0
Seeber et al. 2002	Human	380	8	0
Patty et al. 1935	Human	3,300	1	2
Seeber et al. 2002	Human	10	480	0
Klimisch 1988	Rat	92,239	180	SL
	Rat	92,239	30	2
Pozzani et al. 1959	Rat	8,000	480	SL
Smyth et al. 1962	Rat	2,000	120	0
LaBelle and Brieger 1955	Mouse	103,000	43	3
	Mouse	9,090	240	SL
	Mouse	11,700	240	SL
	Mouse	7850	240	2
Zakhari et al. 1977	Mouse	69,500	45	SL
	Mouse	50,000	45	2
Patty et al. 1935	Guinea pig	100,000	45	3
	Guinea pig	33,000	200	3
	Guinea pig	10,000	480	2
Geller et al. 1979	Baboon	100	480	0
Altenkirch et al. 1978	Rat	10,000	480	2
	Rat	6,000	480	0
Hansen et al. 1992	Mouse	26,000	30	2
	Mouse	10,000	30	1
DeCeaurriz et al. 1981	Mouse	10,745	5	2
Stone et al. 1981	Mouse	5,000	10	1
	Mouse	9,000	10	2
Glowa and Dews 1987	Mouse	10,000	9.5	2
	Mouse	5600	9.5	2
	Mouse	1,000	9.5	0
	Mouse	300	9.5	0
Patty et al. 1935	Guinea pig	3,300	240	0
	Guinea pig	10,000	40	2

[a]Categories: 0, no effect; 1, discomfort; 2, disabling; SL, some lethality; and 3, lethal.

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APPENDIX C

ACUTE EXPOSURE GUIDELINE LEVELS FOR METHYL ETHYL KETONE

Derivation Summary for Methyl Ethyl Ketone

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
200 ppm	200 ppm	200 ppm	200 ppm	200 ppm

Key references:
Dick, R.B., E.F. Krieg, Jr., J. Setzer, and B. Taylor. 1992. Neurobehavioral effects from acute exposures to methyl isobutyl ketone and methyl ethyl ketone. Fundam. Appl. Toxicol. 19(3):453-473.

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Test species/Strain/Number:
Human/24 subjects (Dick et al. 1992); 19 male subjects (Muttray et al. 2002); 24 subjects (Seeber et al. 2002); 4 male subjects (Shibata et al. 2002)

Exposure route/Concentrations/Durations: 200 ppm for 4 h (Dick et al. 1992; Muttray et al. 2002); 200 ppm for 2 h (Shibata et al. 2002); 10-380 ppm (average 188 ppm) for over 4 h (Seeber et al. 2002)

Effects: At 200 ppm, unobjectionable, no neurobehavioral effects, and no other effects reported in additional studies

End point/Concentration/Rationale: NOAEL for irritation and neurobehavioral deficits

Uncertainty factors/Rationale:
Total uncertainty factor: 1
Interspecies: Not applicable
Intraspecies: 1, no susceptible populations were located. The intensity of discomfort associated with 200 ppm is not expected to vary greatly among the general population.

Modifying factor: Not applied

Animal-to-human dosimetric adjustment: Not applicable

(Continued)

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AEGL-1 VALUES Continued

10 min	30 min	1 h	4 h	8 h
200 ppm	200 ppm	200 ppm	200 ppm	200 ppm

Time-scaling: Not applied; a tolerance develops to any irritation

Data adequacy: The database on clinical and monitoring studies is extensive. MEK is rapidly metabolized. Short exposures of healthy subjects and subjects with sMCS at 380 ppm without apparent adverse effects supports the concentration of 200 ppm for the general population.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
4,900 ppm[a]	3,400 ppm[a]	2,700 ppm[a]	1,700 ppm	1,700 ppm

Key reference:
Cavender, F.L., H.W. Casey, H. Salem, J.A. Swenberg, and E.J. Gralla. 1983. A 90-day vapor inhalation toxicity study of methyl ethyl ketone. Fundam. Appl. Toxicol. 3(4):264-270.
Supporting reference:
Altenkirch, H., G. Stoltenburg, and H.M. Wagner. 1978a. Experimental studies on hydrocarbon neuropathies induced by methyl-ethyl-ketone (MEK). J. Neurol. 219(3):159-170.

Test species/Strain/Number:
Rat/Fischer 344/15 males and 15 females (Cavender et al. 1983); Wistar/5 rats (Altenkirch et al. 1978)

Exposure route/Concentrations/Durations:
Inhalation/0, 1,250, 2,500, or 5,000 ppm for 6 h/day, 5 days/week, for 90 days (Cavender et al. 1983); 6,000 ppm for 8 h/day, 7 days/week, for several weeks (Altenkirch et al. 1978)

Effects: At 5,000 ppm, no irritation, no narcosis, and transient weight loss (Cavender et al. 1983); at 6,000 ppm, hyperexcitability followed by somnolence within 5-10 min and gait disturbance after exposures, no neuropathies, animals died of bronchopneumonia in 7th week (Altenkirch et al. 1978).

End point/Concentration/Rationale: NOAEL for neurobehavioral deficits at 5,000 ppm for 6 h

Uncertainty factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1, uptake is greater and faster in rodents compared with humans.
Intraspecies: 3, no susceptible populations identified; metabolism is not expected to vary greatly among individuals; and susceptibility to CNS depression does not vary by more than a factor of 2- to 3-fold among the general population.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applied

(Continued)

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AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
4,900 ppm[a]	3,400 ppm[a]	2,700 ppm[a]	1,700 ppm	1,700 ppm

Time-scaling: The 4- and 8-h exposures were set equal to 1,700 ppm; the 10- and 30-min and 1-h values were time-scaled with the default n value of 3.

Data adequacy: Extensive database of human (irritation, neurotoxicity, and metabolism) and animal studies (baboon, rat, mouse, and guinea pig); animal studies addressed irritation, neurotoxicity, developmental toxicity, and subchronic toxicity; the Cavender et al. (1983) study is supported by a study with rats conducted at 6,000 ppm (Altenkirch et al. 1978); the key study utilized groups of 15 male and 15 female rats; and complete histologic examinations were performed at the end of exposure.

[a]The 10- and 30-min and the 1-h AEGL-2 values are higher than one-tenth of the lower explosive limit (LEL) of MEK in air (LEL = 18,000 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 h
[a]	[a]	4,000 ppm[b]	2,500 ppm[b]	2,500 ppm[b]

Key references:

Fowles, J.R., G.V. Alexeeff, and D. Dodge. 1999. The use of the benchmark dose methodology with acute inhalation lethality data. Regul. Toxicol. Pharmacol. 29(3):262-278.

Hansen, L.F., A. Knudsen, and G.D. Nielsen. 1992. Sensory irritation effects of methyl ethyl ketone and its receptor activation mechanism. Pharmacol. Toxicol. 71(3 Pt. 1):201-208.

Klimisch, H. 1988. The inhalation hazard test; principle and method. Arch. Toxicol. 61(5):411-416.

La Belle, C.W., and H. Brieger. 1955. The vapor toxicity of a composite solvent and its principal components. Arch. Ind. Health 12(6):623-627.

Zakhari, S., M. Leibowitz, P. Levy, and D.M. Aviado. 1977. Acute, oral, intraperitoneal, and inhalational toxicity in the mouse. P. 67-69 in Isopropanol and Ketones in the Environment, L. Golberg, ed. Cleveland, OH: CRC Press.

Test species/Strain/Number:
Rat/unspecified/6 rats (Klimisch 1988); mouse/CF-1/10 per group (Zakhari et al. 1977); mouse/CF-1/4 per group (Hansen et al. 1992); rat/strain not given/6 per group (La Belle and Brieger 1955)

Exposure route/Concentrations/Durations:
Inhalation/92,239 ppm for 30 min or 3 h (Klimisch 1988); 50,000, 60,000, 70,000, 80,000, or 100,000 ppm, for 45 min (Zakhari et al. 1977); 0, 3809, 9136, 12,771, 24,179, or 26,416 ppm, for30 min (Hansen et al. 1992); 7,850, 9,090, 9,260, 12,200, 13,750, 18,100, or 20,200 ppm, for 4 h (La Belle and Brieger 1955)

(Continued)

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AEGL-3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
[a]	[a]	4,000 ppm[b]	2,500 ppm[b]	2,500 ppm[b]

Effects: No deaths at 96,239 ppm for 30 min (Klimisch 1988); no deaths at 50,000 ppm for 45 min (Zakhari et al. 1977); concentration-dependent decrease in respiratory rate and tidal volume; calculated RD_{50} of 31,246 ppm; no deaths at 26,000 ppm for 30 min (Hansen et al. 1992); and no deaths at 7,850 ppm (La Belle and Brieger 1955)

End point/Concentration/Rationale: On the basis of the first three studies, 10,000 ppm would not be life-threatening to humans; at 7,500 ppm for 4-h, maximum likelihood estimate, with a 1% response (MLE_{01}) calculated by Fowles et al. (1999) from data of La Belle and Brieger (1955)

Uncertainty factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1, uptake is greater and faster in rodents than in humans.
Intraspecies: 3, no susceptible populations identified; CNS depression does not vary by more than a factor of 2-3 among the general population.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applied

Time-scaling: $C^n \times t = k$. Default value of n = 3 used when scaling from longer to shorter time intervals; both 4- and 8-h values set equal to 2,500 ppm; 1-h value time-scaled from the 4-h value

Data adequacy: Extensive database of human (irritation, neurotoxicity, and metabolism) and animal studies (baboon, rat, mouse, and guinea pig); animal studies addressed irritation, neurotoxicity, developmental toxicity, and subchronic toxicity; studies were supported by no deaths in rats exposed at 10,000 ppm for several days (Altenkirch et al. 1978) and no deaths in guinea pigs exposed at 10,000 ppm for 13.5 h (Patty et al. 1935).

[a]The 10- and 30-min AEGL-3 value of 10,000 ppm (29,300 mg/m^3) is higher than 50% of the lower explosive limit (LEL) of MEK in air (LEL = 18,000 ppm). Therefore, extreme safety considerations against the hazard of explosion must be taken into account.
[b]The 1-, 4-, and 8-h AEGL-3 values are higher than one-tenth of the LEL of MEK in air (LEL = 18,000 ppm). Therefore, safety considerations against the hazard of explosion must be taken into account.

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4

Perchloromethyl Mercaptan[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 Claudia Troxel (Oak Ridge National Laboratory) and Zarena Post and Susan Ripple (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee 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).

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effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

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

SUMMARY

Perchloromethyl mercaptan is an oily, yellow liquid with an unbearable, acrid odor and a reported odor threshold of approximately 0.001 ppm (Ruth 1986; ACGIH 1991; NIOSH 1996). Although it was used as a chemical warfare agent by the French in the 1915 battle of Champagne, wartime use was abandoned shortly thereafter because of the clear warning properties, the decomposition in the presence of iron and steel, and the easy removal of the vapor by charcoal (Prentiss 1937). Today, perchloromethyl mercaptan is used as an intermediate in the synthesis of dyes and phthalimide fungicides.

Data addressing human and animal toxicity following exposure to perchloromethyl mercaptan vapor are sparse. Only secondary sources described human data; case reports described respiratory and topical exposures to unquantified amounts of perchloromethyl mercaptan; and sources did not provide experimental details. Animal data addressing the lethal and nonlethal effects of perchloromethyl mercaptan were limited to rats, and studies addressing nonlethal effects were limited to repeat-exposure protocols.

Because there were no acute animal toxicity data appropriate for deriving an AEGL-1, the AEGL-1 is based on the repeat-exposure study by Knapp et al. (1987) in which rats were exposed 6 h/day, 5 days/week, for 2 weeks, to 0.02, 0.13, or 1.15 ppm. No effects were reported at 0.02 ppm, mild nasal epithelial changes were noted at 0.13 ppm, and mild nasal epithelial changes and pulmo-

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nary irritation (labored breathing, increased lung weight, pulmonary edema, increased mucous secretion, alveolitis, interstitial fibroplasia, and perivascular edema) were noted at 1.15 ppm. The AEGL-1 point of departure is based on mild nasal epithelial changes noted at 0.13 ppm, which represents a no-observed-adverse-effect level (NOAEL) for notable irritation. This concentration is also a NOAEL for pulmonary irritation. A total uncertainty factor of 10 was applied. An intraspecies uncertainty factor of 3 and an interspecies uncertainty factor of 3 were applied because perchloromethyl mercaptan is highly irritating and corrosive, and much of the toxicity is probably caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly among individuals or among species. No modifying factor was applied because the minor epithelial changes were noted in a repeat-exposure study; it is likely that the epithelial changes following a single exposure would have been less pronounced. The derived value was set equal at all AEGL time-points because the end point is a no-effect level for perchloromethyl mercaptan as a respiratory irritant.

Insufficient data are available to derive values consistent with the AEGL-2 definition. Studies that reported analytic exposure concentrations failed to describe adverse health effects consistent with an AEGL-2 end point. In the absence of specific data that could be used to determine AEGL-2 values, one-third of the AEGL-3 values have been used to establish the AEGL-2 values when the data indicated a steep exposure-based relationship. Therefore, the AEGL-2 values were derived by dividing the AEGL-3 values by 3.

No deaths occurred in male and female rats exposed at 9 ppm for 1 h, while 7 of 10 rats died at 18 ppm (Stauffer Chemical Company 1971). Therefore, 9 ppm represents a no-effect-level for mortality and was selected as the most appropriate basis for the AEGL-3 derivation, given the limited database. All exposed rats developed ocular and mucosal irritation within 5 min of initial exposure; dyspnea, gasping, and "acute depression" were also observed. Necropsy revealed inflamed oral and nasal mucosa. A total uncertainty factor of 10 was applied. An intraspecies uncertainty factor of 3 and an interspecies uncertainty factor of 3 were applied because perchloromethyl mercaptan is highly irritating and corrosive, and much of the toxicity is probably caused by a direct chemical effect on the tissues. This type of port-of-entry effect is not expected to vary greatly among individuals or among species. The intraspecies uncertainty factor of 3 is also supported by the steep dose-response curve, which may be an indication of relatively little variation within a population.

The values are scaled to AEGL time frames using the concentration-time relationship given by the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 1 to 3.5 (ten Berge et al. 1986). Although the mechanism of action appears to be direct contact irritation, it is not appropriate to set the values equal across time because the irritation is no longer considered mild, but rather the AEGL-3 concentration represents a threshold for lethality. Therefore, the irritation is sufficiently severe that continued exposure would produce increased and likely irreversible damage. The value of n could

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not be empirically derived because of inadequate data. Therefore, the default values of n = 1 and 3 were used for extrapolating from shorter to longer and longer to shorter durations of exposure, respectively.

The derived AEGL values are listed in Table 4-1. All values are above the estimated odor threshold of 0.001 ppm; therefore, odor will not provide information on the extent of exposure. Perchloromethyl mercaptan is corrosive to the skin, and skin absorption may provide additional exposure (Stauffer Chemical Co. 1971).

I. INTRODUCTION

Perchloromethyl mercaptan is an oily, yellow liquid with an unbearable, acrid odor (ACGIH 1991; NIOSH 1996). Although it was used as a chemical warfare gas by the French in the battle of the Champagne in 1915, wartime use was abandoned shortly thereafter because of the strong warning odor, decomposition in the presence of iron and steel, and because the vapor could easily be removed by charcoal (Prentiss 1937). Today, perchloromethyl mercaptan is used as an intermediate in the synthesis of dyes and phthalimide fungicides (ACGIH 1991; Shertzer 2001). Production data for perchloromethyl mercaptan were not available. The physicochemical data on perchloromethyl mercaptan are presented in Table 4-2.

2. HUMAN TOXICITY DATA

2.1 Acute Lethality

Althoff (1973) published the case of a 15-year-old male laboratory assistant who was exposed to perchloromethyl mercaptan liquid and vapor when a flask was broken. Approximately 200 mL of perchloromethyl mercaptan spilled onto his clothing and onto the floor. He was taken to the hospital and admitted. Thirty-six hours following exposure, the patient died from massive hemorrhaging pulmonary edema and simultaneous heart, circulatory, and kidney failure from the resultant hypoxia. Damage noted during autopsy included partly hemorrhagic, necrotizing tracheobronchitis and bronchiolitis with numerous mucus obstructions, high-grade diffuse hemorrhagic lung edema, and extreme interstitial edema; and pleural discharge on both sides of the lungs.

2.2. Nonlethal Toxicity

The odor of perchloromethyl mercaptan has been described as unbearable, acrid, and disagreeable (ACGIH 1991; NIOSH 1996). Secondary sources reported an odor threshold of 0.001 ppm (reported as 0.0075 mg/m^3) (Ruth 1986)

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TABLE 4-1 Summary of AEGL Values for Perchloromethyl Mercaptan

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	0.013 ppm (0.099 mg/m^3)	0.013 ppm (0.099 mg/m^3)	0.013 ppm (0.099 mg/m^3)	0.013 ppm (0.099 mg/m^3)	0.013 ppm ([0.099 mg/m^3)	Nasal epithelial changes in rats exposed at 0.13 ppm for 6 h /d, 5 d/wk, for 2 weeks (Knapp et al. 1987)
AEGL-2 (disabling)	0.53 ppm (4.0 mg/m^3)	0.37 ppm (2.8 mg/m^3)	0.30 ppm (2.3 mg/m^3)	0.077 ppm (0.59 mg/m^3)	0.037 ppm (0.28 mg/m^3)	One-third of the AEGL-3 values
AEGL-3 (lethality)	1.6 ppm (12 mg/m^3)	1.1 ppm (8.4 mg/m^3)	0.90 ppm (6.8 mg/m^3)	0.23 ppm (1.7 mg/m^3)	0.11 ppm (0.84 mg/m^3)	No mortality in rats exposed at 9 ppm for 1 h (Stauffer Chemical Co. 1971)

TABLE 4-2 Chemical and Physical Data on Perchloromethyl Marcaptan

Parameter	Value	Reference
Synonyms	Clarisit (war gas); methane sufenyl chloride; PCM; perchloromethanethiol; thrichloromethylsulfenyl chloride	ACGIH 1991
CAS registry no.	594-42-3	ACGIH 1991
Chemical formula	CCl_3SCl	ACGIH 1991
Molecular weight	185.87	ACGIH 1991
Physical state	Liquid	ACGIH 1991
Color	Yellow	ACGIH 1991
Boiling point	147-148°C	Shertzer 2001
Density (air = 1)	6.414	Shertzer 2001
Solubility	Insoluble in water; soluble in ether	ACGIH 1991
Vapor pressure	65 torr at 70ºC 3 mmHg at 20ºC	ACGIH 1991 Shertzer 2001
Specific gravity (water = 1)	1.7 at 20ºC	ACGIH 1991
Conversion factors	1 ppm = 7.60 mg/m^3 1 mg/m^3 = 0.132 ppm	Farr and Kirwin 1994

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and an "olfactory threshold" of 0.24 ppm (reported as 1.8 mg/m^3) (Izmerov et al. 1982). Flury and Zernik (1931) reported severe eye, mouth, and chest irritation in humans following exposure to low (unspecified) concentrations of perchloromethyl mercaptan. A 19-year-old male accidentally exposed ("in the face") to an unknown concentration of perchloromethyl mercaptan experienced irritation of the conjunctiva and respiratory tract mucosa and developed extensive bronchopneumonia within 20 h (Spácilová 1971). He was treated with antibiotics, oxygen, and "cardiotonics", and recovered within 14 days. Prentiss (1937) stated that perchloromethyl mercaptan caused lacrimation at 1.3 ppm (reported as 0.010 mg/L) was intolerable at 9.2 ppm (0.070 mg/L) and was lethal at 390 ppm (3.0 mg/L) after 10 min (no original citations or details provided).

The National Institute for Occupational Safety and Health (NIOSH) conducted a combined environmental and medical evaluation of a chemical plant in which workers were potentially exposed to Folpet, Captan, phthalimide, tetrahdrophthalimide, perchloromethyl mercaptan, carbon tetrachloride, carbon disulfide, mercaptan, and chlorine (Burroughs and Hora 1982). Unfortunately, NIOSH investigators were unable to measure perchloromethyl mercaptan air samples because of an inadequate analytic method. The conclusion of the investigation was that the acute symptoms reported by workers were nonspecific and not necessarily related to occupational exposure, "although the most commonly reported symptoms involved eye irritation, which is typical of exposure to Captan and Folpet."

2.3. Developmental and Reproductive Effects

No human developmental and reproductive toxicity data on perchloromethyl mercaptan were found in the open literature.

2.4. Genotoxicity

No human genotoxicity data on perchloromethyl mercaptan were found in the open literature.

2.5. Carcinogenicity

No data were found in the available literature regarding the carcinogenic potential of perchloromethyl mercaptan.

2.6. Summary

Data addressing toxicity following perchloromethyl mercaptan exposure in humans are sparse. Following exposure to an unknown concentration of perchloromethyl mercaptan vapor and skin contact with the liquid, one fatality oc-

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curred due to massive hemorrhagic pulmonary edema, accompanied by simultaneous heart, circulatory, and kidney collapse (Althoff 1973).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Vernot et al. (1977) determined the 1-h lethal concentration to 50% of the exposed population (LC_{50}) for perchloromethyl mercaptan in rats. Groups of five male or five female Sprague-Dawley rats were exposed to various concentrations of perchloromethyl mercaptan (individual concentrations not given) for 1 h in an exposure chamber (in either bell jar or large desiccators). The 1-h LC_{50} values were calculated by probit analysis of the data and were 11 ppm (95% confidence interval [C.I.]: 10-13) for male rats and 16 ppm (95% C.I.: 13-22) for female rats. When averaged, the 1-h LC_{50} for male and female Sprague-Dawley rats (combined) is 13 ppm.

Groups of 10 Sprague-Dawley rats (five males and five females) were exposed to perchloromethyl mercaptan vapor at concentrations of 9, 18, 124, 382, 822, or 2,342 ppm for 1 h in a 32-liter (L) positive pressure chamber (concentrations given in report as 0.066, 0.133, 0.940, 2.900, 6.250, and 17.800 mg/L/h) (Stauffer Chemical Co. 1971). The vapor was generated using a midget impinger. It is not clear from the text of the original report whether exposure concentrations were nominal or measured. Animals were observed for clinical signs of toxicity and mortality during the exposure and for 14-days thereafter. All animals exhibited eye and mucosa irritation within 5 min of initial exposure, and dyspnea, gasping, and "acute depression" ensued. Mortality occurred in all test groups by 24 h postexposure except for the 9-ppm group (Table 4-3). Necropsy of animals that died revealed pulmonary edema, heart and liver congestion, and inflammation of the pericardial and peritoneal membranes and upper gastrointestinal tract. Oral and nasal mucosa were inflamed at all exposure concentrations. Corneal opacity was present in animals exposed at 124 ppm and greater. The authors calculated a 1-h LC_{50} of 13 ppm (reported as 0.1 mg/L/h).

A 4-h LC_{100} value of 34 ppm (given as 260 mg/m^3) was reported for rats (Izmerov et al. 1982). No other details were provided.

Gage (1970) conducted a series of experiments in which Alderley Park specific-pathogen-free rats were exposed to perchloromethyl mercaptan at 0.5, 2, 10, or 100 ppm in a glass desiccator with wire mesh separating the animals. The appropriate nominal concentration was produced by injecting perchloromethyl mercaptan at a known rate into a metered flow of air using a controlled fluid-feed atomizer, but analytic chamber concentrations were not determined during the exposures. When nominal concentrations were less than 100 ppm, perchloromethyl mercaptan was mixed with acetone. In an acute exposure ex-

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periment, four male rats were exposed at 100 ppm for 1 h. The animals exhibited severe respiratory difficulty, and all died. Postmortem examination revealed pulmonary edema. In another experiment, four male rats were exposed to perchloromethyl mercaptan in acetone for 6 h at 10 ppm. Animals developed lethargy and respiratory difficulty, and three animals died. Necropsy again revealed pulmonary edema. In a series of short-term exposures, four male rats exposed to perchloromethyl mercaptan in acetone 20 times at 2 ppm for 6 h (time between exposures not stated) had initial respiratory difficulty. No animals died. Pulmonary congestion was noted during postmortem examination (conducted the day after the last exposure). In another experiment, four male and four female rats were exposed to perchloromethyl mercaptan in acetone at 0.5 ppm for 20 exposures over 6 h (time between exposures not stated). No signs of toxicity were noted, and all organs were found to be normal during necropsy conducted on the day after the last exposure. The protocol used by Gage was confounded by several factors, including the lack of information on the purity of the chemical, the mixing of the chemical with acetone for exposure purposes, and the lack of analytic verification of chamber concentrations.

3.1.2. Mice

A 2-h LC_{50} value of 38.9 ppm (reported as 296 ± 43 mg/m^3) and a 3-h LC_{50} of 9 ppm were reported for mice following inhalation exposure to perchloromethyl mercaptan (Althoff 1973; Izmerov et al. 1982). No further details were provided. Mice inhaling approximately 46 ppm for 15 min (reported as 0.35 mg/L) died from pulmonary edema within 1-2 days of exposure (Flury and Zernick 1931).

TABLE 4-3 Mortality of Sprague-Dawley Rats Exposed to Perchloromethyl Mercaptan for 1 h

Concentration		Mortality After Exposure					
ppm	mg/L/h	1 h	2 h	6 h	12 h	24 h	48 h
9	0.066	0/10	0/10	0/10	0/10	0/10	0/10
18	0.133	0/10	0/10	2/10	6/10	7/10	7/10
124	0.940	1/10	9/10	10/10	—	—	—
382	2.900	10/10	7/10	10/10	—	—	—
822	6.250	10/10	10/10	—	—	—	—
2,342	17.800	10/10	10/10	—	—	—	—

Source: Stauffer Chemical Co. 1971.

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3.1.3. Cats

Cats exposed to perchloromethyl mercaptan at approximately 46 ppm for 15 min (reported as 0.35 mg/L) died from pulmonary edema within 1-2 days of exposure (Flury and Zernick 1931).

3.2. Nonlethal Toxicity

3.2.1. Rats

Groups of 15 male and female Sprague-Dawley rats were exposed to "cumulative" mean air concentrations of 0, 0.02, 0.13, or 1.15 ppm (reported as 0, 0.13, 1.0, or 8.7 mg/m^3) for 6 h/day, 5 days/week, for 2 weeks (Knapp et al. 1987). At 1.15 ppm, signs consisted of haircoat stains, dyspnea, tremors, and reduced body-weight gain. Necropsy revealed increased lung weight, pulmonary edema, and increased mucous secretion, and microscopic examination of the lungs found alveolitis, interstitial fibroplasia, and perivascular edema. Mild nasal epithelial changes (not further described) were noted in animals exposed at 0.13 and 1.15 ppm.

Groups of 18 male and 18 female Sprague-Dawley CD rats were exposed to perchloromethyl mercaptan vapor in the air at measured concentrations of 0, 0.014, 0.079, or 0.580 ppm (reported as 0, 0.11, 0.60, or 4 mg/m^3) for 6 h/day, 5 days/week, for a total of 70 to 72 exposure days (Knapp and Thomassen 1987). The exposures were conducted in 1.0-m^3-inhalation exposure chambers. No animals died from the exposure, and no exposure-related effects were noted in hematology or clinical chemistry parameters. Exposure-related effects were observed in the high-concentration group. Clinical signs consisted of increased incidences of salivation in males and increased sneezing in males and females starting on test days 18 and 59, respectively. High-concentration-group females had a time-related decrease in absolute body weight starting at week 1 and continuing throughout the study (−6-12% compared with controls). The controls had a total body-weight gain of 64%. Necropsy of the high-concentration groups at study termination revealed increased absolute lung weight and lung weight relative to body weight and brain weight in males (+9%, +16%, and +10%, respectively) and increased lung weight relative to body weight in females (+15%) compared with controls. Other effects noted in animals from the high-concentration group included gross mucus in the trachea in 4 of 18 males and in 2 of 18 females. Microscopic findings of acute inflammation and hypertrophy, and hyperplasia of respiratory nasal epithelium in males and females were reported. Residues of purulent or serum exudate were noted in all males and in 13 of 18 females in the 0.580-ppm group and in one male and one female exposed at 0.079 ppm. The only exposure-related pulmonary lesion was mild-to-minimal focal subacute interstitial pneumonia in five males and one female from the high-concentration group.

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As discussed in Section 3.1.1, Gage (1970) conducted a series of experiments in which Alderley Park specific-pathogen-free rats were exposed to perchloromethyl mercaptan at 100, 10, 2, or 0.5 ppm for various time periods. No deaths occurred in the four male rats exposed at 2 ppm or in the four male or female rats exposed at 0.5 ppm for 20 exposures over 6 h (time between exposures not stated). In the 2-ppm group, initial respiratory difficulty was reported, and pulmonary congestion was noted during postmortem examination. No clinical signs of toxicity or remarkable necropsy findings were reported for rats in the 0.5-ppm group. It should be reemphasized that the protocol used by Gage was compromised by several factors, including the lack of information on the purity of the chemical, the mixing of the chemical with acetone for exposure purposes, and the lack of analytic verification of chamber concentrations.

3.2.2. Other Species

Seven rats, seven guinea pigs, and two dogs were exposed to perchloromethyl mercaptan at a nominal concentration of 1 ppm for 8 h/day, 5 days/week, for 3 months (Hazleton Laboratories 1952). For numerous reasons, this study can be used only to provide descriptive data. The materials and methods and the results sections of the study report were mostly illegible (poor copy quality). It appeared that the laboratory had difficulty with the instrumentation used to deliver the perchloromethyl mercaptan to the exposure chamber. The (legible) summary section failed to discuss or mention control animals, suggesting that control animals were not assigned. At least one of the dogs had parasitic infestation and findings suggestive of bronchopneumonia; the guinea pigs that died appeared to have had pneumonia with septicemia, and the surviving guinea pig had signs of a chronic infection. The study authors suggested that the irritative effects of perchloromethyl mercaptan led to increased susceptibility to secondary infections. However, it is not clear that these infections were not already present prior to or at the start of exposures. The data for all the animals are presented together below.

In summary, six of seven guinea pigs died within the first 3 weeks of exposure. Signs included lacrimation, rhinorrhea, lethargy, and increased respiration. Guinea pigs that died had pneumonia with septicemia, and the surviving guinea pig developed fibrotic lungs and liver findings consistent with a chronic infection. Neither of the dogs died as a result of their exposure. The dogs developed lacrimation, rhinorrhea, nausea and retching, coughing and sneezing, diarrhea, and occasional blood-stained stools. (Note that at least one of the dogs had a parasitic infection.) Microscopic examination of the lungs of one of the dogs revealed bronchiolitis with possible bronchopneuomonia. Clinical signs in rats were not summarized. Microscopic examination of the lungs revealed thin alveolar walls with a hyaline-like appearance, and in some areas, the alveolar walls ruptured and formed emphysematous blebs.

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3.3. Developmental and Reproductive Effects

No developmental and reproductive toxicity data on perchloromethyl mercaptan were found in the available literature.

3.4. Genotoxicity

Perchloromethyl mercaptan was mutagenic in a number of in vitro assays, including *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100 with or without metabolic activation (Stauffer Chemical Company 1982a), the DNA-polymerase-deficient *Escherichia coli* (pol A_1- strain) without metabolic activation (Rosenkranz and Leifer 1980), inhibition of DNA synthesis (via DNA polymerase β inhibition) in isolated bovine liver nuclei (Dillwith and Lewis 1980), induction of mutations at the thymidine kinase locus in cultured L5178Y mouse lymphoma cells with or without metabolic activation (Stauffer Chemical Company 1983a), and induction of morphologic transformations in the BALB/3T3 morphologic transformation assay (Stauffer Chemical Company 1982b). Perchloromethyl mercaptan failed to increase chromosomal aberrations or sister chromatid exchanges in cultured Chinese hamster ovary cells with or without metabolic activation, and there was no increase in micronuclei in the bone marrow of mice in a micronucleus assay (Stauffer Chemical Company 1983b, 1984).

3.5. Carcinogenicity

No data were found in the literature concerning the carcinogenic potential of perchloromethyl mercaptan in animals.

3.6. Summary

A summary of lethal and nonlethal data is presented in Table 4-4. Acute lethality data were available for rats: 1-h inhalation LC_{50} values for perchloromethyl mercaptan vapor were 13 ppm for males and females combined (Stauffer Chemical Co. 1971) and 11 ppm for males and 16 ppm for females for an average of 13.5 ppm for males and females combined (Vernot et al. 1977). Although a 3-h LC_{50} value of 9 ppm and a 2-h LC_{50} value of 39 ppm were reported in mice, these values were published in a secondary source and did not provide any original citation or experimental details (Stauffer Chemical Co. 1971, as cited in Althoff 1973; Eastman Kodak Co. 1979; Izmerov et al. 1982).

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TABLE 4-4 Summary of Inhalation Data in Laboratory Rats

Concentration (ppm)	Exposure Time	Effect	Reference
		Lethal Effects	
18	1 h	Lowest empirical exposure causing mortality (7/10) (males and females); deaths resulting from pulmonary edema, heart and liver congestion, inflammation of upper gastrointestinal tract and pericardial and peritoneal membranes	Stauffer Chemical Co. 1971
11	1 h	Calculated LC_{50} (males)	Vernot et al. 1977
16	1 h	Calculated LC_{50} (females)	Vernot et al. 1977
13	1 h	Calculated LC_{50} (average of males and females)	Vernot et al. 1977
		Nonlethal Effects	
9	1 h	Eye and mucosa irritation, dyspnea, gasping, "acute depression" (severity of signs not defined), inflamed mouth, and nasal mucosa	Stauffer Chemical Co. 1971
0.13	6 h/d, 5 d/wk, for 2 wk	Mild nasal epithelial changes	Knapp et al. 1987
1.15	6 h/d, 5 d/wk, for 2 wk	Haircoat stains, labored breathing, tremors, decreased birth weight., increased lung weight, pulmonary edema, increased mucous secretion, alveolitis, interstitial fibroplasia, and mild nasal epithelial changes	
0.58	6 h/d, 5 d/wk, for 70-72 d	Salivation (day 18) and sneezing (day 59) Mild changes, including decreased female birth weight, increased male and female lung weight relative to body weight, mucous in trachea, respiratory nasal epithelium changes, and focal subacute interstitial pneumonia	Knapp and Thomassen 1987

Data addressing nonlethal effects in animals following perchloromethyl mercaptan exposure are small. Clinical signs in rats surviving a 1-h exposure at 9 ppm included eye and mucosa irritation, dyspnea, gasping, and "acute depression" (Stauffer Chemical Co. 1971). The severity of those signs at this concentration and at the higher concentrations (which resulted in mortality) was not provided; no control group was included. A 2-week repeat-exposure study reported numerous findings in rats exposed at 1.15 ppm, including clinical signs (haircoat stains, labored breathing, tremors, and decreased body weight) and gross and microscopic lung changes (increased lung weight, pulmonary edema,

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increased mucous secretion, alveolitis, and interstitial fibroplasia) (Knapp et al. 1987). Mild nasal epithelial changes were observed in rats repeatedly exposed at 0.13 or 1.15 ppm (Knapp et al. 1987). Minimal effects were observed in rats exposed subchronically at 0.580 ppm; these effects included reduced body weight, increased lung weight, mucous in the trachea, respiratory nasal epithelial changes (acute inflammation and hypertrophy and hyperplasia of respiratory nasal epithelium), residues of purulent serous exudate, and focal subacute interstitial pneumonia (Knapp and Thomassen 1987). No such changes were observed in rats that inhaled 0.014 or 0.079 ppm for 70 to 72 days (Knapp and Thomassen 1987). The descriptive data provided by Gage (1970) and Hazleton Laboratories (1952) are of little use because the protocols used were fundamentally compromised by several factors.

Perchloromethyl mercaptan was generally mutagenic in standard in vitro test systems. No data were found regarding the potential for perchloromethyl mercaptan exposure to cause developmental and reproductive toxicity or to increase carcinogenic risk.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism, Disposition, and Mechanism of Toxicity

Althoff (1973) postulated that two mechanisms of action could be responsible for the toxicity of perchloromethyl mercaptan: one is the direct damage to tissues resulting from contact with the hydrolysis product hydrochloric acid:

$$CCl_3\text{-}S\text{-}Cl + H_2O \rightarrow CCl_3\text{-}SOH + HCl,$$

and the other is inactivation of key enzymes by the reaction of perchloromethyl mercaptan with biologic functional groups, such as amino, hydroxyl, carboxyl, sulfhydryl, or histidyl groups:

$$R\text{-}NH_2 + CCl_3\text{-}S\text{-}Cl \rightarrow CCl_3\text{-}S\text{-}NH\text{-}R + HCl \text{ or } R\text{-}OH + CCl_3\text{-}S\text{-}Cl \rightarrow CCl_3\text{-}S\text{-}O\text{-}R + HCl.$$

Because perchloromethyl mercaptan is insoluble in water, large amounts of HCl are not likely to be produced. This fact explains the deeper lung damage after HCl exposure compared with the relatively mild upper-respiratory-tract damage observed in animals exposed to perchloromethyl mercaptan.

4.2. Structure-Activity Relationships

Structure-activity relationships were not used in the derivation of inhalation exposure guidelines for perchloromethyl mercaptan. Although acute toxic-

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ity data are available for methyl mercaptan, the potency of perchloromethyl mercaptan is greater than that of methyl mercaptan. In rats, the highest nonlethal concentration of perchloromethyl mercaptan is 9 ppm for 1 h, and the 1-h LC_{50} is reported to be 11, 13, or 16 ppm. In comparison, the highest nonlethal concentration of methyl mercaptan in rats is 400 ppm for 4 h, with a 4-h LC_{50} value of 675 ppm in rats and 1,664 ppm in mice (EPA 2008). Therefore, the two chemicals are sufficiently different to preclude useful structure-activity relationship comparison.

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. The authors subjected the individual animal data sets to probit analysis with exposure duration and exposure concentration as independent variables. An exponential function $(C^n \times t = k)$, 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 time periods 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 time periods because the extrapolated values are more conservative in the absence of other data.

5. DATA ANALYSIS FOR AEGL-1 VALUES

5.1. Human Data Relevant to AEGL-1

Ruth (1986) reported an odor threshold of 0.001 ppm, while Izmerov et al. (1982) reported an "olfactory threshold" value in humans of 0.24 ppm. No further information was provided. The odor of perchloromethyl mercaptan is said to be unbearable, acrid, and disagreeable (ACGIH 1991; NIOSH 1996). Prentiss (1937) reported lacrimation at a concentration of 1.3 ppm, but no original citations or experimental details were provided.

5.2. Animal Data Relevant to AEGL-1

There were no acute animal data appropriate for deriving an AEGL-1. Although one study reported eye and mucosa irritation in rats exposed to perchloromethyl mercaptan at 9 ppm for 1 h, the severity of the signs was not provided, and the report stated that dyspnea, gasping, and signs of acute depression

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were also observed (Stauffer Chemical Co. 1971). Other nonlethal data are from repeat-exposure studies. Exposure of rats to perchloromethyl mercaptan for 6 h/day, 5 days/week, for 2 weeks at 0.02 ppm failed to elicit any measurable changes; exposure at 0.13 ppm resulted only in mild nasal epithelial changes (not further defined); exposure at 1.15 ppm resulted in objective clinical signs of intoxication (haircoat stains, labored breathing, tremors, reduced body-weight gain, increased lung weight, pulmonary edema, increased mucous secretion, alveolitis, interstitial fibroplasia, and perivascular edema in the lungs and mild epithelial changes in the nose) (Knapp et al. 1987). No exposure-related changes were observed in rats inhaling perchloromethyl mercaptan at 0.014 or 0.079 ppm for 6 h/day, 5 days/week, for a total of 70 to 72 exposure days (Knapp and Thomassen 1987).

5.3. Derivation of AEGL-1 Values

Because there were no acute animal toxicity data appropriate for deriving an AEGL-1, the AEGL-1 is based on the repeat-exposure study by Knapp et al. (1987) in which rats were exposed to perchloromethyl mercaptan at 0.02, 0.13, or 1.15 ppm for 6 h/day, 5 days/week, for 2 weeks. No effects were reported at 0.02 ppm, mild nasal epithelial changes were noted at 0.13 ppm, and mild nasal epithelial changes and pulmonary irritation (labored breathing, increased lung weight, pulmonary edema, increased mucous secretion, alveolitis, interstitial fibroplasia, and perivascular edema) were noted at 1.15 ppm. The AEGL-1 point of departure is mild nasal epithelial changes noted at a concentration of 0.13 ppm, which represents a NOAEL for notable irritation. This concentration is also a NOAEL for pulmonary irritation. A total uncertainty factor of 10 was applied. An intraspecies uncertainty factor of 3 and interspecies uncertainty factor of 3 were applied because perchloromethyl mercaptan is highly irritating and corrosive, and much of the toxicity is probably caused by a direct chemical effect on the tissues. This type of port-of-entry effect is not expected to vary greatly among individuals or among species, respectively. No modifying factor was applied because the minor epithelial changes were noted in a repeat-exposure study; the epithelial changes following a single exposure probably would have been less pronounced. The derived value was set equal at all AEGL time points because the end point is a no-effect level for irritation.

AEGL-1 values are presented in Table 4-5.

TABLE 4-5 AEGL-1 Values for Perchloromethyl Mercaptan

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1	0.013 ppm (0.099 m^3)	0.013 ppm (0.099 m^3)	0.013 ppm (0.099 m^3)	0.013 ppm (0.099 m^3)	0.013 ppm (0.099 m^3)

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6. DATA ANALYSIS FOR AEGL-2 VALUES

6.1. Human Data Relevant to AEGL-2

No available human data were appropriate for an AEGL-2 derivation for perchloromethyl mercaptan.

6.2. Animal Data Relevant to AEGL-2

Acute animal toxicity data appropriate for use in an AEGL-2 derivation were sparse. Although rats survived a 1-h exposure to perchloromethyl mercaptan at 9 ppm, the severity of the reported clinical signs (eye and mucosa irritation, dyspnea, gasping, and acute depression) was not provided for the various exposure concentrations (Stauffer Chemical Co. 1971). In addition, exposure at 9 ppm was close to the calculated LC_{50} of 13 ppm. The inhalation study conducted by Gage (1970) reported initial respiratory difficulty in rats exposed 20 times at 2 ppm for 6 h. However, the protocol used by Gage was confounded by several factors including lack of information on the purity of the chemical, the mixing of the chemical with acetone for exposure purposes, and the lack of analytic verification of chamber concentrations. Therefore, the descriptive data provided by Gage are of little use.

Rats exposed to perchloromethyl mercaptan for 6 h/day, 5 days/week, for 2 weeks, at 0.13 ppm developed mild nasal epithelial changes, while rats exposed at the next higher concentration (1.15 ppm) developed severe effects, including haircoat stains, labored breathing, tremors, decreased body weight, increased lung weight, pulmonary edema, increased mucous secretion, alveolitis, and interstitial fibroplasia (Knapp et al. 1987). In a subchronic toxicity study, rats exposed at 6 h/day, 5 days/week, for 70-72 days developed only minimal effects at the highest exposure concentration (0.58 ppm) (Knapp and Thomassen 1987). Clinical signs were not present until later in the study (salivation on day 18; sneezing on day 59). Other effects noted in the high-exposure group compared with the controls included reductions in female body weight (−12%), increased lung weight in males and females (relative to body weight, approximately +15%), mucous in trachea in 4 of 18 males and 2 of 18 females, and respiratory nasal epithelium changes in males and females (acute inflammation and hypertrophy and hyperplasia). Residues of purulent or serum exudate were noted in all males and in 13 of 18 females in the 0.580-ppm group. The only exposure-related pulmonary lesion was mild-to-minimal focal subacute interstitial pneumonia in 5 of 18 males and in 1 of 18 females.

6.3. Derivation of AEGL-2 Values

Insufficient data are available to derive values consistent with the AEGL-2 definition. Studies that reported analytic exposure concentrations failed to de-

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scribe adverse health effects consistent with an AEGL-2 end point. In the absence of specific data that could be used to determine AEGL-2 values, one-third of the AEGL-3 values have been used to establish the AEGL-2 values when the data indicated a steep exposure-based relationship. Therefore, the AEGL-2 values were derived by dividing the AEGL-3 values by 3.

AEGL-2 values are presented in Table 4-6.

7. DATA ANALYSIS FOR AEGL-3 VALUES

7.1. Human Data Relevant to AEGL-3

No available human data were appropriate for an AEGL-3 derivation. Human data were limited to case reports describing exposures to unquantified concentrations of perchloromethyl mercaptan; it is likely these accidents involved both skin and respiratory tract contract with the material (Spácilová 1971; Althoff 1973).

7.2. Animal Data Relevant to AEGL-3

No mortality was observed in rats exposed to perchloromethyl mercaptan at 9 ppm for 1 h, while 7 of 10 rats died at 18 ppm (Stauffer Chemical Co. 1971). All exposed rats exhibited clinical signs of eye and mucosa irritation, dyspnea, gasping, and acute depression within 5 min of exposure, and necropsy revealed that the mouth and nasal mucosa were inflamed. On the basis of the mortality in this study, the calculated 1-h LC_{50} was 13 ppm (males and females combined). Vernot et al. (1977) reported 1-h LC_{50} values of 11 ppm for male rats and 16 ppm for female rats. A 4-h LC_{50} of 25 ppm was also reported in rats, and a 2-h LC_{50} value of 38.9 ppm (reported as 296 ± 43 mg/m^3) and a 3-h LC_{50} value of 9 ppm were reported in mice following inhalation exposure to perchloromethyl mercaptan (Althoff 1973; Izmerov et al. 1982). However, no original citations or experimental details were provided to support these values.

7.3. Derivation of AEGL-3 Values

No mortality was observed in male and female rats exposed to perchloromethyl mercaptan at 9 ppm for 1 h, while 7 of 10 rats died at 18 ppm (Stauffer Chemical Company 1971). Therefore, 9 ppm represents a no-effect-level for mortality and was selected as the most appropriate basis for the AEGL-3 derivation, given the limited database. All exposed rats developed ocular and mucosal irritation within 5 min of initial exposure; dyspnea, gasping, and "acute depression" were also observed. Necropsy revealed inflamed mouth and nasal mucosa.

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A total uncertainty factor of 10 was applied. An intraspecies uncertainty factor of 3 and interspecies uncertainty factor of 3 were applied because perchloromethyl mercaptan is highly irritating and corrosive, and much of the toxicity is probably caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly among individuals or among species. The intraspecies uncertainty factor of 3 is also supported by the steep dose-response curve, which may be an indication of relatively little variation within a population.

The values are scaled to AEGL time frames using the concentration-time relationship given by the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 1 to 3.5 (ten Berge et al. 1986). Although the mechanism of action responsible for death appears to be direct contact irritation in the lung, it is not appropriate to set the values equal across time because the irritation is no longer considered mild, but rather the concentration represents the threshold for lethality. Therefore, the irritation is severe enough that continued exposure would result in increased damage. The value of n could not be empirically derived because of inadequate data. Therefore, the default values of n = 1 and 3 were used for extrapolating from shorter to longer and longer to shorter exposure periods, respectively.

AEGL-3 values are presented in Table 4-7.

8. SUMMARY OF AEGLs VALUES

8.1. AEGL Values and Toxicity End Points

A summary of the AEGL values for perchloromethyl mercaptan is presented in Table 4-8. All values are above the estimated odor threshold of 0.001 ppm; therefore, odor will not provide information on the extent of exposure. Perchloromethyl mercaptan is corrosive to the skin and skin absorption may provide additional exposure (Stauffer Chemical Co. 1971).

TABLE 4-6 AEGL-2 Values for Perchloromethyl Mercaptan

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-2	0.53 ppm (4.0 m^3)	0.37 ppm (2.8 m^3)	0.30 ppm (2.3 m^3)	0.077 ppm (0.59 m^3)	0.037 ppm (0.28 m^3)

TABLE 4-7 AEGL-3 Values for Perchloromethyl Mercaptan

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-3	1.6 ppm (12 m^3)	1.1 ppm (8.4 m^3)	0.90 ppm (6.8 m^3)	0.23 ppm (1.7 m^3)	0.11 ppm (0.84 m^3)

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TABLE 4-8 Summary of AEGL Values for Perchloromethyl Mercaptan

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	0.013 ppm (0.099 mg/m^3)	0.013 ppm (0.099 mg/m^3)	0.013 ppm (0.099 mg/m^3)	0.013 ppm (0.099 mg/m^3)	0.013 ppm ([0.099 mg/m^3)
AEGL-2 (disabling)	0.53 ppm (4.0 mg/m^3)	0.37 ppm (2.8 mg/m^3)	0.30 ppm (2.3 mg/m^3)	0.077 ppm (0.59 mg/m^3)	0.037 ppm (0.28 mg/m^3)
AEGL-3 (lethality)	1.6 ppm (12 mg/m^3)	1.1 ppm (8.4 mg/m^3)	0.90 ppm (6.8 mg/m^3)	0.23 ppm (1.7 mg/m^3)	0.11 ppm (0.84 mg/m^3)

The AEGL-1 values were based on mild nasal epithelial changes in rats from a repeat-exposure study. This end point represents a NOAEL for notable discomfort. Data were insufficient to derive AEGL-2 values; therefore, the AEGL-2 values were obtained by dividing the AEGL-3 values by 3. The AEGL-3 values were based on a no-effect level for lethality. At the no-effect level for increased mortality, exposed animals developed eye and mucosa irritation, dyspnea, gasping, and acute depression, and necropsy revealed inflamed oral and nasal mucosa.

One way to evaluate the AEGL values in context of existing empirical data is presented in Figure 4-1. For this plot, the toxicity response was placed into severity categories. The severity categories fit into definitions of the AEGL health effects: no effects; discomfort; disabling; lethal, and partially lethal (an experimental concentration at which some of the animals died and some did not). The effects that place an experimental result into a particular category vary according to the spectrum of data available on a specific chemical and the effects from exposure to that chemical. The concentrations often span a number of orders of magnitude, especially when human data exist. Therefore, the concentration is placed on a log scale. The graph in Figure 4-1 plots the perchloromethyl mercaptan AEGL values along with the existing acute animal toxicity data in terms of the categories assigned to them. From this plot, it is evident that the AEGL values are below any exposure concentration in animals resulting in adverse effects and, therefore, should be protective of human health.

8.2. Comparisons with Other Standards

Published standards and guidance levels for perchloromethyl mercaptan are listed in Table 4-9.

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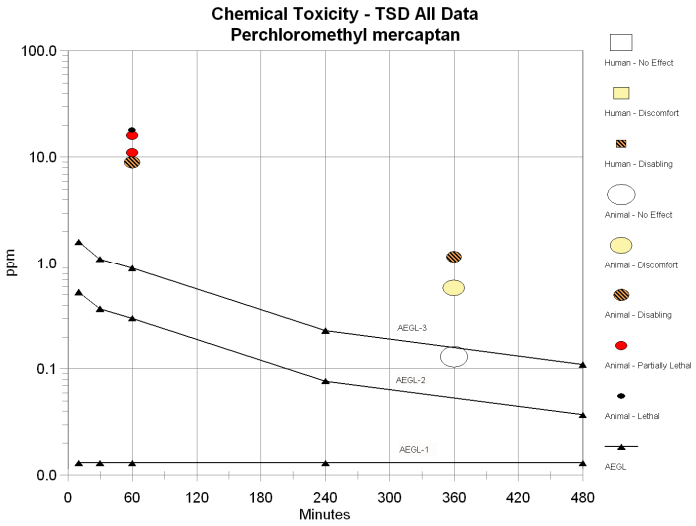

FIGURE 4-1 Category plot of animal toxicity data compared with AEGL values.

TABLE 4-9 Extant Standards and Guidelines for Perchloromethyl Mercaptan

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	0.013 ppm	0.013 ppm	0.013 ppm	0.013 ppm	0.013 ppm
AEGL-2	0.53 ppm	0.37 ppm	0.30 ppm	0.077 ppm	0.037 ppm
AEGL-3	1.6 ppm	1.1 ppm	0.90 ppm	0.23 ppm	0.11 ppm
IDLH (NIOSH)[a]		10 ppm			
TLV-TWA (ACGIH)[b]					0.1 ppm
PEL-TWA (OSHA)[c]					0.1 ppm
REL-TWA (NIOSH)[d]					0.1 ppm
MAK (Germany)[e]					Not established; insufficient data
MAC (The Netherlands)[f]					($0.01 mg/m^3$ = 0.01 ppm)

[a]IDLH (immediately dangerous to life or health, National Institute of Occupational Safety and Health) (NIOSH 1996; 2005) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms or any irreversible health effects. The IDLH for perchloromethyl mercaptan is based on the statement by Prentiss (1937) that perchloromethyl mercaptan is about one-sixth as toxic as phosgene; the phosgene IDLH is 2 ppm.

[b]TLV-TWA (Threshold Limit Value–time-weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 1991, 2008) is the time-weighted average

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concentration for a normal 8-h workday and a 40-h workweek to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[c]PEL-TWA (permissible exposure limits–time-weighted average, Occupational Health and Safety Administration) (OSHA) (29 CFR 1910.1000 [1996]) is analogous to the ACGIH TLV-TWA but is for exposures of no more than 10 h/day, 40 h/week.

[d]REL-TWA (recommended exposure limits–time-weighted average, National Institute for Occupational Safety and Health) (NIOSH 2005) is analogous to the ACGIH TLV-TWA.

[e]MAK (maximale Argeitsplatzkonzentration [maximum workplace concentration]) (Deutsche Forschungsgemeinschaft [German Research Association] (DFG 2007) is analogous to the ACGIH TLV-TWA.

[f]MAC (maximaal aanvaaarde concentratie [maximal accepted concentration]) Dutch Expert Committee for Occupational Standards, The Netherlands) (MSZW 2004) is analogous to the ACGIH TLV-TWA.

8.3. Data Quality and Research Needs

Data addressing human and animal toxicity following exposure to perchloromethyl mercaptan vapors were very limited. Human data were generally limited to case reports describing exposures to an unquantifiable amount of perchloromethyl mercaptan, secondary sources, and/or sources in which the experimental details were not provided. Further studies addressing the acute lethal and nonlethal effects of perchloromethyl mercaptan in animals would be of utility, since available animal data were limited to rats, and studies addressing nonlethal effects were limited to repeat-exposure protocols. No data were available addressing the potential for perchloromethyl mercaptan exposure to cause developmental or reproductive effects or neoplasia.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR PERCHLOROMETHYL MERCAPTAN

Derivation of AEGL-1

Key study:	Knapp et al. 1987
Toxicity end point:	Mild nasal epithelial changes representing a NOAEL for notable discomfort following exposure of rats at 0.013 ppm for 6 h/day, 5 days/week, for 2 weeks.
Time-scaling:	Values were set equal across time because the effects are those of mild irritation.
Uncertainty factors:	3 for interspecies variability 3 for intraspecies variability Combined uncertainty factor of 10
Calculations:	Point of departure/uncertainty factors 0.13/10 = 0.013
10-min, 30-min, 1 h, 4 h, and 8 h AEGL-1:	0.013 ppm for all time points

Derivation of AEGL-2

Key study:	AEGL-3 divided by 3; see AEGL-3 derivation
Toxicity end point:	AEGL-3 divided by 3; see AEGL-3 derivation
Time-scaling:	AEGL-3 divided by 3; see AEGL-3 derivation
Uncertainty factors:	AEGL-3 divided by 3; see AEGL-3 derivation
Calculations:	AEGL-3 values divided by 3
10-min. AEGL-2:	1.6 ppm/3 = .53 ppm
30-min AEGL-2:	1.1 ppm/3 = 0.37 ppm
1-h AEGL-2:	0.90 ppm/3 = 0.30 ppm

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4-h AEGL-2: 0.23 ppm/3 = 0.077 ppm

8-h AEGL-2: 0.11 ppm/3 = 0.037 ppm

Derivation of AEGL-3

Key study: Stauffer Chemical Co. 1971

Toxicity end point: No lethality in rats exposed to 9 ppm for 1 h

Time-scaling: $C^n \times t = k$ (default of n = 1 for shorter to longer exposure periods and n=3 for longer to shorter exposure periods)

Uncertainty factors: 3 for interspecies variability
3 for intraspecies variability
Combined uncertainty factor of 10

Calculations: $(C/\text{uncertainty factors})^n \times t = k$
$[(9 \text{ ppm})/10]^1 \times 1 \text{ h} = 0.9 \text{ ppm-h}$
$[(9 \text{ ppm})/10]^3 \times 1 \text{ h} = 0.729 \text{ ppm-h}$

10-min AEGL-3: $C^3 \times 0.167 \text{ h} = 0.729 \text{ ppm-h}$
$C^3 = 4.365 \text{ ppm}$
$C = 1.63 \text{ ppm} = 1.6 \text{ ppm}$

30-min AEGL-3: $C^3 \times 0.5 \text{ h} = 0.729 \text{ ppm-h}$
$C^3 = 1.458 \text{ ppm}$
$C = 1.13 \text{ ppm} = 1.1 \text{ ppm}$

1-h AEGL-3: $C^1 \times 1 \text{ h} = 0.729 \text{ ppm-h}$
$C^1 = 0.729 \text{ ppm-h}$
$C = 0.90 \text{ ppm}$

4-h AEGL-3: $C^1 \times 4 \text{ h} = 0.9 \text{ ppm-h}$
$C^1 = 0.225 \text{ ppm}$
$C = 0.225 \text{ ppm} = 0.23 \text{ ppm}$

8-h AEGL-3: $C^1 \times 8 \text{ h} = 0.9 \text{ ppm-h}$
$C^1 = 0.1125 \text{ ppm}$
$C = 0.1125 \text{ ppm} = 0.11 \text{ ppm}$

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APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR PERCHLOROMETHYL MERCAPTAN

Derivation Summary for Perchloromethyl Mercaptan

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
0.013 ppm	0.013 ppm	0.013 ppm	0.013 ppm	0.013 ppm

Reference:
Knapp, H.F., S.M. MacAskill, G.M. Zwicker, and G.L. Sprague. 1987. Effects in rats of repeated inhalation exposure to perchloromethyl mercaptan. Toxicologist 7(1):191[Abstact 762].

Test species/Strain/Number: Rat/Sprague-Dawley/15 per exposure group

Exposure route/Concentrations/Durations:
Inhalation at 0.02, 0.13, 1.15 ppm for 6 h/d, 5 d/wk, for 2 wk

Effects:
0.02 ppm: no effects
0.13 ppm: mild nasal epithelial changes
1.15 ppm: clinical signs of haircoat stains, labored breathing, tremors, and reduced body weight gain; necropsy revealed increased lung weight, pulmonary edema, and increased mucous secretion; microscopic examination found alveolitis, interstitial fibroplasia, and perivascular edema in the lungs and mild epithelial changes in the nose

End point/Concentration/Rationale: NOAEL for notable discomfort of 0.13 ppm for 6 h/day

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3 was applied because perchloromethyl mercaptan is highly irritating and corrosive, and much of the toxicity is probably caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly among species

Intraspecies: 3 was applied because perchloromethyl mercaptan is highly irritating and corrosive, and much of the toxicity is probably caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly among individuals, and the steep dose-response curve may be an indication of little variation within a population; (no deaths were observed in rats exposed at 9 ppm but 7 of 10 died at 18 ppm [Stauffer Chemical Company 1971]).

Modifying factor: No modifying factor was applied because the minor epithelial changes were noted in a repeated exposure study; it is likely that the epithelial changes following a single exposure would have been less pronounced.

Animal-to-human dosimetric adjustment: Not applicable

(Continued)

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AEGL-1 VALUES Continued

10 min	30 min	1 h	4 h	8 h
0.013 ppm	0.013 ppm	0.013 ppm	0.013 ppm	0.013 ppm

Time scaling: The derived value was set equal at all AEGL time-points because the end point is a no-effect level for irritation.

Data adequacy: No acute toxicity data were available for use in the derivation of the AEGL-1; therefore, the AEGL-1 values are based on a NOAEL from a repeat-exposure study.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.53 ppm	0.37 ppm	0.30 ppm	0.077 ppm	0.037 ppm

Reference: See "Data adequacy" below.

Test species/Strain/Sex/Number: See "Data adequacy" below.

Exposure route/Concentrations/Durations: See "Data adequacy" below.

Effects: See "Data adequacy" below.

End point/Concentration/Rationale: See "Data adequacy" below.

Uncertainty factors/Rationale: See "Data adequacy" below.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time-scaling: See "Data adequacy" below.

Data adequacy: No acute toxicity data were available for use in the derivation of the AEGL-2. In the absence of specific data that could be used to determine AEGL-2 values, one-third of the AEGL-3 values have been used to establish the AEGL-2 values when the data indicated a steep exposure-based relationship. Therefore, the AEGL-3 values are divided by 3 (see AEGL-3 derivation).

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
1.6 ppm	1.1 ppm	0.90 ppm	0.23 ppm	0.11 ppm

Reference: Stauffer Chemical Company. 1971. Initial Submission: Acute Inhalation Test with Perchloromethyl Mercaptan in Rats. Report No. T-1683. Stauffer Chemical Company, Westport, CT. Submitted by ICI Americas Inc., to U.S. Environmental Protection Agency, August 28, 1992. EPA Document No. 88-920006928. 7 pp.

Test Species/Strain/Number: Rat/Sprague-Dawley/5 per exposure group

Exposure route/Concentrations/Durations:
Inhalation at 9, 18, 124, 382, 822, or 2,342 ppm for 1 h

(Continued)

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AEGL-3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
1.6 ppm	1.1 ppm	0.90 ppm	0.23 ppm	0.11 ppm

Effects:

Concentration (ppm):	Mortality
9	0/10
18	7/10
124	10/10
382	10/10
822	10/10
2,342	10/10

End point/Concentration/Rationale: Exposure at 9 ppm for 1 h did not result in mortality; all exposed rats exhibited clinical signs of eye and mucosa irritation, dyspnea, gasping, and acute depression; necropsy revealed that the mouth and nasal mucosa were inflamed.

Uncertainty factors/Rationale:
Total uncertainty factor: 10

Interspecies: 3 was applied because perchloromethyl mercaptan is highly irritating and corrosive, and much of the toxicity is probably caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly among species.

Intraspecies: 3 was applied because perchloromethyl mercaptan is highly irritating and corrosive, and much of the toxicity is probably caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly among individuals; also supported by the steep dose-response curve, which may be an indication of little variation within a population.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Insufficient data

Time-scaling: $C^n \times t = k$, where n = 3 for extrapolation from longer to shorter durations and n = 1 for extrapolation from shorter to longer durations.

Data adequacy: The AEGL-3 value was based on a concentration not causing lethality and should be protective of human health.

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5

Phosphorus Oxychloride[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 have been defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million [ppm] or milligrams per cubic meter] mg/m^3]) of a substance at or above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-

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

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

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

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

Airborne concentrations below the AEGL-1 represent exposure levels that 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 AEGLs 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

Phosphorus oxychloride is a colorless fuming liquid with a pungent odor. It is stable to over 300°C but is highly reactive with water yielding phosphoric acid and hydrogen chloride. It is used in the manufacture of plasticizers, hydraulic fluids, gasoline additives, fire-retarding agents, and in the manufacture of alkyl and aryl orthophosphate trimesters.

Information regarding exposure of humans to phosphorus oxychloride are qualitative reports that indicate notable dermal, ocular, pharyngeal, and pulmonary irritation following acute and subchronic (intermittent) exposures. Most reports lacked exposure concentrations, with the exception of one report of occupational exposure to phosphorus oxychloride of 1.6-11.2 ppm. Effects often persisted after cessation of exposure, especially in individuals experiencing more severe effects. Neither odor detection data nor lethality data are available for humans.

Quantitative data in animals are limited to reports of lethality. These data include a 4-h LC_{50} (concentration lethal to 50% of test animals) of 44.4 ppm for rats and 52.5 ppm for guinea pigs, and an unverified 4-h LC_{50} of 32 ppm for rats. A 5-15 min exposure of rats and guinea pigs to phosphorus oxychloride at 0.96 ppm was stated to be a “threshold response” in one report. A brief report from industry indicated immediate adverse responses (at 2 min) and death (18 min) after exposure to a very high concentration (25,462 ppm). The studies affirm the extreme irritation properties of phosphorus oxychloride, although the exposures

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described also resulted in lethality. No information was available on reproductive and developmental toxicity, genotoxicity, or carcinogenicity.

There are no definitive data regarding the metabolism or precise mechanism of action of phosphorus oxychloride toxicity. On the basis of the available human and animal toxicity data and the chemical properties of phosphorus oxychloride, it was assumed that the primary effect is damage to mucosal surfaces and, for respiratory effects, subsequent pulmonary edema. The lethal potency of phosphorus oxychloride, however, does not appear to be explained simply by the action of its degradation products (phosphoric acid and hydrogen chloride).

AEGL-1 values were not derived for phosphorus oxychloride. No human or animal data relevant to the derivation of any AEGL-1 for phosphorus oxychloride were located.

AEGL-2 values were not derived for phosphorus oxychloride. No exposure-response data relevant to the derivation of any AEGL-2 were located. Estimating AEGL-2 values by a reduction in AEGL-3 values was considered tenuous and difficult to justify in the absence of such data.

AEGL-3 values were developed using an estimate of the lethality threshold on the basis of a 4-h LC_{50} of 48.4 ppm in rats (Weeks et al. 1964). Although exposure-response data were unavailable, the lethality threshold was estimated as one-third of the 4-h LC_{50} (48.4 ppm ÷ 3 = 16.1 ppm). This is also justified because many respiratory tract irritants have exposure-response relationships in which the transition from progressive irritation and repairable epithelial tissue damage to lethal pulmonary damage occurs abruptly. Because of uncertainties regarding species variability in the lethal response to phosphorus oxychloride and the lack of lethality data in humans, an order-of-magnitude uncertainty adjustment was applied for interspecies variability. Contact irritation resulting in damage to mucosal surfaces appears to be involved in the toxic response to phosphorus oxychloride. This response is probably a function of the extreme reactivity of phosphorus oxychloride and its dissociation products with tissues (especially pulmonary mucosal surfaces), and probably does not vary greatly among individuals. Therefore, the uncertainty adjustment selected for intraspecies variability was 3. A larger uncertainty factor would result in AEGL-3 values that are inconsistent with human data. The concentration exposure and 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. In the absence of an empirically-derived exponent (n), conservative and protective AEGL values were calculated by temporal scaling; n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points.

The AEGL values for phosphorus oxychloride are presented in Table 5-1. The range of interspecies variability remains uncertain because of sparse animal data and the lack of quantitative exposure-response data for humans. The lack of exposure-response data for nonlethal effects in animals or humans is a significant data deficiency.

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1. INTRODUCTION

Phosphorus oxychloride is a colorless, clear, fuming liquid with a musty, pungent odor. No odor threshold data are available. Phosphorus oxychloride is a chlorinating agent used in the manufacture of plasticizers, hydraulic fluids, gasoline additives, and fire retarding agents (O'Neil et al. 2001). It is also used extensively in the manufacture of alkyl and aryl orthophosphate triesters. The physicochemical data on phosphorus oxychloride are presented in Table 5-2. The chemical is stable to >300ºC but is highly reactive with water yielding phosphoric acid and hydrogen chloride. The decomposition reaction is:

$$POCl_3 + 3H_2O \rightarrow H_3PO_4 + 3HCl$$

TABLE 5-1 Summary of AEGL Values for Phosphorus Oxychloride[a]

Classification	10 min	30 min	1 h	4 h	8h	End Point (Reference)
AEGL-1 (Nondisabling)	Not recommended					
AEGL-2 (Disabling)	Not recommended					
AEGL-3 (Lethality	1.1 ppm (6.9 mg/m^3)	1.1 ppm (6.9 mg/m^3)	0.85 ppm (5.3 mg/m^3)	0.54 ppm (3.4 mg/m^3)	0.27 ppm (1.7 mg/m^3)	Estimate of lethality threshold in rats (16.1 ppm); 3-fold reduction in 4-h LC_{50} of 48.4 ppm (Weeks et al. 1964)

[a]Absence of AEGL-1 and AEGL-2 values does not imply that exposure below the AEGL-3 is without adverse effect.

TABLE 5-2 Chemical and Physical Data for Phosphorus Oxychloride

Parameter	Value	Reference
Synonyms	Phosphoryl chloride, phosphorus chloride, phosphorus oxytrichloride, trichlorophosphine oxide, trichlorophosphorus oxide	Fee et al. 1996; O'Neil et al. 2001; RTECS 2009
CAS registry number	10025-87-3	O'Neil et al. 2001
Chemical formula	$POCl_3$	O'Neil et al. 2001
Molecular weight	153.33	O'Neil et al. 2001
Physical state	Liquid	O'Neil et al. 2001
Melting point	1.25°C	O'Neil et al. 2001
Boiling point	105.8°C	O'Neil et al. 2001
Density	1.645 at 25°C	O'Neil et al. 2001
Solubility	Decomposes in water and alcohol	Fee et al. 1996
Vapor pressure	40 mmHg (27.3°C)	HSDB 2009
Conversion factors in air	1 ppm = 6.27 mg/m^3 1 mg/m^3 = 0.16 ppm	NIOSH 2005

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2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data were available regarding the acute lethality of phosphorus oxychloride in humans.

2.2. Nonlethal Toxicity

Most information on acute exposure of humans to phosphorus oxychloride is from secondary sources (ACGIH 1991; O'Neil et al. 2001). The following signs and symptoms were reported for acute exposures: headache, respiratory tract and eye irritation, chest pain, dyspnea, and nephritis. Chronic asthma-like conditions after acute exposure have also been reported (Sassi 1954; HSDB 2009). However, exposure-response data for these responses are lacking. Although there are no reports that provide quantitative data appropriate for AEGL development, they do affirm that the respiratory tract is a primary target for toxic responses following acute inhalation exposure to phosphorus oxychloride.

An accident involving an explosive release of phosphorus oxychloride, hydrogen chloride, oxalic acid, phosphorus pentachloride, and oxalyl chloride was reported by Rosenthal et al. (1978). Eight men and three women, ages 22-56 years, were exposed for approximately 30 sec to 2 min (the time required to escape from the contaminated area). The major signs and symptoms of exposure were wheezing, shortness of breath, conjunctivitis, and coughing. Nine people exhibited effects on ventilatory function; six recovered within a few days. In the other three individuals, disturbances in respiratory function returned to normal after 4 wk in one patient and 2.5 mo in the second, but persisted after 2 y in the third patient. The applicability of this report to AEGL development is questionable because of the lack of data on exposure concentrations and of concurrent exposure to other chemicals that have similar toxic effects.

Sassi (1954) described 20 cases of acute and subchronic occupational exposure in the manufacture of phosphorus oxychloride. Exposure concentrations varied from 10-20 mg/m^3 (1.6-3.2 ppm) for normal conditions to 70 mg/m^3 (11.2 ppm) for accidents. The signs and symptoms of acute exposures included irritation of the eyes and throat, dyspnea, dry cough, and bronchial stenosis (occurring several days after exposure). Long-term exposures resulted in more severe effects, including conditions characterized as asthmatic bronchitis and emphysema. Although concentrations for various exposure situations were provided in the report, there were no information on exposure durations.

Velsicol Chemical Corporation (1978) reported eye irritation in a worker exposed to phosphorus oxychloride. No information was provided on the concentrations to which the worker was exposed nor the severity of the irritation. The worker did, however, return to work; a 3-d "probable length of disability" was noted.

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A health hazard evaluation conducted by the National Institute of Occupational Safety and Health (NIOSH) of the FMC Corporation plant in Nitro, West Virginia, reported that workers with known repeated exposures to phosphorus oxychloride or phosphorus trichloride experienced a significantly higher ($p < 0.001$) prevalence (65%) of respiratory symptoms (chest tightness, wheezing, difficulty breathing) compared with unexposed workers (5%) (Tharr and Singal 1980). However, no correlation was found between results of pulmonary function tests on the workers and exposure to these chemicals. The study involved 37 exposed workers and 22 unexposed workers. Most air samples were below detection limits, although one employee (wearing a chlorine gas mask) was exposed to phosphorus oxychloride at approximately 4 mg/m^3 for about 25 min; no effects reported for this individual.

A follow-up study by NIOSH on 26 of the exposed workers and 11 of the unexposed workers at FMC Corporation reported that half of the exposed workers reported significantly ($p < 0.002$) more episodes of respiratory effects (wheezing, breathlessness, and chest tightness) compared to the unexposed workers who reported no such effects (Moody 1981). Results of pulmonary function tests did not reveal significant effects from exposure to phosphorus oxychloride (or phosphorus trichloride). No significant difference in pulmonary function (FEV_1) was found in the exposed workers compared with the unexposed workers over a 2-y period. The small sample size reduces the power of the study to detect such changes and, therefore, compromises the apparent negative finding. Additionally, it appeared that the pulmonary function tests were performed after the occurrence of the symptoms noted in the questionnaires completed by the workers.

On January 22, 1984, approximately 6,500 gallons of phosphorus oxychloride were released from a large storage tank at a chemical plant in Sauget, Illinois, as a result of an icicle shearing a pipe nipple off the tank (T. Hornshaw, Office of Chemical Safety, Illinois EPA, pers. communication, 2009). The plume affected seven employees, and moved into neighboring Rush City, Illinois. Thirty five citizens were treated at area hospitals, most from a neighborhood approximately one-half mile from the plant. The most common signs and symptoms were respiratory tract irritation and stomach pain. Five citizens were admitted overnight but none were in serious condition, and were later released. All of the affected employees were examined by a company physician and were cleared to resume work the same day. No measurements of airborne concentrations were taken.

2.3. Developmental and Reproductive Toxicity

No human developmental and reproductive toxicity data concerning phosphorus oxychloride were found.

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2.4. Genotoxicity

No human genotoxicity data on phosphorus oxychloride were found.

2.5. Carcinogenicity

No human data were found regarding the carcinogenic potential of phosphorus oxychloride.

2.7. Summary

Most information on the toxic response of humans to phosphorus oxychloride is from secondary reports that lack quantitative exposure-response data. The chemical appears to be extremely irritating to the respiratory tract and other mucous membranes. Both port-of-entry and systemic effects have been reported. Primary reports describe occupational exposures to phosphorus oxychloride, but they involve simultaneous exposures to other irritating chemicals (e.g., hydrogen chloride, oxalic acid, phosphorus pentachloride, oxalyl chloride) and lack information on exposure concentrations and durations. The reports affirm signs and symptoms of nasopharyngeal, ocular, and dermal irritation, and ventilatory dysfunction following acute exposures. Concurrent exposures to other chemicals, especially those having the same effects and targets as phosphorus oxychloride, compromise the usefulness of human exposure data for quantitative determination of AEGL values.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Quantitative data on the acute lethality of phosphorus oxychloride are from a single study in rats and guinea pigs, and an unverified 4-h LC_{50} value for rats.

3.1.1. Rats

Weeks et al. (1964) reported on the acute lethality of phosphorus oxychloride in female rats. The experimental protocol consisted of a group of 20 young adult female rats (strain not specified) exposed to phosphorus oxychloride (concentrations not provided) followed by a 14-d observation period. Another group of 20 rats was similarly exposed to phosphorus oxychloride and ammonia (for neutralization of hydrolysis products). The test vapors were generated by passing dried nitrogen through the liquid test article. The vapors were then mixed

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with influent air before being pumped into the chamber. Test article concentrations were determined by collection and weighing of material on a filter. These samples were also analyzed for phosphorus, nitrogen, and chloride. The test atmospheres were calculated as microgram of phosphorus per liter of air (µg/L) and as micromoles of phosphorus oxychloride per mole of air (µmole/mole). The latter expression assumed no hydrolysis of the test material (hydrolysis, however, was calculated to be about 15%). During exposure, rats exhibited signs of irritation (pawing and scratching of the nose and head) and had porphyrin secretions around the eyes. Gasping and convulsions preceded death which occurred within 48 h. No further details were provided regarding time of deaths. The 4-h LC_{50} for rats was reported as 48.4 µmole/mole (48.4 ppm). Neutralization with ammonia lowered the 4-h LC_{50} to 44.4 µmole/mole (44.4 ppm). Although simultaneous exposure to ammonia reduced or eliminated signs of irritation, it resulted in gross and microscopic pathologic findings (dark red lungs, desquamation of respiratory tract epithelium, and plugging of bronchial and bronchiolar lumens). The LC_{50} values do not necessarily imply that the test material was in a vapor from. In fact, it is probable that vapor and aerosol forms were present in the exposure atmosphere. With the exception of the median lethal concentration values, no other exposure-response data were provided.

In a study by Molodkina (1974), acute inhalation exposure of rats to lethal or near-lethal concentrations of phosphorus oxychloride resulted in immediate signs of irritation (rubbing of faces and restlessness). The rats exhibited inactivity and decreased respiration after 5-15 min, followed by convulsions. Rats that survived showed continued lacrimation and corneal opacities, and ulcers around the mouth several days after exposure ended. The report identified a "threshold concentration" of 0.006 mg/L (0.96 ppm) on the basis of "integrated characteristics." It is unclear as to what effect this threshold pertains or the precise nature of the "integrated characteristics." Information in this report affirms the irritation and lethal capacity of phosphorus oxychloride after acute inhalation exposure.

Details regarding a 4-h LC_{50} of 32 ppm for rats in a 1972 study (Marhold 1972 as cited in RTECS 2009) were unavailable for analysis and could not be verified.

The results of an inhalation study in rats were provided in a brief report by Monsanto (1991). Male Sprague-Dawley rats (number not specified) were exposed to phosphorus oxychloride at 159.7 mg/L (25,462 ppm) for 18 min. Conditions in the 35-L chamber were: 25°C, 85% humidity, and 4.0 L/min airflow. The concentration of the test material was such that there was a fog in the chamber. Within 2 min the rats were having difficulty breathing and their eyes were closed. After 10 min, weakness, convulsions, and collapse were observed, and one rat died. All rats were dead after 18 min. Necropsy revealed lung congestion. No further details were provided.

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3.1.2. Guinea pigs

Weeks et al. (1964) conducted experiments using groups of 10 male guinea pigs. The experimental protocol was the same as that described for the experiments with rats. The response of the guinea pigs was consistent with exposure to an irritating chemical (restlessness, lacrimation, pawing at nose and head). The 4-h LC_{50} was 52.5 μmole/mole (52.5 ppm). Deaths occurred within 48 h after exposure; no further details were provided. Neutralization of the phosphorus oxychloride with ammonia resulted in a lowering of the LC_{50} to 41.3 μ mole/mole (41.3 ppm). As in the study with rats, simultaneous exposure of the guinea pigs to ammonia appeared to decrease the irritation responses to the phosphorus oxychloride but increase overall toxicity. The series of exposures and the respective responses used to obtain the median lethal concentration were not provided and, therefore, no other exposure-response data are available.

The previously discussed (Section 3.1.1) study by Molodkina (1974) also examined the response of guinea pigs to acute inhalation of phosphorus oxychloride. Lacrimation and corneal opacities were reported for animals after acute exposure to lethal or near lethal concentrations. No other details were reported.

3.2. Nonlethal Toxicity

Definitive exposure-response data for nonlethal toxicity in animals were not available. Weeks et al. (1964) and Molodkina (1974) reported that acute inhalation of phosphorus oxychloride (for up to 4 h) by rats and guinea pigs resulted in severe irritation (rubbing of face, lacrimation, porphyrin secretions, desquamation of pulmonary epithelium), but the precise concentrations and exposure durations were not provided. The only exposure-duration data provided were median lethality values. Thus, it is difficult to determine concentrations of phosphorus oxychloride that might cause nonlethal responses without potential for lethality.

3.3. Developmental and Reproductive Toxicity

No animal developmental and reproductive toxicity data concerning phosphorus oxychloride were found.

3.4. Genotoxicity

No animal genotoxicity data on phosphorus oxychloride were found.

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3.5. Carcinogenicity

No animal data were found regarding the carcinogenic potential of phosphorus oxychloride.

3.6. Summary

Quantitative exposure-response toxicity data in animals were from lethality studies rats and guinea pigs (Table 5-3). A report by Weeks et al. (1964) provided an adequate description of the experimental protocol and 4-h LC_{50} value for rats (44.4 ppm) and guinea pigs (52.5 ppm). A study by Molodkina (1974) also examined the toxic response of rats and guinea pigs to inhaled phosphorus oxychloride; exposure to phosphorus oxychloride at 0.96 ppm for 5-15 min was considered a threshold response. However, the characteristics of the responses or what constituted the "threshold" were not provided. A brief report from Monsanto (1991) showed immediate adverse responses (after 2 min) and death (after 18 min) after exposure to phosphorus oxychloride of 25,462 ppm. Acute lethality values from a secondary source could not be verified. The available studies affirm the extreme irritation properties of phosphorus oxychloride, although the exposure concentrations described also resulted in lethality. No information was available regarding reproductive and developmental toxicity, genotoxicity, or carcinogenicity.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No data on the metabolism and disposition of phosphorus oxychloride were found.

TABLE 5-3 Acute Lethality of Phosphorus Oxychloride in Laboratory Animals

Species	Lethality Value	Reference
Rat	4-h LC_{50} = 48.4 ppm	Weeks et al. 1964
Rat	4-h LC_{50} = 32 ppm (not verified)	Marhold 1972 as cited in RTECS 2009
Rat	100% lethality = 25,462 ppm after 18 min	Monsanto 1991
Guinea pig	4-h LC_{50} = 52.5 ppm	Weeks et al. 1964

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4.2. Mechanism of Toxicity

The precise mechanism of toxicity of inhaled phosphorus oxychloride has not been elucidated. The irritant properties of phosphorus oxychloride might be from its decomposition products, phosphoric acid and hydrogen chloride. However, the acute lethality of phosphorus oxychloride appears to be greater than from the decomposition products alone. For example, the 1-h LC_{50} values for phosphoric acid and hydrochloric acid in rats are >212 ppm and 3,124 ppm, respectively, whereas the 1-h LC_{50} for phosphorus oxychloride is 76 ppm (estimated by temporal extrapolation from 4-h data). Although the acute lethality of inhaled phosphorus oxychloride probably results from damage to the respiratory epithelium and pulmonary edema, the role of delivery to this target tissue remains uncertain. Exposure to phosphorus oxychloride might allow the formation of larger concentrations of phosphoric acid and hydrochloric acid in the lungs than would be possible from exposures to each of the chemicals alone. This would cause greater damage and explain, in part, the greater toxicity of phosphorus oxychloride.

4.3. Structure-Activity Relationships

Barbee et al. (1995) conducted an acute toxicity study in which groups of 10 rats were exposed to oxalyl chloride $(COCl)_2$ at 0, 462, 866, 1,232, 1,694, or 2,233 ppm for 1 hr. The 1-h LC_{50} was 1,840 ppm. The acute lethality of oxalyl chloride was similar to that of hydrogen chloride, but oxalyl chloride was much less toxic than phosphorus oxychloride. Because the toxicity of phosphorus oxychloride appears to be greater than that of hydrogen chloride, it is unlikely that the mechanisms of toxicity for the two chemicals are the same. Thus, the development of AEGL values on the basis of analogy to hydrogen chloride production alone might underestimate the toxic potential of phosphorus oxychloride.

Phosphorus trichloride produces many of the same signs and symptoms as phosphorus oxychloride after acute inhalation exposures (Weeks et al. 1964; ACGIH 1991) and also undergoes rapid hydrolysis to hydrogen chloride and phosphonic acid. Data from rats and guinea pigs (Weeks et al. 1964) suggest that the lethal potency of phosphorus oxychloride might be similar to that of phosphorus trichloride. The rat 4-h LC_{50} values for both chemicals are approximately 50 ppm which supports the contention that they have similar toxicity. Information on human exposures to phosphorus trichloride verify a potential for irritation of the respiratory tract, nasopharyngeal region, eyes, and skin, and effects on ventilatory function (Wason et al. 1982, 1984). These human exposure reports provide qualitative information on the toxic response to the chemical, but lack measurements of exposure.

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4.4. Other Relevant Information

4.4.1. Species Variability

Data are insufficient to reliably describe species variations in toxic responses to inhaled phosphorus oxychloride. Rats and guinea pigs appeared to respond similarly in a study by Weeks et al. (1964) and on the basis of an unverified LC_{50} in rats (RTECS 2009).

4.4.2. Concurrent Exposure Issues

No concurrent exposure issues of special concern have been identified that would directly affect the derivation of AEGL values for phosphorus oxychloride. Simultaneous exposure to other irritating or corrosive chemicals would necessitate adjustments in emergency response planning for potential exposures to phosphorus oxychloride.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

Quantitative exposure-response data in humans are not available for development of AEGL-1 values for phosphorus oxychloride. Information on the human experience is based on qualitative descriptions of signs and symptoms of acute exposure. Although exposure concentrations were not provided, the available reports indicate that very short exposures might result in notable respiratory, ocular, and dermal irritation. There is evidence that respiratory effects might persist for an extended period after exposure is ceased.

5.2. Summary of Animal Data Relevant to AEGL-1

Data are not available on responses in animals that would be consistent with AEGL-1 effects.

5.3. Derivation of AEGL-1

Exposure-response data were not available for developing AEGL-1 values for phosphorus oxychloride (Table 5-4).

TABLE 5-4 AEGL-1 Values for Phosphorus Oxychloride

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

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6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Quantitative exposure-response data in humans are not available for development of AEGL-2 values for phosphorus oxychloride. Information regarding the human experience is based on qualitative and semi-quantitative information regarding signs and symptoms (respiratory tract irritation that might persist for extended periods and ocular and dermal irritation) of exposed individuals. The information in these reports suggest very brief exposure to phosphorus oxychloride at low concentrations (1.6-3.2 ppm) might cause irritation severe enough to impair egress from a contaminated area. Additionally, data from animal studies suggest that acute exposure to phosphorus oxychloride might cause contact irritation damage (e.g., corneal opacities) that could be irreversible. However, definitive exposure concentration and duration measurements were lacking for these animal studies, thereby preventing exposure-response assessments for AEGL-2 development.

6.2. Summary of Animal Data Relevant to AEGL-2

Animal data on effect severity consistent with AEGL-2 were based on qualitative descriptions of responses in animals exposed to lethal or near-lethal concentrations. Signs of exposure in these studies were consistent with extreme irritation of the eyes, nasopharyngeal region, and the respiratory tract. However, exposure concentration data and exposure duration data were not available.

6.3. Derivation of AEGL-2

Exposure-response data were not available for developing AEGL-2 values for phosphorus oxychloride (Table 5-5). The lack of information regarding the exposure-response relationship makes estimating AEGL-2 values by reducing AEGL-3 values difficult to justify.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

Information is not available regarding lethality in humans exposed to phosphorus oxychloride.

TABLE 5-5 AEGL-2 Values for Phosphorus Oxychloride

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

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7.2. Summary of Animal Data Relevant to AEGL-3

Lethality data are based on 4-h LC_{50} values for rats and guinea pigs. Two 4-h LC_{50} values are available for rats: 48.4 ppm (Weeks et al. 1964) and 32 ppm (Marhold 1972 as cited in RTECS 2009, unverifiable). A single 4-h LC_{50} for guinea pigs is 52.5 ppm (Weeks et al. 1964). The range of exposure used to determine these median lethal concentrations, however, were not reported. Therefore, it is not possible to assess the exposure-response relationship. The available data suggest that species variability in the lethal response to phosphorus oxychloride is not great. However, there is still uncertainty regarding the range of susceptibility among species because data are available from only one well described study on two species.

7.3. Derivation of AEGL-3

In lieu of additional data, the available 4-h LC_{50} values may be considered for developing AEGL-3 values for phosphorus oxychloride. Because the rat appears to be a slightly more sensitive species than the guinea pig, the 4-h LC_{50} of 48.4 ppm identified by Weeks et al. (1964) was used as the basis for the AEGL-3 values. The 32-ppm value reported in RTECS (2009) was not verified and, therefore, was not used.

In the absence of complete data regarding the exposure-response curve and assuming that the difference between nonlethal and lethal exposures is small, the lethality threshold was estimated to be one-third of the 4-h rat LC_{50} (48.4 ppm/3 = 16.1 ppm). This extrapolation is also justified because many respiratory tract irritants have exposure-response relationships in which the transition from progressive irritation and repairable epithelial tissue damage to lethal pulmonary damage occurs abruptly. A total uncertainty factor of 30 (10 for interspecies variability and 3 for intraspecies variability) was used. The interspecies uncertainty factor of 10 was maintained because there are data on only two species (a single 4-h LC_{50} each for rats and guinea pigs) and no lethality data in humans. Additionally, the study by Weeks et al. (1964) showed rats to be notably more sensitive to phosphorus oxychloride (4-h LC_{50} of 48.4 ppm) than to phosphorus trichloride (4-h LC_{50} of 104. 3 ppm). Although signs of exposure in humans are qualitatively similar to those observed in laboratory animals, there are no quantitative exposure-response data in humans. An intraspecies uncertainty factor of 3 was selected because a critical mechanism of phosphorus oxychloride toxicity appears to involve irritation and destruction of pulmonary mucosal surfaces; lethality resulting, at least in part, from damage to respiratory tract epithelium. It is assumed that a basic contact irritation mechanism would not vary greatly among individuals and that a 3-fold reduction would be sufficient to protect individuals with moderately compromised respiratory function. Further reduction of the AEGL-3 values by a greater uncertainty factor would result in values inconsistent with occupational exposures reported by Sassi

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(1954), where repeated exposures to concentrations up to 3.2 ppm resulted in irritation and minor respiratory difficulties but not death. There are no data available to determine a time-scaling factor. The concentration-exposure-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived exponent (n), and to obtain conservative and protective AEGL values, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points. Because of uncertainties in extrapolating a 4-h exposure to a 10-min exposure, the 10-min AEGL-3 is set equivalent to the 30-min AEGL-3 rather than using exponential scaling. The derivation of AEGL-3 values is shown in Appendix A and the resulting values are summarized in Table 5-6.

8. SUMMARY OF PROPOSED AEGLS

8.1. AEGL Values and Toxicity Endpoints

The available toxicity data for phosphorus oxychloride indicate that irritation of the skin, eyes, nose, and respiratory tract are the most notable and often reported signs of toxicity. Although these end points relevant to AEGL-1 and AEGL-2 values, quantitative exposure-response data are lacking for development of these values. Quantitative data on lethality in animals were available and were considered appropriate for the basis of AEGL-3 development. The data were, however, limited to a single study and two species.

8.2. Comparison with Other Standards and Guidelines

The World Health Organization (WHO 1989) reported that exposure guidelines for phosphorus oxychloride range from 0.05-3 mg/m^3 (0.008-0.48 ppm) in different countries. Standards and criteria for phosphorus oxychloride are presented in Table 5-7.

8.3. Data Quality and Research Needs

Although qualitative data are available regarding the acute inhalation toxicity of phosphorus oxychloride in humans, quantitative exposure-response data are lacking. Animal data include one study reporting LC_{50} values in rats and guinea pigs. The animal data were sufficient for developing AEGL-3 values. However, there are no data pertaining to the nonlethal responses in animals following inhalation exposure to phosphorus oxychloride. There are also insufficient data for determining the range of susceptibility among different species or between the test animal species and humans.

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TABLE 5-6 AEGL-3 Values for Phosphorus Oxychloride

10 min	30 min	1 h	4 h	8h
1.1 ppm	1.1 ppm	0.85 ppm	0.54 ppm	0.27 ppm

TABLE 5-7 Standards and Guidelines for Phosphorus Oxychloride

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	Not recommended				
AEGL-2	Not recommended				
AEGL-3	1.1 ppm	1.1 ppm	0.85 ppm	0.54 ppm	0.27 ppm
TLV-TWA (ACGIH)[a]					0.1 ppm
REL-TWA (NIOSH)[b]					0.1 ppm
REL-STEL (NIOSH)[c]	0. 5 ppm (15 min)				
MAK Spitzenbegrenzung (Germany)[d]					1.33 mg/m^3 (0.2 ppm)
MAC (The Netherlands)[e]					0.6 mg/m^3 (0.1 ppm)

[a]TLV-TWA (Threshold Limit Value-time-weighted average of the American Conference of Governmental Industrial Hygienists) (ACGIH 2003) is the time-weighted average concentration for a normal 8-h workday and a 40-h work week to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.
[b]REL-TWA (recommended exposure limits-time-weighted average, National Institute for Occupational Safety and Health) (NIOSH 2005) is analogous to the ACGIH-TLV-TWA.
[c]REL-STEL (recommended exposure limits-short-term exposure limit, National Institute for Occupational Safety and Health) (NIOSH 2005) is analogous to the ACGIH-TLV-STEL.
[d]MAK Spitzenbegrenzung (Kategorie II,2) [maximum workplace concentration (peak limit category II,2)] (DFG 2002) 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.
[e]MAC (maximaal aanvaarde concentratie [maximum accepted concentration]), Dutch Expert Committee for Occupational Standards, The Netherlands (MSZW 2004) is analogous to the ACGIH-TLV-TWA.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR PHOSPHORUS OXYCHLORIDE

Derivation of AEGL-1

AEGL-1 values are not recommended because insufficient data. Absence of AEGL-1 values does not imply that exposure below the AEGL-3 values are without adverse effects.

Derivation of AEGL-2

AEGL-2 values are not recommended because of insufficient data. Absence of AEGL-2 values does not imply that exposure below the AEGL-3 values are without serious or possibly irreversible adverse effects.

Derivation of AEGL-3

Key study:	Weeks et al. 1964
Toxicity end point:	Lethality threshold of 16.1 ppm in rats, estimated by 3-fold reduction in 4-h LC_{50} of 48.4 ppm.
Scaling:	$C^n \times t = k$ (n = 3 for extrapolating from longer to shorter exposure periods and n = 1 for extrapolating from shorter to longer exposure periods) $(16.1 \text{ ppm})^1 \times 4 \text{ h} = 64.4 \text{ ppm-h}$ $(16.1 \text{ ppm})^3 \times 4 \text{ h} = 16{,}693.12 \text{ ppm-h}$
Uncertainty factors:	10 for interspecies variability 3 for intraspecies variability
10-min AEGL-3	1.1 ppm, set equal to the 30-min AEGL-3
30-min AEGL-3	$C^3 \times 0.5 \text{ h} = 16{,}693.12 \text{ ppm-h}$ $C = 32.2 \text{ ppm}$ 30-min AEGL-3 = 32.2 ppm/30 = 1.1 ppm
1-h AEGL-3	$C^3 \times 1 \text{ h} = 16{,}693.12 \text{ ppm-h}$ $C = 25.56 \text{ ppm}$ 1-h AEGL-3 = 25.56 ppm/30 = 0.85 ppm

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4-h AEGL-3	$C^3 \times 4$ h = 16,693.12 ppm-h C = 16.1 ppm 4-h AEGL-3 = 16.1 ppm/30 = 0.54 ppm
8-h AEGL-3	$C^1 \times 8$ h = 64.4 ppm-h C = 8.05 ppm 8-h AEGL-3 = 8.05 ppm/30 = 0.27 ppm

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APPENDIX B

ACUTE EXPOSURE GUIDELINES FOR PHOSPHORUS OXYCHLORIDE

Derivation Summary for Phosphorus Oxychloride

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Reference: Not applicable				
Test Species/Strain/Number: Not applicable				
Exposure Route/Concentrations/Durations: Not applicable				
Toxicity End Point: Not applicable				
Time Scaling: Not applicable				
Concentration/Time Selection/Rationale: Not applicable				
Uncertainty Factors/Rationale: Not applicable				
Modifying Factor: Not applicable				
Animal to Human Dosimetric Adjustments: Not applicable				
Data Adequacy: Neither quantitative exposure-response data nor odor threshold data were available for assessing AEGL-1 type effects for phosphorus oxychloride. Therefore, AEGL-1 values are not recommended. The absence of AEGL-1 values does not imply that exposure below AEGL-3 levels is without effect.				

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Reference: Not applicable				
Test Species/Strain/Number: Not applicable				
Exposure Route/Concentrations/Durations: Not applicable				
Toxicity End Point: Not applicable				
Time Scaling: Not applicable				
Concentration/Time Selection/Rationale: Not applicable				
Uncertainty Factors/Rationale: Not applicable				
Modifying Factor: Not applicable				
Animal to Human Dosimetric Adjustments: Not applicable				

(Continued)

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AEGL-2 VALUES Continued

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

Data adequacy: Exposure-response data on nonlethal toxic responses were not available for developing AEGL-2 values for phosphorus oxychloride. The absence of such data precludes estimating AEGL-2 values by reducing AEGL-3 values. Therefore, AEGL-2 values are not recommended. The absence of AEGL-2 values does not imply that exposure below AEGL-3 levels is without serious or possibly irreversible effect.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
1.1 ppm	1.1 ppm	0.85 ppm	0.54 ppm	0.27 ppm

Reference: Weeks, M.H., N.P. Mussleman, P.P. Yevich, K.H. Jacobson, and F.W. Oberst. 1964. Acute vapor toxicity of phosphorus oxychloride, phosphorus trichloride and methyl phosphonic dichloride. Am. Ind. Hyg. Assoc. J. 25:470-475.

Test Species/Strain/Number: Rats (strain not specified)/20 per group

Exposure Route/Concentrations/Durations: Inhalation/concentrations varied but not specified/4 h

Toxicity End Point: 4-h LC_{50} (48.4 ppm) for guinea pigs

Time Scaling: $C^n \times t = k$, n = 3 for extrapolating from longer to shorter exposure periods and n = 1 for extrapolating from shorter to longer exposure periods

Concentration/Time Selection/Rationale: A 3-fold reduction of 4-h LC_{50} (48.4 ppm/ 3 = 16.1 ppm) for rats (the more sensitive species) was considered an estimate of the lethality threshold

Uncertainty Factors/Rationale:
Total Uncertainty: 30
Interspecies: 10
Intraspecies: 3 was considered sufficient because the primary mechanism of action involves a direct effect on respiratory epithelium which is unlikely to vary greatly among individuals. The factor also is considered to be adequate for the protection of individuals with moderately compromised respiratory function. Additional reduction of the AEGL-3 values by a greater uncertainty factor would result in AEGL-3 values that are inconsistent with occupational data and other guidelines.

Modifying Factor: None applied

Animal-to-Human Dosimetric Adjustments: Insufficient data

Data Adequacy: LC_{50} values available for only two species. These data were considered sufficient for developing AEGL-3 values. Interspecies variability remains uncertain because of the lack of data in additional species and definitive exposure data in humans.

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APPENDIX C

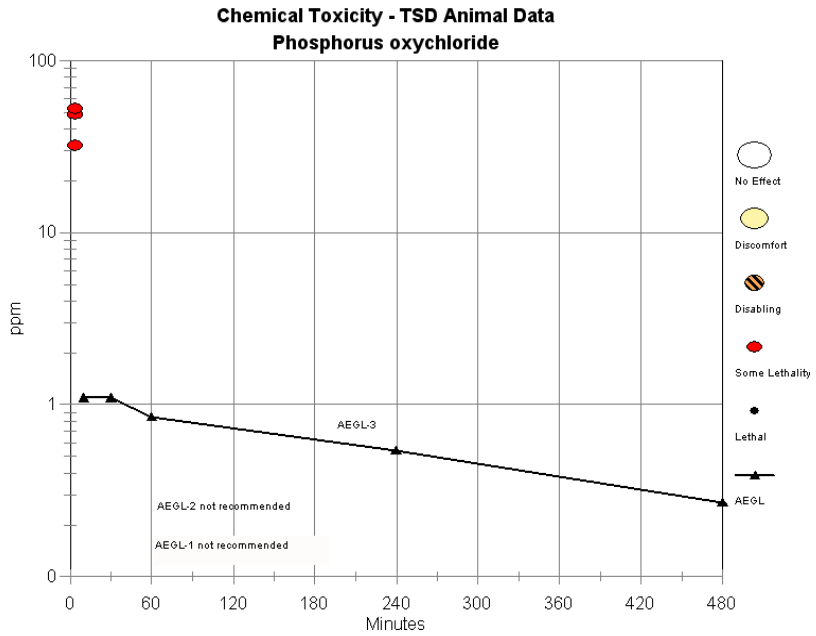

FIGURE 5-1 Category plot for phosphorus oxychloride.

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6

Phosphorus Trichloride[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) and Tom Hornshaw (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee concludes 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).

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effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

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

SUMMARY

Phosphorus trichloride (CAS no. 007719-12-2) is a colorless, clear fuming liquid with a pungent, irritating odor. In the presence of water, the chemical decomposes rapidly in a highly exothermic reaction to phosphonic acid, or hydrogen chloride, and pyrophosphonic acids. The primary use of phosphorus trichloride is for the production of phosphonic acid which, in turn, is used in the production of glyphosphate herbicides. Annual domestic production of 294,000 tons has been reported.

No acute lethality data on humans are available. Qualitative data regarding human exposures indicate signs and symptoms of exposure consistent with a highly irritating chemical; ocular and dermal irritation, respiratory tract irritation, shortness of breath, and nausea.

Lethality data are available for rats, cats, and guinea pigs. Cursory studies conducted nearly 100 years ago in Germany provided preliminary data on lethal and nonlethal effects in cats and guinea pigs following various treatment regimens with inhaled phosphorus trichloride. Although results of the studies indicated the respiratory tract to be a critical target, the methods and results of these studies were not verifiable. Weeks et al. (1964) reported 4-h LC_{50} values of 104.5 ppm and 50.1 ppm for rats and guinea pigs, respectively. An unpublished study by Hazleton Laboratories (1983) identified a no-observed-adverse-effect level (NOAEL) of 3.4 ppm and a lowest-observed-adverse-effect level (LOAEL

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(histopathologic changes in the respiratory tract) of 11 ppm following repeated exposure (6 h/day, 5 days/week for 4 weeks) of rats. There are no data regarding reproductive and developmental toxicity, genotoxicity, or carcinogenicity of phosphorus trichloride. Definitive data regarding the mechanism of action of phosphorus trichloride are unavailable. Decomposition products (hydrogen chloride, phosphonic acid, and pyrophosphonic acids) are responsible, at least in part, for the contact irritation reported by humans, and the irritation and tissue damage observed in animal species.

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. Due to the limited toxicity data for this chemical, an empirical derivation of n was not possible. In the absence of an empirically derived exponent (n), and to obtain conservative and protective AEGL values, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation. Because phosphorus trichloride is a contact irritant, minor irritation effects are not expected to vary with exposure duration (NRC 2001). Therefore, all AEGL-1 values were set at 0.34 ppm (the 3.4 ppm point-of departure adjusted by a total uncertainty factor of 10). The 10-min AEGL-3 values were set equivalent to the 30-min values due to uncertainties in extrapolating from the experimental exposure durations of 4 h and greater.

Quantitative data consistent with AEGL-1 effects were unavailable. Occupational exposures of humans to 1.8-3.6 ppm for 2-6 h (Sassi 1952) and exposure of rats to 3.4 ppm for 6 h/day, 5 days/week for 4 weeks (Hazleton Laboratories 1983) were without notable effect. The occupational exposure data lacked details regarding pairing of the exposure durations (weeks to months) to exposure concentrations. The 3.4 ppm exposure of rats data was considered a NOAEL for AEGL-1 effects. These data as well as the AEGL-1 values are supported by the human experience. The interspecies uncertainty factor was limited to 3 because of the concordance of the animal data with the human experience and because the most sensitive species tested (guinea pig) was only about 2-fold more sensitive. The intraspecies uncertainty factor was limited to 3 because primary effects of phosphorus trichloride (irritation and subsequent tissue damage) appear to be due, in part, to hydrogen chloride and phosphonic acid resulting from chemical dissociation. Additional reduction of the AEGL-1 values would be inconsistent with available human and animal data.

Information consistent with AEGL-2 effects was limited to an occupational exposure report and a multiple exposure study with rats. For occupational exposures, there was notable irritation following 2-6 h of exposure to approximately 14-27 ppm phosphorus trichloride and more severe but reversible irritation following exposures of 1-8 weeks. Reports providing qualitative information but no exposure terms affirmed the potential for respiratory tract irritation following acute exposures to phosphorus trichloride. Data for rats showed upper respiratory tract involvement following multiple exposures (over 4 weeks) to 11 ppm but not to 3.4 ppm (Hazleton Laboratories 1983). For development of

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AEGL-2 values, the 11 ppm exposure in rats was considered a NOAEL for AEGL-2 effects. Uncertainty factor application was the same as for the AEGL-1 tier.

AEGL-3 values were developed based upon a 3-fold reduction of the 4-h LC_{50} (Weeks et al. 1964) as an estimate of the lethality threshold (104.3 ppm/3 = 34.8 ppm). A total uncertainty factor adjustment of 10 was used to develop the AEGL-3 values. Animal data indicated some variability in the toxic response to phosphorus trichloride with guinea pigs being the more sensitive among the species tested but only about 2-fold compared to the rat. Additionally, further reduction of the AEGL-3 values did not appear warranted based upon the human occupational exposure data. Therefore, uncertainty adjustment regarding interspecies variability was limited to 3. To account for intraspecies variability, a factor of 3 was applied. The uncertainty of intraspecies variability was limited to 3 because primary effects of phosphorus trichloride (irritation and subsequent tissue damage) appear to be due, in part, to hydrogen chloride and phosphonic acid resulting from chemical dissociation. Additionally, these products would likely affect all mucosal surfaces in a similar manner and would do so independent of metabolism processes. The total uncertainty factor of 10 may be justified by human exposure data showing that repeated 2 to 6-h exposures of up to 27 ppm were without life-threatening consequences. Furthermore, the results of the Hazleton Laboratories (1983) study showed no fatalities in rats following multiple 6-h exposures to 11 ppm. The AEGL values for phosphorus trichloride are presented in Table 6-1.

TABLE 6-1 Proposed AEGL Values for Phosphorus Trichloride

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (Nondisabling)	0.34 ppm	0.34 ppm	00.34 ppm	0.34 ppm	0.34 ppm	NOAEL of 3.4 ppm in rats exposed 6 h/day, 5 days/week for 4 weeks; no time scaling for irritant (Hazleton Laboratories 1983)
AEGL-2 (Disabling)	2.5 ppm	2.5 ppm	2.0 ppm	1.3 ppm	0.83 ppm	NOAEL for AEGL-2 tier effects; based upon respiratory tract histopathology in rats exposed 6 h/day, 5 days/week for 4 weeks (Hazleton Laboratories 1983)
AEGL-3 (Lethal)	7.0 ppm	7.0 ppm	5.6 ppm	3.5 ppm	1.8 ppm	Estimated lethality threshold based upon 3-fold reduction of rat 4-h LC_{50} (104.3 ppm/3 = 34.8 ppm) (Weeks et al. 1964)[a]

[a]Based upon animal data, lethality may be delayed.

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1. INTRODUCTION

Phosphorus trichloride (CAS No. 007719-12-2) is a colorless, clear, fuming liquid with a pungent, irritating odor (Fee et al. 1996). Odor threshold information is unavailable for this chemical. Domestic production of approximately 294,000 tons has been reported (SRI 1992). The primary use of phosphorus trichloride is for the production of phosphonic acid which, in turn, is used in the production of the herbicide, glyophosphate. Phosphorus trichloride decomposes rapidly in water in highly exothermic reactions. It may also decompose in moist air to hydrochloric acid and hydrated phosphoric acid. The reaction products include phosphonic acid, hydrogen chloride, or pyrophosphonic acids, depending on the mole ratio of water and phosphorus trichloride (Fee et al. 1996). If the mole ratio of water and phosphorus trichloride is greater than 3, the following reaction will occur.

The chemical and physical data on phosphorus trichloride are presented in Table 6-2.

$$PCl_3 + 3\ H_2O \rightarrow H_3PO_3 + 3\ HCl$$

If the mole ratio is 2.5 to 3, reaction products will be a mixture of phosphonic acid and pyrophosphonic acids.

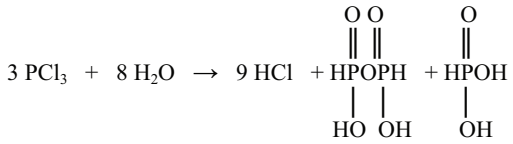

TABLE 6-2 Chemical and Physical Data for Phosphorus Trichloride

Synonyms	Phosphorus chloride, trichlorophosphine	Fee et al. 1996; NIOSH 2005 RTECS 2009
CAS Registry No.	007719-12-2	O'Neil et al. 2001
Chemical formula	PCl_3	O'Neil et al. 2001
Molecular weight	137.33	O'Neil et al. 2001
Physical state	Liquid	O'Neil et al. 2001
Boiling and melting point	76°C/-112°C	O'Neil et al. 2001
Density	1.574	O'Neil et al. 2001
Solubility	Decomposes in water and alcohol	Fee et al. 1996
Vapor pressure	100 mm Hg at 21°C	ACGIH 1991
Conversion factors in air	1 ppm = 5.6 mg/m^3 1 mg/m^3 = 0.18 ppm	Beliles and Beliles 1993

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2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No acute lethality exposure-response data or case reports are currently available.

2.2. Nonlethal Toxicity

Sassi (1952) summarized twenty cases of acute (2-6 h) or "subacute" (1-8 weeks of work) exposures of workers to phosphorus trichloride. The concentration of phosphorus trichloride in the workrooms ranged from 10-20 mg/m^3 (~1.8-3.6 ppm) under normal conditions to 80-150 mg/m^3 (~14-27 ppm) during periods when the plant was "out of order." The method by which the concentrations were determined was not stated in the translated abstract. For the acute exposures, workers experienced a burning sensation in the eyes and throat, photophobia, chest tightness, dry cough, and slight bronchitis which occurred within 2-6 h of exposure. It is unclear, however, if the reported symptoms were associated with the "out of order" condition or were also present to some extent during "normal" operation. For the "subacute" exposures, pharyngeal irritation, coughing, catarrh, dyspnea, and asthmatic bronchitis occurred at 1-8 weeks of exposure. Slight increases in body temperature and moderate leucocytosis with neutrophilia were also reported for both exposures. Signs and symptoms reportedly resolved in 3 to 6 days for the acute exposures and 10-15 days for the subacute exposures.

An abstract by Wason et al. (1982) provided information on an assessment of 27 individuals exposed to phosphorus trichloride released in a railroad accident in 1980. The report indicated that the phosphorus trichloride reacted with water used to disperse the spillage and with air moisture that resulted in the release of phosphoric and hydrochloric acids and phosphorus oxides. No information was provided regarding weather conditions (e.g., wind, temperature, humidity) at the time of the accident. Signs and symptoms were characteristic of exposure to irritants and included burning eyes (86%), shortness of breath (59%), throat irritation (59%), lacrimation (59%), headache (48%), nausea (48%), burning sensation on the skin (44%), and sputum production (41%). Additional effects occurring in 33% or less of the patients included chest pains, wheezing, skin rash, blurred vision, vomiting, and abdominal pain. Lactate dehydrogenase was mildly elevated and serum bilirubin and/or serum transaminases were elevated in three individuals. Results of pulmonary function tests showed greater severity of effect with decreasing distance from the release site. At 2 months, 86% of the individuals who were within 1/16 mile were hypoxemic while only 50% of those 1/16 to 1/8 mile distance were hypoxemic. There were no exposure durations provided (probably >1.5 h as described below) and no exposure concentrations were measured or estimated.

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Wason et al. (1984) reported in more detail on the railroad accident involving spillage of phosphorus trichloride. The report focused on 17 individuals (16 men and one woman, ages 21-59 years), seven of whom were requested to return for follow-up study after the initial medical examination. Signs and symptoms of exposure included eye, skin and throat irritation, nausea, vomiting, blurred vision, headache, and various effects associated with respiration and ventilation (e.g., wheezing, cough, chest pain, dyspnea, sputum production). Chest x-rays of all subjects were normal and there was no evidence of hepatic toxicity. Spirometry tests revealed that the subjects (10 of 17) who were closest (within 110 yards) to the accident site had a significant decrease in vital capacity, maximal breathing capacity, FEV_1, and maximal ventilatory flow rate at 25% of vital capacity. An improvement in the ventilatory changes was seen 1 month later. Subjects closer to the release site appeared to exhibit signs and symptoms of greater severity. It was also found that patients that were exposed for less than 1 h and 30 min had significantly ($p = 0.02$) greater maximal expiratory flow rates at 25% of vital capacity than did those individuals exposed for longer periods. Water was used to disperse the spilled phosphorus trichloride and, as noted in the report, the actual exposure most likely involved phosphoric acid and hydrochloric acid more so than phosphorus trichloride. Eight subjects were exposed for less than 1 h and 30 min and nine were exposed longer (duration not specified). Pulmonary function tests in the seven follow-up patients 1 month after the accident revealed significant improvements in vital capacity, FEV_1, peak expiratory flow rate, and maximal expiratory flow rate at 50% vital capacity. Although this report provides information regarding the nonlethal effects in humans following exposure to phosphorus trichloride, there were no data on the exposure concentrations and it is uncertain as to the precise chemicals (i.e., phosphorus trichloride and/or its degradation products) to which the people were exposed.

A NIOSH health hazard evaluation of workers at the FMC plant in Nitro, West Virginia revealed that those with known repeated exposures to phosphorus oxychloride and/or phosphorus trichloride experienced a significantly higher ($p < 0.001$) prevalence (65%) of occasional respiratory symptoms (chest tightness, wheezing, difficulty breathing) compared to unexposed workers (5%) (Tharr and Singal 1980). However, no correlation was found between results of pulmonary function tests on the workers and exposure to these chemicals. The study utilized 37 exposed workers and 22 unexposed workers. Most air samples were below detection limits although one employee (with respiratory protection of a chlorine gas mask) was exposed to 6 mg phosphorus trichloride/m^3 (1 ppm) for 1 h during a truck-loading operation (no effects were reported for this individual).

A follow-up study conducted by NIOSH on 26 of the exposed workers and 11 of the unexposed workers from the aforementioned FMC Corp. group revealed that half of the exposed workers reported significantly ($p < 0.002$) more episodes of respiratory effects (wheezing, breathlessness, and chest tightness) compared to the unexposed workers who reported no such effects (Moody

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1981). Results of pulmonary function tests did not reveal significant findings regarding effects of phosphorus trichloride (or phosphorus oxychloride) exposure. No significant difference in pulmonary function (FEV_1) was found in the exposed workers vs. the unexposed workers over a 2-year period. The small sample size, however, reduces the power of the study to detect such changes.

Although lacking exposure terms, there is information regarding accidental releases of phosphorus trichloride in Illinois (T. Hornshaw, Office of Chemical Safety, Illinois EPA, personal communication, 2009). Two significant releases of phosphorus trichloride occurred in 1988 from a chemical plant in Sauget, Illinois. The first, on April 17, resulted from overfilling of a railroad tanker, with an estimated 6,000-12,000 pounds released in the railroad yard. The plume caused the evacuation of approximately 22 square blocks, and 417 citizens of neighboring Rush City and East St. Louis, Illinois reported to area hospitals for treatment. Two of these citizens were admitted overnight and subsequently released. Eye and respiratory irritation were the main symptoms reported. The second incident resulted from failure of a rupture disk during start-up procedures at the plant on July 31. It was calculated that no more than 50 pounds of phosphorus trichloride were released from the plant, and the plant's security and industrial hygiene personnel were able to visually track and bound the plume that moved into Rush City. Their reports indicated that the plume traveled approximately 2 miles before dissipating. This plume caused 244 citizens to report to area hospitals for treatment. Eight of these citizens were admitted; seven were kept overnight and released, while the eighth was kept for 3 days before release. This patient's history of asthma contributed to the severity of effects, and the asthma was also aggravated by the exposure to the phosphorus trichloride. The main complaints of the citizens were eye, nose, and throat irritation. No measurements of airborne concentrations were made during either incident.

2.3. Epidemiologic Studies

No epidemiologic studies of phosphorus trichloride toxicity are currently available.

2.4. Developmental and Reproductive Toxicity

Data regarding the reproductive and developmental toxicity of phosphorus trichloride in humans are not available.

2.5. Genotoxicity

No human genotoxicity data for phosphorus trichloride are currently available.

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2.6. Carcinogenicity

Information regarding the potential carcinogenicity of phosphorus trichloride in humans is not available.

2.7. Summary

There are no data regarding lethal exposures of humans to phosphorus trichloride but some information on nonlethal exposures is available. Workers exposed to phosphorus trichloride following a railroad car spill exhibited signs and symptoms consistent with exposure to a highly irritating chemical. Although the reports of this accident describe qualitatively the effects of exposure, there are no quantitative exposure-response terms. Pulmonary function deficits (e.g., vital capacity, FEV_1, peak expiratory flow rate, maximal expiratory flow rate at 50% vital capacity) that correlated with distance from the release showed improvement at 1 month following the exposure. The effects reported could be attributed to phosphorus trichloride decomposition products (phosphonic acid and hydrogen chloride) as well as the parent compound. In an occupational exposure setting, workers experienced a burning sensation in the eyes and throat, photophobia, chest tightness, dry cough, and slight bronchitis following 2-6 h of exposure to approximately 14-27 ppm phosphorus trichloride. Exposure of workers to these levels for 1-8 weeks resulted in pharyngeal irritation, coughing, catarrh, dyspnea, and asthmatic bronchitis. Increases in body temperature and moderate leucocytosis with neutrophilia were also reported for both exposure durations, but all signs and symptoms resolved upon removal from the exposure. The detection of elevated LDH activity in individuals following accidental exposures may imply other organ and tissue damage.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Weeks et al. (1964) reported on the acute lethality of phosphorus trichloride in female rats exposed for 4 h to an atmosphere of phosphorus trichloride generated by passing nitrogen gas through the liquid test material. Chemical analysis was used to determine the amount of the test material in the exposure chamber. The rats were observed for 14 days after removal from exposure. The rats were restless and exhibited labored breathing during the exposure. During the exposure, the eyes were closed and there was considerable porphyrin secretion around the eyes. Deaths occurred over a period of 10 days indicating, under the conditions of this experiment, a notable latency period in the lethal response. The nostrils and paws of the exposed rats exhibited swelling, edema, discolora-

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tion and subsequent sloughing of tissues that was consistent with the activity of a corrosive agent. Microscopic examination revealed necrosis of epithelium and supporting structures in the nostrils but pulmonary damage was considered to be negligible. The investigators noted that the primary site of damage appeared to be the kidneys and was characterized by nephrosis of tubules in the cortico-medullary region. A 4-h LC_{50} of 104.3 ppm was calculated and reported by the investigators. The exposure concentrations tested to obtain this value were not reported and, therefore, there was no information regarding the exposure-response relationship.

3.1.2. Guinea Pigs

Weeks et al. (1964) also examined the lethal effects of phosphorus trichloride on guinea pigs exposed for 4 h. The experimental protocol was as described for the experiments with rats (Section 3.1.1). Based upon the published report, the response of guinea pigs was similar to that of rats; restlessness, signs of ocular and nasopharyngeal irritation, and renal damage. With the exception of the 4-h LC_{50} of 50.1 ppm, no additional exposure-response data were provided.

Results of early inhalation exposure experiments reported by Butjagin (1904) showed that guinea pigs exposed to 623 ppm phosphorus trichloride died shortly after 3 h of exposure.

3.1.3. Cats

Butjagin (1904) reported that test animals (guinea pigs and cats) died shortly after a 3-h exposure to 623 ppm. In another experiment, one cat exposed to 694 ppm died after 306 min.

3.2. Nonlethal Toxicity

3.2.1. Rats

In an unpublished study conducted for the Monsanto Company (Hazleton Laboratories 1983), groups of 15 Sprague-Dawley rats (15/sex/group) were exposed to phosphorus trichloride vapor/aerosol for 6 h/day, 5 days/week for 4 weeks. Over the 4-week period, nominal exposure concentrations were 0.5, 3.0, or 10.0 ppm and analytical concentrations were 0.49, 3.37, and 10.96 ppm. The test atmosphere was generated by passing air (200-990 cc/min depending upon the test concentration group) over the headspace above a non-specified volume of phosphorus trichloride in a flask. The vapor was then carried to the test chambers via Teflon7 tubing. Sample concentrations were determined three times per day by collecting chamber samples in impingers containing 20 mL of sodium hydroxide. The samples were subsequently analyzed in a chloride meter

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and expressed as ppm phosphorus trichloride. Over the 4-week exposure period, concentration excursions deviated from target values by -2.0, + 12.3, and + 9.6% for the low, medium, and high-dose groups, respectively. A control group was exposed to filtered air under the same conditions. No rat died during the exposure period and no treatment-related adverse effects were observed. All rats were sacrificed and necropsied on day 29. Histological alterations in the maxillo- and nasoturbinates and in the lateral wall of the nasal cavity were observed in seven male and four females of the high-dose group; the remaining high-dose rats exhibited no remarkable findings in the nasal cavities and turbinates. Squamous metaplasia of the respiratory epithelium was also present in six males and four females of the high-dose group. There were no treatment-related effects on hematologic or biochemical parameters, and no ophthalmologic effects or body weight/organ weight changes were observed. Under the conditions of this study, 3.4 ppm was considered a NOAEL in rats.

3.2.2. Guinea Pigs

In experiments reported by Butjagin (1904), guinea pigs were exposed to phosphorus trichloride at various concentrations for different durations (1-6 h). Only minor effects (restlessness, salivary and nasal secretions, coughing, and irregular respiration) were observed following 6-h exposure to 0.71 ppm or 1-h exposure to 1.78 to 5.36 ppm. In the report summary, it was also noted that exposures of 50-90 ppm for 1 h produced severe signs of toxicity. The phosphorus trichloride concentrations were determined by measurement of chlorine. It appears that only one to three animals were used for any given exposure and, for some experiments, the same animals were used in multiple tests.

3.2.3. Cats

Butjagin (1904) also conducted experiments with adult cats (2.1- 4.0 kg) exposed to phosphorus trichloride as previously described for guinea pigs. The results were similar to those reported for the guinea pigs; 6-h exposure to 0.71 ppm or 1-h exposure to 1.78 to 5.36 ppm produced signs of restlessness and nasopharyngeal irritation. Six-hour exposures to concentrations of 135 to 303 ppm rapidly produced signs of severe irritation (salivary, nasal, and ocular secretions, breathing through the mouth, irregular and severely labored respiration). Histological examination at 6 to 7 days after exposure revealed severely damaged nasal septum and bronchioles, and pulmonary edema. Inasmuch as these animals were terminated for necropsy, it is likely (based upon the findings) that they might not have survived. In summary, the study author reported that 1-h exposure to 50-90 ppm resulted in severe signs of toxicity. It appears that for at least some of the experiments, the same cats were used.

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3.3. Developmental and Reproductive Toxicity

No data are available regarding the developmental and reproductive toxicity of phosphorus trichloride in animals.

3.4. Genotoxicity

No data are currently available regarding the genotoxicity of phosphorus trichloride.

3.5. Carcinogenicity

No data are available regarding the carcinogenic potential of phosphorus trichloride in animals.

3.6. Summary of Toxicity Data in Animals

Definitive quantitative exposure-response toxicity data in animals were limited. Median lethal exposure concentrations for rats and guinea pigs are available and shown in Table 6-3. A report by Weeks et al. (1964) provided an adequate description of experimental protocol and 4-h LC_{50} value for rats (4-h LC_{50} = 104.3 ppm) and guinea pigs (4-h LC_{50} = 50.1 ppm). Additional data obtained from limited numbers of cats and guinea pigs exposed to various concentrations of phosphorus trichloride for varying durations described both lethal and nonlethal responses (Butjagin 1904). An unpublished study by Hazleton Laboratories (1983) showed that multiple 6-h/day exposures of male and female rats to phosphorus trichloride at 11 ppm over 4 weeks produced only histologic changes in the nasal turbinates while exposure to 3.4 ppm failed to produce any notable effects. The available information affirms that exposure to vapors of phosphorus trichloride may produce dermal, ocular, and nasopharyngeal irritation as well as pulmonary and renal damage. Additionally, on the basis of limited data in rats, cats, and guinea pigs, there appears to be a latency period in the lethal response to phosphorus trichloride.

TABLE 6-3 Acute Lethality of Phosphorus Trichloride in Laboratory Species

Species	Lethality Value	Reference
Rat	4-h LC_{50} : 104.3 ppm	Weeks et al. 1964
Cat	lethality at 306 min, 694 ppm	Butjagin 1904
Cat	lethality at 3 h, 623 ppm	Butjagin 1904
Guinea pig	4-h LC_{50} : 50.1 ppm	Weeks et al.1964
Guinea pig	lethality at 3 h, 623 ppm	Butjagin 1904

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4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Data on the metabolism and disposition of phosphorus trichloride are not currently available.

4.2. Mechanism of Toxicity

The mechanism of toxicity of phosphorus trichloride is currently unknown. The lethal toxicity of phosphorus trichloride does not, however, appear to be explained solely by the activity of the irritant degradation products (hydrogen chloride and phosphonic acid). The rapid exothermic reaction in the presence of water may contribute to localized tissue damage and also explain, in part, the greater toxicity of phosphorus trichloride relative to hydrogen chloride and phosphonic acid.

4.3. Structure-Activity Relationships

Barbee et al. (1995) conducted an acute toxicity study of oxalyl chloride $(COCl)_2$ in which groups of 10 rats were exposed for 1 h to 0, 462, 866, 1,232, 1,694, or 2,233 ppm. The 1-h LC_{50} was found to be 1,840 ppm.

Phosphorus trichloride produces many of the same signs and symptoms as phosphorus oxychloride does following acute inhalation exposures (Weeks et al. 1964; ACGIH 1991) and also undergoes rapid hydrolysis to phosphonic acid and hydrogen chloride.

4.4. Other Relevant Information

4.4.1. Species Variability

Data are insufficient to reliably describe species variability in the toxic response to inhaled phosphorus trichloride.

4.4.2. Concurrent Exposure Issues

No concurrent exposure issues of special concern have been identified that could be directly incorporated in the development of AEGL values for phosphorus trichloride.

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5. DATA ANALYSIS AND PROPOSED AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

Quantitative human data consistent with AEGL-1 effects were not available. Information regarding human exposures to phosphorus trichloride indicates acute exposures result in dermal and ocular irritation, irritation of the respiratory tract, headache, nausea, and shortness of breath.

5.2. Summary of Animal Data Relevant to AEGL-1

The only animal data available that were consistent with AEGL-1 severity effects were those provided in the report by Butjagin (1904). In this study, cats and guinea pigs exposed to phosphorus trichloride concentrations of 0.71 for 6 h or for 1 h to 1.78-5.36 ppm exhibited restlessness, salivary and nasal secretions, coughing, and irregular respiration. Hazleton Laboratories (1983) reported a NOAEL of 3.4 ppm for rats following multiple 6-h/day exposures. This was bounded by a NOEL of 0.5 ppm and LOAEL (11 ppm).

5.3. Derivation of AEGL-1

Data consistent with AEGL-1 effects come from an older study in cats and guinea pigs (Butjagin 1904). There are no odor threshold data and no quantitative data in humans. Because of the uncertainties regarding exposure atmosphere measurements from a study conducted almost 100 years ago and the fact that individual test animals may have been exposed to multiple exposure regimens, the data from Butjagin (1904) were not used in the development of AEGL-1 values. Data from the Hazleton Laboratories study suggested that an exposure above 0.5 ppm may be consistent with AEGL-1 effects as multiple 6-h exposures to this concentration over a 4-week period were without effect. The Hazleton Laboratories study identified 3.4 ppm as a NOAEL for rats receiving multiple 6-h exposures over a period of 4 weeks. Sassi (1952) reported that occupational exposures of 1.8 to 3.6 ppm for 2-6 h occurred under normal operating conditions of a plant manufacturing phosphorus trichloride. However, it is unclear if these exposures were associated with any health effects and, therefore, can not be assumed to represent no-effect exposures. In lieu of additional data the experimentally determined NOAEL 3.4 ppm was considered a NOAEL for development of AEGL-1 values. Data for humans and animals indicated some variability in the toxic response to phosphorus trichloride. Therefore, uncertainty adjustment regarding interspecies variability was limited to 3. To account for intraspecies variability, a factor of 3 was applied. The uncertainty of intraspecies variability was limited to 3 because primary effects of phosphorus trichloride (irritation and subsequent tissue damage) appear to be due, in part, to hydrogen chloride and phosphonic acid resulting from chemical dissociation. The direct-

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contact corrosive effects resulting from these dissociation products would be similar for any mucosal surface and would be independent of biotransformation or other physiological processes. The attenuated uncertainty factors may be justified by the limited human exposure data (Sassi 1952), suggesting that humans could experience 2- to 6-h exposures of up to 3.6 ppm with no apparent effect and that AEGL-1 development is based upon an exposure that was without a discernible effect. The AEGL-1 values for phosphorus trichloride are shown in Table 6-4 and their derivations shown in Appendix A. The AEGL-1 values, based upon the 6-h exposure of rats to 3.4 ppm and a total uncertainty factor of 10, are equivalent because the contact irritation expected from exposure to phosphorus trichloride is not expected to vary over time (NRC 2001).

6. DATA ANALYSIS AND PROPOSED AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Quantitative exposure-response data in humans are not available for development of AEGL-2 values for phosphorus trichloride. Information regarding the human experience is limited to qualitative notations regarding signs and symptoms (ocular, dermal, and respiratory tract irritation, and ventilatory effects). The information in these reports suggests that acute exposure to phosphorus trichloride could cause irritation severe enough to impair egress from a contaminated area. Sassi (1952) reported that workers experienced a burning sensation in the eyes and throat, photophobia, chest tightness, dry cough, and slight bronchitis following 2-6 h of exposure to approximately 14-27 ppm phosphorus trichloride. Although these effects could possibly impair escape, thereby qualifying as AEGL-2 tier effects, the method(s) by which the exposure concentrations were determined was not reported. Exposure concentrations were not provided in other reports (with the exception of the anecdotal data by Tharr and Singal 1980) and information on exposure duration was limited.

6.2. Summary of Animal Data Relevant to AEGL-2

Quantitative data in animals regarding effect severity consistent with AEGL-2 were limited to data on guinea pigs and cats reported by Butjagin (1904). The robustness of these data are, however, poor due to the small numbers of animals in each experiment (one to three) and the fact that some of the animals were apparently used in more than one experiment. This becomes a significant concern considering the additive nature of irritation and tissue damage and the possible latency in activity for some adverse effects of phosphorus trichloride (e.g., pulmonary damage and renal toxicity). Consistent with human acute exposure reports, the predominant response by animals is characterized by

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TABLE 6-4 AEGL-1 Values for Phosphorus Trichloride

AEGL Level	10-min	30-min	1-h	4-h	8-h
AEGL-1	0.34 ppm	0.34 ppm	0.34 ppm	0.34 ppm	0.34 ppm

ocular, nasopharyngeal, and pulmonary irritation and subsequent tissue damage. Animal data are not sufficient to provide a meaningful exposure-response relationship. The responses of cats and guinea pigs in the Butjagin study were reportedly more severe at higher concentrations and occurred more quickly. In the Butjagin (1904) report, cats and guinea pigs exposed to 5.36 ppm for 1 h exhibited restlessness, signs of nasopharyngeal irritation, and irregular respiration. A 6-h exposure of cats to concentrations of 135 to 303 ppm resulted in signs of severe irritation and respiratory distress. Histological examination of the cats exposed to 135 to 303 ppm revealed perforated nasal septa, bronchial damage, and pulmonary edema. Additionally, Weeks et al. (1964) noted renal damage in rats exposed to lethal concentrations of phosphorus trichloride. However, exposure-response data were not provided regarding this effect. The Hazleton Laboratories study (1983) in rats showed that multiple 6-h exposures to 11 ppm over a 4-week period produced histologic alterations in the nasal turbinates but no effects on ophthalmologic hematologic or biochemical parameters, and no overt signs of toxicity. Because the nasal lesions were the result of multiple exposures (5 days/week) over 4 weeks and not of a severity consistent with the AEGL-2 tier, a threshold for AEGL-2 effects in rats is likely at an undetermined concentration above 11 ppm for a single 6-h exposure.

6.3. Derivation of AEGL-2

Data upon which to base AEGL-2 development are limited. Sassi (1952) reported on occupational exposures of 2-6 h durations to concentrations of 14-27 ppm that produced effects that could be considered only marginally consistent with AEGL-2. As previously noted, the animal data reported by Butjagin (1904) are deficient for the purpose of AEGL development. Although the results from the Hazleton Laboratories (1983) study in rats exposed to phosphorus trichloride for 6 h/day, 5 days/week for 4 weeks did not define a response consistent with AEGL-2 severity, the 11 ppm exposure that resulted in histopathologic alterations in the respiratory tract may be considered a NOAEL for AEGL-2 severity effects. Uncertainty factor application and time scaling were as described for AEGL-1. Data from available reports suggest that humans are not especially sensitive to the effects of phosphorus trichloride when compared to laboratory animals. As such further reduction of AEGL values by the application of greater uncertainty factors dose not appear warranted. The AEGL-2 values for phosphorus trichloride are shown in Table 6-5 and their derivation outlined in Appendix A.

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TABLE 6-5 AEGL-2 Values for Phosphorus Trichloride

AEGL Level	10 min	30 min	1 h	4 h	8 h
AEGL-2	2.5 ppm	2.5 ppm	2.0 ppm	1.3 ppm	0.83 ppm

7. DATA ANALYSIS AND PROPOSED AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

Quantitative data are not available regarding lethality in humans exposed to phosphorus trichloride.

7.2. Summary of Animal Data Relevant to AEGL-3

Weeks et al. (1964) provided 4-h LC_{50} values of 104.3 ppm and 50.1 ppm, respectively, for rats and guinea pigs. In early experiments by Butjagin (1904), guinea pigs and cats exposed to 623 ppm phosphorus trichloride died within 3 h, and a cat exposed to 694 ppm died after 306 min of exposure. In the absence of any additional quantitative data, the median lethality values derived by Weeks et al. may be considered as a basis for AEGL-3 development and also serve to a limited extent as an index of species variability. Because the exposure-response data used to derive the median lethality values were not provided, it is not possible to determine the exposure-response relationship.

7.3. Derivation of AEGL-3

Because the median lethality values provided by Weeks et al. (1964) represent the only quantitatively determined estimates regarding the lethal response to acute inhalation of phosphorus trichloride, they may be considered as the basis for AEGL-3 development. The 4-h LC_{50} values for rats (104.3 ppm) and guinea pigs (50.1 ppm) suggest a species variability. In the absence of exposure-response data, the lethality threshold was estimated as a 3-fold reduction of the rat 4-h LC_{50} (104.3 ppm/3 = 34.8 ppm) and used as the point-of-departure for AEGL-3 derivation. The guinea pig was only about 2-fold more sensitive, but the use of the guinea pig 4-h LC_{50} of 16.7 ppm (50.1 ppm/3 = 16.7 ppm) to derive AEGL-3 values would be overly conservative and result in AEGL values that are inconsistent with human exposure information.

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. Due to the limited toxicity data for this chemical, an empirical derivation of n was not possible. In the absence of an empirically derived exponent (n), and to obtain conservative and protective AEGL values, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation.

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Because of the uncertainty in extrapolating from a 4-h exposure to a 10-min exposure, the latter was set equal to the 30-min AEGL-3.

A total uncertainty factor adjustment of 10 was used to develop the AEGL-3 values. Data for humans and animals indicate some variability in the toxic response to phosphorus trichloride with guinea pigs being the more sensitive (~2-fold) among the laboratory animals. Limited data regarding human exposures showed that 2- to 6-h exposures to 14-27 ppm were not life-threatening (Sassi 1952). Therefore, uncertainty adjustment regarding interspecies variability was limited to 3. To account for intraspecies variability, a factor of 3 was applied. The uncertainty of intraspecies variability was limited to 3 because primary effects of phosphorus trichloride (irritation and subsequent tissue damage) appear to be due, in part, to hydrogen chloride and phosphonic acid resulting from chemical dissociation. The activity of these dissociation products would damage any mucosal surface regardless of an individual predisposition to the effects of chemicals with more complex mechanisms of toxicity. The attenuated uncertainty factors may be further justified by limited human exposure data (Sassi 1952) suggesting that humans could experience repeated exposures of up to 27 ppm without life-threatening consequences. The resulting AEGL-3 values are presented in Table 6-6 and their derivation is shown in Appendix A. Because the lethal response in guinea pigs and rats was delayed up to 10 days, note of possible delayed response has been made regarding AEGL-3 values.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

The AEGL-1 values are based upon a NOAEL from a laboratory study in which rats received multiple exposures over a period of 4 weeks. Although a conservative assumption, the use of a NOAEL in the development of the AEGL-1 values may be justified by the relative paucity of definitive exposure-response data, and the fact that limited information regarding the human experience indicates that 2- to 6-h exposures to 1.8-3.6 ppm was without effect. The AEGL-2 values were based on histopathologic alterations detected in the respiratory tract of rats following multiple exposures over 4 weeks. The effects on the respiratory tract were consistent with mode of action of phosphorus trichloride and, therefore, were considered a NOAEL for the AEGL-2 tier effect level (i.e., the effects were neither disabling nor irreversible). Information regarding the human experience suggests that 2- to 6-h exposures to 1.8-3.6 ppm were without effect and that exposure to 14-27 ppm resulted in irritation of the eyes and upper respiratory tract, photophobia, chest tightness, and bronchitis. Therefore, further reduction of the AEGL-2 values does not appear to be warranted. The AEGL-3 values were developed based upon lethality data in laboratory species. The AEGL-3 values were developed based upon a 4-h LC_{50} value for rats provided in a study by Weeks et al. (1964). Data pertaining to the human experience also indicate respiratory involvement as a critical effect.

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8.2. Comparison with Other Standards and Criteria

Existing standards and criteria for phosphorus trichloride are presented in Table 6-7.

TABLE 6-6 AEGL-3 Values for Phosphorus Trichloride

AEGL Level	10 min	30 min	1 h	4 h	8 h
AEGL-3[a]	7.0 ppm	7.0 ppm	5.6 ppm	3.5 ppm	1.8 ppm

[a]Based upon animal data, lethality may be delayed.

TABLE 6-7 Extant Standards and Guidelines for Phosphorus Trichloride

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	0.34 ppm	0.34 ppm	0.34 ppm	0.34 ppm	0.34 ppm
AEGL-2	2.5 ppm	2.5 ppm	2.0 ppm	1.3 ppm	0.83 ppm
AEGL-3	7.0 ppm	7.0 ppm	5.6 ppm	3.5 ppm	1.8 ppm
ERPG-1 (AIHA)[a]	_	_	0.5 ppm	_	_
ERPG-2 (AIHA)	_	_	3 ppm	_	_
ERPG-3 (AIHA)	_	_	15 ppm	_	_
EEGL (NRC)[b]	_	_	_	_	_
IDLH (NIOSH)[c]	_	25 ppm	_	_	_
TLV-TWA (ACGIH)[d]					0.2 ppm
REL-TWA (NIOSH)[e]					0.2 ppm
PEL-TWA (OSHA)[f]	_	_	_	_	0.5 ppm
TLV-STEL (ACGIH)[g]	_	_	_	_	0.5 ppm
REL-STEL (NIOSH)[h]	_	_	_	_	0.5 ppm
PEL-STEL(OSHA)[i]	_	_	_	_	_
MAK (Germany)[j]	_	_	_	_	0.5 ppm
MAK Spitzenbegrenzung (Germany)[k]	_	_	_	_	_
Einsaztoleranzwert (Germany)[l]	_	_	_	_	_
MAC (The Netherlands)[j]	_	_	_	_	0.2 ppm

[a]ERPG (emergency response planning guidelines, American Industrial Hygiene Association) (AIHA 2009).
The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.

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The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action.
The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects.
[b]EEGL (emergency exposure guidance levels, National Research Council) (NRC 1984)is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace, but avoids death, other severe acute effects and long-term or chronic injury.
[c]IDLH (immediately dangerous to life or health, National Institute for Occupational Safety and Health) (NIOSH 1996) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms, or any irreversible health effects.
[d]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 work week, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.
[e]REL-TWA (recommended exposure limits-time-weighted average, National Institute for Occupational Safety and Health) (NIOSH 2005) is defined analogous to the ACGIH-TLV-TWA.
[f]PEL-TWA (permissible exposure limits-time-weighted average, Occupational Health and Safety Administration) (OSHA) (29 CFR 1910.1000 [1999]) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week.
[g]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 4 times per day. There should be at least 60 min between successive exposures in this range.
[h]REL-STEL (recommended exposure limits-short-term exposure limit, National Institute for Occupational Safety and Health) (NIOSH 2005) is defined analogous to the ACGIH TLV-STEL.
[i]PEL-STEL (permissible exposure limits-short-term exposure limit, Occupational Health and Safety Administration) (OSHA) (29 CFR 1910.1000 [1999]) is analogous to the ACGIH TLV-STEL.
[j]MAK (maximale Arbeitsplatzkonzentration [maximum workplace concentration], Deutsche Forschungsgemeinschaft [German Research Association]) (DFG 1999) is analogous to the ACGIH TLV-TWA.
[k]MAK Spitzenbegrenzung (Kategorie II,2) [maximum workplace concentration (peak limit category II,2] (DFG 2003) 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.
[l]MAK Einsatztoleranzwert [maximum workplace concentration, action tolerance levels] (Vereinigung zur Förderung des deutschen Brandschutzes e.V. [Federation for the Advancement of German Fire Prevention]) constitutes a concentration to which unprotected firemen and the general population can be exposed to for up to 4 h without any health risks.

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[j]MAC (maximaal aanvaarde concentratie [maximum accepted concentration]). Dutch Expert Committee for Occupational Standards, The Netherlands (MSZW 2004) is analgous to the ACGIH-TLV-TWA.

8.3. Data Adequacy and Research Needs

The overall robustness of the data base for phosphorus trichloride toxicity is poor. The lack of data creates substantial uncertainty regarding the exposure-response relationship for the toxic response to this chemical. Although qualitative data are available regarding the acute inhalation toxicity of phosphorus trichloride in humans, quantitative exposure-response data are lacking. Quantitative exposure-response data are severely limited for nonlethal responses in animals. These deficiencies result in an incomplete picture of the exposure concentration-response curve and exposure duration-response for phosphorus trichloride. Additional data are also needed regarding the mechanism of action, possible systemic effects (e.g., renal toxicity), and latency in the toxic responses (e.g., pulmonary damage) following acute inhalation exposure to phosphorus trichloride. The relationship between the AEGL values and available data are shown in the Category Plot in Appendix C.

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APPENDIX A

DERIVATION OF AEGL VALUES

Derivation of AEGL-1 Values

Key study:	Hazleton Laboratories 1983
Toxicity end point:	NOAEL of 3.4 ppm for rats following multiple exposure at 6 h/day, 5 days/week for 4 weeks.
Scaling:	No time scaling was applied for AEGL-1 because the contact irritation expected from exposure to phosphorus trichloride vapors is not expected to vary over time. This approach is consistent with the AEGL Standing Operating Procedures (NRC 2001).
Uncertainty factors:	Interspecies UF = 3; the attenuation of this uncertainty factor is justified by the fact that the guinea pig appears to be the most sensitive species tested. Intraspecies UF = 3; contact irritation and subsequent tissue damage appear to be due, in part, to hydrogen chloride and phosphonic acid resulting from chemical dissociaton and direct corrosive action of these components on mucosal surfaces. Additional application of uncertainty factor adjustment would provide AEGL-1 values that are inconsistent with limited data on human exposures. All AEGL-1 values were equivalent to the point-of-departure (3.4 ppm for 6 h) adjusted by a total uncertainty factor of 10 (3.4 ppm/10 = 0.34 ppm) because the contact irritation expected from exposure to phosphorus trichloride vapors is not expected to vary over time. This approach is consistent with the AEGL Standing Operating Procedures (NRC 2001).

Derivation of AEGL-2

Key study:	Hazleton Laboratories 1983

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Toxicity end point:	LOAEL of 11 ppm for respiratory tract histopathologic changes in rats following multiple exposures at 6 h/day, 5 days/week for 4 weeks.
Scaling:	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). Due to the limited toxicity data for this chemical, an empirical derivation of n was not possible. In the absence of an empirically derived exponent (n), and to obtain conservative and protective AEGL values, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation. $(11 \text{ ppm})^1 \times 6 \text{ h} = 66 \text{ ppm-h}$ (n = 1) $(11 \text{ ppm})^3 \times 6 \text{ h} = 7{,}986 \text{ ppm}^3\text{-h}$ (n = 3)
Uncertainty factors:	Interspecies UF = 3; the attenuation of this uncertainty factor is justified by the fact that the guinea pig appears to be the most sensitive species tested and because limited human exposure data (Sassi 1952) indicate that humans have experienced routine occupational exposures of up to 3.6 ppm without effect. Intraspecies UF = 3; contact irritation and subsequent tissue damage appear to be due, in part, to hydrogen chloride and phosphoric acid resulting from chemical dissociaton and direct corrosive action of these components on mucosal surfaces. Adjustments using a greater level of uncertainty would provide AEGL-2 values that are inconsistent with limited data on human exposures.
10-min AEGL-2	The 10-min AEGL-2, was set equivalent to the 30-min value (2.5 ppm) due to uncertainties in extrapolating from the 6-h experimental exposure duration to a 10-min duration.
30-min AEGL-2	$C^3 \times 0.5 \text{ h} = 7{,}986 \text{ ppm}^3\text{-h}$ C = 25.2 ppm 30-min AEGL-2 = 25.2 ppm/10 = 2.5 ppm (14 mg/m^3)

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1-h AEGL-2	$C^3 \times 1$ h = 7,986 ppm^3-h C = 20.0 ppm 1-h AEGL-2 = 20.0 ppm/10 = 2.0 ppm (11 mg/m^3)
4-h AEGL-2	$C^3 \times 4$ h = 7,986 ppm^3-h C = 12.6 ppm 4-h AEGL-2 = 12.6 ppm/10 = 1.3 ppm (7.3 mg/m^3)
8-h AEGL-2	$C^1 \times 8$ h = 66 ppm-h C = 8.25 ppm 8-h AEGL-2 = 8.25 ppm/10 = 0.83 ppm (4.6 mg/m^3)

Derivation of AEGL-3

Key study:	Weeks et al. 1964
Toxicity end point:	Lethality threshold estimated as 3-fold reduction in the 4-h LC_{50} for rats (104.3 ppm/3 = 34.8 ppm); delayed response possible.
Scaling:	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). Due to the limited toxicity data for this chemical, an empirical derivation of n was not possible. In the absence of an empirically derived exponent (n) and to obtain conservative and protective AEGL values, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation. $(34.8 \text{ ppm})^1 \times 4$ h = 139.2 ppm-h (n = 1) $(34.8 \text{ ppm})^3 \times 4$ h = 168,576.8 ppm^3-h (n = 3)
Uncertainty factors:	Interspecies UF = 3; the attenuation of this uncertainty factor is justified by the fact that the guinea pig appears to be the most sensitive species tested and because limited human exposure data (Sassi 1952) indicate that humans have experienced exposures of up to 27 ppm without life-threatening consequences.

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	Intraspecies UF = 3; contact irritation and subsequent tissue damage appear to be due, in part, to hydrogen chloride and phosphonic acid resulting from chemical dissociaton and direct corrosive action of these components on mucosal surfaces. Additional application of uncertainty factor adjustment would provide AEGL-3 values that are not consistent with limited data on human exposures or with the results of repeated exposures in rats wherein exposure to 11 ppm 6 h/day, 5 days/week for 4 weeks showed only histologic changes in the upper respiratory tract and no overt signs of toxicity
10-min AEGL-3	Due to uncertainties in extrapolating from a 4-h to 10-min exposure, the 10-min AEGL-3 is set equivalent to the 30-min value (7.0 ppm).
30-min AEGL-3	$C^3 \times 0.5$ h = 168,576.8 ppm^3-h C = 69.6 ppm 30-min AEGL-3 = 69.6 ppm/10 = 7.0 ppm (39 mg/m^3)
1-h AEGL-3	$C^3 \times 1$ h = 168,576.8 ppm^3-h C = 55.2 ppm 1-h AEGL-3 = 55.2 ppm/10 = 5.6 ppm (31 mg/m^3)
4-h AEGL-3	$C^3 \times 4$ h = 168,576.8 ppm^3-h C = 34.8 ppm 4-h AEGL-3 = 34.8 ppm/10 = 3.5 ppm (20 mg/m^3)
8-h AEGL-3	$C^1 \times 8$ h = 139.2 ppm-h C = 17.4 ppm 8-h AEGL-3 = 17.4 ppm/10 = 1.8 ppm (10 mg/m^3)

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APPENDIX B

ACUTE EXPOSURE GUIDELINES FOR FOR PHOSPHORUS TRICHLORIDE

Derivation Summary for Phosphorus Trichloride

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
0.34 ppm	0.34 ppm	0.34 ppm	0.34 ppm	0.34 ppm

Reference: Hazleton Laboratories 1983

Test Species/Strain/Number: Sprague-Dawley rats; 15/sex/group

Exposure Route/Concentrations/Durations: Inhalation exposure (whole-body) to 0, 0.5, 3.0, or 10.0 ppm (nominal) for 6 h/day, 5 days/week for 4 weeks

Toxicity End Point: No effects noted at 3.4 ppm (analytical) following multiple exposure of rats over 4 weeks

Time Scaling: No time scaling was applied for AEGL-1. All AEGL-1 values were equivalent to the point-of-departure (3.4 ppm for 6 h) adjusted by a total uncertainty factor of 10 (3.4 ppm/10 = 0.34 ppm) because the contact irritation expected from exposure to phosphorus trichloride vapors is not expected to vary over time. This approach is consistent with the AEGL Standing Operating Procedures (NRC 2001).

Concentration/Time Selection/Rationale: In the absence of exposure-response data specific for AEGL-1 effects, the exposure to 3.4 ppm at 6 h/day, 5 days/week for 4 weeks was selected as a conservative basis for AEGL development.

Uncertainty Factors/Rationale: Total uncertainty application of 10

Interspecies UF = 3: The interspecies uncertainty factor was limited to 3 because of the concordance of the animal data with the human experience and because the most sensitive species tested (guinea pig) was only about 2-fold more sensitive.

Intraspecies UF= 3: The intraspecies uncertainty factor was limited to 3 because primary effects of phosphorus trichloride (irritation and subsequent tissue damage) appear to be due, in part, to hydrogen chloride and phosphonic acid resulting from chemical dissociation. Furthermore, the AEGL-1 is based upon a conservative assumption and additional reduction of the AEGL-1 values would be inconsistent with available human and animal data.

Modifying Factor: Not applicable

Animal-to-Human Dosimetric Adjustments: Not applicable

Data adequacy: Neither human nor animal quantitative exposure-response data were available regarding effects consistent with AEGL-1 definition.. The 3.4-ppm exposure of rats over 4 weeks was selected as a NOAEL for AEGL-1. Although likely to be a conservative basis for developing AEGL-1 values, it may be justified due to the relative paucity of data on the toxic response to this chemical.

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AEGL-2 VALUES

10 min	30-min	1 h	4 h	8 h
2.5 ppm	2.5 ppm	2.0 ppm	1.3 ppm	0.83 ppm

Reference: Hazleton Laboratories 1983

Test Species/Strain/Number: Sprague-Dawley rats; 15/sex/group

Exposure Route/Concentrations/Durations: Inhalation exposure (whole-body) to 0, 0.5, 3.0, or 10.0 ppm (nominal) for 6 h/day, 5 days/week for 4 weeks

Toxicity End Point: Histopathologic alterations in respiratory tract in rats exposed to 11 ppm (analytical), 6 h/day, 5 days/week for 4 weeks. There were no concurrent hematologic or biochemical alterations indicative of a toxic response, and there were no ophthalmologic effects. The 11 ppm exposure concentration is considered a NOAEL for AEGL-2 tier effects.

Time Scaling: 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. Due to the limited toxicity data for this chemical, an empirical derivation of n was not possible. In the absence of an empirically derived exponent (n), and to obtain conservative and protective AEGL values, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation. For 10-min AEGL-2, values were set at equivalence to the 30-min values due to uncertainties in extrapolating from the experimental exposure durations of 4 h or greater.

Concentration/Time Selection/Rationale: The multiple exposure of rats to 11 ppm over 4 weeks was considered a conservative estimate and NOAEL for AEGL-2 effects (i.e., the effects were neither disabling nor irreversible).

Uncertainty Factors/Rationale: Total uncertainty application of 10.
Interspecies UF = 3: The interspecies uncertainty factor was limited to 3 because of the concordance of the animal data with the human experience and because the most sensitive species tested (guinea pig) was only about 2-fold more sensitive.
Intraspecies UF = 3: The intraspecies uncertainty factor was limited to 3 because primary effects of phosphorus trichloride (irritation and subsequent tissue damage) appear to be due, in part, to hydrogen chloride and phosphonic acid resulting from chemical dissociation. Furthermore, the AEGL-2 is based upon histopathologic changes in the respiratory tract that were not necessarily irreversible or disabling. Additional reduction of the AEGL-2 values would be inconsistent with available human and animal data.

Modifying Factor: Not applicable

Animal-to-Human Dosimetric Adjustments: Not applicable

Data adequacy: Limited information regarding the human experience indicated that 2- to 6-h exposures to 1.8-3.6 ppm were without effect and that exposure to 14-27 ppm irritation of the eyes and upper respiratory tract, photophobia, chest tightness, and bronchitis. Because the effects were neither disabling nor irreversible, the end point used for AEGL-2 development is considered a NOAEL for AEGL-2 effects.

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AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
7.0 ppm	7.0 ppm	5.6 ppm	3.5 ppm	1.8 ppm

Reference: Weeks, M.H., N.P. Mussleman, P.P. Yevich, K.H. Jacobson, and F.W. Oberst. 1964. Acute vapor toxicity of phosphorus oxychloride, phosphorus trichloride and methyl phosphonic dichloride. Am. Ind. Hyg. J. 25: 470-475.

Test Species/Strain/Number: female rats /strain not specified/20 per group

Exposure Route/Concentrations/Durations: inhalation/median lethal concentrations derived but exposure concentrations not specified/4 h

Toxicity End Point: estimated lethality threshold by 3-fold reduction of rat 4-h LC_{50} of 104.3 ppm

Time Scaling: 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. Due to the limited toxicity data for this chemical, an empirical derivation of *n* was not possible. In the absence of an empirically derived exponent (n), and to obtain conservative and protective AEGL values, temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation.

$(34.8\ ppm)^1 \times 4\ h = 139.2\ ppm\text{-}h$ (*n* = 1)

$(34.8\ ppm)^3 \times 4\ h = 168{,}576.8\ ppm^3\text{-}h$ (*n* = 3)

Concentration/Time Selection/Rationale: a 3-fold reduction of the rat 4-h LC_{50} (104.3 ppm/3 = 34.8 ppm) was used as an estimate of the lethality threshold.

Uncertainty Factors/Rationale:

Total Uncertainty:	10
Interspecies UF = 3	Data for humans and animals indicate some variability in the toxic response to phosphorus trichloride but LC_{50} values for rodents exhibited approximately a 2-fold difference.
Intraspecies UF = 3	The uncertainty for intraspecies variability was limited to 3 because primary effects of phosphorus trichloride (irritation and subsequent tissue damage) appear to be due, in part, to hydrogen chloride and phosphonic acid resulting from chemical dissociation and the direct corrosive action of these on mucosal surfaces. The overall uncertainty factor adjustment of 10 may be justified by limited human exposure data suggesting that humans could experience exposures of up to 27 ppm without life-threatening consequences. Furthermore, the results of a multiple exposure studies in rats (11 ppm 6 h/day, 5 days/week for 4 weeks) showed only histologic changes in the upper respiratory tract and no overt signs of toxicity.

Modifying Factor: None applied

Animal-to-Human Dosimetric Adjustments: Insufficient data

(Continued)

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AEGL-3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
7.0 ppm	7.0 ppm	5.6 ppm	3.5 ppm	1.8 ppm

Data adequacy: Lethality data are limited to two species and quantitative data for humans are limited. However, comparison of the AEGL-3 values with available data does not support application of uncertainty adjustment greater than that currently applied. Data suitable for determining exposure-time relationships are also lacking and impact on temporal extrapolation efforts. A delayed response is possible as demonstrated in the Weeks et al. (1964) study in which deaths of guinea pigs occurred up to 10 days post exposure.

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APPENDIX C

CATEGORY PLOT FOR PHOSPHORUS TRICHLORIDE

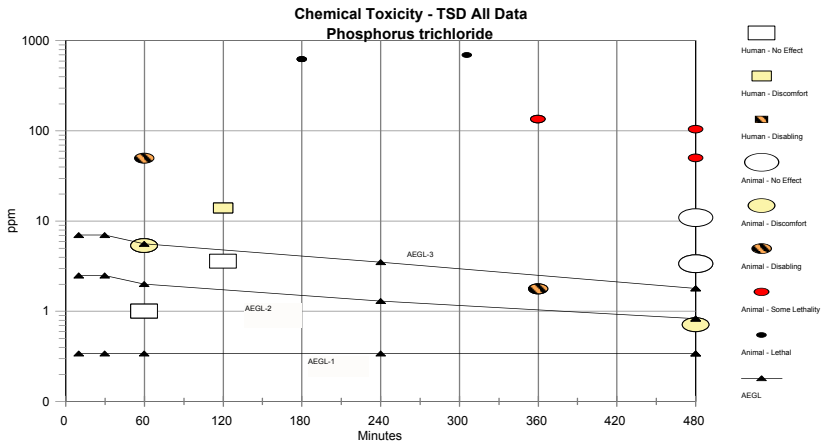

FIGURE 6-1 Category plot for phosphorus trichloride.

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7

Sulfuryl 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 min to 8 h. Three levels—AEGL-1, AEGL-2 and AEGL-3—are developed for each of five exposure periods (10 and 30 min, 1 h, 4 h, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million 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, non-sensory 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) and Steven Barbee (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee concludes 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).

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

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

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

SUMMARY

Sulfuryl chloride, a colorless to light yellow liquid with a pungent odor, is used as chlorinating, sulfonating, and chlorosulfonating agent in organic synthesis. It is generally used in closed systems, thereby limiting exposure potential.

No information is available regarding exposure of humans to sulfuryl chloride. Because it decomposes to hydrochloric acid and sulfuric acid upon contact with water, it may assumed that exposure would result in notable irritation and corrosive action on the eyes and respiratory tract. Due to this decomposition, metabolism is irrelevant in the toxic response to sulfuryl chloride.

Inhalation exposure data in animals are limited to lethality studies in laboratory rats, all of which confirm toxic effects (dyspnea, ocular irritation, and respiratory tract irritation leading to pulmonary hemorrhage and death) consistent with severe irritation and /or corrosive activity. One-hour LC_{50} values of 59 to 242 ppm and a 4-h LC_{50} of 159 ppm have been reported for rats. There was some discrepancy regarding the lethal toxicity of sulfuryl chloride in rats exposed for one or four hours. However, all studies demonstrated that exposure of rats produces clinical signs of ocular and respiratory tract irritation, dyspnea, and body weight loss. Necropsy findings consistently indicated concentration-related pulmonary involvement. Although death may occur during exposure at higher concentrations, post-exposure observation has shown that lethality may be delayed for several days at lower concentrations.

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Data were insufficient for development of AEGL-1 values. All exposure regimens in the rat studies resulted in effects that were considered of greater severity than those of the AEGL-1 tier. Specifically, signs of ocular and respiratory tract irritation in rats exposed for one hour to sulfuryl chloride concentrations as low as 31 ppm also exhibited pulmonary hemorrhage upon necropsy.

Toxicity studies on sulfuryl chloride were conducted primarily to assess lethality. All nonlethal exposures in these studies resulted in respiratory tract damage (necrosis, hemorrhage) that was detectable at the end of the 3 to14-day post-exposure observation periods. Lethality threshold estimates (e.g., LC_{01}, $BMCL_{05}$) from all studies resulted in exposure concentrations that were less than the nonlethal concentrations in the respective studies. Therefore, it was not possible to determine a data-driven estimate of the threshold for AEGL-2 severity effects. Because lethality threshold estimates tended to be less than nonlethal experimental exposures and because of the apparent steep exposure-response curve for sulfuryl chloride, AEGL-2 values were estimated by a three-fold reduction of the AEGL-3 values (NRC 2001).

A 4-h $BMCL_{05}$ of 70.1 ppm calculated from the Haskell Laboratory study (DuPont 1982; Kelly and Stula 1983) was used as the POD for deriving AEGL-3 values. Although this is a somewhat more conservative approach than use of an LC_{01} (70.6 ppm) as an estimate of the lethality threshold, its selection may be justified by the known respiratory tract damage observed from nonlethal exposures and the potential uncertainty regarding latent-occurring health effects (including lethality beyond the 3 to 14-day observation periods of the animal studies). Because the effects of sulfuryl chloride appear to be contact tissue damage resulting from the degradation products (sulfuric acid and hydrochloric acid) not resulting from metabolic processes and because rodents will receive a greater dose to target tissues than would humans, the uncertainty factor for interspecies variability was limited to 3. An intraspecies uncertainty factor of 3 was considered sufficient to account for individual variability in direct-contact toxic response to corrosive agents. Additional uncertainty was considered unnecessary because a 4-h exposure of rats to 84 ppm in the DuPont (1982) study was not lethal, and multiple exposures of rats to 55 ppm was not lethal (Kelly and Stula 1983). The exposure concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, *n*, ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived chemical-specific scaling exponent, temporal scaling for AEGL-3 values was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC 2001).

Results of gentoxicity assays of sulfuryl chloride are equivocal and no carcinogenicity bioassays have been conducted. The AEGL values for sulfuryl chloride are summarized in Table 7-1.

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1. INTRODUCTION

Sulfuryl chloride, a colorless to light yellow liquid with a pungent odor, is used as chlorinating, sulfonating, and chlorosulfonating agent in organic synthesis of such chemicals as chlorophenol and chlorothymol (O'Neil et al. 2001). Approximately 10,000 to 20,000 metric tons of sulfuryl chloride were produced worldwide in 2001 (OECD 2005).

The chemical and physical data on DMF are presented in Table 7-2.

TABLE 7-1 Summary of AEGL Values for Sulfuryl Chloride

Classification	10-min	30-min	1-h	4-h	8-h	End Point (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Not recommended; insufficient data
AEGL-2 (Disabling)	4.7 ppm 26 mg/m^3	4.7 ppm 26 mg/m^3	3.7 ppm 20 mg/m^3	2.3 ppm 13 mg/m^3	1.2 ppm 6.6 mg/m^3	Data insufficient for derivation of AEGL-2 threshold. Due to steep exposure-response relationship, AEGL-2 values estimated as one-third reduction of AEGL-3 values (NRC 2001)
AEGL-3 (Lethality)	14 ppm 77 mg/m^3	14 ppm 77 mg/m^3	11 ppm 61 mg/m^3	7.0 ppm 39 mg/m^3	3.5 ppm 19 mg/m^3	$BMCL_{05}$ of 70.1 ppm estimated as lethality threshold in rats following 4-h exposure to sulfuryl chloride (DuPont 1982; Kelly and Stula 1983)

TABLE 7-2 Chemical and Physical Data for Sulfuryl Chloride

Parameter	Value	Reference
Synonyms	Sulfuryl dichloride; sulfonyl chloride; sulphuric acid dichloride; sulfuric oxychloride	IUCLID 2000; O'Neil et al. 2001
CAS Registry No.	7791-25-5	O'Neil et al. 2001
Chemical formula	Cl_2O_2S	O'Neil et al. 2001
Molecular weight	134.96	O'Neil et al. 2001
Physical state	Liquid	O'Neil et al. 2001
Boiling/melting point	69.3°C/-54.1°C	O'Neil et al. 2001
Density	1.67 g/cm^3 at 20°C	OECD 2005
Solubility in water	Hydrolyzes in water	O'Neil et al. 2001
Vapor pressure	148 hPa at 20°C	OECD 2005
Conversion factors in air	1 mg/m^3 = 0.18 ppm 1 ppm = 5.51 mg/m^3	

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2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data were available regarding lethality in humans following inhalation exposure to sulfuryl chloride.

2.2. Nonlethal Toxicity

No information was available regarding the nonlethal effects of sulfuryl chloride in humans. No odor threshold or odor detection limits were available for sulfuryl chloride.

2.3. Developmental/Reproductive Effects

No human developmental/reproductive toxicity data were available regarding sulfuryl chloride.

2.4. Genotoxicity

No human genotoxicity data were available.

2.5. Carcinogenicity

No data were found in the available literature regarding the carcinogenic potential of sulfuryl chloride in humans.

2.6. Summary

There are no human exposure data regarding inhalation of sulfuryl chloride.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

In a Haskell Laboratory study (DuPont 1982; Kelly and Stula 1983), groups of 10 male Crl:CD7 rats (7-8 weeks old, 233-274g) were exposed (head-only) to 84.4, 134, 155, 207, or 273 ppm sulfuryl chloride (100% purity) for four

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hours. The rats were observed for 14 days post exposure. All exposed rats exhibited red nasal discharge lasting up to two days post exposure. Rats surviving the exposures exhibited severe weight loss for one to two days post exposure. The response of exposure groups are summarized in Table 7-3. The estimated 4-h LC_{50} was reported as 159 ppm. A lethality threshold estimate (4-h LC_{01}) of 70.6 ppm was independently estimated using the method of Litchfield and Wilcoxon (1949) (see Appendix B).

One-hour LC_{50} values (Table 7-4) for sulfuryl chloride indicating a gender-related variability in lethal response have been reported (Bayer AG 1993a; IUCLID 2000). No experimental details were available regarding these values.

An acute inhalation exposure experiment conducted by Western Research Center (Stauffer Chemical Company 1969) provided lethality data for rats exposed to sulfuryl chloride for one hour. In this study, groups of 10 rats (200 g, gender and strain not specified) were exposed to sulfuryl chloride at concentrations of 0.240, 0.394, 0.600, 1.110, 1.400, or 2.180, mg/l (equivalent to 43, 71, 108, 200, 252, and 392 ppm). Rats in all exposure groups exhibited dyspnea and hyperactivity. Exposures at "larger doses" exhibited heavy nasal and pulmonary discharges that were expelled from the mouth. Nasal irritation increased with exposure concentration. Necropsy at 14 days following the 0.240 mg/l (43 ppm) exposure revealed necrosis and erythema in the nasal passages. The lethality data are summarized in Table 7-5.

TABLE 7-3 Toxicity of Sulfuryl Chloride in Male Rats Following a Single 4-h Head Only Inhalation Exposure

Exposure in ppm (mean ± s.d)	Exposure concentration range (ppm)	Mortality
84.4 ± 7.7	80-103	0/10
134 ± 39.9	70-110	2/10 (1 During exposure and 1 within 24 h)
155 ± 19.9	135-195	8/10 (6 During exposure; 2 within 24 h)
207 ± 23.4	172-240	7/10 (All died during exposure)
273 ±16.5	225-294	10/10 (All during exposure)

Source: DuPont 1982.

TABLE 7-4 Inhalation Toxicity in Rats Exposed to Sulfuryl Chloride

Gender	Lethality Value	Source
Male	1-h LC_{50} = 131 ppm	Bayer AG 1993a; IUCLID 2000
Female	1-h LC_{50} = 242 ppm	Bayer AG 1993a; IUCLID 2000

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TABLE 7-5 Lethality in Rats Following 1-h Inhalation Exposure to Sulfuryl Chloride

Exposure concentration (ppm)	Mortality ratio	Time-to-death
43	0/10	–
71	8/10	1-18 h
108	8/10	1-16 h
200	10/10	1-10 h
252	10/10	1-5 h
392	10/10	1-5 h

Source: Stauffer Chemical Company 1969.

In a later study, a 1-h LC_{50} of 0.33 mg/L (~59.4 ppm) for male and female rats (200 g, strain, age not specified) was reported by Western Research Center (Stauffer Chemical Company 1970). Purity of the test article was specified as "> 1% < 100%". Results of this study are shown in Table 7-6. Exposed rats exhibited concentration-related increased severity of lacrimation, erythema around the eyes and ears, salivation, and dyspnea. All dead rats exhibited grossly hemorrhagic lungs with severe erythema of the gastrointestinal tract. Rats in the low-dose groups also exhibited areas of pulmonary hemorrhage. Total post-exposure observation time was not specified although it may be inferred that the rats were observed for at least 72 h.

3.2. Nonlethal Toxicity

3.2.1. Rats

In the study reported by Kelly and Stula (1983), male Sprague-Dawley rats (10/group) exposed head-only to a nonlethal exposure of 84.4 ppm sulfuryl chloride exhibited reddish exudate around the eyes and nostrils. Notable body weight loss for two days following exposure was also reported for these rats. The rats were observed for up to 14 days post exposure. No gross or histopathologic findings were reported.

In a 14-day inhalation exposure study, groups of 10 male Sprague-Dawley rats were exposed to sulfuryl chloride (17, 55, or 166 mg/m^3, equivalent to 3.1, 9.9, or 29.9 ppm) for 6 h/day, 5 days/week (Kelly and Stula 1983). The highest concentration caused excessive weight loss after two exposures and was reduced to 100 mg/m^3 (19.8 ppm) which resulted in the death of two rats after only 8 exposures. Fourteen-day exposure to the lower concentrations was not lethal but produced a concentration-related increase in blood urea nitrogen and histopathologic evidence of respiratory tract damage. Exposure to the lowest dose also exacerbated naturally occurring murine pneumonitis.

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TABLE 7-6 Lethality of Rats Exposed to Sulfuryl Chloride for 1 h

Exposure concentration	Mortality ratio	Time to death
0.174 mg/l (31.3 ppm)	0/10	–
0.346 mg/l (62.3 ppm)	6/10	16-72 h
0.695 mg/l (125.1 ppm)	10/10	8-12 h

Source: Stauffer Chemical Company 1970.

3.3. Developmental/Reproductive Effects

Information was not available regarding the developmental/reproducetive toxicity of sulfuryl chloride.

3.4. Genotoxicity

Sulfuryl chloride was negative in an Ames test with *Salmonella typhimurium* TA 100 (up to 4000 μg/plate) with and without metabolic activation (Bayer AG 1993b). In another assay (Bayer AG 1989) with *Salmonella typhimurium* TA 100, there was a significant dose-dependent increase in the number of revertants with no metabolic activation. However, tests with strains TA98, TA 1535, and TA 1537 were negative with and without activation (Bayer AG 1989).

3.5. Carcinogenicity

Information was not available regarding the carcinogenicity of sulfuryl chloride.

3.6. Summary

Toxicity data for sulfuryl chloride are limited to lethality studies in rats. One-hour LC_{50} values for rats ranged from 59-242 ppm. The 1-h LC_{50} estimates from one study (Bayer 1987) suggested a gender-related sensitivity in lethality; 1-h LC_{50} of 131 and 242 ppm for male and females, respectively. A 4-h LC_{50} of 159 ppm was reported for male rats. Because sulfuryl chloride decomposes to hydrochloric acid and sulfuric acid upon contact with water, it may be assumed that much of its toxicity is attributable to corrosive activity of these products on contacted tissues (e.g., respiratory tract). Exposure of test animals to nonlethal concentrations of sulfuryl chloride was associated with signs of ocular and respiratory irritation, body weight loss, and respiratory tract damage. There is a notable discrepancy among the available toxicity data; results of the Stauffer Chemical Company 1-h exposure studies appear to suggest much greater toxicity for sulfuryl chloride than do data from other studies.

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4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No information was available regarding the metabolism of sulfuryl chloride. Substantial decomposition to sulfuric acid and hydrochloric acid upon contact with moisture (e.g., respiratory tract epithelial surfaces) is expected based upon the chemical properties of sulfuryl chloride.

4.2. Mechanism of Toxicity

No experimental data were available regarding the mechanism of toxicity of sulfuryl chloride. Corrosive activity and subsequent damage to epithelial tissue would be expected from the decomposition products of sulfuric acid and hydrochloric acid.

4.3. Structure-Activity Relationships

Structure-activity relationships were not utilized for AEGL development. Sulfur chloride (S_2Cl_2) is sufficiently different from sulfuryl chloride in its water solubility (less soluble), its degradation products (hydrochloric acid, sulfur, and sulfur dioxide for sulfur chloride versus hydrochloric acid and sulfuric acid for sulfuryl chloride), and acute toxicity (animal data indicate that sulfur chloride is notably less toxic than sulfuryl chloride). Acute inhalation exposure toxicity data in animals show that sulfuryl chloride is notably more toxic than its degradation products.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No human exposure data are available with which to develop AEGL-1 values.

5.2. Animal Data Relevant to AEGL-1

There were no data with which to develop AEGL-1 values for sulfuryl chloride.

5.3. Derivation of AEGL-1

The lowest concentrations tested in available animal studies were associated with evidence of respiratory tract damage. No exposure-response data are

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available to differentiate AEGL-1 type effects from those that may progress to more serious effects. The continuum of toxic responses is likely a function of the corrosive action of the sulfuryl chloride degradation products, hydrochloric and sulfuric acid. The sulfur chloride concentrations at which the corrosive activity of these products becomes more than minor irritation is unclear. Therefore, AEGL-1 values are not recommended (Table 7-7).

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human exposure data were available with which to develop AEGL-2 values.

6.2. Animal Data Relevant to AEGL-2

Rats exposed to 0.174 mg/l (31.3 ppm sulfuryl chloride for one hour exhibited signs of toxicity consistent with contact irritation and respiratory tract damage (lacrimation, erythema around the eyes and ears, salivation, dyspnea, and pulmonary hemorrhage) (Stauffer Chemical Company 1970). Reddish exudate around the eyes and nostrils was also observed in rats exposed to 84.4 ppm (lowest concentration tested) for four hours (DuPont 1982; Kelly and Stula 1983). Neither of these exposures were associated with lethality. Overall, the animal data clearly showed evidence of pulmonary damage in the absence of lethality. In addition, body weight losses were reported for rats at nonlethal concentrations. Repeated (3.1 or 9.9 ppm for 6 h/day, 5 days/week) nonlethal exposures exacerbated naturally occurring murine pneumonitis (Kelly and Stula 1983).

6.3. Derivation of AEGL-2

The reviewed toxicity studies were conducted primarily to assess lethality. Lethality threshold estimates (e.g., LC_{01}, $BMCL_{05}$) from all studies resulted in exposure concentrations that were less than the nonlethal concentrations in the respective studies. However, all nonlethal exposures resulted in respiratory tract damage (necrosis, hemorrhage) that was detectable at the end of the 3 to 14-day post-exposure observation periods. Because lethality threshold estimates tended to be less than nonlethal experimental exposures and because of the apparent steep exposure-response curve for sulfuryl chloride, AEGL-2 values (Table 7-8) were estimated by a three-fold reduction of the AEGL-3 values (NRC 2001).

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TABLE 7-7 AEGL-1 Values for Sulfuryl Chloride

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1	NR	NR	NR	NR	NR

NR: not recommended; insufficient data.

TABLE 7-8 AEGL-2 Values for Sulfuryl Chloride

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	4.7 ppm 26 mg/m^3	4.7 ppm 26 mg/m^3	3.7 ppm 20 mg/m^3	2.3 ppm 13 mg/m^3	1.2 ppm 6.6 mg/m^3

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human exposure data were available with which to develop AEGL-3 values.

7.2. Animal Data Relevant to AEGL-3

Lethality data in animals are limited to rats. In acute inhalation studies conducted at Haskell Laboratory (DuPont 1982; Kelly and Stula 1983), rats were exposed (head-only) to 84.4, 134, 155, 207, or 273 ppm sulfuryl chloride (100% purity) for four hours. Exposure to 84.4 ppm was without lethality and provided a 4-h LC_{50} of 159 ppm. Stauffer Chemical Company (1970) reported a 1-h LC_{50} value of 59 ppm and Bayer (1987) reported 1-h LC_{50} values of 131 ppm and 242 ppm for male and female rats, respectively. A 4-h $BMCL_{05}$ of 70.1 ppm (EPA 2005) and an LC_{01} of 70.6 ppm (Litchfield and Wilcoxon 1949) were derived from the 4-h exposure-response data of the DuPont (Kelly and Stula 1983) study.

7.3. Derivation of AEGL-3

The 4-h $BMCL_{05}$ of 70.1 ppm calculated from the Haskell Laboratory study (DuPont 1982; Kelly and Stula 1983) was used as the point-of-departure for deriving AEGL-3 values (Appendix B). This is a more conservative approach than use of the LC_{01} (70.6 ppm) as an estimate of the lethality threshold using these data. This may be justified by the known respiratory tract damage observed in nonlethal exposures and the potential uncertainty regarding latent-occurring health effects, including lethality, beyond the observation periods utilized in the animal studies. The Haskell Laboratory studies were used for AEGL

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development in preference to alternate data sets because they contained greater detail than other reports, utilized nose-only exposures, and specified purity of the test article. The interspecies uncertainty factor was limited to 3 because the effects of sulfuryl chloride consist of contact tissue damage of degradation products (sulfuric acid and hydrochloric acid), and not from metabolites, and because rodents will receive a greater dose to target tissues than would humans. An intraspecies uncertainty factor of 3 was considered sufficient to account for individual variability in direct-contact toxic response to corrosive agents. Additional adjustment was considered unnecessary because a 4-h exposure of rats to 84 ppm in the DuPont (1982) study was not lethal, and multiple exposures of rats to at least two 6-h exposures to 29.9 ppm followed by up to seven additional 6-h exposures to 19.8 ppm were not lethal (Kelly and Stula 1983). In the absence of an empirically derived chemical-specific scaling exponent, temporal scaling for AEGL-3 values was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC 2001). Because of uncertainties in extrapolating from the 4-h experimental durations upon which the $BMCL_{05}$ is based to a 10-min AEGL exposure period, the 10-min AEGL-3 value was set equivalent to the 30-min value (NRC 2001). AEGL-3 values for sulfuryl chloride are presented in Table 7-9 and their derivation shown in Appendix A.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

The AEGL values for sulfuryl chloride are summarized in Table 7-10. The AEGL-3 values are based upon a lethality threshold ($BMCL_{05}$ of 70.1 ppm) estimated from 4-h exposure data in rats. The available lethality studies in rats utilized post exposure observation periods up to 14 days and, therefore, accounted to some extent for the latency in lethal response to chemicals causing pulmonary damage via corrosive activity. Date were insufficient for determining a threshold for AEGL-2 severity effects. Therefore, the AEGL-2 values were derived by a three-fold reduction of the AEGL-3 values. Because all exposure concentrations tested produced effects greater than AEGL-1 severity, AEGL-1 values were not developed and are not recommended. A comparison of the AEGL values to the available animal toxicity data (Appendix D) reveals that all AEGL concentrations are well below those causing any effects in animals.

TABLE 7-9 AEGL-3 Values for Sulfuryl Chloride

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-3	14 ppm 77 mg/m^3	14 ppm 77 mg/m^3	11 ppm 61 mg/m^3	7.0 ppm 39 mg/m^3	3.5 ppm 19 mg/m^3

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TABLE 7-10 AEGL Values for Sulfuryl Chloride

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	4.7 ppm 26 mg/m^3	4.7 ppm 26 mg/m^3	3.7 ppm 20 mg/m^3	2.3 ppm 13 mg/m^3	1.2 ppm 6.6 mg/m^3
AEGL-3 (Lethality)	14 ppm 77 mg/m^3	14 ppm 77 mg/m^3	11 ppm 61 mg/m^3	7.0 ppm 39 mg/m^3	3.5 ppm 19 mg/m^3

NR: not recommended; insufficient data.

8.2. Comparisons with Other Standards and Guidelines

No standards or guidelines are currently available for sulfuryl chloride.

8.3. Data Adequacy and Research Needs

Human exposure data for sulfuryl chloride were unavailable. The currently available toxicity information for sulfuryl chloride is limited to data from acute lethality studies and one repeated exposure study in rats. Due to the known degradation of sulfuryl chloride to hydrochloric acid and sulfuric acid, the toxic effects are qualitatively predicable. The available lethality data in rats were sufficient for development of AEGL-3 values although there are apparent discrepancies among the available data sets. Exposure-response data were insufficient for assessing with confidence a point-of departure for AEGL-2 severity effects. It may be assumed that the continuum of the toxic response from irritation to lethality may be attributed to sulfuryl chloride-induced respiratory tract damage but the precise exposure at which this occurs is uncertain. Data were insufficient for deriving AEGL-1 values.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR SULFURYL CHLORIDE

Derivation of AEGL-1 for Sulfuryl Chloride

Data were insufficient for developing AEGL-1 values for sulfuryl chloride. All exposure regimens in the available studies resulted in effects greater than those consistent with AEGL-1.

Derivation of AEGL-2 for Sulfuryl Chloride

Lethality thresholds (e.g., LC_{01}, $BMCL_{05}$, one-third of LC_{50}) estimated from the Stauffer Chemical (1969, 1970) and from the DuPont studies (DuPont 1982; Kelly and Stula 1983) reports were less than the respective nonlethal exposures reported in these studies. For this reason and because exposure-response data were insufficient for determination of a threshold for AEGL-2 severity effects, derivation of AEGL-2 values by a three-fold reduction of AEGL-3 values was considered appropriate. The resulting AEGL-2 values are:

10-min AEGL-2:	4.7 ppm
30-min AEGL-2:	4.7 ppm
1-h AEGL-2:	3.7 ppm
4-h AEGL-2:	2.3 ppm
8-h AEGL-2:	1.2 ppm

Derivation of AEGL-3 Sulfuryl Chloride

Key studies:

DuPont (E.I. du Pont de Nemours & Co). 1982. Inhalation Median Lethal Concentration (LC_{50}) of Sulfuryl Chloride. Haskell Laboratory Report No. 387-82. Haskell Laboratory for Toxicology and Industrial Medicine. E. I. du Pont de Nemours and Co., Inc.

Kelly, D.P., and E.F. Stula. 1983. Acute and subacute inhalation toxicity of sulfuryl chloride in rats. Toxicologist 3(1):62 [Abstract 248].

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Critical effect:	$BMCL_{05}$ of 70.1 ppm estimated as lethality threshold in rats following 4-h exposure to sulfuryl chloride.
Time scaling:	$C^n \times t = k$ where $n = 1$ or 3. In the absence of an empirically derived chemical-specific scaling exponent, temporal scaling for both AEGL-2 and AEGL-3 values was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC 2001).
Uncertainty factors:	Total uncertainty factor adjustment was 10. Interspecies: The effects of sulfuryl chloride are mediated by contact tissue damage resulting from the degradation of sulfuryl chloride to sulfuric acid and hydrochloric acid and not the result of metabolic processes. In addition, rodents will receive a greater dose to target tissues than would humans. Therefore, the uncertainty factor for interspecies variability was limited to 3. Intraspecies: An intraspecies uncertainty factor of 3 was considered sufficient to account for individual variability in direct-contact toxic response to corrosive agents and for individuals with compromised respiratory function.
Calculations:	$(70.1 \text{ ppm})^1 \times 4 \text{ h} = 280.4 \text{-ppm-h}$ $(70.1 \text{ ppm})^3 \times 4 \text{ h} = 1{,}377{,}888 \text{ ppm}^3\text{-h}$
10-min AEGL-3	Due to uncertainties in extrapolating from the 4-h POD to 10-min exposure duration, the 10-min AEGL-3 is set equivalent to the 30 min AEGL-3 (14 ppm)
30-min AEGL-3	$C^3 \times 0.5 \text{ h} = 1{,}377{,}888 \text{ ppm}^3\text{-h}$ $C^3 = 2{,}755{,}777 \text{ ppm}^3\text{-h}$ $C = 140$ ppm UF application: 140 ppm/10 = 14 ppm

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1-h AEGL-3	$C^3 \times 1$ h = 1,377,888 ppm^3-h C^3 = 1,377,888 ppm^3-h C = 111 ppm UF application: 111 ppm/10 = 11 ppm
4-h AEGL-3	$C^1 \times 4$ h = 280.4 ppm-h C = 70 ppm UF application: 70 ppm/10 = 7.0 ppm
8-h AEGL-3	$C^1 \times 8$ h = 280.4 ppm-h C = 35 ppm UF application: 35 ppm/10 = 3.5 ppm

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APPENDIX B

LC_{50} AND BENCHMARK DOSE CALCULATIONS FOR SULFURYL CHLORIDE

DuPont (E.I. du Pont de Nemours & Co). 1982. Inhalation Median Lethal Concentration (LC_{50}) of Sulfuryl Chloride. Haskell Laboratory Report No. 387-82. Haskell Laboratory for Toxicology and Industrial Medicine, E. I. du Pont de Nemours and Co., Inc.

Rats (male); all exposure concentrations expressed in ppm

Dose	Mortality	Observed%	Expected%	Observed-Expected	Chi-Square
84.400	0/10	0 (2.60)	2.81	-0.21	0.0002
134.000	2/10	20.00	30.77	-10.77	0.0544
155.000	8/10	80.00	51.23	28.77	0.3314
207.000	7/10	70.00	85.30	-15.30	0.1866
273.000	10/10	100 (97.40)	96.75	0.65	0.0013

Values in parentheses are corrected for 0 or 100% Total = 0.5739

LC_{50} = 153.718 (133.380 - 177.158)*
Slope = 1.32 (1.19 - 1.47)*
*These values are 95% confidence limits

Total animals = 50
Total doses = 5
Animals/dose = 10.00
Chi-square = total chi-square × animals/dose = 5.7391
Table value for chi-square with 3 degrees of freedom = 7.8200

LC_{84} = 203.516
LC_{16} = 116.105
FED = 1.15
FS = 1.11
A = 1.08

Probit Model $Revision: 2.1
$ Date: 2000/02/26 03:38:53 $
Input Data File: C:\BMDS\SO2CL2.(d)
Gnuplot Plotting File: C:\BMDS\SO2CL2.plt
Mon Nov 27 11:22:45 2006

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Exposure	Expected Lethal Dose Values (ppm)
$LC_{0.1}$	47.752
$LC_{1.0}$	70.619
$LC_{5.0}$	93.383
LC_{10}	105.974
LC_{25}	127.633
LC_{50}	153.718
LC_{75}	185.134
LC_{90}	222.972
LC_{99}	334.600

Benchmark Dose: $BMCL_{05}$ Rat lethality data DuPont 1982; Kelly and Stula 1983).

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 = -14.2564
Slope = 2.83606

Asymptotic Correlation Matrix of Parameter Estimates
(*** 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)

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	Intercept	Slope
Intercept	1	-1
Slope	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0	NA
Intercept	-17.8499	4.6632
Slope	3.54497	0.917185

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	-16.1167			
Fitted model	-19.3819	6.53043	3	0.08847
Reduced model	-34.4972	36.761	4	< .0001
AIC: 42.7638				

Goodness of Fit

Dose	Est._Prob.	Expected	Scaled Observed	Size	Residual
84.4000	0.0168	0.168	0	10	-0.4128
134.0000	0.3131	3.131	2	10	-0.7709
155.0000	0.5115	5.115	8	10	1.825
207.0000	0.8542	8.542	7	10	-1.381
273.0000	0.9791	9.791	10	10	0.462

Chi-square = 6.22
DF = 3
P-value = 0.1015

Benchmark Dose Computation
Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
BMD = 96.6681
BMDL = 70.1015

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APPENDIX C

TIME SCALING CALCULATIONS

The relationship between dose and time for any given chemical is a function of the physical and chemical properties of the substance and the unique toxicological and pharmacological properties of the individual substance. Historically, the relationship according to Haber (1924), commonly called Haber's Law or Haber's Rule (i.e., $C \times t = k$, where C = exposure concentration, *t* = exposure duration, and *k* = a constant) has been used to relate exposure concentration and duration to effect (Rinehart and Hatch 1964). This concept states that exposure concentration and exposure duration may be reciprocally adjusted to maintain a cumulative exposure constant (*k*) and that this cumulative exposure constant will always reflect a specific quantitative and qualitative response. This inverse relationship of concentration and time may be valid when the toxic response to a chemical is equally dependent upon the concentration and the exposure duration. However, an assessment by ten Berge et al. (1986) of LC_{50} data for certain chemicals revealed chemical-specific relationships between exposure concentration and exposure duration that were often exponential. This relationship can be expressed by the equation $C^n \times t = k$, where *n* represents a chemical specific, and even a toxic end point specific, exponent. The relationship described by this equation is basically the form of a linear regression analysis of the log-log transformation of a plot of C vs t. Ten Berge et al. (1986) examined the airborne concentration (C) and short-term exposure duration (t) relationship relative to death for approximately 20 chemicals and found that the empirically derived value of *n* ranged from 0.8 to 3.5 among this group of chemicals. Hence, it was shown that the value of the exponent (*n*) in the equation $C^n \times t = k$ quantitatively defines the relationship between exposure concentration and exposure duration for a given chemical and for a specific health effect end point. Haber's Rule is the special case where $n = 1$. As the value of *n* increases, the plot of concentration vs time yields a progressive decrease in the slope of the curve. In the absence of an empirically derived chemical-specific scaling exponent, temporal scaling for both AEGL-2 and AEGL-3 values for sulfuryl chloride was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC 2001).

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APPENDIX D

ACUTE EXPOSURE GUIDELINES FOR SULFURYL CHLORIDE

Derivation Summary for Sulfuryl Chloride

AEGL-1 VALUES

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

Reference: Not applicable

Test Species/Strain/Number: Not applicable

Exposure Route/Concentrations/Durations: Not applicable

Effects: Not applicable

End Point/Concentration/Rationale: Not applicable

Uncertainty Factors/Rationale: Not applicable

Modifying Factor: None applied

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: Not applicable

Data Adequacy: Data were insufficient for developing AEGL-1 values. Test exposures in all available studies resulted in greater than AEGL-1 effects (respiratory tract damage) in animals.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
4.7 ppm	4.7 ppm	3.7 ppm	2.3 ppm	1.2 ppm

Reference: NA

Test Species/Strain/Sex/Number: NA

Exposure Route/Concentrations/Durations: inhalation (see AEGL-3)

Effects: NA; estimated as one-third of AEGL-3

End Point/Concentration/Rationale: Due to inadequate data and uncertainties regarding a definitive threshold for AEGL-2 level effects, the AEGL-2 values were estimated as one-third of the AEGL-3.

Uncertainty Factors/Rationale: Total uncertainty factor: See AEGL-3

Modifying Factor: None applied

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: See AEGL-3

Data Adequacy: Nonlethal exposure of rats to sulfuryl chloride produced effects of respiratory irritation and pulmonary damage, dyspnea, and body weight loss. Estimated lethality thresholds were less than experimental exposures that were not lethal. Therefore, the AEGL-2 values were derived as one-third of the AEGL-3 values.

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AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
14 ppm	14 ppm	11 ppm	7.0 ppm	3.5 ppm

References:

DuPont (E.I. du Pont de Nemours & Co). 1982. Inhalation Median Lethal Concentration (LC_{50}) of Sulfuryl Chloride. Haskell Laboratory Report No. 387-82. Haskell Laboratory for Toxicology and Industrial Medicine, E. I. du Pont de Nemours and Co., Inc.

Kelly, D.P., and E.F. Stula. 1983. Acute and subacute inhalation toxicity of sulfuryl chloride in rats. Toxicologist 3(1):62 [Abstract 248].

Test Species/Strain/Sex/Number:10 male Crl:CD7 rats (7-8 weeks old, 233-274g)

Exposure Route/Concentrations/Durations: Inhalation (head-only) exposure to 84.4, 134, 155, 207, or 273 ppm sulfuryl chloride (100% purity) for four hours; 14-day observation

Effects:

Exposure Conc. (ppm)	Mortality
84.4	0/10
134	2/10
155	8/10
207	7/10
273	10/10

End Point/Concentration/Rationale: The 4-h $BMCL_{05}$ of 70.1 ppm calculated from the Haskell Laboratory study (DuPont 1982; Kelly and Stula 1983) was used as the point-of-departure for deriving AEGL-3 values. Although a somewhat more conservative approach than use of the LC_{01} (70.6 ppm), it may be justified by the known respiratory tract damage observed for nonlethal exposures and the potential for latent-occurring health effects, including lethality, beyond the 3 to 14-day observation periods utilized in the animal studies.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10

Interspecies: The interspecies uncertainty factor was limited to 3 because contact tissue damage results from the degradation products (sulfuric acid and hydrochloric acid) and not metabolism processes, and because rodents will receive a greater dose to target tissues than would humans.

Intraspecies: An intraspecies uncertainty factor of 3 was considered sufficient to account for individual variability in direct-contact toxic response to corrosive agents. Additional uncertainty was considered unnecessary because a 4-h exposure of rats to 84 ppm in the DuPont (1982) study was not lethal, and multiple exposures of rats to 55 ppm was not lethal (Kelley and Stula 1983).

Modifying Factor: None applied

(Continued)

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AEGL-3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
14 ppm	14 ppm	11 ppm	7.0 ppm	3.5 ppm

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: In the absence of an empirically derived chemical-specific scaling exponent, temporal scaling for both AEGL-2 and AEGL-3 values was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC 2001).

Data Adequacy: Toxicity data were available for only one species, although the mode of action is likely very similar across species. Data were sufficient for AEGL-3 development.

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APPENDIX E: CATEGORY PLOT FOR SULFURYL CHLORIDE

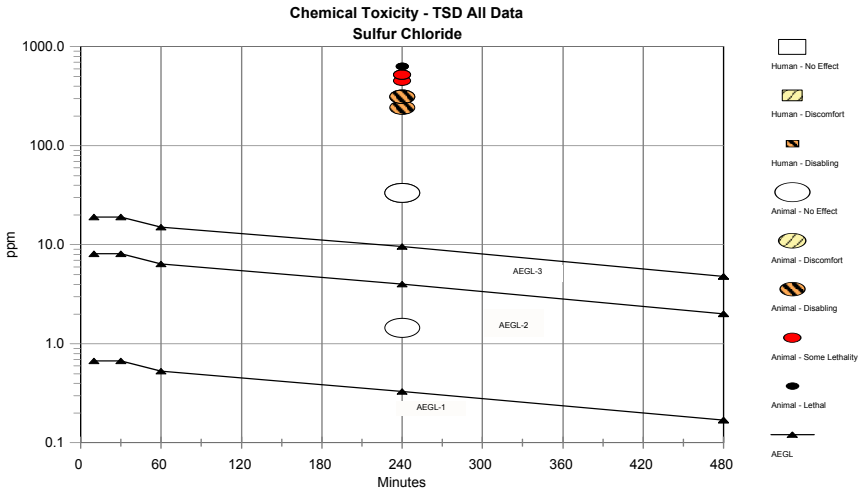

FIGURE 7-1 Category plot for sulfuryl chloride.

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