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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 U.S. Department of Defense (DOD), the U.S. Department of Energy (DOE), the U.S. 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 seventh volume in the series

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

Acute Exposure Guideline Levels for Selected Airborne Chemicals. It reviews the AEGLs for acetone cyanohydrin, carbon disulfide, monochloroacetic acid, and phenol for scientific accuracy, completeness, and consistency with the NRC guideline reports.

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

Two 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 two of the committtee's interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for monochloroacetic acid and phenol (*Thirteenth Interim Report of the Committee on Acute Exposure Guideline Levels*, 2005) and acetone cyanohydrin and carbon disulfide (*Fourteenth Interim Report of the Committee on Acute Exposure Guideline Levels*, 2006): Deepak K. Bhalla (Wayne State University), David W. Gaylor (Gaylor and Associates, LLC), and Sam Kacew (University of Ottawa).

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of this volume before its release. The review of the interim report completed in 2005 was overseen by Sidney Green, Jr. (Howard University). The review of the interim report completed in 2006 was overseen by Robert A. Goyer, professor emeritus, University of Western Ontario. Appointed by the NRC, they were responsible for making certain that an independent examination of the interim reports were carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The committee gratefully acknowledges the valuable assistance provided by the following persons: Ernest Falke, Marquea D. King, Iris A. Camacho, and Paul Tobin (all from EPA); George Rusch (Honeywell, Inc.). The committee acknowl-

edges James J. Reisa, director of the Board on Environmental Studies and Toxicology, and Susan Martel, senior program officer for toxicology, for their helpful guidance. Kulbir Bakshi, project director for his work in this project, and Raymond Wassel for bringing the report to completion. Other staff members who contributed to this effort are Ruth Crossgrove (senior editor), Mirsada Karalic-Loncarevic (manager of the Technical Information Center), Radiah Rose (editorial projects manager), Aida Neel (program associate), and Korin Thompson (project assistant). Finally, we would like to thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

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

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 7

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

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

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

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

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

exposures at high levels but of short duration, usually less than 1 hour (h), and only once in a lifetime for the general population, which includes infants , 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 by the federal government to identify, review, and interpret relevant toxicologic and other scientific data and to develop acute exposure guideline levels (AEGLs) for high-priority, acutely toxic chemicals. The NRC's previous name for acute exposure levels—community emergency exposure levels (CEELs)—was replaced by the term AEGLs to reflect the broad application of these values to planning, response, and prevention in the community, the workplace, transportation, the military, and the remediation of Superfund sites.

AEGLs represent threshold exposure limits (exposure levels below which adverse health effects are not likely to occur) for the general public and are applicable to emergency exposures ranging from 10 minutes (min) to 8 h. Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 min, 30 min, 1 h, 4 h, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

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

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

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

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

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

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

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

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

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

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

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

REVIEW OF AEGL REPORTS

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

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

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

Because of the enormous amount of data presented in AEGL reports, the NRC committee cannot verify all of the data used by NAC. The NRC committee

relies on NAC for the accuracy and completeness of the toxicity data cited in the AEGL reports. Thus far, the committee has prepared six reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b). This report is the seventh volume in that series. AEGL documents for acetone cyanohydrin, carbon disulfide, monochloroacetic acid, and phenol are each published as an appendix in this report. The NRC committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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Appendixes

1

Acetone Cyanohydrin[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). AEGL-1, AEGL-2, and AEGL-3, as appropriate, will be developed for each of five exposure periods (10 and 30 min and 1, 4, and 8 h) and will be distinguished by varying degrees of severity of toxic effects. The recommended exposure levels are considered applicable to the general population, including infants and children and other individuals who may be sensitive or susceptible. The three AEGLs have been defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million [ppm] or milligrams per cubic meter [mg/m^3]) of a substance above which it is

[1]This document was prepared by the AEGL Development Team composed of Peter Griem (Forschungs- und Beratungsinstitut Gefahrstoffe GmbH) and Chemical Managers Larry Gephart and Ernest V. Falke (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guideline reports (NRC 1993, 2001).

predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m³) 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/m³) 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 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 sensitive subpopulations, it is recognized that certain individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Acetone cyanohydrin is a colorless to yellowish liquid with a characteristic bitter almond odor due to the presence of free hydrogen cyanide (HCN). The major use of acetone cyanohydrin is in the production of methacrylic acid and its esters; the latter are used for the production of plexiglass. Further uses of acetone cyanohydrin are in the production of acrylic esters, polyacrylic plastics. and synthetic resins, as well as in the manufacture of insecticides, pharmaceuticals, fragrances, and perfumes. Acetone cyanohydrin decomposes spontaneously in the presence of water to acetone and HCN.

Fatalities and life-threatening occupational intoxication have been described after accidental inhalation, skin contact, and ingestion. Initial symptoms after mild exposure to acetone cyanohydrin range from cardiac palpitation, headache, weakness, dizziness, nausea, and vomiting to nose, eye, throat, and skin irritation. Acetone cyanohydrin behaves as its molar equivalent in cyanide both in vitro and in vivo. All the pharmacologic actions of cyanide result from cyanide's reversible complex with the ferric (+3) state of mitochondrial cytochrome c oxidase also known as ferrocytochrome c oxygen oxidoreductase. Cessation of electron transport across the inner mitochondrial membrane results in inhibition of oxygen utilization and causes hypoxia and cellular destruction.

Four studies exposed rats repeatedly to acetone cyanohydrin at about 10, 30, and 60 ppm for 6 h/day (d), 5 d/week (wk) for a total of 4 weeks (Monsanto

1986a; using groups of 10 male and 10 female rats), 10 weeks (Monsanto 1982b; using groups of 15 male rats) and 14 weeks (Monsanto 1986b; using groups of 15 male and 15 female rats) or for 6 h/d for 21 days (Monsanto 1982c; using groups of 15 female rats). Death was observed at 60 ppm after the first exposure in three animals of the Monsanto (1986a) study but not in subsequent exposures or in the other studies conducted under similar protocols. Preceding death, respiratory distress, prostration, convulsions, and tremors were obvious. In all studies, exposure at 60 and 30 ppm caused signs of irritation (red nasal discharge, clear nasal discharge, perioral wetness, and encrustations) during the first and subsequent weeks of exposure. At 10 ppm, red nasal discharge was not observed in one study (Monsanto 1986a); its incidence was not increased compared with the concurrent control group in two studies (Monsanto 1982b,c), but it was increased compared with the control group in the fourth study (Monsanto 1986b). No other signs of intoxication were reported in these four studies.

The derivation of AEGL-1 values was based on the facts that acetone cyanohydrin decomposes spontaneously to HCN and acetone and that local and systemic toxic effects of acetone cyanohydrin are due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-1 values (on a ppm basis) derived for HCN (NRC 2002) to acetone cyanohydrin. This procedure is supported by similar values that would be derived on the basis of available acetone cyanohydrin studies in rats (derivation basis would be exposure at 9.2 ppm for 6 h/d, 5 d/wk for 4 weeks, which did not result in red nasal discharge [Monsanto 1986a]) using a total uncertainty factor of 10.

The odor threshold of acetone cyanohydrin has not been firmly established. Shkodich (1966) published the odor threshold for acetone cyanohydrin in water (0.06 milligrams per liter [mg/L]). However, the odor would necessarily be the consequence of a mixed presentation of the HCN and acetone cyanohydrin concentrations in air. Since no definitive reports on the odor threshold of acetone cyanohydrin were located in the literature, no level of distinct odor awareness (LOA) was derived.

The derivation of AEGL-2 values was based on the facts that acetone cyanohydrin decomposes spontaneously to HCN and acetone and that the systemic toxicity of acetone cyanohydrin is due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-2 values (on a ppm basis) derived for HCN (NRC 2002) to acetone cyanohydrin. This procedure is supported by similar values that would be derived on the basis of available acetone cyanohydrin studies in rats using a total uncertainty factor of 10 (derivation basis would be exposure at 29.9 ppm for 6 h/d, 5 d/wk for 4 weeks, which caused signs of irritation, while the next higher concentration produced respiratory distress, prostration, convulsions and tremors, Monsanto [1986a]).

The derivation of AEGL-3 values was based on the facts that acetone cyanohydrin decomposes spontaneously to HCN and acetone and that the systemic toxicity of acetone cyanohydrin is due to free cyanide. Once absorbed, a dose of

acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-3 values (on a ppm basis) derived for HCN (NRC 2002) to acetone cyanohydrin. This procedure is supported by the close similarity of acetone cyanohydrin and HCN regarding death in rats: Blank (1983) reported that 3 of 10 rats died after the first exposure to HCN at 68 ppm; the subsequent two exposures on the following days caused no additional deaths. This finding closely resembles that of Monsanto's (1986a) report of death of 3 of 20 animals after the first exposure to acetone cyanohydrin at 60 ppm (the actual exposure concentration on the first day might have been slightly higher than the average 59.6 ppm); no additional deaths were found in the 19 subsequent exposures. The derived values are listed in Table 1-1 below.

1. INTRODUCTION

Acetone cyanohydrin is a colorless to yellowish liquid with a characteristic bitter almond odor due to the presence of free HCN (ACGIH 1996). The major use of acetone cyanohydrin is in the preparation of -methacrylic acid and its esters; the latter are used for the production of plexiglass. Further uses of acetone cyanohydrin are in the production of acrylic esters, polyacrylic plastics, and synthetic resins as well as an intermediate in the manufacture of insecticides, pharmaceuticals, fragrances, and perfumes (OECD 1997). About 0.5-1 million metric tons of acetone cyanohydrin is produced worldwide annually (IUCLID 2000) principally by reaction of HCN with acetone. Chemical and physical properties of acetone cyanohydrin are listed in Table 1-2.

TABLE 1-1 Summary of AEGL Values for Acetone Cyanohydrin[a,b]

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (Nondisabling)	2.5 ppm (8.8 mg/m³)	2.5 ppm (8.8 mg/m³)	2.0 ppm (7.0 mg/m³)	1.3 ppm (4.6 mg/m³)	1.0 ppm (3.5 mg/m³)	Application of AEGL-1 values for HCN (NRC 2002)
AEGL-2 (Disabling)	17 ppm (60 mg/m³)	10 ppm (35 mg/m³)	7.1 ppm (25 mg/m³)	3.5 ppm (12 mg/m³)	2.5 ppm (8.8 mg/m³)	Application of AEGL-2 values for HCN (NRC 2002)
AEGL-3 (Lethal)	27 ppm (95 mg/m³)	21 ppm (74 mg/m³)	15 ppm (53 mg/m³)	8.6 ppm (30 mg/m³)	6.6 ppm (23 mg/m³)	Application of AEGL-3 values for HCN (NRC 2002)

[a]Acetone cyanohydrin decomposes spontaneously in the presence of water to yield HCN and acetone. Therefore, both acetone cyanohydrin and HCN concentrations should be considered.
[b]Cutaneous absorption may occur; direct skin contact with the liquid should be avoided.

TABLE 1-2 Chemical and Physical Data for Acetone Cyanohydrin

Parameter	Data	Reference
Molecular formula	$(CH_3)_2C(OH)CN$	IUCLID 2000
Molecular weight	85,1	E.I. du Pont de Nemours and Co. 1998
CAS Registry Number	75-86-5	IUCLID 2000
Physical state	Liquid	E.I. du Pont de Nemours and Co. 1998
Color	Colorless	E.I. du Pont de Nemours and Co. 1998
	Colorless to yellowish	ACGIH 1996
Synonyms	2-Propanone cyanohydrin; 2-cyano-2-propanol; 2-cyano-2-hydroxypropane; hydroxyisobutyronitrile; 2-methyl-lactonitrile; 2-hydroxy-2-methyl-propionitrile; Acetoncyanhydrin	IUCLID 2000
Vapor pressure	1.07 hPa at 20°C	IUCLID 2000
	0.8 mm Hg at 20°C	E.I. du Pont de Nemours and Co. 1998
	1 mm Hg at 25°C	E.I. du Pont de Nemours and Co. 1998
	1.6 hPa at 40°C	Grybat et al. 2003
	12.5 hPa at 72°C	Grybat et al. 2003
Density	0.932 g/cm^3 at 19°C	IUCLID 2000
	0.9267 g/cm^3 at 25°C	IUCLID 2000
Melting point	−19°C to −20°C	IUCLID 2000
Boiling point	81°C at 30.7 hPa	IUCLID 2000
	82°C at 23 mm Hg	E.I. du Pont de Nemours and Co. 1998
	95°C at 1013 hPa (decomposition to acetone and HCN)	IUCLID 1996
Solubility	Very soluble in water, alcohol and ether	E.I. du Pont de Nemours and Co. 1998
Odor	Characteristic bitter almond odor of free HCN	ACGIH 1996
Explosive limits in air	2.2 % (LEL) to 12 % (UEL)	IUCLID 2000
Conversion factors	1 ppm = 3.5 mg/m³	E.I. du Pont de Nemours and Co. 1998
	1 mg/m³ = 0.28 ppm	

Since the elimination reaction of HCN from acetone cyanohydrin is an endothermic reaction, the decomposition of acetone cyanohydrin is accelerated by heat. At temperatures of 120°C or higher, acetone cyanohydrin decomposes with

the evolution of HCN (IUCLID 2000). Rather than acting as mere diluents, water and ethanol (especially in the presence of amines) exert specific dissociative effects on acetone cyanohydrin (Stewart and Fontana 1940). The very rapid breakdown of acetone cyanohydrin with moisture would present some challenges in any accidental spill or release. Because acetone cyanohydrin breaks down so readily to HCN and the toxicity is due to HCN, both materials are present in a mixture and the ratio of the two could be rapidly changing. Therefore, both materials would need to be tracked to give an indication of the risk.

Acetone cyanohydrin in air can be specifically determined using solid sorbent sampling (samples should be stored water-free and frozen to avoid decomposition), elution with a water-free solvent (ethylacetate), and gas chromatographic analysis (Glaser and O'Connor 1985; NIOSH 1985). Methods for total cyanide determination involving sampling in alkaline solutions or infrared spectroscopy also are available (Singh et al. 1986). Electrochemical detectors for HCN and Draeger tubes for HCN will not detect acetone cyanohydrin. However, these devices can be used to detect HCN that will form rapidly in a case of acetone cyanohydrin release because of its decomposition to acetone and HCN.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Although deaths have occurred from exposures to acetone cyanohydrin, specific exposure concentrations and exposure periods have not been reported (Sunderman and Kincaid 1953; NIOSH 1978; DECOS 1995; ACGIH 1996). Fatalities and life-threatening poisonings with clonic-tonic convulsions in workers have been described after inhalation (Krefft 1955) and skin contact (Sunderman and Kincaid 1953; Thiess and Hey 1969) as well as after accidental ingestion (Sunderman and Kincaid 1953). Following mild exposure to acetone cyanohydrin, patients presented with cardiac palpitation; headache; weakness; dizziness; nausea; vomiting; and nose, eye, throat, and skin irritation (Ballantyne and Marrs 1987; DECOS 1995).

2.2. Nonlethal Toxicity

No relevant studies documenting nonlethal effects in humans after a single inhalation exposure to acetone cyanohydrin were located in the available literature. Cases of intoxication in workers after dermal contact with acetone cyanohydrin have been reported (Lang and Stintzy 1960; Zeller et al. 1969).

Sunderman and Kincaid (1953) described at least three pumpers who lost consciousness during the packing operation of acetone cyanohydrin. The men recovered after they had been revived on exposure to fresh air and cleaning their hands. No permanent injury apparently occurred following these exposures. It had been noted that the pumpers usually had their hands covered with grease.

When the employees had covered their hands, the effects of acetone cyanohydrin were minimal, suggesting dermal penetration of acetone cyanohydrin as the principal route of exposure in these cases. The symptoms following mild exposure to acetone cyanohydrin were predominantly cardiac palpitation, headache, nausea, and vomiting. No details about the exposure conditions were reported.

Oral exposure to acetone cyanohydrin may occur as a consequence of its liberation from linamarin, a cyanogenic glycoside found in cassava and other plant foodstuffs (Conn 1979). Linamarin is the common name given to a molecule composed of glucose and acetone cyanohydrin. Since toxic effects of linamarin usually become evident only after long-term, low-dose exposure, toxicity data for linamarin are not considered relevant to AEGL development and thus are not presented here.

Shkodich (1966) reported that according to a majority of people smelling and tasting acetone-cyanohydrin-containing water, the sensory threshold of smell for this substance is at a concentration of 0.06 mg/L and that of aftertaste is 0.48 mg/L. No experimental details were reported.

2.3. Developmental and Reproductive Toxicity

No studies documenting potential developmental or reproductive toxicity of acetone cyanohydrin exposure in humans were located in the available literature.

2.4. Genotoxicity

No studies documenting the genotoxic potential of acetone cyanohydrin exposure in humans were located in the available literature.

2.5. Carcinogenicity

No studies documenting the carcinogenic potential of acetone cyanohydrin exposure in humans were located in the available literature.

2.6. Summary

Deaths associated with inhaled acetone cyanohydrin have occurred, but exposure concentrations are unknown. Likewise, airborne exposure concentrations for those who survived the initial acute intoxication were not provided, but in each instance, there was ample opportunity for skin absorption. No information on developmental or reproductive effects, genotoxicity, or carcinogenicity was located.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Lethality data are available for the rat; only one study reporting lethality in mice was located. The lethality data are summarized in Table 1-3.

3.1.1. Rats

Smyth et al. (1962) exposed groups of six albino rats to acetone cyanohydrin vapors that were produced by passing a 2.5-L/min-air-stream through a fritted glass disc immersed in 50 mL of acetone cyanohydrin. Doses were logarithmically distributed, differing by a factor of two (doses were not stated explicitly). The observation period was 14 d. After exposure for 4 h, two of six rats were killed at 62.5 ppm and six of six rats were killed at 125 ppm. The maximum time rats could be exposed to saturated vapor (about 1,300 ppm) without producing any deaths was 5 min. No other signs of toxicity were reported.

Izmerov et al. (1982) reported an LC_{40} (concentration that is lethal for 40% of test organisms) of 185 mg/m³ (51.8 ppm) for 2 h in rats (no details reported).

Sunderman and Kincaid (1953) using saturated vapors of commercially available acetone cyanohydrin reported that six of six rats died after 1.5 min. When the free HCN contained in the acetone cyanohydrin was removed by precipitation with silver nitrate before exposure, the authors found that collapse occurred after an average time of 4 min and 50 % mortality after 10 min (the exact number of animals not stated).

Monsanto (1986a) exposed groups of 10 female and 10 male Sprague-Dawley rats to acetone cyanohydrin at 0, 10, 30, or 60 ppm for 6 h/d, 5 d/wk for 20 exposure days (28 days in total). Concentrations in the exposure chamber were calculated by dividing the net amount of acetone cyanohydrin delivered to the chamber per unit time by the airflow per unit time and, in addition, measured by a Miran infrared analyzer (using the C-N triple bond frequency, which detects both acetone cyanohydrin and HCN) four times daily. For the total exposure period, mean analytic concentrations (± standard deviation [SD]) were determined as 9.2 ± 0.9, 29.9 ± 1.2, and 59.6 ± 1.4 ppm, respectively. In the highest exposure group, respiratory distress, tremors or convulsions or both, foaming at the mouth, and prostration were observed in four males following the first exposure. Three of the four animals died. No deaths occurred in the 29.9-ppm group (see section 3.2.4 for nonlethal effects). In three other studies conducted under similar protocols, no deaths were observed at 60 ppm for 6 h/d (Monsanto 1982b,c, 1986b) (see sections 3.2.1 and 3.3.1). The authors suggested that the differences between the 28-d study and the 14-week study (Monsanto 1986b) were possibly due to the very steep dose-response for acetone

TABLE 1-3 Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Rat	Saturated vapor (about 1,300 ppm)	1.5 min (time to death)	6/6 animals died during exposure period; using commercially available acetone cyanohydrin	Sunderman and Kincaid 1953
Rat	Saturated vapor (about 1,300 ppm)	10 min (time to death)	6/6 animals died during exposure period; using commercial acetone cyanohydrin with free HCN removed	Sunderman and Kincaid 1953
Rat	125	4 h	6/6 animals died	Smyth et al. 1962
Rat	62.5	4 h	2/6 animals died	Smyth et al. 1962
Rat	59.6	6 h/d, 5 d/wk, 4 wk	3/20 animals died (deaths occurred after first exposure during which exposure to an elevated concentration may have occurred)	Monsanto 1986a
Rat	58.6	6 h/d, 7 d/wk, 21 d	No deaths in 24 animals	Monsanto 1982c
Rat	57.7	6 h/d, 5 d/wk, 14 wk	No deaths in 30 animals	Monsanto 1986b
Rat	57.2	6 h/d, 5 d/w, 48 d	No deaths in 15 animals	Monsanto 1982b
Rat	51.8	2 h	LC_{40}	Izmerov et al. 1982
Mouse	574	2 h	LC_{50}	Gabor et al. 1962
Mouse	19.6	2 h	LC_{30}	Izmerov et al. 1982

cyanohydrin or to the normal variation in experimental animals of the same strain. Evaluation of the nominal and analytic concentrations revealed that the animals in the 60-ppm group may have been exposed to a slightly higher concentration during the second half of the first day: the nominal concentration of 64.8 ppm for the first day was the highest of all days (mean for the other 19 exposure days was 60.4 ± 1.8 ppm), likewise, the last two analytic concentrations measured during the first day (55.5, 60.5, 63.5, and 63.5 ppm; mean 60.8 ± 3.8) were greater than those measured on all subsequent exposure days (the highest individual value for exposure days 2-20 was 61.5 ppm; mean for exposure days 2-20 was 59.5 ± 1.4 ppm).

3.1.2. Mice

Gabor et al. (1962) exposed albino mice to different acetone cyanohydrin concentrations (0.5-3 mg/L [40-840 ppm]) for 2 h. Deaths were reported as 0 of 10 mice at 140 ppm, 0 of 10 at 280 ppm, 8 of 10 at 420 ppm, 18 of 44 at 560 ppm, 4 of 10 at 700 ppm, and 10 of 10 at 840 ppm. The authors found a 50% narcosis level at 1.65 mg/L (462 ppm) and calculated a LC_{50} of 2.05 mg/L (574 ppm). The mouse strain, analytic methods, and post-exposure observation period were not reported.

Izmerov et al. (1982) reported an LC_{30} of 70 mg/m³ (19.6 ppm) for 2 h in mice (no details were reported).

3.2. Nonlethal Toxicity

No studies were located that evaluated nonlethal consequences of acetone cyanohydrin after a single inhalation exposure. Studies using repeated inhalation exposure reported signs of irritation, such as red nasal discharge and perioral wetness. These data are summarized in Table 1-4.

3.2.1. Rats

Monsanto (1986a) exposed groups of 10 female and 10 male Sprague-Dawley rats to mean acetone cyanohydrin concentrations of 9.2 ± 0.9, 29.9 ± 1.2, and 59.6 ± 1.4 ppm, respectively, for 6 h/d, 5 d/wk for 20 exposure days (28 days in total) (see section 3.1.1). Three of 20 animals that inhaled 59.6 ppm died after the first exposure. The three animals that died and another animal that survived showed respiratory distress, prostration, tremors and/or convulsions (observed in three of the four animals), and foaming of the mouth (observed in two of the four animals). During the first week of exposure, red nasal discharge was reported in 0 of 20 control animals, 0 of 20 animals in the 10-ppm group, 4 of 20 animals in the 30-ppm group, and 2 of 20 animals in the 60-ppm group (the authors reported incidences of irritation only for whole weeks, but not for single days). Reduced ($p > 0.05$) body weight was found in the high-exposure group. No gross or microscopic lesions attributable to acetone cyanohydrin exposure were observed. Total serum protein was reduced in male rats at all exposure concentrations but only statistically significant in the mid- and high-exposure groups.

Monsanto (1986b) conducted exposures of 15 female and 15 male Sprague-Dawley rats to acetone cyanohydrin at 0, 10, 30, or 60 ppm for 6 h/d, 5 d/wk for 14 weeks. Concentrations in the exposure chamber were calculated by dividing the net amount of acetone cyanohydrin delivered to the chamber per unit time by the airflow per unit time and, in addition, measured by a Miran

TABLE 1-4 Summary of Nonlethal Signs of Acetone Cyanohydrin Exposure in Laboratory Animals

Species	Target [analytic] concentration (ppm)	Exposure Time	Effect	Reference
Rat	60 [57.2]	6 h/d, 5 d/wk, 48 d	Red nasal discharge in 14/15 animals vs. 10/15 in controls and perioral wetness/red stain in 8/15 animals vs. 2/15 in controls during first 10-d period; 15 males tested	Monsanto 1982b
Rat	60 [58.6]	6 h/d, 7 d/wk, 21 d	Red nasal discharge and encrustations during week 1 in 12/24 animals vs. 6/24 controls; 24 females tested	Monsanto 1982c
Rat	60 [59.6]	6 h/d, 5 d/wk,4 wk	Respiratory distress, prostration, tremors and/or convulsions in 4/20, red nasal discharge in 2/20 animals vs. 0/20 in controls during week 1; 3/20 males died after first day; 10 females and 10 males tested	Monsanto 1986a
Rat	60 [57.7]	6 h/d, 5 d/wk, 14 wk	Bloodlike discharge about the nose in 20/30 animals vs. 6/30 in controls and clear nasal discharge in 2/30 animals vs. 0/30 in controls during week 1; no deaths occurred; 15 females and 15 males tested	Monsanto 1986b
Rat	30 [28.5]	6 h/d, 5 d/wk, 48 d	Red nasal discharge in 12/15 animals vs. 10/15 in controls and perioral wetness/red stain in 4/15 animals vs. 2/15 in controls during first 10-d period; 15 males tested	Monsanto 1982b
Rat	30 [30.4]	6 h/d, 7 d/wk, 21 d	Red nasal discharge and encrustations during week 1 in 10/24 animals vs. 6/24 controls; 24 females tested	Monsanto 1982c
Rat	30 [29.9]	6 h/d, 5 d/wk, 4 wk	Red nasal discharge in 4/20 animals vs. 0/20 in controls during week 1; 10 females and 10 males tested	Monsanto 1986a
Rat	30 [28.6]	6 h/d, 5 d/wk, 14 wk	Bloodlike discharge about the nose in 18/30 animals vs. 6/30 in controls and clear nasal discharge in 3/30 animals vs. 0/30 in controls during week 1; 15 females and 15 males tested	Monsanto 1986b
Rat	10 [10.0]	6 h/d, 5 d/wk, 48 d	Red nasal discharge during week 1 in 10/15 animals vs. 10/15 in controls; 15 males tested	Monsanto 1982b

(Continued)

TABLE 1-4 Continued

Species	Target [analytic] concentration (ppm)	Exposure Time	Effect	Reference
Rat	10 [10.7]	6 h/d, 7 d/wk, 21 d	Red nasal discharge and encrustations during week 1 in 9/24 animals vs. 6/24 in controls; 24 females tested	Monsanto 1982c
Rat	10 [9.2]	6 h/d, 5 d/wk, 4 wk	No signs of irritation; 10 females and 10 males tested	Monsanto 1986a
Rat	10 [10.1]	6 h/d, 5 d/wk, 14 wk	Bloodlike discharge about the nose in 17/30 animals vs. 6/30 in controls and clear nasal discharge in 3/30 animals vs. 0/30 in controls during week 1; 15 females and 15 males tested	Monsanto 1986b

infrared analyzer (using the C-N triple bond frequency, which detects both acetone cyanohydrin and HCN). For the total exposure period, mean concentrations (±SD) were determined as 10.1 ± 0.9, 28.6 ± 1.8, and 57.7 ± 2.9 ppm, respectively. No deaths were observed. During the first week of treatment, bloodlike discharge about the nose was observed in 6 of 30 control animals, 17 of 30 animals in the 10-ppm group, 18 of 30 animals in the 30 ppm group, and 20 of 30 animals in the 60-ppm group; clear nasal discharge was reported in 0 of 30, 3 of 30, 3 of 30, and 2 of 30 animals, respectively (the authors reported incidences of irritation only for whole weeks, but not for single days). No exposure related signs of toxicity or changes in hematologic or clinical chemistry parameters were observed. No effect on body weight was found. No gross or microscopic lesions attributable to acetone cyanohydrin were observed.

Monsanto (1982b) exposed male Sprague-Dawley rats (15/dose group) by inhalation to acetone cyanohydrin at 0, 10, 30, or 60 ppm for 6 h/d, 5 d/wk for 48 exposure days (69 days in total). Concentrations in the exposure chamber were calculated by dividing the net amount of acetone cyanohydrin delivered to the chamber per unit time by the airflow per unit time and, in addition, measured by a Miran infrared analyzer (using the C-N triple bond frequency, which detects both acetone cyanohydrin and HCN). For the total exposure period, mean concentrations (±SD) were determined as 10.0 ± 1.0, 28.5 ± 1.9, and 57.2 ± 3.0 ppm, respectively. For the period of exposure days 1-10, red nasal discharge was observed in 10 of 15 concurrent control animals and in 10 of 15, 12 of 15, and 14 of 15 animals that inhaled 10, 30, or 60 ppm, respectively; perioral wetness and red stain was observed in 2 of 15, 2 of 15, 4 of 15, and 8 of 15 animals, respectively. (The authors did not report the incidence of signs of irritation for single days.)

Monsanto (1982c) exposed female Sprague-Dawley rats (24/dose group) by inhalation to acetone cyanohydrin at 0, 10, 30, or 60 ppm for 6 h/d, 7 d/wk for 21 d. Concentrations in the exposure chamber were calculated by dividing the net amount of acetone cyanohydrin delivered to the chamber per unit time by the airflow per unit time and, in addition, measured by a Miran infrared analyzer (using the C-N triple bond frequency, which detects both acetone cyanohydrin and HCN). For the total exposure period, mean concentrations (±SD) were determined as 10.7 ± 0.4, 30.4 ± 2.1, and 58.6 ± 2.3 ppm, respectively. During the first week of exposure, red nasal discharge or encrustations were observed in 6 of 24 animals of the control group and in 9 of 24, 10 of 24, and 12 of 24 animals exposed to 10, 30, and 60 ppm, respectively. (The authors reported incidences of irritation for whole weeks only but not for single days.)

3.3. Developmental and Reproductive Toxicity

3.3.1. Rats

No studies documenting potential developmental or reproductive toxicity

of acetone cyanohydrin after a single inhalation exposure were located in the available literature.

In fertility studies, Monsanto (1982b) exposed male Sprague-Dawley rats (15/dose group) by inhalation to acetone cyanohydrin concentrations (±SD) of 0, 10.0 ± 1.0, 28.5 ± 1.9, or 57.2 ± 3.0 ppm for 6 h/d, 5 d/wk for 48 exposure days (69 days in total) (see section 3.2.1 for details and signs of irritation). After the treatment period, each male was mated consecutively with three untreated females. There were no adverse effects of inhaled acetone cyanohydrin in males as indicated by mortality, mean body weights (the high-exposure group showed a lower mean body weight, which was not significantly different from that of the concurrent control group), clinical observations and necropsy (males were killed about 3 weeks after the end of the exposure period). The number of live implants and pre- and post-implantation losses were comparable for females mated with untreated or treated males. The authors concluded that exposure to acetone cyanohydrin at 60 ppm failed to demonstrate any potential for reproductive toxicity in male rats.

In fertility studies, Monsanto (1982c) exposed female Sprague-Dawley rats (24/dose group) by inhalation to acetone cyanohydrin at 0, 10.7 ± 0.4, 30.4 ± 2.1, and 58.6 ± 2.3 ppm for 6 h/d, 7 d/wk for 21 days (see section 3.2.1 for details and signs of irritation). There was no indication of a treatment-related adverse effect on body weight during exposure or during gestation. After cessation of exposure, the females were mated with untreated males. At examination on gestational days 13-15, fertility of mated females was comparable between the treated groups and the control group for mating efficiency, pregnancy rates, number of live implants, and pre- and post-implantation losses. The authors concluded that repeated inhalation of acetone cyanohydrin at 60 ppm failed to demonstrate any adverse effects on fertility of female rats.

Monsanto (1982a, 1983) treated groups of 25 pregnant Sprague-Dawley rats by gavage to 0, 1, 3, or 10 mg of acetone cyanohydrin per kilogram (kg) per day on days 6-15 of gestation. No deaths were observed. Maternal toxicity was evident by slight reductions in body-weight gain in the mid- and high-dose groups. Statistically significant differences between the high-dose group and controls were observed for the reduction of the number of corpora lutea per dam and the number of implantations per dam. Numbers of viable fetuses per dam, post-implantation losses per dam (nonviable fetuses, early and late resorptions), mean fetal body weight, and fetal sex distribution for all dose groups were comparable with controls. The incidence of malformations and developmental variations for all fetuses of treated animals were comparable with the concurrent control group fetuses.

3.4. Genotoxicity

In tests using different *Salmonella* strains, acetone cyanohydrin failed to yield a reproducible positive response. No mutagenic activity was observed in

vitro using the Chinese hamster ovary (CHO) gene mutation assay. No significant increases in the frequency of chromosome aberrations were observed in bone marrow cells of Sprague-Dawley rats (24 rats/sex/group) taken 6, 12, 24, or 48 h after administration of acetone cyanohydrin at 0, 1.5, 5, or 15 mg/kg by gavage (IUCLID 2000; E.I. du Pont de Nemours and Co. 1998).

3.5. Carcinogenicity

No information regarding the carcinogenic potential of acetone cyanohydrin exposure was located in the available literature. Genotoxicity studies with cyanide salts were generally negative, and no cancers were induced in rats in a 2-y feeding study with HCN (NRC 2002).

3.6. Summary

Inhalation data were available mainly for the rat. During exposure of rats, death was observed at saturated concentration (about 1,300 ppm) after 1.5 or 10 min (Sunderman and Kincaid 1953) or 5 min (Smyth et al. 1962). Other studies (failing to provide experimental details) reported death of two of six rats after 4 h at 62.5 ppm (Smyth et al. 1962), an LC_{40} of 51.8 ppm in rats, an LC_{30} of 19.6 ppm in mice (Izmerov et al., 1982), and an LC_{50} of 574 ppm for 2 h in mice (Gabor et al. 1962). In a series of studies exposing rats repeatedly at about 60 ppm for 6 h/d, deaths in 3 of 20, 0 of 20, 0 of 24, and 0 of 15 animals were observed (Monsanto 1982b,c, 1986a,b). Preceding death, respiratory distress, prostration, convulsions, and tremors were observed after the first exposure at 60 ppm (Monsanto 1986a). In the other three studies, exposure at 60 ppm and, in all studies, exposure at 30 ppm caused red nasal discharge and encrustations during the first week of exposure. At 10 ppm, the incidence of red nasal discharge was significantly increased in one of the four Monsanto studies.

4. SPECIAL CONSIDERATIONS

4.1. Stability, Metabolism, and Disposition

Upon release into moist air, acetone cyanohydrin decomposes to yield HCN and acetone. This process is accelerated by heat and catalyzed by the presence of water. In dilute aqueous solutions, acetone cyanohydrin will fully decompose. The half-life for decomposition is pH dependent and was calculated for a 0.1% solution as 57 min at pH 4.9, 28 min at pH 6.3, and 8 min at pH 6.8 (ICI 1993). From the rate constant for decomposition at pH 7 and 26°C of 4.47 h^{-1}, a half-life of 9 min was calculated (Ellington et al. 1987).

In the humid air and the moist mucosa of the respiratory tract, acetone cyanohydrin decomposes to yield its molar equivalent in HCN and acetone. This

reaction is a result of the physical chemistry of acetone cyanohydrin (Stewart and Fontana 1940), and it is not known to be enzyme-catalyzed in animals or humans (Kaplita and Smith 1986; DECOS 1995).

Acetone cyanohydrin is miscible with water and is taken up by the moist respiratory passages. The pulmonary retention of acetone cyanohydrin has not been reported, but it is probably in the range for HCN (about 58%; ATSDR 1997), acrylonitrile (about 50%; ATSDR 1990), and acetone (70-80%; ATSDR 1994). Cyanide concentrations in liver and brain of CD-1 mice were similar after a single intraperitoneal injection of an equimolar dose of acetone cyanohydrin or sodium cyanide. After injection of acetone cyanohydrin at 9 mg/kg, 108.0 ± 27.5 and 30.0 ± 4.6 mmol/kg were found in liver and brain, respectively. After a single injection of a single dose of sodium cyanide at 4.8 mg/kg, cyanide concentrations in liver and brain were 87.8 ± 31.2 mmol/kg and 24.9 ± 4.8 mmol/kg, respectively (Willhite and Smith 1981).

With regard to the metabolism of cyanide, it is important to distinguish between low-dose cyanide metabolism, which occurs under circumstances in which cyanide is present in physiologic concentrations, and high-dose cyanide disposition, in which amounts of cyanide are far in excess of those present under normal physiologic conditions. Low-dose cyanide metabolism involves incorporation via vitamin B_{12}-dependent enzymes of cyanide into the C_1-metabolite pool from which it can be eliminated as carbon dioxide. Under physiologic conditions, the normal capacity of rhodanese to handle cyanide is not overwhelmed, and circulating cyanide remains in metabolic equilibrium with the C_1-metabolic pool (DECOS 1995; ATSDR 1997).

At high doses of cyanide, the metabolic pathway via the C_1-metabolite pool becomes quickly saturated, and detoxification involving enzymatic thiocyanate formation occurs. The enzyme rhodanese (E.C. 2.8.1.1) catalyzes the transfer of a sulfane sulfur atom from sulfur donors, such as thiosulfate, to cyanide, which acts as a sulfur acceptor, thus forming thiocyanate (DECOS 1995; ATSDR 1997). The activity of rhodanese is variable between species and tissues but is high in liver and kidney in most species (Ballantyne and Marrs 1987). The quantitative contribution to thiocyanate formation of beta-mercaptopyruvate-cyanide sulfurtransferase (E.C. 2.8.1.2), which is found in blood, liver, and kidney and catalyzes the transfer of a sulfur atom from 2-mercaptopyruvate to cyanide forming pyruvate and thiocyanate, is not known (DECOS 1995). The half-life time for the conversion of cyanide to thiocyanate from a nonlethal dose in humans is between 20 and 60 min (ATSDR 1997).

A minor pathway for cyanide detoxification is the formation of 2-aminothiazoline-4-carboxylic acid from cyanide and cystine. This reaction occurs spontaneously both in vitro and in vivo and is not enzyme-dependent. The reaction product has been identified in urine of experimental animals and in humans exposed to high concentrations of cyanide (Wilson 1987; Wood and Cooley 1956).

Acetone is oxidized in the liver by cytochrome P450 2E1 to acetol. Acetol in turn can be used for gluconeogenesis, that is, biosynthesis of glucose, either

via further oxidation to methylglyoxal in the liver or extrahepatically via reduction to L-1,2-propanediol, which can return to the liver where it is oxidized to L-lactaldehyde and further to L-lactate, which is then incorporated into glucose. Alternatively, L-1,2-propanediol can be degraded to acetate and formate in the liver (Casazza et al. 1984; Kosugi et al. 1986).

Data regarding the excretion of acetone cyanohydrin per se are not available. The cyanide metabolic products thiocyanate, cyanocobalamin, and 2-aminothiazole-4-carboxylic acid are excreted into urine. HCN and carbon dioxide are expired (DECOS 1995; ATSDR 1997).

4.2. Mechanism of Toxicity

Acetone cyanohydrin behaves as its molar equivalent in cyanide both in vitro and in vivo. All of the pharmacologic actions of cyanide result from cyanide's reversible complex with the ferric (+3) state of mitochondrial cytochrome c oxidase, also known as ferrocytochrome c–oxygen oxidoreductase. This enzyme is also known as cytochrome aa3, and it is the terminal oxidase in aerobic metabolism of all animals, plants, yeasts, and some bacteria. This enzyme is a heme-copper lipoprotein, and cytochromes a and a3 are combined in the same large oligomeric protein molecule. Mammalian cytochrome c oxidase contains two molecules of heme A and two copper atoms. This helical protein also contains 820 amino acids. The integrity of the disulfide groups to maintain the 30% helix structure is essential to the oxidase mechanism. Cessation of the mitochondrial electron transport results in inhibition of oxygen utilization and causes hypoxia and cellular destruction.

The interaction of cytochrome c oxidase with cytochrome c was reviewed by Lemberg (1969). The reaction proceeds by first-order kinetics with respect to the concentration of cytochrome c (Smith et al. 1979). Once absorbed, cyanide complexes with many metal ions and interferes with the activities of at least 39 heme zinc, copper, and disulfide enzymes (e.g., catalase and peroxidase) whose activities depend on either metals as cofactors or prosthetic groups (Dixon and Webb 1964). Cyanide also binds to nonhematin metal containing enzymes, like tyrosinase, ascorbic acid oxidase, xanthine oxidase, amino acid oxidase, formic dehydrogenase, and various phosphates. The cyanide concentration required for cytochrome c oxidase inhibition is 26 orders of magnitude less than that required for inhibition of these other enzymes. Thus, it is the critical position of cytochrome c oxidase in aerobic metabolism that makes its inhibition felt earliest, so the effects of HCN on other enzyme systems have scant chance to appear (Rieders 1971). The oxidase-HCN (not CN) (Stannard and Horecker 1948; Gibson and Greenwood 1963) complex is dissociable (Swinyard 1975).

Willhite and Smith (1981) measured the inhibition of the oxidation of purified bovine cardiac cytochrome c in vitro by a number of nitriles. In the presence of potassium cyanide (KCN) or acetone cyanohydrin, the reaction was inhibited in a concentration-dependent fashion. The addition of acetone cyano-

hydrin inhibited the reaction in a manner kinetically similar to the addition of KCN. Since the inhibitory effects of KCN and acetone cyanohydrin were observed at pH 6.0 and the pKa of HCN is 9.2, the data indicate that the inhibitory species is the undissociated acid HCN, as suggested previously (Stannard and Horecker 1948; Gibson and Greenwood 1963).

4.3. Structure-Activity Relationships

Willhite and Smith (1981) demonstrated that the behavior of acetone cyanohydrin parallels that of its molar equivalent of cyanide in vivo. For example, the intraperitoneal LD_{50} (lethal dose with 50% lethality) in mice for acetone cyanohydrin (equivalent to 2.65 mg of cyanide ion per kilogram) is similar to that of sodium cyanide at 2.54 mg of cyanide ion per kilogram; mean time-to-death was 5 min for both compounds. Pretreatment with sodium nitrite or thiosulfate (standard cyanide antidotes) protected mice against lethal doses of acetone cyanohydrin and HCN. The authors also studied the acute toxicity in mice for a series of seven aliphatic nitriles (acetonitrile, propionitrile, acrylonitrile, *n*-butyronitrile, malononitrile, succinonitrile, and acetone cyanohydrin) and sodium cyanide. Only the latter two compounds produced death within 5 min. All other nitriles produced death at widely varying intervals from a few minutes to many hours. Pretreatment with the liver toxicant carbon tetrachloride protected mice against death from all nitriles, except acetone cyanohydrin, suggesting that all nitriles examined (except for acetone cyanohydrin) possess little if any acute toxicity in the absence of normal hepatic function and that these nitriles (except acetone cyanohydrin) underwent hepatic metabolism to release cyanide, accounting for their acute toxicity. In contrast, acetone cyanohydrin did not require metabolic activation and released its cyanide moiety spontaneously in vivo.

Johannsen and Levinskas (1986) undertook a structure-activity comparison of acetone cyanohydrin, lactonitrile, four mononitriles (acetonitrile, propionitrile, *n*-butyronitrile, and acrylonitrile) and two dinitriles (succinonitrile and adiponitrile). The authors observed that with regard to oral and dermal LD_{50}, as well as repeated administration, acetone cyanohydrin was the most potent compound tested. For other nitriles, the time to onset of signs of toxicity in rats was between 50 and 300 min after exposure, and for acetone cyanohydrin ,a rapid onset of signs (within 5 min) before death was found. The authors concluded that the signs of acetone cyanohydrin toxicity resembled those seen after exposure to sodium cyanide.

4.4. Other Relevant Information

4.4.1. Effects of Cyanides and Acetone in Humans

Since acetone cyanohydrin exerts toxicity through rapid release of cyanide, it is appropriate to take into consideration relevant studies describing ef-

fects in humans after exposure to cyanide (summarized in NRC 2002). Several studies reporting effects after repeated occupational exposure to cyanides are available; however, accurate empirical exposure data usually were not reported.

Bonsall (1984) described the case of a worker who was exposed to HCN during inspecting a tank containing a thin layer of hydrazodiisobutyronitrile. The tank had been washed with water, which resulted in hydrolysis of the nitrile into HCN and acetone. The man collapsed after 3 min, was fitted with a breathing apparatus after another 3 min and removed from the tank after 13 min. At this time, the worker was unconscious with imperceptible breathing and dilated pupils and was covered with chemical residue. Immediately after the accident, a concentration of HCN of about 500 mg/m³ (450 ppm) was measured. The victim was administered sodium thiosulfate and was discharged from the hospital 2 weeks later without apparent sequelae.

El Ghawabi et al. (1975), compared the symptoms of 36 workers exposed to HCN in three electropating factories in Egypt with a control group; employment ranged between 5 and 17 years. None of the workers in either the exposed or control groups were smokers. Cyanide exposure resulted from a plating bath that contained copper cyanide, sodium cyanide, and sodium carbonate. Concentrations of cyanide in the breathing zone of the workers ranged from 4.2 to 12.4 ppm (means in the three factories: 6, 8, and 10 ppm). Fifteen-minute air samples were collected in sodium hydroxide and analyzed colorimetrically. Symptoms reported most frequently by exposed workers compared with the referent control group were, in descending order of frequency: headache, weakness, and changes in taste and smell. Lacrimation, vomiting, abdominal colic, precordial pain, salivation, and nervous instability were less common. The authors made no attempt to correlate the incidences of these symptoms with concentrations. Although there were no clinical manifestations of hypothyroidism or hyperthyroidism, 20 of the workers had thyroid enlargement to a mild or moderate degree; this condition was accompanied by higher ^{131}I uptake compared with the referent controls. Exposed workers also had significantly higher blood hemoglobin, lymphocyte cell counts, cyanmethemoglobin, and urinary thiocyanate levels than controls. Urinary thiocyanate levels were correlated with cyanide concentration in workplace air. Two workers in the factory with a mean exposure of 10 ppm suffered psychotic episodes; recovery occurred within 36 to 48 h. Although the sample size was small, the study used well-matched controls and included a biologic index of exposure (urinary thiocyanate). The NRC Subcommittee on Spacecraft Maximum Allowable Concentrations, in evaluating the El Ghawabi et al. (1975) data, concluded that "8 ppm would likely produce no more than mild CNS effects (e.g., mild headache), which would be acceptable for 1-h exposures" of healthy adults (NRC 2000).

Blanc et al. (1985) surveyed and examined 36 former employees of a silver reclaiming facility to determine acute and potential residual adverse health effects resulting from occupational HCN exposure. The study was prompted by a worker fatality from acute cyanide poisoning. The workers had been chronically exposed to airborne cyanide at time-weighted-average (TWA) concentra-

tions (taken 24 h after the plant had closed down) of at least 15 ppm. The most frequent symptoms included headache, dizziness, nausea or vomiting, and a bitter or almond taste, eye irritation, loss of appetite, epistaxis, fatigue, and rash. The most prevalent symptoms (headache, dizziness, nausea or vomiting, and a bitter or almond taste) were consistent with cyanide poisoning. A concentration-response relationship corresponding to high- and low-exposure jobs was demonstrated, but exact breathing zone concentrations were not quantified. Some symptoms exhibiting a dose-response trend occurring 7 or more months after exposure had ceased. Mild abnormalities of vitamin B_{12}, folate, and thyroid function were detected, and those results suggested cyanide and/or thiocyanide involvement. The NRC (2000) pointed out that the 24-h TWA of 15 ppm was measured 1 day after the plant had ceased operation, suggesting that these workers may have been exposed to cyanide at more than 15 ppm.

Leeser et al. (1990) reported a cross-sectional study of the health of cyanide-salt production workers. Sixty-three cyanide production workers employed for 1 to 40 years were compared with 100 referent workers from a diphenyl oxide plant. Workers were examined before and after a block of six 8-h shifts. All workers had full medical examinations, routine clinical chemistry tests, and blood samples taken for measurement of blood cyanide and carboxyhemoglobin. In addition, circulating levels of vitamin B_{12} and thyroxin (T4) were measured. Atmospheric cyanide was monitored with static monitors, Draeger pump tests, and personal monitoring. For the personal monitoring, air was drawn through bubblers that contained sodium hydroxide. Cyanide collected in the sodium hydroxide solution was measured using an anion-selective ion electrode. All results (34 samples) were between 0.01 and 3.6 mg/m³ (0.01 and 3.3 ppm). Geometric mean values for eight job categories ranged between 0.03 and 1.05 mg/m³ (0.03 and 0.96 ppm). Values for only one job category (eight personal samples) averaged 0.96 ppm. Results of routine Draeger pump tests (area samples) were between 1 and 3 ppm (measurement method not stated). This increased exposure was reflected in an increase in mean blood cyanide level in the workers following a block of six 8-h shifts, and there was an increase of 5.83 µmol during the 6-ppm exposure compared with a decrease of 0.46 µmol across the shift block in the spring. Static monitors on all floors, set to trigger alarms at 10 ppm, failed to sound during the study. Circulating cyanide concentrations in exposed workers, though low, were generally higher than in control workers, and the highest levels were measured in cyanide-exposed nonsmokers compared with the nonsmoking control group (cyanide-exposed nonsmokers, 3.32 µmol; controls, 1.14 µmol; $p < 0.001$). For ex-smokers, the difference was smaller (cyanide exposed, 2.16 µmol; controls, 1.46 µmol), and for current smokers, the blood cyanide level was higher in the control group (2.94 µmol for cyanide workers who smoked; 3.14 µmol for controls who smoked). The percentage of workers reporting shortness of breath and lack of energy was higher in cyanide workers than in the diphenyl oxide plant workers. These differences were partially explained by the greater number of cyanide workers who were shift workers. Slightly higher hemoglobin values and lymphocyte counts in the cyanide

workers were not dose-related. Results of clinical and physical examinations and evaluation of medical histories failed to reveal any exposure-related health problems.

Compared with cyanide, the acute toxicity of acetone is low (ATSDR 1994). This fact is reflected in comparatively high values for the TLV (Threshold Limit Value) (ACGIH 1997) of 500 ppm for 8 h with a 750-ppm STEL (short-term exposure limit), the IDLH (immediately dangerous to life and health concentrations) of 2,500 ppm (NIOSH 1996), and the EEGL (emergency exposure guidance levels) of 1,000 ppm for 24 h and 8,500 ppm for 1 h (NRC 1984). Acetone and its metabolic products (Casazza et al. 1984; Kosugi et al. 1986; Gentry et al. 2003) contribute only insignificantly to the toxicity of acetone cyanohydrin.

4.4.2. Lethality of HCN in Animals

Only one study was located that evaluated lethality of HCN in rats for an exposure time comparable to that of the 6-h studies of Monsanto (1982b,c, 1986a,b) using acetone cyanohydrin.

Five male and five female Sprague-Dawley Crl:CD rats were exposed to HCN at 68 ppm in a stainless steel chamber for 6 h/d for 3 days (Blank 1983). HCN was generated by passing nitrogen over the liquid contained in a 500-mL flask. The concentration in the cage was measured with an infrared analyzer. During the exposures, hypoactivity and quick shallow breathing were observed in all animals. During the first day, three males exhibited anoxia and hypoxia followed by convulsions (one male). One male rat died during the exposure, a second male died during the post-exposure observation period, and a third male was found dead prior to the second day of exposure. Two additional males and all five females exhibited breathing difficulties following the first exposure. No additional mortality was observed following the second and third days of exposure; body weights by the third day were below pre-exposure weights. Necropsy of the three dead males revealed cyanosis of the extremities, moderate-to-severe hemorrhage of the lung, lung edema, tracheal edema, blanched appearance of the liver, singular occurrences of blood engorgement of the heart and surrounding vessels, chromorhinorrhea, urine-filled bladder, and gaseous distension of the gastrointestinal tract. Survivors were sacrificed following the last exposure. Of the seven survivors, three females developed slight-to-moderate pulmonary hemorrhage.

4.4.3. Species Variability

Because of the lack of sufficient data, the potential interspecies variability for acute inhalation toxicity of acetone cyanohydrin cannot be assessed directly. However, data on acute lethality after oral administration (Table 1-5) indicate that lethal doses are similar for different species.

TABLE 1-5 Summary of Oral LD_{50} Data for Acetone Cyanohydrin

Species	LD_{50} (mg/kg)	Reference
Rat	17	Smyth et al. 1962
Rat	13.3	Shkodich 1966
Rat	17.8	Marhold 1972
Mouse	14	Marhold 1972
Mouse	15	Hamblin 1953, personal commun., as cited in Sunderman and Kincaid 1953
Mouse	2.9	Shkodich 1966
Guinea pig	9	Shkodich 1966
Rabbit	13.5	Shkodich 1966

Likewise, nearly identical LD_{50} values have been found in rats and mice after parenteral application: An LD_{50} value of 8.7 mg/kg (95% confidence interval [CI], 8-9 mg/kg) (mean time to death, 5 ± 1 min) was found after intraperitoneal injection in CD-1 male mice (Willhite and Smith 1981), and one of 8.5 mg/kg was found after subcutaneous injection in male albino rats (Magos 1962).

For HCN, LC_{50} values for various species differ by a factor of 2-3 (ATSDR 1997), and an interspecies extrapolation factor of 2 was used for derivation of AEGL-3 and -2 values for HCN (NRC 2002).

4.4.4. Intraspecies Variability

People at potentially increased risk for toxic effects caused by exposure to acetone cyanohydrin include those with chronic exposure to cyanide (e.g., heavy smokers) or cyanogenic glycosides from edible plants (e.g., cassava or lima beans) and those with an inadequate detoxification of cyanide (reviewed in NRC 2002). The latter condition can result from inadequate dietary intake of vitamin B_{12} and/or sulfur-containing amino acids as well as from inborn metabolic errors, such as the genetic component responsible for Leber's hereditary optic atrophy, which is possibly associated with a reduction in rhodanese activity, dominantly inherited optic atrophy, and recessively inherited optic atrophy (DECOS 1995). However, for a single acute exposure to high acetone cyanohydrin concentrations, the interindividual differences are probably not great because the decomposition of acetone cyanohydrin to cyanide is not dependent on metabolism and the cyanide detoxification pathway becomes quickly saturated at higher exposure concentrations. Due to conservatism of the cytochrome c oxidase during evolution, interindividual differences in the affinity of cyanide binding to its target receptor are unlikely to occur.

For HCN, an intraspecies extrapolation factor of 3 has been used for derivation of AEGL-3 and -2 values for HCN (NRC 2002).

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

The odor threshold of acetone cyanohydrin has not been firmly established. Shkodich (1966) published the odor threshold for acetone cyanohydrin in water (0.06 mg/L). However, the odor would necessarily be the consequence of a mixed presentation of the HCN and cyanohydrin concentrations in air. Human data on irritation effects of acetone cyanohydrin are lacking.

Since the effects of acetone cyanohydrin are due to the release of cyanide after its rapid decomposition, data on exposure of humans to cyanide are relevant. In humans occupationally exposed to cyanide, no adverse effects have been found after exposure to a geometric mean cyanide concentration of 1 ppm (Leeser et al. 1990). At concentrations of 6-10 ppm, there were increased complaints of mild headache after repeated occupational exposure (El Ghawabi et al. 1975).

5.2. Animal Data Relevant to AEGL-1

During the first week of repeated 10-ppm 6-h exposure studies in rats, there was no sign of red nasal discharge in one study (Monsanto 1986a). The incidence of nasal discharge was not increased compared with concurrent control groups in two studies (Monsanto 1982b,c), but it was increased compared with the control group in a fourth study (Monsanto 1986b). No other adverse effects were reported in these four studies.

5.3. Derivation of AEGL-1

Human data on acetone cyanohydrin relevant for the derivation of AEGL-1 are lacking. One study in rats (Monsanto 1986a) reported red nasal discharge (which was interpreted as a sign of local irritation in the upper respiratory tract) in 4 of 20 animals at 29.9 ppm and in 2 of 20 animals at 59.6 ppm, but not in control animals and in animals exposed to 9.2 ppm, during the first week of repeated 6-h/d exposures. However, red nasal discharge was not consistently seen in any of the other Monsanto studies and, when present, was not always dose-responsive. In addition, control animals varied widely in terms of whether that end point was present or not. In light of the variability of the red nasal discharge in repeat studies, it seemed a poor end point on which to base the AEGL-1. Also, the repeat exposures used in the Monsanto studies were not appropriate for the derivation of AEGL-1 values.

The pathogenesis of red nasal discharge in rats is not entirely clear. In the case of acetone cyanohydrin, it may be related to local tissue hypoxia leading to vasodilatation and subsequent extravasation of red blood cells, which could explain the lack of histopathologic findings. Red nasal discharge in rats occurs at the plexus antebrachii, which is very prominent in the rat. In the rat, extravasation of red blood cells visible as red nasal discharge is caused easily not only by locally acting chemicals, but also by stress, dry air, or upper respiratory tract infections.

The derivation of AEGL-1 values was based on the facts that acetone cyanohydrin decomposes spontaneously to HCN and acetone and that the local and systemic toxic effects of acetone cyanohydrin are due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-1 values (on a ppm basis) derived for HCN (NRC 2002) to acetone cyanohydrin. This procedure is supported by similar values that would be derived on the basis of available acetone cyanohydrin studies in rats. The derivation basis would be an exposure at 9.2 ppm for 6 h/d, 5 d/wk for 4 weeks, which did not result in red nasal discharge (Monsanto 1986a). Using the default time scaling procedure and a total uncertainty factor of 10, AEGL-1 values of 2.1, 2.1, 1.7, 1.1, and 0.69 ppm would be derived for the 10- and 30-min and 1-, 4-, and 8-h periods, respectively.

The AEGL-1 values for acetone cyanohydrin are set at the same values (on a ppm basis) as the AEGL-1 values for HCN (NRC 2002). The values are listed in Table 1-6.

Because no definitive reports on the odor threshold of acetone cyanohydrin were located in the literature (see section 5.1), no level of distinct odor awareness (LOA) was derived.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

Human exposure data relevant for the derivation of AEGL-2 values are lacking. Because the effects of acetone cyanohydrin are caused by the release of cyanide after rapid decomposition of acetone cyanohydrin, data on exposure of humans to cyanide are relevant. Chronic occupational exposure to cyanide concentrations of about 6-10 ppm produced mild CNS effects (mild headache) (El Ghawabi et al. 1975); more distinct symptoms were reported for occupational exposures of 15 ppm and higher (Blanc et al. 1985).

6.2. Animal Data Relevant to AEGL-2

Four studies using repeated 6-h inhalation exposures of rats, performed

TABLE 1-6 AEGL-1 Values for Acetone Cyanohydrin[a]

AEGL	10 min	30 min	1 h	4 h	8 h
AEGL-1	2.5 ppm (8.8 mg/m³)	2.5 ppm (8.8 mg/m³)	2.0 ppm (7.0 mg/m³)	1.3 ppm (4.6 mg/m³)	1.0 ppm (3.5 mg/m³)

[a]Acetone cyanohydrin decomposes spontaneously in the presence of water to yield HCN and acetone. Therefore, both acetone cyanohydrin and HCN concentrations should be considered.

according to good laboratory practice, reported signs of irritation at an exposure concentration of about 30 ppm (Monsanto 1982b,c, 1986a,b), such as red nasal discharge and encrustations and perioral wetness and red stain. Red nasal discharge was also observed at about 10 ppm in two of the four studies. At higher concentrations of about 60 ppm in one study (Monsanto 1986a), respiratory distress, prostration, and tremors and/or convulsions were observed after the first exposure in 4 of 20 animals, and of these, three animals died. No studies showing irreversible, nonlethal effects in animals were available in the literature.

6.3. Derivation of AEGL-2

The derivation of AEGL-2 values was based on the facts that acetone cyanohydrin decomposes spontaneously to HCN and acetone and that the systemic toxicity of acetone cyanohydrin is due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-2 values (on a ppm basis) derived for HCN (NRC 2002) to acetone cyanohydrin. This conclusion is supported by very similar AEGL-2 values that would be derived on the basis of chemical-specific data: in the Monsanto (1986a) study, repeated exposures to 29.9 ppm acetone cyanohydrin for 6 h/d, 5 d/wk for 4 weeks resulted in irritation, but not in respiratory distress, which was observed in 4of 20 animals during the first exposure at 60 ppm. Using the default time-scaling procedure and a total uncertainty factor of 10, AEGL-2 values of 6.8, 6.8, 5.4, 3.4, and 2.5 ppm would be derived for the 10- and 30-min and 1-, 4-, and 8-h periods, respectively.

The AEGL-2 values for acetone cyanohydrin are set at the same values (on a ppm basis) as the AEGL-2 values for HCN (NRC 2002). The values are listed in Table 1-7.

TABLE 1-7 AEGL-2 Values for Acetone Cyanohydrin[a]

AEGL	10 min	30 min	1 h	4 h	8 h
AEGL-2	17 ppm (60 mg/m³)	10 ppm (35 mg/m³)	7.1 ppm (25 mg/m³)	3.5 ppm (12 mg/m³)	2.5 ppm (8.8 mg/m³)

[a]Acetone cyanohydrin decomposes spontaneously in the presence of water to yield HCN and acetone. Therefore, both acetone cyanohydrin and HCN concentrations should be considered.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

Human exposure data relevant for the derivation of AEGL-3 values are not available.

7.2. Animal Data Relevant to AEGL-3

Reliable LC_{50} studies for acetone cyanohydrin performed according to good laboratory practice are not available. Single-exposures killed two of six rats that inhaled 62.5 ppm for 4 h (Smyth et al. 1962). The LC_{40} was 51.8 ppm for 2 h in rats, and the LC_{30} was 19.6 ppm for 2 h in mice (Izmerov et al. 1982); however, due to the small number of animals in the study by Smyth et al. (1962), the lack of information on the rodent strain and the number of animals used in the study by Izmerov et al. (1982), and the failure of both studies to report experimental details, a thorough evaluation of these data is not possible.

The study by Sunderman and Kincaid (1953) used saturated acetone cyanohydrin vapor that led to death within 1.5 or 10 min. Likewise, Smyth et al. (1962) reported death of rats after 5 min of exposure to saturated vapor concentrations.

Four studies, performed according to good laboratory practice, exposed rats repeatedly to acetone cyanohydrin at about 60 ppm for 6 h/d (Monsanto 1982b,c, 1986a,b). Lethal effects were reported in only one of the studies (Monsanto 1986a): 3 of 10 males died after the first exposure, none of 10 female rats died, and no further deaths of males were observed in subsequent exposures. No deaths occurred in the other studies that used 15 males and 15 females (Monsanto 1986b), 24 females (Monsanto 1982c), or 15 males (Monsanto 1982b).

In the HCN study by Blank (1983), 3 of 10 rats died after the first exposure to at 68 ppm for 6 h.

7.3. Derivation of AEGL-3

The derivation of AEGL-3 values was based on the facts that acetone cyanohydrin decomposes spontaneously to HCN and acetone and that the systemic toxicity of acetone cyanohydrin is due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-3 values (on a ppm basis) derived for HCN (NRC 2002) to acetone cyanohydrin. This conclusion is supported by very similar observations of lethal effects in rats: Blank (1983) reported that 3 of 10 rats died after the first exposure to HCN at 68 ppm, and the subsequent two exposures on the following days caused no additional deaths. This finding closely resembles that of Monsanto (1986a) reporting death of 3 of 20 animals after the first exposure to acetone cyanohydrin at 60 ppm (as

discussed in section 3.1.1, the actual exposure concentration on the first day might have been slightly higher than the average 59.6 ppm), and no additional deaths were found in the 19 subsequent exposures.

The AEGL-3 values for acetone cyanohydrin are set at the same values (on a ppm basis) as the AEGL-3 values for HCN (NRC 2002). The values are listed in Table 1-8.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

The AEGL values for various levels of effects and various time periods are summarized in Table 1-9. They were derived using the following key studies and methods.

The derivation of AEGL values was based on the facts that acetone cyanohydrin decomposes spontaneously to HCN and acetone and that the local and systemic toxicity of acetone cyanohydrin is due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL values (on a ppm basis) derived for HCN (NRC 2002) to acetone cyanohydrin.

All inhalation data are summarized in Figure 1-1. The data were classified into severity categories chosen to fit into definitions of the AEGL health effects.

TABLE 1-8 AEGL-3 Values for Acetone Cyanohydrin[a]

AEGL	10 min	30 min	1 h	4 h	8 h
AEGL-3	27 ppm (95 mg/m³)	21 ppm (74 mg/m³)	15 ppm (53 mg/m³)	8.6 ppm (30 mg/m³)	6.6 ppm (23 mg/m³)

[a]Acetone cyanohydrin decomposes spontaneously in the presence of water to yield HCN and acetone. Therefore, both acetone cyanohydrin and HCN concentrations should be considered.

TABLE 1-9 Summary of AEGL Values for Acetone Cyanohydrin[a,b]

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	2.5 ppm (8.8 mg/m³)	2.5 ppm (8.8 mg/m³)	2.0 ppm (7.0 mg/m³)	1.3 ppm (4.6 mg/m³)	1.0 ppm (3.5 mg/m³)
AEGL-2 (Disabling)	17 ppm (60 mg/m³)	10 ppm (35 mg/m³)	7.1 ppm (25 mg/m³)	3.5 ppm (12 mg/m³)	2.5 ppm (8.8 mg/m³)
AEGL-3 (Lethal)	27 ppm (95 mg/m³)	21 ppm (74 mg/m³)	15 ppm (53 mg/m³)	8.6 ppm (30 mg/m³)	6.6 ppm (23 mg/m³)

[a]Acetone cyanohydrin decomposes spontaneously in the presence of water to yield HCN and acetone. Therefore, both acetone cyanohydrin and HCN concentrations should be considered.
[b]Cutaneous absorption may occur; direct skin contact with the liquid should be avoided.

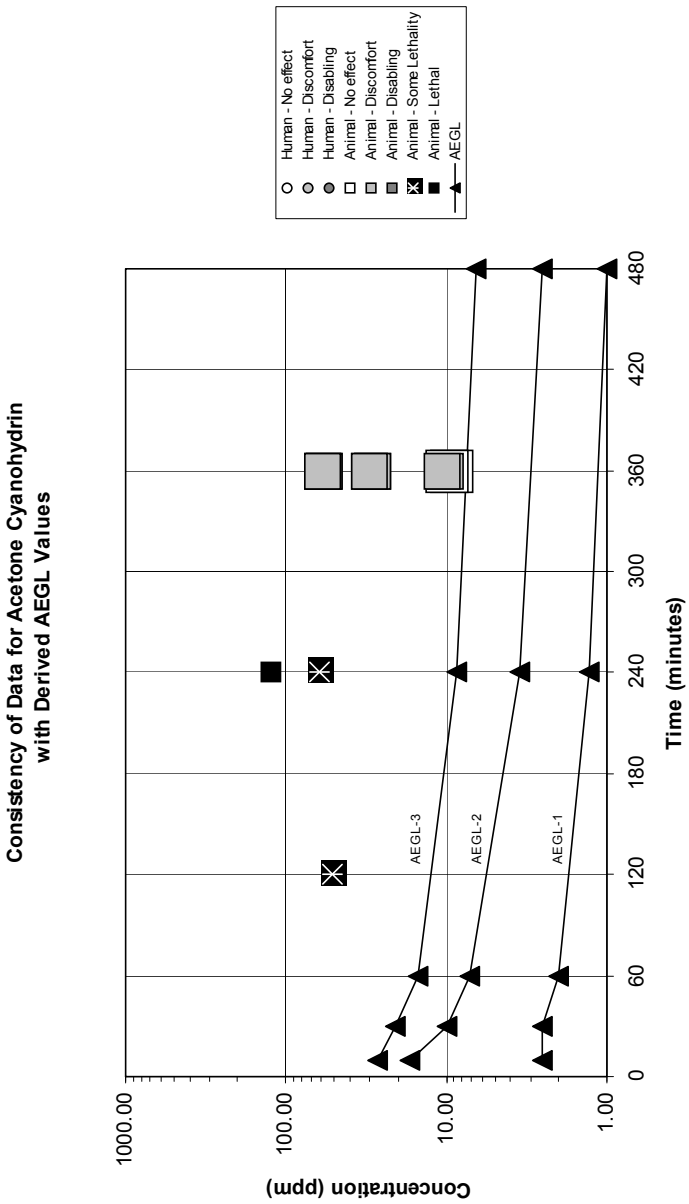

FIGURE 1-1 Categorical representation of acetone cyanohydrin inhalation data.

The category severity definitions are "no effect," "discomfort," "disabling," "lethal," "some lethality" (at an experimental concentration in which some of the animals died and some did not, this label refers to the animals that did not die), and "AEGL." Note that the AEGL values are designated as triangles without an indication to their level. AEGL-3 values are higher than the AEGL-2 values, and the AEGL-2 values are higher than the AEGL-1 values.

8.2. Comparison with Other Standards and Criteria

Standards and guidance levels for workplace and community exposures are listed in Table 1-10.

8.3. Data Adequacy and Research Needs

Definitive exposure-response data for acetone cyanohydrin in humans are not available. Data from earlier animal studies were often compromised by uncertain quantitation of exposure atmospheres, small numbers of animals, and poor data presentation. Four more recent repeated inhalation exposure studies in rats sponsored by Monsanto Company utilized accurate and reliable methods for characterizing concentrations. However, repeat exposure studies were considered of limited relevance for the derivation of AEGL values.

TABLE 1-10 Extant Standards and Guidelines for Acetone Cyanohydrin

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	2.5 ppm	2.5 ppm	2.0 ppm	1.3 ppm	1.0 ppm
AEGL-2	17 ppm	10 ppm	7.1 ppm	3.5 ppm	2.5 ppm
AEGL-3	27 ppm	21 ppm	15 ppm	8.6 ppm	6.6 ppm
WEEL (AIHA)[a]	5 ppm for 15 min				2 ppm
TLV ceiling (ACGIH)[b]	4.7 ppm as cyanide				
REL ceiling (NIOSH)[c]	1 ppm				

[a]AHIA WEEL (American Industrial Hygiene Association, workplace environmental exposure level) (AIHA1999) represent workplace exposure concentrations to which, it is estimated, nearly all employees could be repeatedly exposed without adverse effects. WEELs are expressed as time-weighted-average values for different time periods.
[b]ACGIH TLV ceiling (American Conference of Governmental Industrial Hygienists, Threshold Limit Value) (ACGIH 1996) is defined as a 15-min TWA exposure concentration, which should not be exceeded at any time during the workday. Because acetone cyanohydrin behaves qualitatively and quantitatively both in vitro and in vivo exactly as does its molar equivalent in free cyanide, the TLV for acetone cyanohydrin is assigned to be identical to that for free HCN.
[c]NIOSH REL ceiling (National Institute of Occupational Safety and Health, recommended exposure limits) (NIOSH 1978)is defined analogous to the ACGIH TLV ceiling. NIOSH based the value on the assumption that acetone cyanohydrin was approximately 18.3 times as toxic as acetonitrile by inhalation.

With regard to toxic effects, the similarity between acetone cyanohydrin and HCN concerning both the mechanism of toxic effects and dose-response relationships was considered high enough to apply the AEGL-1, AEGL-2, and AEGL-3 values derived for HCN to acetone cyanohydrin on a part per million basis. In contrast to HCN, appropriate studies are not available for acetone cyanohydrin in exposed workers for the derivation of AEGL-1 or in well-performed inhalation exposure studies evaluating neurotoxic or lethal effects for the derivation of AEGL-2 and AEGL-3 values. However, the available results of studies in rats are in good agreement with HCN studies. LC_{50} studies for acetone cyanohydrin performed according to good laboratory practice would strengthen the derived AEGL-3 values.

It Because of the steep dose-response relationship, concentrations of AEGL-2 and AEGL-3 values differ only by a factor of 1.6 to 2.6, which could cause problems in regulatory applications of AEGL values especially when it is considered that uncertainties of measurements and dispersion (plume) calculations can be in the same order of magnitude or even higher.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR ACETONE CYANOHYDRIN

AEGL-1 VALUES[a]

10 min	30 min	1 h	4 h	8 h
2.5 ppm	2.5 ppm	2.0 ppm	1.3 ppm	1.0 ppm

Reference: The AEGL-1 values for acetone cyanohydrin are set at the same values (on a ppm basis) as the AEGL-1 values for HCN.

NRC (National Research Council). 2002. Hydrogen cyanide. Pp. 211-276 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 2. Washington, DC: National Academy Press,.

Test Species/Strain/Number: Not applicable.

Exposure Route/Concentrations/Durations: Not applicable.

Effects: Not applicable.

End Point/Concentration/Rationale: Human data on acetone cyanohydrin relevant for the derivation of AEGL-1 are lacking. One study in rats (Monsanto 1986a) reported red nasal discharge (which was interpreted as a sign of local irritation in the upper respiratory tract) in 4/20 animals at 29.9 ppm and in 2/20 animals at 59.6 ppm, but not in control animals and in animals exposed at 9.2 ppm during the first week of repeated 6-h/d exposures. However, red nasal discharge was not consistently seen in any of the other Monsanto (1982b,c, 1986b) studies and, when present, was not always dose-responsive. In addition, control animals varied widely in terms of whether that end point was present. In light of the variability of the red nasal discharge in repeat studies, it seemed a poor end point on which to base the AEGL-1. Also, the repeat exposures used in the Monsanto studies were not appropriate for the derivation of AEGL-1 values.

The pathogenesis of red nasal discharge in rats is not entirely clear. In the case of acetone cyanohydrin, it may be related to local tissue hypoxia leading to vasodilatation and subsequent extravasation of red blood cells, which could explain the lack of histopathologic findings. Red nasal discharge in rats occurs at the plexus antebrachii, which is very prominent in the rat. In the rat, extravasation of red blood cells visible as red nasal discharge is caused easily not only by locally acting chemicals but also by stress, dry air, or upper respiratory tract infections.

The derivation of AEGL-1 values was based on the facts that acetone cyanohydrin decomposes spontaneously to HCN and acetone and that the systemic toxicity of acetone cyanohydrin is due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-1 values (on a ppm basis) derived for HCN (NRC 2002) to acetone cyanohydrin.

Uncertainty Factors/Rationale: Not applicable.

Time Scaling: Not applicable.

(Continued)

AEGL-1 VALUES Continued

10 min	30 min	1 h	4 h	8 h
2.5 ppm	2.5 ppm	2.0 ppm	1.3 ppm	1.0 ppm

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Not applicable.

Data Quality and Support for AEGLs: Similar values would be derived on the basis of available acetone cyanohydrin studies in rats (derivation basis would be an exposure of 9.2 ppm for 6 h/d, 5 d/wk for 4 weeks that did not result in red nasal discharge [Monsanto 1986a]) using a total uncertainty factor of 10.

[a]Acetone cyanohydrin decomposes spontaneously in the presence of water to yield HCN and acetone. Therefore, both acetone cyanohydrin and HCN concentrations should be considered.

AEGL-2 VALUES[a]

10 min	30 min	1 h	4 h	8 h
17 ppm	10 ppm	7.1 ppm	3.5 ppm	2.5 ppm

Reference: The AEGL-2 values for acetone cyanohydrin are set at the same values (on a ppm basis) as the AEGL-2 values for HCN.

NRC (National Research Council). 2002. Hydrogen cyanide. Pp. 211-276 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 2. National Academy Press, Washington, DC.

Test Species/Strain/Sex/Number: Not applicable.

Exposure Route/Concentrations/Durations: Not applicable.

Effects: Not applicable.

End Point/Concentration/Rationale: The derivation of AEGL-2 values was based on the facts that acetone cyanohydrin decomposes spontaneously to HCN and acetone and that the systemic toxicity of acetone cyanohydrin is due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-2 values (on a ppm basis) derived for HCN (NRC 2002) to acetone cyanohydrin.

Uncertainty Factors/Rationale: Not applicable.

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Not applicable.

Time Scaling: Not applicable.

Data Quality and Support for AEGLs: Very similar values would be derived on the basis of available acetone cyanohydrin studies in rats (derivation basis would be an exposure of 29.9 ppm for 6 h/d, 5 d/wk for 4 weeks that caused red nasal discharge as a sign of irritation, and the next higher concentration produced respiratory distress, prostration, convulsions, and tremors [Monsanto 1986a]) using a total uncertainty factor of 10.

[a]Acetone cyanohydrin decomposes spontaneously in the presence of water to yield HCN and acetone. Therefore, both acetone cyanohydrin and HCN concentrations should be considered.

AEGL-3 VALUES[a]

10 min	30 min	1 h	4 h	8 h
27 ppm	21 ppm	15 ppm	8.6 ppm	6.6 ppm

Reference: The AEGL-3 values for acetone cyanohydrin are set at the same values (on a ppm basis) as the AEGL-3 values for HCN.

NRC (National Research Council). 2002. Hydrogen cyanide. Pp. 211-276 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 2. National Academy Press, Washington, DC.

Test Species/Strain/Sex/Number: Not applicable.

Exposure Route/Concentrations/Durations: Not applicable.

Effects: Not applicable.

End Point/Concentration/Rationale: The derivation of AEGL-3 values was based upon the facts that acetone cyanohydrin decomposes spontaneously to HCN and acetone and that the systemic toxicity of acetone cyanohydrin is due to free cyanide. Once absorbed, a dose of acetone cyanohydrin behaves in a manner identical to that of its molar equivalent in absorbed free cyanide. It is appropriate to apply the AEGL-3 values (on a ppm basis) derived for HCN (NRC 2002) to acetone cyanohydrin.

Uncertainty Factors/Rationale: Not applicable.

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Not applicable.

Time Scaling: Not applicable.

Data Quality and Support for the AEGLs: Support comes from the close similarity of acetone cyanohydrin and HCN regarding death in rats: Blank (1983) reported that 3 of 10 rats died after the first exposure to HCN at 68 ppm, but the subsequent two exposures on the following days caused no additional deaths. This finding closely resembles that of Monsanto (1986a) reporting death of 3 of 20 animals after the first exposure to acetone cyanohydrin at 60 ppm (the actual exposure concentration on the first day might have been slightly higher than the average 59.6 ppm), and no additional deaths were found in the 19 subsequent exposures.

[a]Acetone cyanohydrin decomposes spontaneously in the presence of water to yield HCN and acetone. Therefore, both acetone cyanohydrin and HCN concentrations should be considered.

2

Carbon Disulfide[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 [ppm] or milligrams per cubic meter [mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory

[1]This document was prepared by the AEGL Development Team composed of Jens-Uwe Voss (Toxicological Advisory Services, Chemical Hazard and Risk Assessment and Chemical Managers George Rodgers 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 has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guideline reports (NRC 1993, 2001).

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

Pure carbon disulfide (CS_2) is a colorless, mobile, refractive liquid with a sweetish aromatic odor similar to chloroform. Commercial and reagent grade products are yellowish with an unpleasant, repulsive odor of decaying radish or overcooked cauliflower. Due to its high volatility, low flash point, low autoignition temperature, and wide range of explosive limits in air, CS_2 poses an acute fire and explosion hazard. The most important industrial use of CS_2 has been in the manufacture of regenerated cellulose rayon by the viscose process.

A wide range of odor thresholds from 0.0243 mg/m^3 to 23.1 mg/m^3 (0.0078 to 7.4 ppm) for CS_2 were reported. Amoore and Hautala (1983) reported a geometric mean air odor threshold of 0.11 ppm (standard error [SD], 0.058 ppm) Leonardos et al. (1969) determined an odor recognition threshold of 0.21 ppm. AIHA (1997), in a critical overview of odor thresholds for chemicals, reported a range of all referenced values from 0.016 to 0.42 ppm. No geometric mean and no "range of acceptable values" for CS_2 were presented, and the use of the 0.21 ppm threshold was rejected because it represented a 100% recognition concentration. Few data are available with respect to concentrations of CS_2 causing odor annoyance. In one controlled human study (Lehmann 1894), 180-240 ppm caused "moderate odor annoyance," and there were no complaints to exposures at 10-20 ppm in a toxicokinetic study (Rosier et al. 1987).

The database is not sufficient to calculate a level of distinct odor awareness (LOA). It also must be taken into account that strong smelling decomposi-

tion products of CS_2 are rapidly formed under the influence of light and air. Therefore, the odor threshold and the hedonic tone of CS_2 will markedly change with the presence and formation of such impurities. CS_2 is rapidly absorbed from the respiratory tract and distributed throughout the body, the highest concentration occurring in lipid rich tissues. Dithiocarbamates and similar products build up the so-called "acid-labile" CS_2 by the reaction of CS_2 with NH_2, SH, and OH groups of amino acids, proteins, and amines. Although unbound CS_2 is eliminated rapidly after the termination of exposure, the acid labile part shows a longer half-life and may accumulate with repeated exposure.

On acute exposure, CS_2 acts on the central nervous system (CNS) in humans and animals. In humans, acute effects on the CNS following CS_2 exposure manifest in dizziness, headaches, autonomic nervous system reactions, nausea, vertigo, vomiting, central paralysis, and narcosis. In animals (rats, mice, rabbits, cats, and dogs), acute exposure led to reduced activity but also hyperexcitability, stupor, ataxia, tremors, convulsions, deep narcosis, and finally respiratory arrest and death. Irritation of eyes and mucous membranes occur only at concentrations already affecting the CNS. However, low concentrations without notable effects on the CNS led to an inhibition of xenobiotic biotransformation reactions, inhibition of ethanol metabolism via the alcohol and aldehyde dehydrogenase pathway, and alterations of carbohydrate and energy metabolism in the liver.

In several toxicokinetic studies in humans, occasional slight headaches but no other subjective symptoms were reported to occur in some individuals at exposure concentrations in the range of 17-51 ppm (Harashima and Masuda 1962; Teisinger and Soucek 1949). Inhibition of biotransformation was observed in humans after 6 h of exposure to CS_2, at 10 ppm, the lowest concentration tested (Mack et al. 1974). In rats, 8 h of exposure to 20 ppm, the lowest concentration tested, also inhibited biotransformation of drugs and solvents and caused a decrease of the glycogen content of the liver. All effects were rapidly reversible within about 24 h, and no increase of liver enzymes in serum was observed (Freundt and Dreher 1969; Freundt and Kuttner 1969; Kürzinger and Freundt 1969; Freundt and Schauenburg 1971; Freundt et al. 1974b, 1976a; Freundt and Kürzinger 1975). In one controlled human study, two volunteers were exposed to concentrations from about 180 ppm to more than 3,000 ppm (Lehmann 1894). In this study, CNS symptoms and irritation of eyes and throat occurred at 260-420 ppm. CNS symptoms increased in severity with exposure concentration and time. Severe CNS effects that continued after exposure ended were seen at about 2,000 ppm. Concentrations from 2,000 ppm increasing to above 3,000 ppm led to seminarcotic state and irregular respiration.

The AEGL-1 values are based on studies investigating CS_2-induced inhibition of ethanol metabolism in humans (Freundt and Lieberwirth 1974a; Freundt et al. 1976b). In this controlled study, volunteers were exposed to CS_2 at 20 ppm for 8 h by inhalation and simultaneously or afterwards took in alcoholic beverages to obtain a blood ethanol level of 0.75 grams per liter (g/L) (75 mg/deciliter [dL]). Each person served as his or her own control. CS_2 exposure

caused a 50-100% increase in acetaldehyde in blood as compared with conditions without CS_2. The effect occurred when alcohol was taken up during the CS_2 exposure, and similarly when the alcohol uptake started 8 h after the end of CS_2 exposure. Apparently, CS_2 inhibits the metabolism of ethanol at the second step of the pathway, that is, the oxidation of acetaldehyde via aldehyde dehydrogenase (ALDH). The observed increase of acetaldehyde in the controlled studies was asymptomatic, that is, no disulfiram effect ("Antabuse syndrome" with flush, hypotension, and tachycardia) was observed. However, alcohol intolerance has repeatedly been mentioned in workers occupationally exposed to unknown (most probably higher) concentrations of CS_2, and in its guidelines, the German Society for Occupational and Environmental Medicine includes alcohol intolerance as a further adverse effect induced by CS_2 (Drexler 1998).

There are different forms of ALDHthat differ in their activity. The presence of the ALDH2(2) allele (which is common in Asians but rare or absent in Caucasians) results in lower ALDH activity and thus higher levels of acetaldehyde after ingestion of alcohol as compared with persons in which the normal enzyme is present. Although individuals homozygous in ALDH2(2) are considered hypersusceptible to ethanol (many avoid drinking ethanol at all), individuals heterozygous in ALDH are considered as a sensitive subgroup within the normal population. In this group, an additional increase of the acetaldehyde concentration due to a CS_2-mediated ALDH inhibition may lead to an disulfiram effect (Antabuse syndrome) or aggravate otherwise mild symtpoms.

An intraspecies factor of 3 was applied to account for the protection of the sensitive subpopulation. Extrapolation was made to the relevant AEGL time points using the relationship $C^n \times t = k$, where C = exposure concentration, t = exposure duration, k = a constant, and n represents a chemical-specific exponent. The default of n = 3 was used for shorter exposure periods, due to the lack of experimental data for deriving the concentration exponent. For the AEGL-1 for 10 min, the AEGL-1 for 30 min was applied because the derivation of AEGL values was based on a study with a long experimental exposure period of 8 h, and no supporting studies using short exposure periods were available that characterized the concentration time–response relationship. The derived AEGL-1 values are above the odor thresholds but below the concentrations reported to cause moderate odor annoyance (see above).

The derivation of the AEGL-2 is based on the no-observed-exposure level (NOEL) of 1,000 ppm for behavioral alterations in rats exposed to CS_2 for 4 h (Goldberg et al. 1964). At the next higher concentration of 2,000 ppm, an inhibition of the escape (and also the avoidance) response was observed. A total uncertainty factor of 10 was used. The interspecies uncertainty factor was reduced to 3 because of the similarity of acute effects produced by agents affecting the CNS seen in rodents compared with humans. Moreover, use of a default interspecies uncertainty factor of 10 would have resulted in values that are contradicted by experimental human studies in which no serious or escape-impairing effects were reported during or following 6-8 h of exposure to 80 ppm. An intraspecies uncertainty factor of 3 was applied to account for sensitive individuals

because the threshold for CNS impairment is not expected to vary much among individuals. Time scaling was performed according to the regression equation $C^n \times t = k$, using the default of n = 3 for shorter exposure periods (30 min and 1 h) and n = 1 for longer exposure periods (8 h), because of the lack of suitable experimental data for deriving the concentration exponent. For the 10-min AEGL-2, the 30-min value was used because the derivation of AEGL-2 values was based on a long experimental exposure period (4 h), and no supporting studies using short exposure periods were available for characterizing the concentration-time-response relationship.

The AEGL-3 was based on a study with rats (Du Pont 1966). In that study, all six animals exposed to 3,500 ppm for 4 h died during or within 2 h after exposure, whereas none of six rats exposed to 3,000 ppm died during the exposure or within the 14-day post-exposure observation period. A total uncertainty factor of 10 was used. An interspecies uncertainty factor of 3 was applied because the acute effects on the CNS are not expected to vary much between species. Moreover, use of a default interspecies uncertainty factor of 10 would have resulted in values that are contradicted by experimental human studies in which no life-threatening effects were reported during or following 6-8 h exposure to 80 ppm. An intraspecies uncertainty factor of 3 was applied to account for sensitive individuals because the threshold for CNS impairment is not expected to vary much among individuals. Time scaling was performed according to the regression equation $C^n \times t = k$, using the default of n = 3 for shorter exposure periods (30 min and 1 h) and n = 1 for longer exposure periods (8 h), because of the lack of suitable experimental data for deriving the concentration exponent. For the 10-min AEGL-3, the 30-min value was used because the derivation of AEGL-3 values was based on a long experimental exposure period (4 h), and no supporting studies using short exposure periods were available for characterizing the concentration-time-response relationship. A summary of AEGL values is shown in Table 2-1.

1. INTRODUCTION

Pure CS_2 is a colorless, mobile, refractive liquid with a sweetish aromatic odor similar to chloroform. Under the action of light (and air), CS_2 is decomposed with the formation of yellow decay products and a disagreeable odor. Similarly, commercial and reagent grade products are yellowish with a repulsive odor of decaying radish (WHO 1979). The odor was also described as "disagreeable, sweet" (Ruth 1986) or that of overcooked cauliflower.

CS_2 is released into the environment from natural sources such as soil, marshes, lakes, and volcanoes. The total global emission of CS_2 and the anthropogenic share of the total emission is not well-known. However, according to more recently modelled scenarios, it is suggested that the majority of CS_2 may be produced through human activity, rather than naturally (Environment-Canada/Health Canada 2000).

TABLE 2-1 Summary of AEGL Values for Carbon Disulfide[a]

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (Nondisabling)	17 ppm (52 mg/m^3)	17 ppm (52 mg/m^3)	13 ppm (42 mg/m^3)	8.4 ppm (26 mg/m^3)	6.7 ppm (21 mg/m^3)	Increase in blood acetaldehyde in humans with moderate intake of alcohol (Freundt et al. 1976b)
AEGL-2 (Disabling)	200 ppm (620 mg/m^3)	200 ppm (620 mg/m^3)	160 ppm (490 mg/m^3)	100 ppm (310 mg/m^3)	50 ppm (160 mg/m^3)	NOEL for behavioral changes in rats (inhibition of escape response) (Goldberg et al. 1964)
AEGL-3 (Lethality)	600 ppm (1,480 mg/m^3)	600 ppm (1,480 mg/m^3)	480 ppm (990 mg/m^3)	300 ppm (930 mg/m^3)	150 ppm (470 mg/m^3)	No lethality in rats (Du Pont 1966)

[a]Cutaneous absorption may occur. Liquid CS_2 is a severe skin irritant and direct skin contact with the liquid must be avoided.

CS_2 was discovered by Lampadius in 1796 by heating a mixture of pyrite (FeS_2) and charcoal. Commercially, CS_2 has been prepared by directing sulfur vapor over glowing coals. In the Western industrial countries, this process has been replaced by the reaction of methane and sulfur at temperatures between 500 and 700°C and a pressure between 4 and 9 bar ("methane process"). The CS_2 is separated from H_2S and by-products by liquefaction, distillation, and treatment with sodium hydroxide. The product thus purified contains a maximum of 0.02% impurities (BUA 1993).

About 1 million tons of CS_2 was produced commercially worldwide in 1984. Since that time, production has been decreasing and was estimated at about 900,000 tons in 1990 (BUA 1993). The most important industrial use of CS_2 has been in the manufacture of regenerated cellulose rayon by the viscose process and of cellophane. CS_2 has also been used for the production of carbon tetrachloride which served as a starting chemical for the synthesis of fluorocarbon propellants and refrigerants (ATSDR 1996). This application has been of declining importance in recent years. Smaller amounts of CS_2 are needed as a solvent, for example, in the purification of sulfur, and for the manufacture of dithiurams, dithiocarbamates, and trithiocarbamates used as fungicides and vulcanization accelerators; for the manufacture of xanthates used as flotation agents in mineral refining processes; and for the synthesis of some other sulfur compounds. CS_2 has also been used for soil fumigation, for example, in viniculture for fighting vine lice, and in veterinary medicine (BUA 1993; Environment Canada/Health Canada 2000).

Chemical and physical properties of CS_2 are presented in Table 2-2. Because of its high volatility, low flash point, low autoignition temperature, and the wide range of explosive limits in air, CS_2 poses an acute fire and explosion hazard.

TABLE 2-2 Chemical and Physical Data for Carbon Disulfide

Parameter	Data	Reference
Synonyms	Carbon bisulphide, carbon disulphide, carbon sulfide, dithiocarbonic anhydride, sulphocarbonic anhydride	HSDB 2007
Chemical formula	CS_2	
Molecular weight	76.14 g mol^{-1}	ATSDR 1996
CAS Reg. No.	75-15-0	ATSDR 1996
Physical state	Liquid at room temperature	ATSDR 1996
Solubility	2.94 g/L in water (20°C); soluble in ethanol, benzene, ether	ATSDR 1996; Beauchamp et al. 1983
Vapor pressure	400 mm at 28°C 300 mm at 20°C 100 mm at −5.1°C 40 mm at −22.5°C	Henschler and Greim 1975; Weast 1973
Vapor density (air = 1)	2.62	Beauchamp et al. 1983
Liquid density (water = 1)	1.2632 (20°C)	Weast 1973
Melting point	−111.53°C	Weast 1973
Boiling point	46.25°C	Weast 1973
Explosive limits in air	1-50%	Beauchamp et al. 1983
Flash point	−29.62°C	Beauchamp et al. 1983
Autoignition temperature	100°C	Beauchamp et al. 1983
Conversion factors (at 25°C)	1 ppm = 3.114 mg/m^3 1 mg/m^3 = 0.321 ppm	Calculated according to NRC 2001

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

According to Flury and Zernik (1931), exposure to very high concentrations of CS_2 is followed by acute disturbance of consciousness; delirium; loss of reflexes, including loss of pupil reaction; total paralysis; and respiratory arrest. The authors stated that exposure to CS_2 at 4,800 ppm for 30 min to 1 h will immediately or later result in death, and 3,200-3,850 ppm over the same period of time will be life-threatening. The same statement is made by Bittersohl et al.(1972). Furthermore, they stated that "hyperacute intoxication" with very high concentrations exceeding 10 mg/L (3,200 ppm) will immediately lead to loss of reflexes, coma, and death. No details or references are presented.

2.1.1. Reports

Death has been reported in a community in India following an accidental release of large amounts of CS_2, hydrogen sulfide, and sulfuric acid from a viscose rayon plant (Kamat 1994). Due to the lack of exposure data and the concomitant exposure to other chemicals, no conclusions valid for the derivation of AEGL values can be derived from these data.

There are few reports of acute poisonings following oral ingestion. In a fatal case in which the patient had swallowed "a glass" of CS_2, the victim soon became unconscious and died about 2 h after drinking the liquid (Davidson and Feinleib 1972). Generally, 30-60 mL is reported to be fatal (WHO 1993). However, ingestion of about 18 g of CS_2 (about 15 mL) was reported to be lethal in three occasions. Prior to death, spasmodic tremors, prostration, dyspnoea, cyanosis, peripheral vascular collapse, hypothermia, mydriasis, convulsions, and coma developed. Death occurred within a few hours (Fielder et al. 1981).

2.2. Nonlethal Toxicity

Without giving any references, Bittersohl et al. (1972) stated that at about 300 ppm, slight symptoms in humans will occur after several hours of exposure, marked symptoms of intoxication at 400 ppm, severe symptoms at 1,150 ppm after 30 min, and life-threatening effects at 3,200-3,800 ppm. Furthermore, they stated that acute intoxications at concentrations higher than 1 mg/L (320 ppm) will lead to narcosis lasting for minutes followed by severe headaches and nausea. No details or any references are presented in this textbook, but some of the data agree with those presented in the summarizing table in Lehmann (1894). This table is also presented by Flury and Zernik (1931) and Lehmann and Flury (1938), and the same values are repeatedly presented by other reports (NRC 1984; AIHA 1992; OSHA 1999).

2.2.1. Reports

In an accident, about 30,000 L of CS_2 spilled from a broken railroad tank car. As a result of this spill, about 500 people were temporarily evacuated from the adjacent area. Five people were seen at a local hospital, and one of them was admitted. During inspection of the contaminated area, a flash fire occurred in which four people were trapped for a short period of time, but no injuries resulted. No further details were reported (NTSB 1998).

Spyker et al. (1982) reported an accident in which CS_2 leaking from a railroad tank car caught fire and was extinguished. An airborne concentration of 20 ppm CS_2 was measured at a site outside the town later during transfer of CS_2 from the leaking tanker, but no measurement data were reported from the town or from the area during emergency operations. About 600 residents of an adja-

cent area were evacuated; 27 subjects, mostly police and firefighters, who were exposed to unknown concentrations of CS_2 were examined at a hospital. Most of the victims complained of headaches (16 of 27), nausea (14 of 27), and dizziness (16 of 27). Burning of throat, lips, and skin (11 of 27) and shortness of breath or chest pain (4 of 27) also occurred; two victims complained of impotence, and vomiting was seen in one. Spirometry, single breath CO-diffusing capacity, and arterial blood gas measurements were made in all four victims having shortness of breath or chest pain and in seven others who appeared clinically to be the most severely ill. Vital capacity and the partial pressure of arterial O_2 were lower on the day of exposure than 9 days later. No significant changes were observed in forced vital capacity, forced expiratory volume, or diffusing capacity. None of the patients evaluated appeared to have sustained injury lasting beyond the first few post-exposure days (Spyker et al. 1982). It is not reported but likely that these victims were exposed not only to CS_2 but also to the toxic and irritant products of CS_2 burning, especially sulfur dioxide and acid mists.

Following acute exposure to high concentrations of CS_2, fainting and loss of consciousness was observed in about one third of 123 victims in an accidental release of large amounts of CS_2, hydrogen sulfide, and sulfuric acid from a viscose rayon plant in India (Kamat 1994).

A 42-year-old woman who had used CS_2 for a few years to control insects in warehouses accidentally ingested about 5 mL of CS_2 from a used soft drink bottle (Yamada 1977). After 5 h of induced vomiting, numbness in the lips and nausea and noninduced vomiting occurred. Within 12 h, abdominal pain, pyrexia, and wave-form agitation appeared, and she was hospitalized with conspicuous agitation, hyperesthesia, accentuated tendon reflex of extremities and positive Babinski reaction in lower extremities. Transient ECG abnormalities were seen (sinus tachykardia and sharp P wave) 16 h after ingestion. Repeated illusion and delusions appeared after discharge. Abnormal EEG, such as sudden group of theta waves of higher potential and light-induced theta waves, was observed 2 days after the accident for about a week. The patient appeared healthy 2 months later.

2.2.2. Occupational Exposures

Acute effects of exposure to CS_2 are described in occupational medicine and toxicology handbooks and reports. Many serious cases of intoxication have occurred among workers exposed to CS_2 in the cold vulcanization of rubber during the 19th century and later in the viscose rayon production (Davidson and Feinleib 1972). In these reports, exposure concentrations, based on estimates but not on measurements, are either lacking or are stated without any reference. Also, these reports describe cases in which acute symptoms occurred in workers who previously had been exposed for weeks to years to unknown concentrations of CS_2. In view of the chronic effects of CS_2 on the nervous system, it seems

likely that such "acute" poisonings were actually acute exposure and acute outbreak of symptoms superimposed on chronic inhalation exposure. Therefore, it is unknown to what extent the effects described were due to acute exposure to CS_2. Eye irritation in workers in the viscose-producing industry has also been described. However, this effect is considered to be mainly caused by hydrogen sulfide, which always is present together with CS_2 in the viscose production process (BUA 1993; Greim 1999). Acid mists may also contribute to the effects.

Gordy and Trumper (1938) described six cases of intoxication in workers who had been employed for at least 11 months. Especially in one case, the early effects are probably due to acute poisoning: A 27-year-old woman described to be in generally good health had been working in the rayon industry for 6 years as a reeler of artificial silk. On a day when she handled incompletely dried viscose, symptoms began with violent headache, faintness, restlessness, weeping, screaming, laughing, and loss of consciousness. After recovering consciousness, the victim felt as "though she had been beaten all over." She spit blood and had "bloody bowel movements" and was semiconscious and stuporous most of the rest of the day. No data regarding the possible concentration of CS_2 were presented. The victim also complained of long-lasting effects after this episode. Repeated spells occurred from that day on, lasting about 15 min and consisting of headaches and numbness in various parts of the body. Her hands and feet felt as though they were asleep. She developed psychotic episodes characterized by auditory hallucinations, vasomotor instability, and disturbance of vision.

In a short notice, Münchinger (1958) briefly summarized medical and neurologic findings in 100 workers in a Swiss viscose factory. The workers were 24-66 years old. Exposure duration varied between 1 and 39 years, and the mean CS_2 concentration at the workplace was reported to fluctuate between 5 and 35 mg/m^3 (1.6-11.2 ppm). Peak or maximum exposures were not reported. About two-thirds of the workers complained about subjective symptoms, especially alcohol intolerance, sleep disorders, noticeable tiredness at work, and irritability. About one third each complained of gastrointestinal problems and had pathologic cardiovascular findings or respiratory tract disease. Medical and psychiatric examination revealed in about two-thirds of the workers alterations of the functions of the autonomic, peripheral, and CNS compatible with a mild-to-moderate psychoorganic syndrome. No detailed evaluation was presented.

Alcohol intolerance in subjects exposed to CS_2 has been mentioned in several other reports, and in its guidelines, the German Society for Occupational and Environmental Medicine points to alcohol intolerance as a further adverse effect induced by CS_2 (Drexler 1998). Freundt et al. (1976b) cite several early reports regarding the development of alcohol intolerance in workers manufacturing rubber or viscose rayon. Reports date back to as early as 1856 and 1910 (Williams 1937), when exposure was probably very high. However, precise data regarding the concentration of CS_2, the amount of alcohol intake, and the temporal relationship were not available. Djuric (1971) noticed that in a group of vis-

cose factory workers exposed to "pretty high concentrations" of CS_2, slight intolerance to alcohol may occur.

Vigliani (1954) described findings in Italian viscose rayon factories. From 1940 to 1941, he observed 100 cases of CS_2 poisoning. Outbreaks of poisonings occurred in two plants after war-time measures led to bad ventilation, lengthened work shifts up to 12 h/d, and improper handling. The concentrations in the two plants ranged from a minimum of 0.11 mg/L (35 ppm) in the churn to a maximum of 2.5 mg/L (800 ppm) in the staple bleaching. In the staple rooms, the workers were exposed 4-5 h/d to CS_2 concentrations between 1 and 2 mg/L (320-640 ppm). Concentrations higher than 0.5 mg/L (160 ppm) with a maximum of 2 mg/L (640 ppm) were reported to poison workers in 2 to 6 months. In the 100 cases described, symptoms (in decreasing frequency) included polyneuritis, gastric disturbances, headaches, vertigo, sexual weakness, tremors, myopathy, psychoses, extrapyramidal symptoms, opticoneuritis, hemiparesis, and pseudobulbar paralysis. Concentrations of 0.40 to 0.50 mg/L (130-160 ppm) caused toxicity after 1 or more years of work. Some cases of mild poisoning were also seen in workers exposed to 0.2-0.3 mg/L (64-96 ppm).

A great number of epidemiologic studies on the chronic effects of CS_2 in occupationally exposed workers have been carried out, and these studies have been repeatedly reviewed and summarized (Davidson and Feinleib 1972; Henschler and Greim 1975, 1997; WHO 1979; Fielder et al. 1981; Beauchamp et al. 1983; BUA 1993; ATSDR 1996; Griem 1999 EnvironmentCanada/Health Canada 2000; WHO 2000). A detailed description of the findings from the epidemiologic studies is beyond the scope of this document, because these studies do not provide data that could be used for the derivation of AEGLs.

Briefly, in chronic intoxication with CS_2, almost every organ of the body may be affected. Generalized, subjective symptoms, such as tiredness, sleeplessness, headaches, irritability, excitability, nausea, digestive disorders, reduction of libido, neurasthenia, and dizziness, have been reported. Further effects include gastritis, ulcers, liver disfunction, paresis, paralysis, myopathy, and cardiac arrhythmia. Exposure to very high concentrations might result in psychoses, hallucinations, delirium, and dementia. In chronic exposure, the most common effects are polyneuritis with paresthesia, ataxia, reflex disorders, and atonia. In the vascular system, hypertonia and arteriosclerosis-like lesions in the vessels of the brain, coronary heart disease, lesions of the kidney, pancreas, and eye might develop. Increased levels of blood lipids have also been reported (Greim 1999).

Neurotoxic effects were described to occur in workers exposed for decades to concentrations lower than 30 mg/m³ (10 ppm). Increased mortality from cardiac infarction, neurotoxicity, and changes in blood lipids have been described at concentrations of about 20 mg/m³ (6 ppm) (Greim 1999). An exposure-response analysis concluded that the lowest levels associated with reductions in peripheral nerve conduction velocity in CS_2-exposed humans range from 13 to <31 mg/m³ (4 to <10 ppm) (EnvironmentCanada/Health Canada 2000).

2.2.3. Experimental Studies

The findings of clinical volunteer studies with controlled exposure are summarized in Table 2-3. The study of Lehmann (1894) covered a very wide range of exposure concentrations. In this study, two healthy young males were exposed to different concentrations of CS_2 vapour in exposure chambers. CS_2 was evaporated inside the exposure chamber from liquid material by means of a fan. To determine the concentration of CS_2 in air, CS_2 was absorbed in ethanolic potassium hydroxide, and the xanthogenate formed was determined by titration. In the course of the whole study, the exposure concentrations varied between 0.55 mg/L (180 ppm) and 6.67 mg/L (3,370 ppm), and the exposures lasted from 1 h to 4 h 45 min. The data from all experiments are summarized in Table 2-3. Signs of respiratory tract irritation (tickle in the throat and dry cough) occurred in most experiments, but always at concentrations that also caused effects on the CNS. In summary, exposure to 0.55-0.76 mg/L (180-240 ppm) for up to 4 h 45 min caused moderate odor annoyance but no further subjective symptoms. CNS symptoms (dizziness and headaches) and irritation of eyes and throat were observed at 0.8-1.3 mg/L (180-240 ppm). With increasing concentration, the symptoms, especially those on the CNS, occurred more rapidly, became more pronounced, and persisted after exposure ended for several hours or even overnight. Concentrations of about 2,000 ppm caused severe intoxication with difficulty performing tasks, anxiety, nausea, progressing dizziness, and beginning central paralysis. After exposure, staggered gait, strong dazed feeling, autonomic nervous system reactions (sudden salivation, increased pulse, and vomiting) and up to 2 days of feeling ill were recorded. Concentrations increasing from 2,000 ppm to above 3,000 ppm resulted in semi-narcotic state and irregular respiration.

In some toxicokinetic studies with exposure CS_2 concentrations of 20-50 ppm, the presence or absence of signs of toxicity was briefly mentioned.

Nine persons who had never previously been in contact with CS_2 were exposed in 11 experiments to CS_2 at 17-30 ppm (in one case to 51 ppm) for 1 to 4 h. The concentration of CS_2 in the air was kept constant during the experiment within ±6 µg/L (1.9 ppm) and was determined every 15 min colorimetrically with diethylamine and copper reagent. Other than an occasional slight headache, the volunteers were reported to be free of symptoms (Teisinger and Soucek 1949).

In another toxicokinetic study, five "normal men" were exposed via a plastic face mask to CS_2 at 20 or 25 ppm for 1.5-2.1 h. The concentration of CS_2 in the air was kept constant during the experiment within ±1 ppm and was determined every 30 min (no further details reported). None of the subjects noticed any immediate or delayed effects from the vapor exposure, and in each case, blood pressure, heart rate, and respiratory rate were normal throughout the experiment (McKee et al. 1943).

TABLE 2-3 Summary of Acute Nonlethal Effects in Controlled Humans Studies after Inhalation of Carbon Disulfide

Subjects	Exposure Duration	Exposure Concentration	Effect/Remarks	Reference
2 male (m) volunteers	Up to 4 ¾ h	0.55-0.76 mg/L (180-240 ppm)	Moderate odor annoyance, no other subjective symptoms	Lehmann 1894
	Up to 4 h	0.8-1.3 (260-420)	Tension in the eyes, slight dizziness, headache, slight cough, feeling of exhaustion, at the end: slight lacrimation, burning of eyes, persistent headaches	
		0.7-2.55 mg/L (435-820 ppm)	Tickle in the throat, burning eyes, tingling; slight headaches, temporary impairment of reading ability, feeling of heat in the forehead, cough, slight dizziness. After end of exposure: strong, persistent headaches, irritation of larynx, cough attacks, palpitations, dizziness, anxiety, reddened face, increased pulse, paleness and cold sweat, unmotivated laughing ("mirth")	
	3 h and 30 min	About 2-3 mg/L (640-960 ppm)	Unmotivated laughing ("mirth"), intermittent stinging headaches, dizziness After exposure: Severe, persisting headache, congestion at night, feeling dazed next day	
	Up to 2 h	3.4-3.7 mg/L (1,100-1,190 ppm)	Immediate feeling of pressure in the head, dizziness, nausea, vertigo, increased pulse, intense headaches, skin of face feeling hot; increased pulse rate, tingling and paresthesia in arms	
	1 h	5.75-6.67 mg/L (1,850-2,140 ppm)	After end of exposure: persistent headaches Rapidly developing headache, pressure in the head, feeling of heat in the face, irritation of pharynx progressing to cough, nausea; persistent hiccups; anxiety, increased pulse, increasing dizziness, beginning central paralysis, mental capabilities highly impaired, difficulty to perform tasks After end of exposure: staggered gait, strong dazed feeling, sudden salivation with increased pulse; vomiting, headaches persisting until next morning, disturbed sleep, 2 d of feeling ill	

	½ h, then 1 h	6.8 mg/L (2,180 ppm) 10.5 mg/L (3,370 ppm)	>30 min: strong dizziness, nausea, seminarcotic state, tingling, shallow, irregular respiration with deep gasping in between; After exposure: leg muscle aches, feeling nervous and upset, intermittent headaches for 12 d	
9 volunteers	1-4 h	17-30 ppm (one exp: 51 ppm)	Occasional slight headaches, no details reported	Teisinger and Soucek 1949
Not reported	0.5-2 h	38-52 ppm	Slight headache in some of the subjects	Harashima and Masuda 1962
6 volunteers	4-50 min	3 ppm 10 ppm 20 ppm	No complaints or objective symptoms of intoxication after each experiment	Rosier et al. 1987
5 m volunteers	1.5-2.1 h	20-25 ppm	No subject noted immediate or delayed effects; normal blood pressure, heart and respiratory rate	McKee et al. 1943
19 m volunteers	6 h	10-80 ppm	≥10 ppm: inhibition of aminopyrine metabolism	Mack et al. 1974
11 m volunteers	8 h	40-80 ppm	In combination with ethyl alcohol (0.7 g/L [70 mg/dL]): rise in serum bilirubin, no elevation of hepatic enzymes in serum	Freundt and Lieberwirth 1974b
12 m volunteers	8 h	20-80 ppm	With synchronous or subsequent intake of ethyl alcohol (0.75 g/L [75 mg/dL]): increase in blood acetaldehyde to twice of control values, no disulfiram effect	Freundt et al. 1976b
4 trained staff members		0.21 ppm	Odor recognition threshold	Leonardos et al. 1969

In a further pharmacokinetic study, six healthy male volunteers of ages 27-36 years were exposed to CS_2 at concentrations of 10 and 20 ppm at rest and to 3 and 10 ppm under a 50-Watt (W) level of exercise (Rosier et al. 1987). The mean inhaled concentrations were within 4.1% (at 3 ppm), 1.6% (at 10 ppm), and 3.1% (at 20 ppm) of the proposed value. Every experiment consisted of four periods of 50 min exposure to CS_2 with a resting period of 10 min between two consecutive exposures. All volunteers were informed of the practical implications of the experiments. There were no complaints or objective signs of CS_2 intoxication after each experiment.

In another toxicokinetic study, six male volunteers were exposed through face mask to CS_2 concentrations ranging from 28 to 52 ppm for 0.5-2 h. Their bodies were covered from neck to hip by synthetic resin clothing through which air was blown to collect and determine CS_2 excreted via the skin. Apart from a slight headache in three of the six subjects, no signs of toxicity were reported (Harashima and Masuda 1962). Because of the absence of controls, exclusion of the symptom from response to the experimental procedure was not possible.

In a further toxicokinetic study, about 10 persons (probably workers of a factory where CS_2 was used, but no details were reported) were exposed in a 140-m^3 chamber to CS_2 at concentrations of 300 µg/L (96 ppm) for 8 h and 445 µg/L (143 ppm) for 5 h (Demus 1964). The exposure concentration was continuously monitored and reported to deviate no more than ±5% from the nominal concentration. The authors did not report the occurrence of any symptoms of intoxication, nor did they explicitly state the absence of such effects.

The inhibition of oxidative *N*-demethylation of amidopyrine by CS_2 was studied by Mack et al. (1974). Experiments were conducted on healthy male adults of ages 21-40 years instructed to discontinue drug intake and to restrict alcohol intake a few weeks prior to the experiments. Groups of four persons were exposed to CS_2 at 0, 10, 20, 40, or 80 ppm for 6 h. Exposures were carried out in an 8-m^3 dynamic exposure chamber (air exchange 8-15 times per hour). The CS_2-air mixture entered under uniform pressure through a vent at one edge. The exposure mixture was prepared in a spherical glass mixing vessel by evaporation of liquid CS_2 into a rotametrically metered stream of air. Continuous dropwise addition of CS_2 according to the desired concentration was obtained with an automatic infusion apparatus (Perfusor type 71100, Braun). Constant evaporation was maintained by heating the spherical mixing vessel over a 50-degree water bath. The CS_2-air mixture was diluted to the desired concentration with ambient air in another larger mixing drum. Permanent circulation of the chamber atmosphere was achieved by a vent in the middle of the roof. The CS_2 concentrations actually prevailing within the chamber were monitored before and during the entire exposure period with an automatically recording infrared analyzer (Uras 1, Hartmann & Braun) that was mounted outside and connected with the exposure chamber by a glass tube. At the start of each experiment, the individuals received amidopyrine orally at 7 mg/kg of body weight. Metabolites (aminoantipyrine [AAP], 4-AAP, and *N*-acetyl-AAP) were assayed in urine sampled 3-33 h after the start of the exposure. A concentration of CS_2 at 10 ppm

was sufficient to result in a significant deficit in the excretion of free and total 4-AAP during the exposure. Both the intensity and the duration of the effect showed a well-defined dose-response relationship. The excretion deficit was reversible and compensated for during the subsequent excretion phase. Further experiments with 6 h of exposure at 20 ppm revealed that the effect was no longer detectable at 18 h after exposure. Exposure to CS_2 at 20 ppm 6 h/d for 5 days produced an inhibitory reaction identical to that seen after a single 6-h exposure to 40 ppm.

Reports of alcohol intolerance in workers occupationally exposed to CS_2 prompted the investigation of this phenomenon in experimental studies. Ethanol is mainly oxidatively metabolized by two pathways, one (predominant) pathway via the cytosolic alcohol dehydrogenase (ADH) and, to a lesser extent, a second pathway via the microsomal CYP2E1 (see Figure 2-1). Both result in the formation of acetaldehyde, which is further oxidized by mitochondrial aldehyde dehydrogenae (ALDH) to acetate. Finally, acetate enters the intermediary metabolism of the cell.

Apparently, CS_2 inhibits the metabolism of ethanol at the second step of the pathway, that is, the oxidation of acetaldehyde via ALDH. The effect of CS_2 on the blood acetaldehyde concentration in subjects who had ingested alcoholic beverages was investigated in volunteers (Freundt and Lieberwirth 1974a; Freundt et al. 1976b). Twelve healthy males of ages 20-32 years were asked not to take alcohol or medicine several days prior to the experiment. Exposure conditions and alcohol intake were performed as described above (Freundt and Lieberwirth 1974b). Acetaldehyde and ethanol were determined by gas chromatographic headspace analysis in blood samples taken from the antecubital vein at hourly intervals. In all experiments, CS_2 exposure had no significant effect on the blood alcohol concentration. The mean blood alcohol concentration obtained was about 0.75 g/L (75 mg/dL) and remained fairly constant during the experiments. In alcoholized control subjects, the blood acetaldehyde concentration determined was approximately 6×10^{-3} g/L (140 μM). During a simultaneous 8-h exposure of four volunteers to CS_2 at 20 ppm, the blood acetaldehyde concentration rose significantly by about 50%. Exposure to CS_2 at 40 or 80 ppm for 8 h resulted in a slight further increase of blood acetaldehyde. In a further experiment with four volunteers, administration of alcohol (about 0.5 g/L [50 mg/dL] blood alcohol) for 8 h, instituted 16 h (that is, the next morning) after the 8-h exposure to CS_2 at 20 ppm, the blood acetaldehyde concentration reached slightly more than twice the control value. A nearly identical quantitative effect was also seen after repeated exposure to CS_2 at 20 ppm for 8 h/d on 5 consecutive days and simultaneous administration of ethanol only on the last day. Under the conditions used, no signs of a disulfiram effect (Antabuse syndrome) of alcohol intolerance in any the subjects were noted.

The influence of inhaled CS_2 on serum parameters was studied in volunteers who also received alcohol (Freundt and Lieberwirth 1974b). Exposures were carried out in an 8-m^3 dynamic exposure chamber (air exchange 15 times

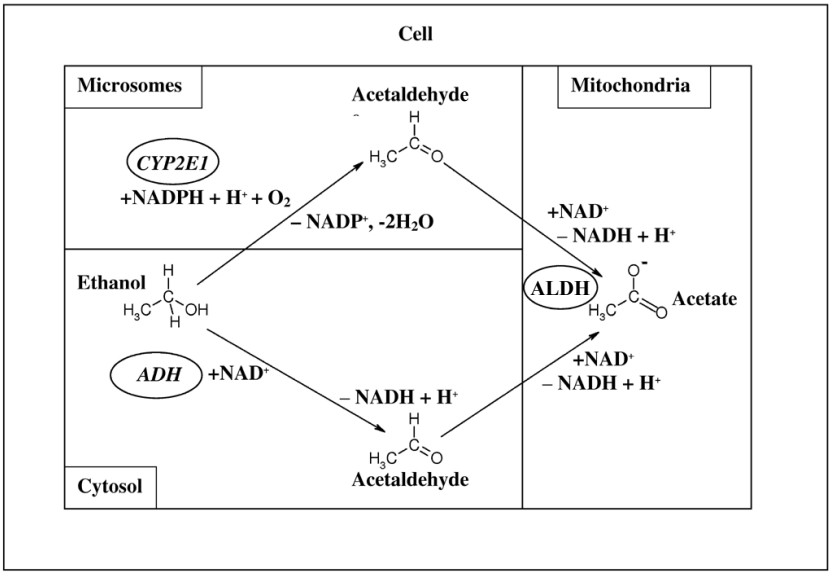

FIGURE 2-1 Oxidative pathways of ethanol metabolism. Abbreviations: ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; CYP2E1, cytochrome P-450 2 E1.

per hour) as described by Mack et al. (1974). Eleven healthy male volunteers of ages 20-32 years were asked not to take alcohol or medicine several days prior to the experiment. Volunteers (number in parentheses) were exposed to CS_2 at 0 (11), 40 (5), or 80 (4) ppm for 8 h. The volunteers received alcohol (0.57 mL/kg of body weight) in orange juice (3.01 mL/kg of body weight) at the beginning of the exposure and alcohol at 0.047 mL/kg of body weight in orange juice at 0.18 mL/kg of body weight every 15 min until the end of exposure. Standardized meals were served 1.5, 3, and 5 h after start of exposure. The mean blood ethanol concentration obtained was 0.7 g/L (70 mg/dL) (range 0.58 to 0.85 g/L [58 to 85 mg/dL], determined by gas chromatography). For the evaluation of serum parameters, the pretreatment values in each group served as the control values. Alcohol intake alone significantly lowered blood glucose by about 12%. In subjects with alcohol intake who were exposed to CS_2 at 40 ppm, no significant changes of any serum parameters (cholesterol, calcium, inorganic phosphate, total bilirubin, albumin, total protein, uric acid, urea-*N*, glucose, lactate dehydrogenase [LDH], alkaline phosphatase, and aspartate aminotransferase [ASAT]) were found. However, the blood glucose level was about 13% lower at the end of the treatment period. At 80 ppm, the decrease in blood glucose reached statistical significance. At this concentration, a significant rise of the serum total bilirubin concentration by 61% as compared with preexposure also was observed, and the bilirubin concentration just exceeded the normal range. However, a nearly identical bilirubin concentration was observed in the group

that only received alcohol. Here, the increase was not significant because the pretreatment level was higher than that observed in the 80-ppm group. No significant changes were observed in serum parameters (cholesterol, calcium, inorganic phosphate, albumin, total protein, uric acid, urea-*N*, LDH, alkaline phosphatase, and ASAT).

In the same study, four volunteers were exposed to CS_2 at 20 ppm for 8 h without simultaneous alcohol intake. After exposure, a 30% decrease of the mean blood glucose level was observed. The decrease did not reach statistical significance. No significant changes were noted on any of the serum parameters mentioned above. When this group subsequently received alcohol (as decribed above) over a period of 16-24 h after the exposure to CS_2, a 108% increase in the serum total bilirubin concentration to above the upper normal range and slight nonsignificant increases (18-52%) in serum albumin, total protein, uric acid, and alkaline phosphatase were observed.

Finally, in this study four volunteers were exposed to CS_2 at 20 ppm for 8 h/d for 5 days. Only during the last exposure, alcohol (as described above) was given. During the 4 days of exposure to CS_2 alone, nonsignificant decreases in blood glucose levels (up to 12%) were seen each day. The only significant change observed was a 55% increase in serum total bilirubin on day 3. At the end of day 5, the total serum bilirubin was increased by about 50% and the blood glucose was significantly decreased by 18%. However, throughout the study, all blood glucose determinations were within the normal range.

Lehmann (1894) described the odor of concentrated vapors of freshly purified CS_2 as resembling the odor of chloroform and the odor of more diluted vapors from the same samples as resembling a mixture of chloroform and decaying radish (or overcooked cauliflower). The author also reported that exposure of a single volunteer at 0.55-0.76 mg/L (180-240 ppm) for up to 4 h 45 min caused moderate odor annoyance.

Leonardos et al. (1969) determined the odor recognition threshold for CS_2 under controlled laboratory conditions using a standardized and defined procedure. The CS_2 used was of the highest purity that was commercially available from large-scale production.. Four trained panel staff members were selected. Prior to exposure to at least five different concentrations in an odor test room, the panel examined the odor over water at various dilutions to become acquainted with the odor type and to develop a common terminology for describing the odor. The order of presentation of concentrations in the test room was on a random basis, and observations were separated by a minimum of a 25-min break. A positive response was indicated for each concentration at which the panelist described the odor of the chemical. The threshold was taken as the lowest concentration at which the panelist could define the odor and that which could be consistently recognized at higher concentrations. The odor threshold represents that concentration at which all four panelists could positively recognize the odor. A threshold of 0.21 ppm was determined. The value from this study served as the basis for the derivation of the Emergency Response Planning Guidelines 1 (ERPG-1) value for CS_2 of 1 ppm (AIHA 1992).

Amoore and Hautala (1983) reported a geometric mean air odor threshold of 0.11 ppm (standard error, 0.058 ppm) for CS_2. Data were derived from six available original literature references, which were not explicitly reported.

A wide range of odor thresholds from 0.0243 to 23.1 mg/m³ (0.0078 to 7.4 ppm) for CS_2 were reported in a compilation of data from the industrial hygiene literature (Ruth 1986). The author did not explicitly report from which references the values for individual chemicals were taken. No value regarding irritating concentrations was reported.

In a critical overview of odor thresholds for chemicals, all the referenced values ranged from 0.016 to 0.42 ppm, but no geometric mean and no "range of acceptable values" for CS_2 were presented (AIHA 1997). The use of the 0.21-ppm threshold (see above) was rejected in this overview because this value represents a 100% recognition concentration.

In instances where CS_2 was swallowed, the following symptoms were reported: spasmodic tremor, Cheyne-Stokes respiration, large pupils, pallor, decreased body temperature, and finally coma. Less serious manifestations included paresthesias, weakness and unsteadiness of arms and legs, and hemiparesis (Davidson and Feinleib 1972).

Liquid CS_2 is a severe skin irritant and vesicant. In workers in the spinning operation of viscose plants, serous and hemorrhagic blisters on the skin of fingers occurred. Recurrent blisters may develop several weeks after cessation of contact (Hueper 1936).

2.3. Reproductive and Developmental Toxicity

Data regarding the reproductive or developmental toxicity of acute exposure of humans to CS_2 were not available.

Studies have been carried out on occupational cohorts chronically exposed to CS_2. A detailed description of these findings is beyond the scope of this document, but there are several reviews (Henschler and Greim 1975; WHO 1979; Fielder et al. 1981; Beauchamp et al. 1983; BUA 1993; ATSDR 1996; Greim 1999; EnvironmentCanada/Health Canada 2000) from which the following conclusions can be derived. Reports of reduced sperm counts and changes in sperm morphology and of changes in hormone levels that had been presented in earlier studies could not be confirmed in more recent studies. Significant effects in recent studies were found on workers' libido (between 1 and 30 mg/m³ [0.32 and 10 ppm]) and potency (above 30 mg/m³). In females, spontaneous abortions and menstruation disorders were described. The concentrations reported range from below 10 mg/m³ (3.2 ppm) to far above 30 mg/m³ (10 ppm). Some evidence for an increase in malformations of the heart and CNS has been presented. Two early reports of an increased frequency of spontaneous abortions associated with maternal or paternal employment in the viscose rayon industry could not be confirmed in more recent studies.

2.4. Genotoxicity

In an in vitro study, lymphocytes from 25- to 40-year-old male volunteers were incubated with CS_2 in gas-tight vessels for 30 min (Garry et al. 1990). In the presence, but not in the absence, of a metabolic activation system (S-9 from rat liver), CS_2 led to a significant concentration-dependent increase in the number of sister chromatid exchanges (SCE). Chromosomal aberrations were not increased.

In a further in vitro study using WI-38 human lung fibroblasts, the unscheduled DNA synthesis (UDS) was not increased by CS_2 (0.1-5 mL/L of medium) in the absence of a metabolic activation system. In the presence of mouse liver S-9, a slight but significant amount of UDS was observed. Unexpectedly, the positive control substance benzo(*a*)pyrene failed to induce UDS in this study (Belisles et al. 1980).

In human sperm exposed to CS_2 in vitro, a significant increase in the frequency of chromosomal aberrations and of chromosomal breaks were seen (Le and Fu 1996).

2.5. Carcinogenicity

A mortality cohort study was carried out on 2,291 workers with chronic occupational CS_2 poisoning diagnosed during the years 1970-1990. The general population of Poland was the reference population. With respect to neoplastic diseases, the analysis in male subjects showed a statistically significant excess of deaths from colon cancer (standard mortality ratio = 233; 9 cases). All these cases were noted in workers of the two oldest rayon plants, and a detailed future analysis is required to derive further conclusions (Peplonska et al. 1996).

The number of deaths due to neoplasms was compared in a cohort of rayon plant workers and in a cohort of paper mill workers from 1967 to 1982. No significant differences were found (Nurminen and Hernberg 1984).

A nested case-control study in a cohort of rubber workers indicated a significantly increased odds ratio for exposure to CS_2, and development of and also death from lymphocytic leukemia when specific exposures in the group to a variety of different solvents other than benzene (jobs with benzene exposure were excluded from the study) were analyzed (Wilcosky et al. 1984). However, cautious attention must be paid to a number of factors: The number of cases examined was small, a large number of solvents were considered in the analysis, many of these solvents were used in mixtures so that identifying single agents was not possible, historical exposure was estimated from the designation "permitted to use" but not from actual use, and confounding factors from nonoccupational or other occupational exposures were not taken into account.

A number of epidemiologic studies on mortality in workers exposed to CS_2, especially in the viscose rayon industry, have been presented. However, these studies focus on the association between exposure and mortality from car-

diovascular diseases, and other findings are poorly described. The available data have been reviewed and summarized (WHO 1979; ATSDR 1996; BUA 1993; EnvironmentCanada/Health Canada 2000). Overall, there was no consistent evidence of an increase in mortality from all cancers combined or from cancers at any specific site.

2.6. Summary

In experimental studies, a wide overall range of odor thresholds from 0.0243 mg/m³ to 23.1 mg/m³ (0.0078 to 7.4 ppm) were reported (Ruth 1986). Because CS_2 decomposes rapidly under the influence of air and light, resulting in the formation of foul smelling decay products, it is to be expected that the odor detection and recognition threshold of CS_2 will vary widely, depending on the purity of the substance and the conditions.

The most sensitive effect following exposure to CS_2 was an inhibition of biotransformation reactions. In an experimental study on oxidative *N*-demethylation of amidopyrine, exposure to CS_2 at 10-80 ppm caused a concentration-dependent, reversible inhibition of the urinary excretion of metabolites, indicating inhibition of oxidative biotransformation (Mack et al. 1974).

In several experiments, volunteers were exposed to CS_2 in combination with controlled intake of alcohol. The blood ethanol concentration was about 0.7 g/L (70 mg/dL) representing a level which may be often obtained in "lifestyle activities." Exposure to CS_2 at 20-80 ppm for 8 h caused a 50% increase in the concentration of acetaldehyde in blood compared with "alcohol-only" values of the same subjects. A similar effect was seen when the intake of alcohol started 16 h after exposure to CS_2 at 20 ppm and after 8 h/d for 5 consecutive days of exposure to CS_2 at 20 ppm with alcohol intake only on the last day. Under the conditions of the study, there were no complaints about a disulfiram effect (Antabuse syndrome) or other subjective signs of intoxication (Freundt and Lieberwirth 1974a; Freundt et al. 1976b).

Exposure to CS_2 at 80 ppm for 8 h in subjects given alcohol also led to a significant 60% rise of total serum bilirubin. This effect also occurred when the alcohol intake started 16 h after CS_2exposure at 20 ppm. Other serum parameters, including liver enzymes in serum (LDH, alkaline phosphatase, ASAT), were in the normal range (Freundt and Lieberwirth 1974b).

Occasional slight headache was reported in volunteers exposed to CS_2 at 17-51 ppm for 0.5 to 4 h. No other symptoms were reported (Teisinger and Soucek 1949; Harashima and Masuda 1962). The volunteers were reported to be free of symptoms at exposures to CS_2 at 3-25 ppm (McKee et al. 1943; Rosier et al. 1987) for 1.5 to 2.1 h. Odor annoyance was described by volunteers exposed to CS_2 at 180-240 ppm. No other symptoms were reported. CNS symptoms and irritation of eyes and throat occurred at 260-420 ppm. CNS symptoms increased in severity with exposure concentration and time. Severe CNS effects, which continued after the exposure ended, were seen at about 2,000 ppm. Concentra-

tions from 2,000 ppm increasing to above 3,000 ppm resulted in semi-narcotic state and irregular respiration.

Studies in occupationally exposed workers also show that the primary effect of acute intoxication is on the CNS. Often, symptoms such as psychoses remained for a long period of time afterward (Gordy and Trumper 1938). However, these reports described cases in workers who previously had been exposed for weeks to years. In view of the chronic effects of CS_2 on the nervous system, such "acute" poisonings probably were acute exposures and acute outbreaks superimposed by chronic exposure. No concentrations were reported in such acute cases.

Deaths have been reported following exposures to high concentrations in accidents. Due to the lack of exposure data and the concomitant exposure to H_2S and sulfuric acid, no conclusions valid for the derivation of the AEGL can be derived from these data. According to Flury and Zernik (1931), exposure to CS_2 at 4,800 ppm for 30 min to 1 h will immediately or later result in death, and exposure at 3,200-3,850 ppm over the same period of time will be life-threatening. The same statement was made by Bittersohl et al. (1972). Furthermore, they stated that "hyperacute intoxication" with very high concentrations exceeding 10 mg/L (3,200 ppm) will immediately lead to loss of reflexes, coma, and death. No details or references were presented in these secondary sources.

Data regarding reproductive or develomental toxicity following acute exposure were not available. Epidemiologic studies have provided conflicting evidence of effects on reproduction, spontaneous abortions, and malformations. These studies were carried out in workers with chronic exposure to CS_2.

Data on genotoxicity are very limited. CS_2 increased the frequency of SCE in vitro in human lymphocytes in the presence but not in the absence of a metabolic activation, system. Chromosomal aberrations were not increased (Garry et al. 1990). A further in vitro study using WI-38 human lung fibroblasts found no increased UDS in the absence of a metabolic activation system. In the presence of a metabolic activation system, a slight but significant amount of UDS was observed. No valid conclusions can be drawn because, unexpectedly, the positive control substance benzo(*a*)pyrene failed to induce UDS in this study (Belisles et al.1980).

A number of epidemiologic studies on mortality in workers exposed to CS_2, especially in the viscose rayon industry, have been presented. However, these studies focused on the association between exposure and mortality from cardiovascular diseases, and other findings are poorly described. Overall, the database with respect to cancer is limited. There is no consistent evidence of an increase in mortality from all cancers combined or from cancers at any specific site.

3. ANIMAL TOXICITY DATA

In this TSD, the presentation and the discussion of animal toxicity studies

have been limited to acute exposure studies and to studies with repeated exposure. These were evaluated with respect to the presence or absence of acute toxic effects that are of relevance for the derivation of AEGL values.

3.1. Acute Lethality

Studies were performed on rats, mice, rabbits, and cats. Data are summarized in Table 2-4.

3.1.1. Rats

Six male CD-rats per group were exposed to CS_2 at 3,000 ppm and 3,500 ppm for 4 h in a 16-L exposure chamber (Du Pont 1966). At the higher exposure concentration, analytically determined values as monitored hourly by gas chromatography were about 8.8% higher than nominal values. Because of instrumental difficulties, no analytic confirmation was performed at 3,000 ppm. The data indicate a very steep concentration-response curve for lethality: Whereas all six rats exposed at 3,500 ppm died during exposure or less than 2 h later, none of six rats exposed at 3,000 ppm died during exposure or within the 14-day post-exposure observation period. During exposure, animals suffered from tachypnea, ptosis, incoordination, chromodacryorrhea (release of red fluid from nasolacrimal glands), and gasping. Weight loss, hyperexcitability, and dyspnea were observed 24 h post-exposure. At 3,500 ppm, besides the effects described above, salivation, aimless wandering, and prostration were noted. Necropsy of two rats exposed at 3,500 ppm revealed pleural effusion, dark red and edematous lungs, petechial lung hemorrhages, and pulmonary hyperemia. Changes in other organs were also seen but not reported.

Without further details, a 2-h LC_{50} (concentration that is lethal to 50% of a test group) of 25,000 mg/m³ (8,025 ppm) for rats is reported by Izmerov et al. (1982). No treatment-related deaths were noted in male and female Fischer rats exposed to CS_2 at 0, 50, 500, or 800 ppm for 6 h/d, 5 d/wk for 2, 4, 8, or 13 weeks as described by Sills et al. (1998) (see 3.2.2). Nonlethal effects observed in this study are reported in section 3.2.2 (Moser et al. 1998).

In a subchronic study, Fischer 344 rats and Sprague-Dawley rats (15 males and 15 females per group) were exposed to analytically confirmed concentrations of CS_2 at 0, 50, 300, and 800 ppm for 6 h/d, 5 d/wk for at least 89 consecutive calendar days (ToxiGenics 1983a,b,c). There was no mortality in Fischer 344 rats. One male Sprague-Dawley rat exposed at 800 ppm was found dead on study day 41, and one male Sprague-Dawley rat exposed to 50 ppm was sacrificed in extremis on study day 50 of the study. Nonlethal effects observed in this study are reported in section 3.2.2.

TABLE 2-4 Summary of Lethal Effects in Animals after Acute Inhalation Exposure to Carbon Disulfide

Species	Exposure	Concentration	Effect/Remarks	Reference
Rat	2 h	25,000 mg/m³ (8025 ppm)	LC_{50}	Izmerov et al. 1982
	4 h	3,500 ppm	6/6 died	Du Pont 1966
	4 h	3,000 ppm	0/6 died	
	4 h/d, 5 d/wk, 2 wk	2,000 ppm	No death after one exposure; 2/10 died after 10 exposures	Goldberg et al. 1964
	2 h	0.15% (1500 ppm)	0/12 died	Savolainen and Järvisalo 1977
	6 h/d, 5 d/wk, 13 wk	800 ppm	F344 rats: no mortality S-D rats: 1/15 m died at day 41	ToxiGenics 1983b; ToxiGenics 1983c
	6 h/d, 5 d/wk, 13 wk	800 ppm	No treatment related deaths	Moser et al. 1998
Mouse	2 h	10,000 mg/m³ (3,210 ppm)	LC_{50}	Izmerov et al. 1982
	30 min	4,500 ppm	"Average lethal concentration," 17/30 animals died	Kuljak et al. 1974
	30 min/d, 3 d	3,000 ppm	21/30 animals died	
	6 h/d, 2-5 d	800 ppm	No death after one exposure; 21/57 died in group on high-fat diet; no death in group on normal diet	Lewis et al. 1999
	6 h/d, 5 d/wk, 13 wk	800 ppm	4/30 died 13th wk	ToxiGenics 1983a
	1 h	220 ppm	LC_{50}	Gibson and Roberts 1972
Rabbit	6 h, 15 min	3,220 ppm	2½ h: lying on its side; narcosis at the end; death after 7 d	Flury and Zernik 1931

(Continued)

TABLE 2-4 Continued

Species	Exposure	Concentration	Effect/Remarks	Reference
Rabbit	6 h	3,000 ppm	4/6 died and 2/6 moribund and euthanized after exposure	PAI 1991
	6 h/d, 13 d	1,200 ppm	Developmental toxicity study 2/24 dams died	PAI 1991
Cat	48 min	112 mg/L (36,000 ppm)	Lying on its side, convulsions, 1¾ h: narcosis, died after half a day	Lehmann and Flury 1938
	3 h, 8 min	≥23 mg/L (≥7,400 ppm)	Died during exposure	Lehmann 1894
	2 h 15 min	6,450 ppm	40 min: lying on its side, convulsions; later narcosis; death after 1 d	Flury and Zernik 1931
	4 h 15 min	3,220 ppm	1¾ h: lying on its side, convulsions; after 4 h: narcosis, death after 1 d	
Guinea pig	15 min	≥54 mg/L (≥17,300 ppm)	Increasing paralysis, death	Lehmann 1894
	30 min	≥23 mg/L (≥7,400 ppm)	Died without convulsions	

An oral LD_{50} of 3,188 mg/kg of body weight was reported by Izmerov et al. (1982). In another study, following oral administration of undiluted CS_2 to male Sprague-Dawley rats, an LD_{50} of 1,200 mg/kg of body weight was determined (Kanada et al. 1994). No further details were presented in these studies. After intraperitoneal (i.p.) injection of undiluted CS_2 to male Sprague-Dawley rats, an LD_{50} of 0.84 mL/kg of body weight (1,060 mg/kg) was reported (de Gandarias et al. 1992).

In a further study, the toxicity of CS_2 in Sprague-Dawley rats of different age was compared (Green and Hunter 1985). CS_2 was given intraperitoneally in corn oil vehicle. The 24-h LD_{50} was estimated by the "up-and-down" method. CS_2 was found least toxic to 20-day-old male rats (LD_{50}, 1,545 mg/kg) and most toxic to 1-day-old rats (LD_{50}, 583 mg/kg).

3.1.2. Mice

Gibson and Roberts (1972) exposed male Swiss-Webster mice to calculated CS_2 concentrations of 54, 110, 230, and 550 ppm, respectively, for 60 min. The actual concentrations of CS_2 were not measured. An "approximate LC_{50}" of 220 ppm was reported. Further data presented indicate a steep concentration-response curve for lethality: Whereas animal lethality precluded time studies of liver function exceeding 2 h at 230 ppm, such studies could be carried out over 24 h at 110 ppm. Izmerov et al. (1982) reported a 2-h LC_{50} of 10,000 mg/m³ (3,210 ppm) for mice. No details were presented.

Kuljak et al. (1974) exposed mice (sex and strain not reported) to CS_2 in a desiccator through which air mixed with CS_2 was passed at a rate of 1.2 L/h by means of a vacuum pump. A gas meter and a series of three impingers in which the CS_2 was absorbed were placed between the desiccator and the vacuum pump. CS_2 was determined by a xanthogenate method. The "average lethal concentration" (LC_m) was determined by straight-line graphic interpolation. Exposure to 4,500 ppm (reported to represent the LC_m) for 30 min killed 17 of 30 animals. In a further experiment on mice pretreated with glutathione (100 mg/kg i.p.) 2 h prior to exposure to CS_2 at 4,500 ppm for 30 min, 8 of 30 animals died.

Lewis et al. (1999) studied the effects of CS_2 on the development of atherogenic lesions. Female C57BL/6 mice were exposed to analytically confirmed concentrations of CS_2 at 50, 500, or 800 ppm for 6 h/d, 5 d/wk for 1, 4, 8, 12, 16, or 20 wk. Immediately after the first exposure, half of each group in the six subgroups (to be exposed for 1, 4, 8, 12, 16, or 20 wk) were placed on a control standard diet, and half were on an atherogenic high-fat diet. In the high-fat diet groups exposed at 800 ppm, 21 of 60 mice died during the first week of exposure. Not all animals died on the same day, and none died after a single exposure to CS_2 (J.G. Lewis, personal communication). Necropsies failed to disclose the cause of death. Nonlethal effects of this study are described in section 3.2.3.

In a subchronic study, B6C3F1 mice were exposed to analytically confirmed concentrations of CS_2 at 0, 50, 300, and 800 ppm for 6 h/d, 5 d/wk for at least 89 consecutive calendar days (ToxiGenics 1983a). Four mice exposed at 800 ppm died during the last week of the study. Nonlethal effects observed in this study are reported in section 3.2.3.

Male Swiss-Webster mice were given CS_2 in corn oil orally by intubation or intraperitoneally so that each animal received oil-CS_2 solution at 10 mL/kg (Gibson and Roberts 1972). Neither the exact number of animals nor the different CS_2 concentrations used were reported. The median lethal dose of CS_2 (within a 24-h period) for oral administration was 3,020 mg/kg and for i.p. administration was 1,890 mg/kg.

Without further details, Izmerov et al. (1982) reported an oral LD_{50} of 2,780 mg/kg for mice.

3.1.3. Rabbits

In an unpublished range finding experiment for a reproductive or developmental toxicity study, six pregnant New Zealand rabbits were exposed to CS_2 at 3,000 ppm for 6 h on the 6th day of gestation (PAI 1991); four of the six animals died during exposure, and the two others were moribund at the end of exposure and were sacrificed. No gross lesions were observed, but the animals exhibited tremors, labored breathing, and apparent anoxia. The four animals that died during exposure did not struggle or convulse prior to death.

Without further details, Izmerov et al. (1982) reported an oral LD_{50} of 2,550 mg/kg. Brieger (1949) reported that rabbits (no further details given) injected intravenously with CS_2 at 0.5 mL (0.63 g) died within 20 min.

3.1.4. Cats

Flury and Zernik (1931) reported that individual cats exposed to CS_2 at 3,220 ppm for 4.25 h and to 6,450 ppm for 2.25 h became anesthetized during exposure and died after 1 and 7 days, respectively.

3.1.5. Guinea pigs

Lehmann (1894) reported that one guinea pig exposed to at least 7,400 ppm died within 30 min, and another one exposed to at least 17,300 ppm died within 15 min.

An oral LD_{50} of 2,125 mg/kg was reported, but no details were given (Izmerov et al. 1982). Following i.p. administration of CS_2 at 400 mg/kg, three of four male guinea pigs died within 24 h (DiVincenzo and Krasavage 1974).

3.2. Nonlethal Toxicity

Studies with inhalation exposure were performed with monkeys, rats, mice, rabbits, dogs, and cats. A number of studies with repeated inhalation exposure have reported acute effects in laboratory animals after the first exposure or at the end of the daily exposure period. Nonlethal effects are summarized in Table 2-5.

3.2.1. Nonhuman primates

Aversive thresholds to electric shock stimulation were studied in squirrel monkeys (*Saimiri sciureus*) (Weiss et al. 1979). Individual animals were placed in an exposure chamber and restrained at the waist. The animal faced a T-shaped bar fixed to a strain gauge. A computer-controlled, constant current shock stimulator delivered the aversive stimulus to the electrodes placed on the tail and foot. The strain gauge output was fed to the inputs of a computer. A large force requirement of 300 g enhanced the sensitivity of the experiment to the toxicologic insult. The shock level was raised by 2% of the total range each time an increment was programmed (every 2 seconds [s]) and reduced by the same amount after each response. The bar had to be released to initiate a new response, continued application of such a force did not further lower the shock. The concentration of CS_2 in the exposure chamber was monitored continuously.

Experiments with one monkey revealed a stable performance under control conditions without exposure to CS_2. The aversive threshold rose for the first few minutes and subsequently undulated within narrow limits. This undulating response is explained by the tendency of the animal to wait for the shock level to rise by several steps before emitting a train of responses which lowers the shock level. In a 2-h exposure to CS_2 at about 600 ppm, a radically altered response pattern was observed: During the first 30 min, the animal responded erratically and tolerated higher shock levels than under control conditions. Long gaps without responding and an inadequate force exerted (responses less than 300 g did not reduce the shock) when the monkey did react contributed to this effect. During the last 30 min of exposure, response forces met the criterion as often as in the control session, but the aversive threshold remained elevated beyond control values suggesting an anesthetic and/or an analgesic effect. This effect was also seen in a second monkey that maintained a shock level 50% above its own control value.

Additional experiments with lower exposure concentrations over longer periods of time were reported to produce equivalent effects. While the first monkey whose performance is described above displayed a similar response to an exposure of 18 h to 70 ppm, the highest concentration required to produce such an effect in a group of four monkeys trained as described above was 200 ppm.

TABLE 2-5 Summary of Acute Nonlethal Effects in Animals after Inhalation Exposure to Carbon Disulfide

Species, Strain, Number, Sex	Exposure	Concentration	Effect	Reference
Squirrel monkey, 2	2 h	600 ppm	Rise in electric shock tolerance, diminution of response force	Weiss et al. 1979
Squirrel monkey, 4	18 h	70-200 ppm		
Rat	10 min	1,660-81,100 ppm	No overt clinical signs of toxicity, transient slight to moderate weight loss	Du Pont 1981
Rat	4 h	3,000 ppm	0/6 animals died; tachypnea, ptosis, incoordination, gasping, hyperexcitability	Du Pont 1966
Rat, CFE, f	4 h	2,000 ppm	Behavioral alterations	Goldberg et al. 1964
Rat	4 h/d	5 mg/L (1,600 ppm)	Exposure well tolerated, no signs of toxicity apart from animals being more subdued	Heubusch and DiStefano 1978
Rat, S-D, 12	2 h	0.15% (1,500 ppm)	No deaths; slightly somnolent after exposure, recovery within 46 h	Savolainen and Järvisalo 1977
Rat, Wistar, 4, m	4 h	1,370 ppm	30% depression of response to electric seizure	Frantik et al. 1994
Rat, Wistar, 8-30, m	4 h/d, 2 d	4.0 mg/L (1280 ppm)	Myocardial damage only in animals pretreated with phenobarbitone (PB) + noradrenaline (or PB + cold-stress)	Chandra et al. 1972
Rat, Wistar, 7, m	18 h	2.5 mg/L (800 ppm)	Severe narcosis, reduced cardiac and respiratory rate, straightening of hind limbs, reduced body temperature; uncoupling of oxidative phosphorylation in brain mitochondria	Tarkowski and Sobczak 1971
Rat, Porton, 6, m	15 h	2.5 mg/L (800 ppm)	Ataxia, tremors, occasional convulsions; 25% lowering of blood glucose; alterations of brain amino acid metabolism	Tarkowski and Cremer 1972
Rat, Wistar, 7, f	12 h	2.4 mg/L (770 ppm)	No visible signs of toxicity reported; Brain: ultrastructural alterations of mitochondria, increase in ATP, decrease in ADP and AMP	Tarkowski et al. 1980

Rat, 6	4 h/d	800 ppm	No deaths; drowsiness shortly after start of exposure	Battig and Grandjean 1964
Rat, F 344, 9 m, 9 f	6 h/d, 5 d/wk, 2-13 wk	50, 500, 800 ppm	No treatment-related deaths	Moser et al. 1998
Rat, 18, m	6 or 7 h	0.15 mg/L (50 ppm) 1.2 mg/L (385 ppm) 2.4 mg/L (770 ppm)	No effect increase in spontaneous motor activity decrease of spontaneous motor activity (ca. 60%), motor performance, and avoidance reactions	Frantik 1970
Rat, S-D, 4-6, m	4 h and 8 h	2 mg/L (640 ppm)	Decrease of brain, adrenal, heart noradrenaline; decrease of adrenal adrenaline; dncrease of adrenal dopamine	McKenna and DiStefano 1977b
Rat, 6, m	4 h/d; 2 d	2 mg/L (640 ppm)	Decreased noradrenaline concentration in brain; increase in amphetamine-induced stereotypes	Magos et al. 1974
Rat, Porton-Wistar, 4, m	16 h	2 mg/L (640 ppm)	No obvious sign of toxicity after exposure; brain: increase of dopamine, decrease of noradrenaline	Caroldi et al. 1987
Rat, S-D, 6, m	10 h/d; 14 d	600-800 ppm	≥600 ppm, each day: narcotic-like stupor during exposure; after 14 h return to normal levels of alertness and activity 600 ppm, ≥9 d: circling behavior, retropulsion 800 ppm, ≥4 d: circling behavior, retropulsion	Wilmarth et al. 1993
Rat, Wistar, 14, m	6 h	500 ppm	Reduced activity level, not strongly irritating or prenarcotic	Kivisto et al. 1995
Rat, Wistar, 5-15, f	8 h	20 ppm 100 ppm 400 ppm	Decrease of liver glycogen Increased oxygen consumption No change of serum ASAT, ALAT, LDH, biliary BSP-clearance; increased hepatic lactate	Freundt and Kürzinger 1975
Rat, Wistar, 5 or 10, f	8 h	200 ppm	No hepatic damage	Freundt et al. 1974a

(Continued)

TABLE 2-5 Continued

Species, Strain, Number, Sex	Exposure	Concentration	Effect	Reference
Rat, S-D, 4-6, m	8 h	0.2 mg/L (64 ppm)	Decrease of brain noradrenaline	McKenna and DiStefano 1977b
Rat, Wistar, 5-15, f	8 h	20 ppm	Increase in hepatic microsomal lipid, inhibition of microsomal drug biotransformation	Freundt et al. 1974b; Freundt and Kuttner 1969
Rat, S-D, 20-23 f	6 h/d, gestation day 6-20	100, 200, 400, 800 ppm	No deaths of dams ≥400 ppm: reduced weight gain	Saillenfait et al. 1989
Mouse	20 min	11,000 ppm	Narcosis; recovery after termination of exposure	Flury and Zernik 1931
Mouse, H, 8, f	2 h	2,600 ppm	30% depression of response to electric seizure	Frantik et al. 1994
Mouse, CD-1, 4-5, m,	30 min	120 ppm 580 ppm 2,270 ppm 3,700 ppm	No effect on behavioral response Decreased responding in most mice Decreased responding in all mice Responding abolished	Liang et al. 1983
Mouse, CD-1, 12, m	30 min	2,000 ppm 2,242 ppm 3,700 ppm	Decreased behavioral response in some mice calculated EC_{50} abolished response in all mice	Glowa and Dews 1987
Rabbit, 1	2 h 15 min	6,450 ppm	50 min: lying on its side, convulsions, narcosis, recovery	Flury and Zernik 1931
Rabbit, 1	3 h	10.4 mg/L (3,340 ppm)	Swaying, lying on its side, loss of reflexes, recovery after end of exposure	Lehmann 1894
Rabbit, 1	2 h 15 min	9.3 mg/L (2,990 ppm)	Swaying, lying on its side, restlessness, paralysis, nystagmus, recovery	
Rabbit, 1	3 h 30	7.6 mg/L (2,440 ppm)	Swaying, lying on its side, convulsions, paralysis, recovery after about 1 h	

Rabbit, 2	3 h	4.3-4.7 mg/L (1,380-1,510 ppm)	Variable respiration, restlessness	
Rabbit, 1	9 h	2.64 mg/L (850 ppm)	No marked symptoms noted, animal takes up food during exposure	
Rabbit, 3	8 h	1.2 -1.34 mg/L (385-430 ppm)	Decreasing respiration rate, no further symptoms	
Rabbit	10 h	0.2 mg/L (64 ppm)	No signs of acute toxic effects observed	Lehmann 1894
Rabbit	6 h/d, 13 d	1,200 ppm	Developmental toxicity study Dams: reduced weight gain, ataxia, tremors, wheezing, labored respiration	PAI 1991
Rabbit	6 h/d, 5 d/wk, 17 wk	750 ppm	No signs of acute toxicity observed	Cohen et al. 1959
Dogs, mixed, 8	8 h/d, 5 d/wk, 10-15 wk	400 ± 102 ppm	During exposure: sleep Immediately after exposure: drowsiness, staggered and stumbled gait, trembling and shaking, restlessness, later excited, noisy Death after 10-15 wk	Lewey et al. 1941
Cat, 1	1 h 6 min	75 mg/L (24,100 ppm)	Lying on its side, convulsions after 30 min, recovery after end of exposure	Flury and Zernik 1931
Cat, 5	0.5-2.5 h/d, 24-92 d	8-10 mg/L (2,570-3,210 ppm)	Salivation, dyspnoea, restlessness, excitement at first, apathy later, tremor, sometimes coma	Ferraro et al. 1941
Cat, 2	2 h 15 min	10.4 mg/L (3,340 ppm)	Shaking, repeated vomiting, convulsions, collapse, salivation, slow recovery	Lehmann 1894
Cat, 1	2 h 30 min	9.3 mg/L (2,990 ppm)	Shaking, shivering, vomiting, tonic-clonic convulsions, variable respiration	

(Continued)

TABLE 2-5 Continued

Species, Strain, Number, Sex	Exposure	Concentration	Effect	Reference
Cat, 1	3 h 20 min	7.6 mg/L (2,440 ppm)	Vomiting, dyspnoea, salivation, tonic convulsions, decreasing respiration rate	
Cat, 1	3 h	4.7 mg/L (1,510 ppm)	Increased respiration, lying on its side, clonic and tonic convulsions, salivation	
Cat, 2	9 h	2.64 mg/L (850 ppm)	Slow respiration, vomiting, clonic convulsions, lying on its side; recovery after exposure	
Cat, 1	8 h	1.34 mg/L (430 ppm)	Slow respiration, dozing, defecation, variable respiration rate	
Cat, 1	8 h	1.2 mg/L (385 ppm)	Slow respiration, no marked effects	
Cat, 1	10 h	0.2 mg/L (64 ppm)	No toxic effects observed	

3.2.2. Rats

Exposure of six rats to CS_2 at 3,000 ppm for 4 h resulted in no deaths during exposure or within the 14-day post-exposure observation period (Du Pont 1966). During exposure, animals suffered from tachypnea, ptosis, incoordination, chromodacryorrhea (release of red fluids from nasolacrimal glands), and gasping. Weight loss, hyperexcitability, and dyspnea were observed 24 h post-exposure. The data of this study indicate a very steep concentration-response curve since all of six rats exposed to 3,500 ppm for 4 h died during exposure or before 2 h post-exposure (see section 3.1.1).

In an upper respiratory tract irritation study, four rats per group were exposed head-only to analytically confirmed concentrations of CS_2 at 1,660, 8,760, 35,100, or 81,100 ppm for 10 min. No respiratory rate depression was observed in response to CS_2 exposure. At 1,660 ppm but not at higher concentrations, dark red eyes were observed 24 h to 6 days post-exposure. No overt clinical signs of toxicity were noted. However, a slight-to-moderate transient weight loss (no further data) was observed 24 h post-exposure at all exposure concentrations (Du Pont 1981).

Frantik et al. (1994) studied the inihibition of propagation and maintenance of the electrically evoked seizure discharge in rats and mice. Concentration-effect regressions were determined for 48 common solvents including CS_2 in male Wistar rats. The animals were exposed individually for 4 h to analytically confirmed concentrations. Three concentrations of solvent were selected in the linear part of the concentration-response curve (between 25% and 75% of maximum effect, if possible). (For some not explicitly named solvents, the concentrations had to be lowered to avoid respiratory tract irritancy.) Measurements were carried out within 1 min after removal of the animals from the exposure chamber. A short electrical impulse was applied through ear electrodes. Of six time characteristics recorded, the duration of tonic extension of hindlimbs was the most sensitive and reproducible response measure in rats. All data were processed using linear regression analysis to estimate the concentration of solvent in air evoking 37% of the maximum possible effect. In the case of CS_2, a concentration of 1,370 ppm and a slope of regression of 0.029%/ppm were calculated. The lowest effect concentration that for most solvents could be proved statistically was 10%. For CS_2, the EC_{10} can be calculated as follows: $EC_{10,4\ h,rat}$ = 1,370 ppm-27% ÷ (0.029%/ppm) = 440 ppm. (EC_{10} is the exposure concentration of a toxicant causing a defined effect on 10% of a test population.)

Behavioral Studies

Goldberg et al. (1964) studied the effects of CS_2 exposure on animal behavior in an experimental system (as described in Goldberg et al. 1962). Behavioral training experiments were conducted in a chamber with a metal grid floor

and a wooden pole with a rough surface attached to the chamber top, which served as an escape or safety area. During the training phase, female Carworth Farms Elias rats aged 30-40 days were placed in the chamber for 15 s with no stimulus. Then, a series of electric shocks (100 volts, 20 ms, 10 pulses/s) was delivered to the floor for 30 s concurrent with the activation of a buzzer. The stimuli were immediately terminated when the rat successfully climbed the pole as escape area. The response to the shock and the buzzer was considered an unconditioned response (escape response). When the animal had learned to consistently show the proper escape reaction, the stimuli were dissociated, and the animal climbed the pole in response to the buzzer alone (conditioned response, avoidance response).

Prior to vapor inhalation experiments, animals were examined for their response to the avoidance and escape stimuli. Effect measurement was done on a quantal basis, that is, the percentage of rats that showed an inhibition of the response. Eight to 10 rats were used in both control and experimental groups with different chemicals, including CS_2. Rats were exposed 4 h/d, 5 d/wk for 2 weeks to analytically confirmed concentrations of CS_2 at 250, 500, 1,000, and 2,000 ppm.

Responses were determined on days 1, 2, 3, 4, 5 and 10 before, during, and 2 h after removal from exposure. Tests made within 2 h after termination of exposure gave maximum effects. Up to 1,000 ppm, no effects were seen after one or two exposures. From the third exposure to CS_2 at 1,000 ppm, the fourth at 500 ppm, and the fifth at 250 ppm, an inhibition of avoidance response was seen without an accompanying effect on the escape response. At 2,000 ppm, an inhibition of the avoidance response was obtained in 50% of the animals after one and two exposures. Repeated exposure at 2,000 ppm resulted in progressive effects on both avoidance and escape response, and the avoidance response showed inhibition in all animals after 10 days. At this concentration, several rats did not escape when the shock was presented, even though they appeared capable. Two animals receiving this concentration died within a few days following the last exposure.

Studies Mainly to Investigate Effects on Liver

The acute effects on hepatic energy potential and functions were studied in female Wistar rats (Kürzinger and Freundt 1969; Freundt and Kürzinger 1975). The animals were exposed to CS_2 at 0, 20, 100, 200, or 400 ppm for 8 h, as described by Freundt et al. (1974a). A significant, concentration-dependent decrease in the glycogen content of the liver was observed at all concentrations. The decrease of liver glycogen was associated with an increase of hepatic lactate, an increase of hepatic inorganic phosphate levels, and an increased oxygen consumption of hepatic tissue slices ex vivo after exposure. Furthermore, the exposed animals showed an increase in whole-body oxygen uptake, a fall in

body temperature, and a decrease of body weight. Up to 400 ppm, no cytotoxic effects occurred (no changes in serum activity of ASAT, alanine aminotransferase [ALAT], and LDH). All parameters were normal 24 h after exposure to the highest concentration.

Effects of CS_2 on the biotransformation of various xenobiotics were studied by Freundt and Dreher (1969); Freundt and Kuttner (1969); and Freundt et al. (1976a). Female Wistar rats were exposed to CS_2 at 20, 50, 100, 200, and 400 ppm for up to 8 h in an exposure chamber as described by Freundt et al. (1974a). Immediately after termination of exposure, animals were treated with various xenobiotics, and the urinary excretion of xenobiotic metabolites was followed. At all concentrations of CS_2 tested, the excretion of the following metabolites was significantly delayed (indicating inhibition of phase I drug-metabolizing pathways): trichloroethanol and trichloroacetic acid from trichloroethene, 4-OH-antipyrine from antipyrine, acetaminophenol from acetanilide and phenacetin, and 4-aminoantipyrine from aminopyrine. All effects were reversible within 6-36 h. Furthermore, CS_2 led to a concentration-dependent significant increase in the hexobarbital sleeping time in rats. In contrast, the (phase II) *N*-acetylation and glucuronidation of drugs were not markedly affected up to 400 ppm. Further investigations revealed that under the conditions of the described exposure, CS_2 reversibly increased the hepatic microsomal lipid content, and the microsomal NADPH-cytochrome c-reductase activity and the total microsomal P-450 content remained within the normal range (Freundt and Schauenburg 1971; Freundt et al. 1974b).

The effects of CS_2 on the blood levels of acetaldehyde in ethanol-treated rats were studied in female Wistar rats, which were exposed once to CS_2 at 20 and 400 ppm, respectively, for 8 h or received 12 repetitive exposures at 400 ppm at 40-h intervals (every other day) (Freundt and Netz 1973; Freundt et al. 1976b). Exposures were carried out as described by Freundt et al. (1974a). Subsequently, rats were given ethanol at 2 g/kg (20% solution, i.p.; blood level about 2.5-3 g/L [250-300 mg/dL]) and left exposed to CS_2 for up to 4 h to the time of blood collection. In the presence as in the absence of CS_2, the blood ethanol concentration decreased linearily, and the regression of the blood elimination curves was not significantly different from that of controls. The acetaldehyde concentration in blood rose after administration of ethanol and was about 30% higher in animals exposed to CS_2 at 20 ppm. Single or repeated exposure to 400 ppm produced a slight additional increase in blood acetaldehyde (up to 1.5-fold of control values). In similar experiments, oral treatment of rats with disulfiram (Antabuse) (1 g/kg of birth weight) increased blood acetaldehyde levels up to five-fold. Intravenous administration of acetaldehyde to rats treated with CS_2 at 400 ppm for 8 h or with disulfiram revealed that the rate of acetaldehyde elimination from blood was significantly lowered by CS_2 and by disulfiram exposure (control $t_{1/2}$: 1 min 45 s; CS_2-treated: 2 min 24 s; disulfiram-treated animals: 2 min 48 s).

In a metabolism study, Kivisto et al. (1995) exposed seven groups of two male Wistar rats per group to analytically confirmed concentrations of CS_2 at 50 ppm or 500 ppm for 6 h. Exposure at 500 ppm was reported to reduce the activity level of the rats. No further details regarding toxic effects were mentioned.

Studies Mainly on Brain Metabolism

Savolainen and Järvisalo (1977) exposed female Sprague-Dawley rats to CS_2 at 0 or 0.15% (1,500 ppm) for 2 h.Littermate animals were treated with phenobarbitone (PB) in drinking water (0.1% w/v) for 7 day prior to the experiment. No details of the exposure conditions were reported. Immediately after CS_2 exposure, the animals were slightly somnolent, but none of the animals died during the experiment. After 1 h, 4 h, and 46 h of exposure, ^{14}C-leucine incorporation; protein and RNA content; and activity of acid proteinase, creatine kinase, and nonspecific cholinesterase in brain showed some minor transient changes, but the interpretation of the data is hardly understandable since no statistical evaluation was presented. At the same exposure conditions, CS_2 alone had no effect on liver cytochrome P-450 concentration and transiently lowered 7-ethoxycoumarin *O*-deethylase (EOD) activity. In rats pretreated with PB, cytochrome P-450 was decreased by 50% and EOD-activity even more (Järvisalo et al. 1977).

Tarkowski and Cremer (1972) exposed male Porton-strain rats to analytically confirmed concentrations of CS_2 at 0 or 2.5 mg/L (800 ppm) continuously for 15 h. As acute signs of poisoning, CS_2-exposed animals suffered from ataxia, tremors, and occasional convulsions. At termination of exposure, the animals showed a moderate hypoglycemia.Changes in the concentration of amino acids in brain were observed, most notably, a 70% increase in glutamine and an increased labeling of brain glutamine from [1-^{14}C]butyrate.

Tarkowski and Sobczak (1971) exposed male Wistar rats to analytically monitored concentrations of CS_2 at 0 or 2.5 mg/L (800 ppm) continuously for 18 h. As main symptoms of acute CS_2 poisoning, severe narcosis, reduced cardiac and respiratory rate, straightening of hind limbs, and lower body temperature were reported. In brain mitochondria from CS_2-exposed animals, disorders of oxidative phosphorylation (suggesting uncoupling of oxidative phosphorylation) but a decreased ATPase activity were found. No such effect was seen in a further study after exposure to CS_2 at 0 or 2.4 mg/L (770 ppm) for 12 h (Tarkowski et al. 1980). Some ultrastructural morphologic changes with swelling and damage of cristae in the brain mitochondria also were observed.

Effects on Catecholamines

Male Sprague-Dawley rats were exposed to analytically confirmed concentrations of CS_2 at 2,000 mg/m³ (640 ppm) for 4, 6, 8, and 8 h, respectively

(McKenna and DiStefano 1977b). No signs of toxicity were mentioned to occur during exposure, nor did the authors explicitly state the absence of such effects. Exposure to CS_2 caused a time-dependent decrease of noradrenaline and a slight transient increase of dopamine in brain. A similar decrease of noradrenaline after 8 h was seen in the adrenal glands and in the heart, .64 ppm was the minimum concentration at which a decrease of noradrenaline could be seen. Similar effects on brain dopamine and noradrenaline following a single exposure to CS_2 at 2,000 mg/m³ (640 ppm) for 1 h or repeated 4 h/d for 2 days were also described in another study (Magos et al. 1974).

Caroldi et al. (1987) exposed male Porton-Wistar rats to an analytically monitored concentration of CS_2 at 2,000 mg/m³ (640 ppm) for 4 h or 16 h. No obvious signs of toxicity were noted. Similar to the observations described above (McKenna and DiStefano 1977b), CS_2 exposure increased the dopamine concentration in brain and decreased the concentration of noradrenaline in a time-dependent manner.

Behavioral Studies with Repeated Inhalation Exposure

The study of Goldberg et al. (1964) is described at the beginning of this section 3.2.2. Battig and Grandjean (1964) exposed rats (about 4 months old, sex and strain not reported) to CS_2 at 0 or 800 ppm for 4 h/d up to 3 wk. Analysis of the chamber atmosphere revealed that the initial concentration of 800 ppm during the first 2.5 h dropped to 550-750 ppm and did not decrease further. No animal died during exposure. The rats exposed to CS_2 displayed marked drowsiness from shortly after the start of exposure. The avoidance reaction to painful electric shocks was studied after onset of each exposure. Compared with the corresponding control group, the acquisition curve of the exposed rats rose later and at a lower rate. In the second week, the frequency of avoidance reactions was stable in both groups but was much lower in the group exposed to CS_2.

Frantik (1970) exposed male albino rats (strain not reported) to CS_2 at 0, 0.15, 1.2 or 2.4 mg/L (0, 50, 385, or 770 ppm) for 6 h/d, 5 d/wk for 10 months. A second experiment was carried out with rats exposed at 0, 1.2, or 2.4 mg/L (0, 385, or 770 ppm) for 7 h/d, 5 d/wk from their seventh month of life on. No details regarding incubation conditions were presented. Acute toxic effects on behavioral characteristics and motor capacity were measured 0-60 min after termination of the daily exposure. At 50 ppm, no effects were observed. At 385 ppm, immediately after the first exposure to CS_2, an increase in spontaneous motor activity was observed. This effect did not reappear after further exposures. At 770 ppm, changes after the first exposure for 6 h and especially 7 h involved reduction of spontaneous motor activity by about 60%, an inert nature of conditioned avoidance reactions, and a decrease in motor performance (maximum speed, static and dynamic endurance). These effects resembled those induced by barbiturates or tranquillizers. They persisted partly for 24 h and had completely

disappeared after 3 days without exposure. After subsequent exposure to the same concentration, the pattern was not repeated but, instead, enhanced activity, compared with control, was seen.

Studies on Effects on the Heart with Repeated Inhalation Exposure

Chandra et al. (1972) studied the effect of CS_2 on the myocardium of male Wistar rats exposed at 4 mg/L (1,280 ppm) for 4 h/d for 1 or 2 days. Some groups also received PB, noradrenaline (NA), both substances, or an additional cold stress at 4°C overnight instead of NA. Treatment with CS_2 alone or combined with PB or NA did not result in histologic lesions of the myocardium. Slight myocardial lesions were seen in control animals pretreated with PB and NA. Myocardial lesions were more pronounced in rats exposed to CS_2 in combination with PB and NA or PB and cold stress.

Studies on Effects on the Liver with Repeated Inhalation Exposure

Effects of CS_2 on the liver were studied in female Wistar rats (Freundt et al. 1974a). Inhalation exposure to 200 ppm for 8 h/d for 7 days caused no fatty infiltration of the liver. Similarly, 3-day pretreatment with phenobarbital (80 mg/kg i.p.) followed by 8-h exposure to CS_2 at 20 or 200 ppm and a narcotic dose of hexobarbital (100 mg/kg i.p.) caused no appreciable fat accumulation in liver cells and no rise in serum ASAT and ALAT. In contrast, oral administration of CS_2 (1 mL/kg) caused a moderate accumulation of fat in the liver that became severe and was accompanied by a rise of serum ASAT in animals also pretreated with phenobarbital.

Neurotoxicity Studies with Repeated Inhalation Exposure

Rats exposed to CS_2 at 5,000 mg/m³ (1,600 ppm) for 4 h/d for 1-6 days showed no signs of toxicity apart from being more subdued. Urination was increased and defecation was decreased. A time-dependent activation of brain tyrosine hydroxylase (TH) was observed. TH activation rose above control after day 2 of exposure, reached 140% of control by day 4, and declined thereafter (Heubusch and DiStefano 1978).

Wilmarth et al. (1993) exposed male Sprague-Dawley rats to analytically monitored concentrations of CS_2 at 0, 600 or 800 ppm for 10 h/d for 14 consecutive days. Both CS_2 concentrations resulted in narcotic-like stupor during exposure. After a 14-h recovery period, there was a return to normal levels of alertness and activity. At 800 ppm, animals began to display retropulsion and circling behavior on day 4 of treatment and developed hindlimb display and signs of mild ataxia by day 7. On day 15, rats displayed a fine whole-body

tremor and had severe ataxia or suffering complete hindlimb paralysis. In rats exposed to 600 ppm, circling behavior and retropulsion were noted from day 9. At termination, signs of mild ataxia and moderate hindlimb paralysis were apparent. In the brain of rats exposed to CS_2, an increase in the phosphorylation of endogenous MAP-2 (microtubuli associated protein) and in the autophosphorylation of Ca^{2+}-/calmodulin-dependent protein kinase II were observed.

In a collaborative National Institute of Environmental Health Sciences (NIEHS) study, the onset and temporal progression of neurotoxicity as manifested in multiple functional and structural alterations were investigated (Harry et al. 1998; Manuel 1998). Male and female F344 rats (9 rats/sex and time) were exposed to analytically confirmed concentrations of CS_2 at 0, 50, 500, or 800 ppm for 6 h/d, 5 d/wk for 2, 4, 8, or 13 weeks, as described by Sills et al. (1998). A summary of the results was presented by Harry et al. (1998). Within 2 weeks of exposure to either 500 or 800 ppm, an increased expression of nerve-growth factor receptor mRNA in the sciatic nerve (indicating alterations in the relationship between axon und Schwann cells) of all animals was found, and that increased during further exposure (Toews et al. 1998). Neurofilament crosslinking in the spinal cord was observed as early as 2-4 weeks at all exposure levels. In erythrocytes, covalent modification of globin was observed at all CS_2 concentrations, and that was paralled by spectrin crosslinking (Valentine et al. 1998). Postural abnormalities at all exposure durations, mostly seen at 800 ppm, were described as hunched posture early on, progressing to diminished postural control at the end of the study. Within 2 weeks at 800 ppm, gait abnormalities occurred. At 500 ppm and 800 ppm, from 4 weeks on, neuromotor alterations progressed to a reduction of grip strength of hind and forelimbs (Moser et al. 1998). Axonal swelling, axonal degeneration, and electrophysiologic alterations in the peripheral nerves or the spinal cord occurred at the two highest concentrations in later stages (from 8 weeks on) of the study (Herr et al. 1998; Sills et al. 1998; Valentine et al. 1998).

Studies With Noninhalation Exposure

Herr et al. (1992) observed alterations in flash (FEP) and pattern reversal (PREP) evoked potentials in rat brain after a single i.p. dose of CS_2 at 100, 200, 400, or 500 mg/kg in corn oil. Repeated administration of CS_2 (200 mg/kg i.p., 30 days) produced similar, but more pronounced effects.

3.2.3. Mice

Flury and Zernik (1931) reported that mice exposed to CS_2 at 11,000 ppm were lying on the side after 15 min and were anesthetized after 20 min. Quick recovery was seen after exposure ended.

Lewis et al. (1999) studied the effects of CS_2 on the development of early lesions of atherosclerosis and arterial fatty deposits in C57BL/6 mice (for ex-

perimental details, see section 3.1.2.). Exposure of mice that were fed a standard diet with CS_2 at 500 or 800 ppm induced a small but significant increase in the rate of fatty deposit formation under the aortic valve leaflets after 12 weeks. No effects were seen at 50 ppm. In contrast, in animals on a high-fat diet, a marked enhancement was observed of the rate of fatty deposit formation in mice at 50, 500, and 800 ppm over the animals on high-fat diet alone.

The inihibition of propagation and maintenance of the electrically evoked seizure discharge was studied in rats and mice as described above (Frantik et al. 1994, see section 3.2.2). All data were processed using linear regression analysis to estimate the concentration of solvent in air evoking 30% of the maximum possible effect. In case of CS_2, a concentration of 2,600 ppm and a slope of regression of 0.008%/ppm were calculated. The lowest effect concentration that for most solvents could be proven statistically was 10%. For CS_2, the EC_{10} can be calculated as follows:

$$EC_{10,\ 4\ h,\ mouse} = 2600\ ppm - 20\% \div (0.008\%/ppm) = 100\ ppm.$$

The effects of exposure to CS_2 were studied on two different behavioral responses in male CD-1 mice (Liang et al. 1983). One response was the interruption of a single light beam passing immediately behind a small hole in the wall of a mouse chamber that was placed in a sealed exposure chamber. The other response was the consecutive interruption of each of three radial light beams spaced around a circular runway. Both responses were maintained under a fixed interval 60-s schedule of milk presentation. Acute, cumulative concentration-effect functions were determined by step-wise increases in the (analytically confirmed) concentration of CS_2 in the chamber at 30-min intervals until responding was abolished. A concentration of 120 ppm was without effect, 580 ppm decreased responding in most mice, 2,200 ppm decreased responding in all mice, and 3,700 ppm abolished responding. Recovery from these acute effects was slow; full recovery required 6 h.

Similar experiments and results were described in a second report of the same study group (Glowa and Dews 1987). Responding (the interruption of a photocell beam located behind a nose-poke hole) was studied under the fixed-interval 60-s schedule of milk presentation as above. CS_2 slightly increased rates of responding at concentrations of 100-600 ppm, 2,000 ppm decreased responding in some mice, and 3,700 ppm abolished responding in all mice. Responding did not recover in any of the mice 30 min after exposure ended. The calculated EC_{50} for decreased responding was 2,242 ± 307 (S.D.) ppm CS_2.

3.2.4. Rabbits

Lehmann (1894) conducted a series of experiments with rabbits and cats in which individual animals were exposed to various (calculated) concentrations of CS_2. There were no differences in the acute toxic effects of freshly purified

and distilled, colorless CS_2 and of impure yellow technical products with the distinct odor of decaying radish or overcooked cauliflower.

No clear signs of acute toxic effects were seen up to 850 ppm. From 1,380 ppm upward, signs of effects on the CNS increased from restlessness and swaying to convulsions, nystagmus, paralysis, and finally narcosis at 6,450 ppm (Table 2-5). All animals recovered after the exposure ended.

During and at the end of exposure of rabbits to an analytically confirmed concentration of CS_2 at 1,100 ppm for 6 h/d for 12 days (Brieger 1949), only minor changes in the ECG were observed. Similarily, the histologic examination of the heart showed only minor changes of individual muscle fibers.

No signs of acute toxicity were observed in rabbits exposed for 6 h/d, 5 d/wk for 16 weeks to CS_2 at 250 ppm, followed by 5 weeks of exposure at 500 ppm, and a further 17 weeks of exposure at 750 ppm (Cohen et al. 1959).

Exposure of the skin of rabbits to liquid CS_2 caused blisters and ulcers that often resembled severe chemical burns. Severe degenerative changes in the local subcutaneous peripheral nerves have also been described in this study (Hueper 1936).

3.2.5. Dogs

Lewey et al. (1941) exposed dogs to analytically monitored concentrations of CS_2 at 400 ppm for 8 h/d, 5 d/wk for 10-15 weeks. At the end of the daily exposure, the dogs were drowsy, they staggered and stumbled, trembled and shook, ran restlessly through the room, caving in one leg at one moment and on another the next. The dogs were very thirsty, but did not eat for hours after end of exposure. They slept most of the time during exposure, but were excited and noisy afterwards. During the course of the study, the dogs developed behavioral changes and showed decreased pupillary reflexes after 2 weeks of exposure, followed by loss of cornea reflexes and signs of polyneuropathy with ataxia, tremor, and muscular weakness with loss of power and tendon reflexes. Behavioral changes with agressiveness also occurred. Retinal angiopathy, possibly as an early sign of arteriosclerosis, developed from the fifth week on. In the heart, significant deviations from the ECG of normal dogs indicated myocardial derangement. All animals died between weeks 10 and 15 of exposure.

3.2.6. Cats

Flury and Zernik (1931) reported that a cat exposed to 24,100 ppm for about 1 h showed convulsions during exposure but recovered afterwards. No details were reported.

Lehmann (1894) conducted a series of experiments with rabbits and cats in which individual animals were exposed to various concentrations of CS_2 (see section 3.2.4). No differences were observed in the acute toxic effects of freshly

purified and distilled, colorless CS_2 and of impure yellow technical products with the distinct odor of decaying radishes (or overcooked cauliflower).

Signs of slight effects on the CNS with slowed respiration and dozing developed at about 400 ppm (Table 2-5). Severe signs of toxicity including convulsions became obvious after exposure to 850 ppm for 9 h and 1,510 ppm for 3 h, respectively. Shivering, shaking, vomiting, and collapse additionally occurred when the concentration was increased up to 3,340 ppm for 2.25 h. The two cats exposed to this concentration slowly recovered after exposure.

3.3. Reproductive and Developmental Toxicity

3.3.1. Rats

No studies were available in which animals were exposed only once.

An overview of developmental or reproductive toxicity with rats is given in Figure 2-2. Saillenfait et al. (1989) exposed pregnant Sprague-Dawley rats to measured concentrations of CS_2 at 0, 100, 200, 400, or 800 ppm for 6 h/d during gestational days 6-20. No maternal toxicity or adverse effects on the developing embryo or fetus were seen at 100 and 200 ppm. Exposure to 400 or 800 ppm CS_2 resulted in dose-related reduction of maternal weight gain and fetal body weight. When gravid uterine weight was subtracted from the dam's body weight gain, the maternal weight was still significantly suppressed indicating maternal toxicity. The only observed effects in fetuses were an increase in unossified sternebrae, an index of delayed fetal development, at 800 ppm and a slight, nonsignificant increase in club foot at 400 ppm.

Belisles et al. (1980) exposed rats to monitored concentrations of CS_2 at 0, 20, or 40 ppm for 7 h/d, 5 d/wk for 3 weeks prior to mating. Animals were divided into two groups that were exposed to the same concentration as used in the pregestational exposure and exposed during gestation days 0-18 or 6-18. Following mating, groups of rats not exposed pregestationally were exposed to 20 or 40 ppm on days 0-18 or days 6-18 of gestation. There were no effects on dams and no embryotoxic, fetotoxic, or teratogenic effects except for a slight but nonsignificant increase in resorptions and reductions in live fetuses in two groups (20 ppm, exposed during gestation, and 40 ppm, exposed both pregestationally and during gestation).

In a further study, female CD rats were exposed to CS_2 at 0, 125, 250, and 500 ppm for 6 h/d for 14 days prior to mating through day 19 of gestation (WIL Research Laboratories, Inc. 1992; Nemec et al. 1993). The dams were allowed to deliver normally, and both pups and dams were observed through day 21 of lactation. No maternal, developmental, or reproductive toxicity was observed at 125 or 250 ppm. Maternal toxicity (irritation, decreased food consumption), dystocia, fetotoxicity (increased mortality, reduced pup viability, decreased litter size, and total litter loss) were observed at 500 ppm.

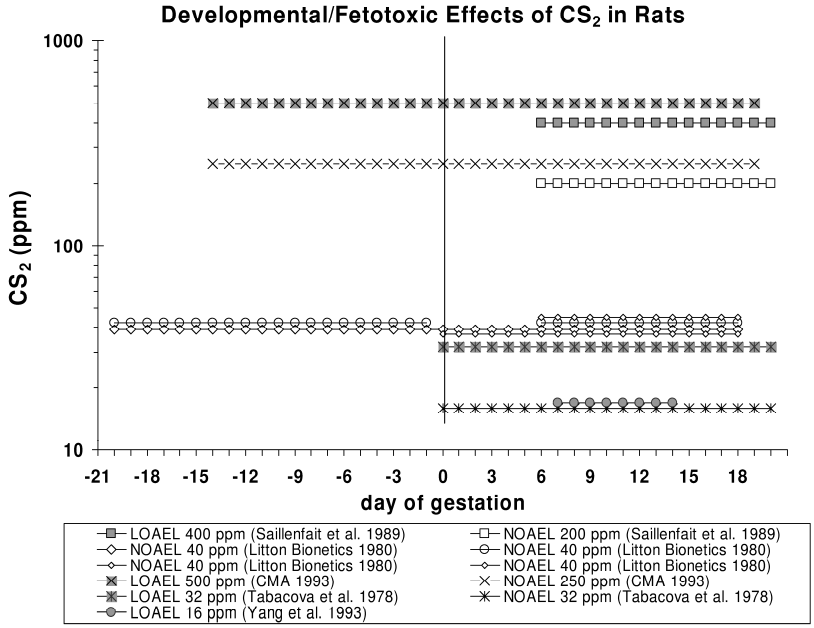

FIGURE 2-2 Overview of developmental and fetotoxicity studies with CS_2 in rats.

In a developmental study (Tabacova et al. 1978), pregnant Wistar rats were exposed to CS_2 at 0, 50, 100, and 200 mg/m³ (0, 16, 32, 64 ppm), respectively, for 8 h/d throughout gestation (21 days). Behavioral deviations were reported to occur in offsprings at all groups exposed to CS_2, and developmental toxicity including malformations (club foot, hydrocephalus) and fetotoxicity were described to be significantly increased at 64 ppm, but no details were presented. The authors stated that, on the whole, the "malformations proved to be relatively mild and compatible with the further life of the progeny."

Tabacova et al. (1983) further described the results of studies in which F_1 animals that had been prenatally exposed to CS_2 were reared until maturity and mated to produce an F_2 generation. During pregnancy, the F_1 females were again exposed to CS_2 at the same concentrations as the F_0 females throughout gestation. Data were presented for groups exposed at 0, 0.03, 10, 100, and 200 mg/m³ (0.01, 3.2, 32, 64 ppm), respectively, but again the experimental conditions and the observations made were not described in detail. The lower exposure levels (0.01 and 3.2 ppm) were reported to be nontoxic and nonteratogenic in the F_1-generation. When pregnant F_1 females were exposed during gestation, increased malformations and alterations in behavioral tests were reported to occur in the F_2-generation at the two lower concentrations.

Behavioral and neurotoxic effects of prenatal exposure to CS_2 in rats were studied also by Lehotzky et al. (1985). Pregnant female Lati:CFY rats were ex-

posed to nominal concentrations of 0, 10, 700, or 2,000 mg/m³ (0, 3.2, 225, 640 ppm) for 6 h/d from day 7 through 15 of gestation. They reported that CS_2 caused a dose-related mortality in dams with probably 33% mortality at 640 ppm, but no details were presented. Perinatal mortality of pups was reported to increase with increasing concentration of CS_2, and performance in behavioural tests were reported to be poorer in offspring from CS_2 exposed dams, but again, detailed data and any statistical evaluations were lacking.

Yaroslavskii (1969) exposed Wistar rats throughout pregnancy to CS_2 at 0 or 2,000 mg/m³ (640 ppm) for 2 h/d. No details of the experimental procedures were described. The number of corpora lutea was not significantly different between the control and the exposed group. The preimplantation losses in CS_2-exposed animals were higher than that of control animals. The mean duration of pregnancy and the mean fetal weights were not affected by CS_2 treatment.

According to a short English abstract, teratogenic effects in the skeletal system and the CNS were observed when pregnant rats were exposed to CS_2 at 50 mg/m³ (16 ppm) or 150 mg/m³ (48 ppm) from day 7 through day 14 of gestation (Yang et al. 1993). The full original report was published in a Chinese source in Chinese and was not available for evaluation.

Zenick et al. (1984) studied the effects of CS_2 on the reproductive system of male Long-Evans rats exposed to monitored concentrations of 0 or 600 ppm for 6 h/d, 5 d/wk for 10 weeks. CS_2 had no effect on body-weight gain and mating behavior after 1 week, but reproductive parameters (ejaculation latency, sperm count and mount latency) were affected after 4-10 weeks. Similar alterations were observed in previous study in which copulatory behavior was assessed 8-10 h after exposure (Tepe and Zenick 1982). No treatment-related effects on hormone levels, histology of the reproductive organs, and organ weights (except for a lower prostate weight) were observed. The authors further report that no treatment-related effects on epididymal sperm counts and reproductive organ weights were seen in a pilot study after exposure to CS_2 at 900 ppm for 12 weeks.

Oral exposure of CD rats to CS_2 at 0, 100, 200, 400, or 600 mg/kg of birth weight per day during the period of organogenesis on day 6-15 led to maternal toxicity (reduced weight gain) at all doses. Fetal weight was reduced at 200 mg/kg of birth weight, but there were no significant differences in the incidence of malformations or resorptions at any dose level.

3.3.2. Mice

No studies were available in which animals were exposed only once.

Yaroslavskii (1969) (see above) also exposed albino mice throughout pregnancy to CS_2 at 0 or 2,000 mg/m³ (640 ppm) for 2 h/d.The number of corpora lutea was not significantly different between control and exposed animals, but the preimplantation and postimplantation losses were significantly higher in CS_2-exposed animals.

3.3.2. Rabbits

No studies were available in which animals were exposed only once. In a developmental study (Gerhart et al. 1991; PAI 1991), New Zealand rabbits were exposed by inhalation to CS_2 at 0, 60, 100, 300, 600, or 1,200 ppm for 6 h/d on gestation days 6-18 and the uterine contents examined on gestation day 29. At 1,200 ppm, severe maternal toxicity, including death, was observed. No exposure-related signs of maternal toxicity were observed at lower concentrations. Embryotoxic effects (postimplantation loss, total resorptions, reduced fetal weight) were seen in the 600- and 1,200-ppm exposure groups. In the 1,200-ppm group, the total incidence of skeletal and visceral malformations was significantly increased. Malformations in the lower dose groups did not appear to be dose-related and were within the range of historical control data presented by the authors. In a similar protocol, as described above for rats, Belisles et al. (1980) exposed rabbits to CS_2 at 0, 20, or 40 ppm for 7 h/d, 5 d/wk for 3 weeks before mating and further on to 20 or 40 ppm on days 0-21 or days 7-21 of gestation. Similarly, animals exposed pregestationally were divided into two groups that were exposed to the same concentration as used in the pregestational exposure and exposed during gestation days 0-21 or 7-21. There was a high level of mortality in rabbits, which was not exposure-related and which makes interpretation of the rabbit study difficult, but there was no evidence of an exposure-related maternal toxicity, fetotoxicity, or developmental abnormalities.

New Zealand White rabbits received CS_2 at 0, 25, 75, or 150 mg/kg of body weight each day on gestational days 6 to 19 and were examined on gestational day 30 for gross, visceral, and skeletal malformations. Significant maternal toxicity occurred at 75 and 150 mg/kg. Fetotoxicity (increased resorptions) was seen at all doses, but the incidence of malformations was only significantly increased at maternally toxic doses (Jones-Price et al. 1984).

3.4. Genotoxicity

Genotoxicity tests with CS_2 were reviewed and summarized (Beauchamp et al. 1983; BUA 1993; ATSDR 1996).

No mutagenic activity, with or without metabolic activation (S-9 from rat and from hamster liver), of CS_2 was observed in bacterial test systems using various strains of *S. typhimurium* or *E. coli* (Hedenstedt et al. 1979; Donner et al. 1981; Haworth et al. 1983) or in a host-mediated assay using CD-1 mice with *S. typhimurium* TA 98 (Belisles et al. 1980). No mutagenicity was observed in a sex-linked recessive lethality assay in *Drosophila melanogaster* after oral or inhalation exposure to CS_2 (Donner et al. 1981; Beauchamp et al. 1983).

Exposure of rats to CS_2 at concentrations of 60 and 120 mg/m³ (20-40 ppm) 7 h/d for up to 5 days did not increase the frequency of chromosomal aberrations in bone marrow cells (Belisles et al. 1980). At the same concentrations,

no dominant lethal mutations in rats and no dose-related increase in sperm abnormalities in rats or mice were observed, but the validity of these findings is limited since there was a lack of a positive response in positive control rats in this study (Belisles et al. 1980).

3.5. Carcinogenicity

A/J-mice were exposed to CS_2 for 6 h/d, 5 d/wk for 6 months (Adkins et al. 1986). At 900 mg/m³, the number of lung adenomas was slightly, but significantly, increased when compared with the number in the corresponding controls but not when compared with the number in the historical controls. The frequency of carcinomas in the lungs and other organs was not increased. The rate of spontaneously occurring lung adenomas is high in this specific strain of mice, and known carcinogens show a considerably higher increase in lung adenomas. On the other hand, only one concentration was tested, and the test duration was relatively short.

The results of a long-term study sponsored by the National Cancer Institute (NCI) with rats and mice administered CS_2 by gavage were considered inadequate for the evaluation of carcinogenicity because of poor survival of both species (Beauchamp et al. 1983). No further data from experimental carcinogenicity studies were available.

3.6. Summary

As in humans, the observed acute toxic effects of CS_2 in animals are mainly on the CNS. Irritation of eyes and/or mucous membranes occurs at concentrations that already have effects on the CNS.

With respect to lethality, the data for rats indicate a steep concentration-reponse curve: Whereas none of six rats survived a 4-h exposure to CS_2 at 3,500 ppm, all six rats survived at 3,000 ppm (Du Pont 1966). No rats died after exposure at 2,000 ppm for 4 h (Goldberg et al. 1964) or at 1,500 ppm for 2 h (Savolainen and Järvisalo 1977). In rabbits, death ocurred in animals after single exposures to 3,000 ppm or 3,200 ppm for 6 h (Lehmann 1894; Flury and Zernik 1931; PAI 1991). Individual cats died after exposure at 6,450 ppm for 2.25 h or after exposure at 3,200 ppm for 4.25 h (Lehmann 1894).

For mice, LC_{50} values of 3,210 ppm (2 h) (Izmerov et al. 1982) and 4,500 ppm (30 min) were reported ("average lethal concentration," Kuljak et al. 1974). A further LC_{50} of 220 ppm (1 h) (Gibson and Roberts 1972) is exceedingly low. The concentrations in this study were not measured, and the data are in contrast with other observations regarding lethal effects in this and other species in acute and in repeated exposure studies. It is likely that this value is erroneous,[2] and no conclusions will be drawn from it.

[2]A higher sensitivity of the mouse strain used can be ruled out since the oral and i.p. LD_{50} (3,020 and 1,890 mg/kg, respectively) also presented in the study are in accordance with data from other studies.

No treatment related deaths were observed in rats and mice following repeated exposures for at least 2 weeks to CS_2 at 800 ppm (ToxiGenics 1983a,b,c; Wilmarth et al. 1993; Moser et al. 1998; Lewis et al. 1999). In one study with mice, about 30% of the mice died that were given a high-fat diet after the first exposure to CS_2 at 800 ppm (Lewis et al. 1999). Necropsy did not reveal the cause of death in these animals. This observation deserves further investigation.

At nonlethal concentrations, acute effects on the nervous system including neurobehavioral alterations, alterations of catecholamine levels, and effects on the liver have been studied.

In squirrel monkeys, limited data from one study (Weiss et al. 1979) show behavioral alterations in response to an aversive electric shock during exposure to CS_2 at 600 ppm for 2 h. When the exposure period was extended to 18 h, effects were seen in four monkeys at concentrations between 70 and 200 ppm. In rats, effects on the CNS were observed in several studies. Activity was reduced at 500 ppm for 6 h but was reported as not strongly irritating or prenarcotic (Kivisto et al. 1995). A little higher concentration of 600 ppm but longer exposure period of 10 h caused narcotic-like stupor (Wilmarth et al. 1993). The effect of exposure time is obvious in three studies in rats exposed to CS_2 at 770-800 ppm: No visible signs of toxicity were reported after 12 h; ataxia, tremors, and occasional convulsions occurred after 15 h, and severe narcosis was seen after 18 h (Tarkowski and Sobczak 1971; Tarkowski and Cremer 1972; Tarkowski et al. 1980). Rats exposed to 1,500 ppm for 2 h or to 2,000 ppm for 4 h were slightly somnolent or more subdued, but exposure was reported to be otherwise well tolerated (Savolainen and Järvisalo 1977; Heubusch and DiStefano 1978).

At 640-800 ppm, metabolic and/or ultrastructural alterations, such as changes in amino acid concentrations (Tarkowski and Cremer 1972), mitochondrial swelling, disorders of oxidative phosphorylation (Tarkowski et al. 1980; Tarkowski and Sobczak 1971), and raised dopamine/noradrenaline ratio, were observed in rat brain. The latter effects were also demonstrated in heart and in adrenal glands. The lowest concentration of CS_2 at which a decrease of noradrenaline in brain was observed was 64 ppm (8 h exposure) (Magos et al. 1974; McKenna and DiStefano 1977b).

The inhibition of propagation and maintenance of electrically evoked seizure discharge in rats was studied by Frantik et al. (1994). The duration of tonic extension of hindlimbs served as the most sensitive and reproducible effect. The concentration of CS_2 evoking 37% of maximum response was 1,370 ppm. By means of linear regression analysis, an EC_{10} of 440 ppm was calculated. In mice, 30% of maximum possible effect was seen at 2,600 ppm, and the calculated EC_{10} was 100 ppm.

In rats, acute exposure to CS_2 at 2,000 ppm for 4 h caused an inhibition of the escape and avoidance response in a pole climbing test in 12% and 50% of the animals, respectively; no such effects were seen after one 4-h exposure to 1,000 ppm (Goldberg et al. 1964). In a neurobehavioral study in mice, a decreased response (determination of activity in response to milk presentation as stimulus) was seen after 30 min of exposure to 580 ppm in some animals. Re-

sponse was decreased in all mice at 2,200 ppm and abolished at 3,700 ppm (Liang et al. 1983). The calculated EC_{50} for decreased responding was 2,242 ppm (Glowa and Dews 1987).

It is likely that these inhibitions of response are related to the narcotic effects of CS_2. These effects are described in other studies following acute exposure at similar and lower concentrations (see above). Battig and Grandjean (1964) also reported that rats were drowsy shortly after a 4-h exposure to 800 ppm. Frantik (1970) described a reduction in spontaneous motor activity, a decrease in motor performance, and an inert nature of conditioned avoidance reactions in rats after a single exposure to CS_2 at 770 ppm for 6 or 7 h. The effects completely disappeared after 3 days without exposure and were not recurring after further exposures.

However, Goldberg et al. (1964) also described that the response to CS_2 at 2,000 ppm became more pronounced after further exposures for up to 10 days and that the effects were then seen at lower concentrations down to 250 ppm. This could indicate a cumulative effect of CS_2. In view of the rapid elimination of free CS_2 (see section 4.1.2), this seems unlikely. More conceivably, the results could be explained as the onset of first chronic effects related to structural damages in the nervous system—effects that are seen after about 2 weeks of exposure in other studies, for example, the NIEHS study (Moser et al. 1998; Valentine et al. 1998).

Effects on liver metabolism, but no signs of histologic liver damage, were observed in rats at concentrations of CS_2 as low as 20 ppm. In the same concentration range, CS_2 exposure was followed by a reversible inhibition of phase-I biotransformation reactions (Freundt and Dreher 1969; Freundt and Kuttner 1969; Freundt et al. 1976a). In rats given alcohol, exposure to CS_2 at 20 ppm led to a 30% increase in blood acetaldehyde concentration and to a prolongation of the half-life of elimination of acetaldehyde from blood (Freundt et al. 1976b; Freundt and Netz 1973).

All developmental or reproductive toxicity studies were performed with repeated exposure to CS_2 during selected phases of embryonal development or during the whole period of gestation (and in some studies including pregestational exposure). No studies were available in which developmental or reproductive toxicity was investigated after a single exposure. CS_2 showed embryotoxic, fetotoxic, and teratogenic effects in developmental toxicity studies at doses of low or no maternal toxicity. In rats, a slight weight reduction in fetal weight (6%) was seen at 400 ppm and a 22% reduction at 800 ppm in one study with exposure to CS_2 during gestational days 6-20; both concentrations reduced maternal weight (Saillenfait et al. 1989). When rat dams were exposed 14 days prior to mating through gestation day 19 to 500 ppm, fetotoxicity was observed, and difficulty with delivery and total litter loss occurred in some dams (WIL Research Laboratories, Inc. 1992; Nemec et al. 1993). Results from further studies with rats (Hinkova and Tabacova 1978; Lehotzky et al. 1985; Yang et al. 1993) reporting teratogenic effects and/or behavioral alterations in offsprings of dams exposed to lower concentrations (16 ppm) of CS_2 cannot be evaluated be-

cause of insufficient presentation of data. In rabbits (dams exposed to CS_2 on days 6-18 of gestation), postimplantation loss was increased and fetal body weight decreased at 600 ppm; teratogenic effects were observed at 1,200 ppm (Gerhart et al. 1991; PAI 1991).

CS_2 was not mutagenic in bacterial test systems with and without metabolic activation (Hedenstedt et al. 1979; Donner et al. 1981; Haworth et al. 1983) or in a host-mediated assay with male rats (Belisles et al. 1980). No increase of chromosomal aberrations were seen in bone marrow of rats in vivo and in a dominant lethal assay (Belisles et al. 1980); however, the exposure concentrations were low (20-40 ppm). Overall, the database with respect to mutagenicity of CS_2 is insufficient for evaluation.

The carcinogenicity of CS_2 cannot be assessed. A screening study of lung tumor induction in A/J-mice showed a slight but significant increase in lung adenomas but not carcinoma (Adkins et al. 1986). No adequate carcinogenicity studies were available.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

4.1.1. Human data

As shown in controlled exposure studies, CS_2 is rapidly and extensively absorbed through the respiratory tract. Unmetabolized CS_2 is mainly excreted via the lungs. Uptake through the skin was demonstrated from aqueous solutions of CS_2.

In a pharmacokinetic study (Teisinger and Soucek 1949), nine persons were exposed to analytically monitored concentrations of CS_2 at 17-30 ppm (in one case to 51 ppm) for 1-4 h. In the first 15 min of exposure, about 80% of inhaled CS_2 was retained. After 45 min and until the end of exposure, uptake decreased to about 40%. The percentage absorbed did not depend on the concentration in the inhaled air. The blood:air coefficient of CS_2 after 90-120 min was 2.2 on average. At the end of exposure, the concentration of CS_2 in blood fell rapidly to 25% of the value present at the end of exposure within 1 h, and CS_2 disappeared from blood after 2 h. Only a small portion (about 5%) of CS_2 was eliminated by the lungs, and this elimination was largely completed 2 h after termination of exposure. Only minor amounts of unchanged CS_2 could be detected in urine.

In a further study, volunteers inhaled CS_2 at 38-52 ppm through face masks for 0.5-2 h (Harashima and Masuda 1962). During the first 10 min of exposure, on average, 51% of the inhaled CS_2 was exhaled in breath, and this percentage increased to 65% after 40 min when equilibrium was about reached. After exposure ceased, the concentration of CS_2 in exhaled breath declined rapidly with a half-life in the order of 10 min. There was a high variation between

individuals in the actual amount of absorbed CS_2 that was exhaled after exposure (8-48%, average 23%). Less than 1% of unchanged CS_2 was excreted through the skin.

Herrmann et al. (1982; 1983; 1985; 1989) conducted a series of toxicokinetic studies on inhalational uptake of CS_2 in nonexposed and occupationally exposed workers. Up to12 test persons were exposed to analytically monitored concentrations of CS_2 at 6-108 mg/m³ (1.9-35 ppm) via face mask. During the first 5-min interval, individual retention ranged from 47% to 80%. After 30 min of exposure, individual retention values decreased to 38-71% (n = 11; mean retention 48.7%). Regression analysis revealed that the retention increased significantly but slightly with increasing exposure concentration. Moderate exercise (100 W) decreased the retention after 30 min to 15-37%. In a further experiment with constant light exercise (25 W), the initial retention of about 50% dropped to about 33% after 30 min and was constant thereafter to the end of exposure (after 4 h). Demus (1964) obtained similar mean retention values of 51.6% (range 43.5-60%, n = 11 individuals) after 30 min, 36.8% (26-43.5%) after 2 h and 31.7% (20-40%) after 5 h at CS_2 exposure concentrations of 53-445µg/L (17-142 ppm).

Interindividual variation in the uptake of CS_2 by inhalation proved significantly influenced by the amount of body fat. In a study (Rosier et al. 1987), six male human volunteers were exposed to CS_2 at 10 and 20 ppm at rest and to 3 and 10 ppm under light physical exercise (50 W) for four consecutive periods of 50 min each. At rest, the retention values were about 40% at 10 ppm and 20 ppm. At physical exercise, the retention values decreased to about 28% at 3 ppm and 10 ppm. The most important fraction of the interindividual variation observed could be explained by the differences in percentage of body fat. During exposure, only an apparent steady state was reached. The exhaled concentration of CS_2 followed over 180 min after exposure could be described by means of a biphasic elimination. There was an initial very fast decrease with a half-life of 1.1 min followed by a second slower decrease with a half-life of 109.7 min. The total amount of CS_2 being exhaled in 180 min varied from 5.4 to 37.9%. Again, it could be shown that interindividual differences in body fat significantly determined this parameter.

Studies regarding the distribution of CS_2 in humans were not available. Limited data are available on the metabolism of CS_2 in humans. In vitro studies have shown that CS_2 combines with amino acids in human blood, and the so-called "acid-labile" CS_2 (see section 4.1.2) is mainly (90%) found in the erythrocytes (Lam and DiStefano 1983; 1986).

Metabolites of CS_2 are primarily excreted via the kidney. Several sulfur-containing urinary metabolites were identified including thiourea, 2-thio-5-thiazolidinone, and 2-thiothiazolidine-4-carboxylic acid (TTCA). These substances are formed by the reaction of CS_2 with glutathione, cysteine, glycine, and other amino acids. Less than 5% of the CS_2 taken up is excreted as TTCA. However, the excretion of TTCA is linearly correlated with the CS_2 exposure occurring at today's workplaces. Therefore, this parameter is used in biologic

monitoring (Drexler 1998). Recently, from the urine of workers exposed to CS_2, 2-thioxothiazolidin-4-carbonylglycine (TTCG) was identified as a metabolite of CS_2. This compound is suggested to be a precursor of TTCA (Amarnath et al. 2001).

4.1.2. Animal Data

A number of studies have shown that CS_2 is rapidly absorbed through the respiratory tract. Absorption of gaseous CS_2 through the skin of rabbits was also demonstrated (Cohen et al. 1958).

The toxicokinetics of CS_2 in rats was studied as part of the collaborative NIEHS study (Moorman et al. 1998) (see section 3.2.2). Male and female F344 rats were exposed nose-only to CS_2 at 50, 500, and 800 ppm for 180 min, and blood samples were taken 4, 8, 15, 30, 60, and 180 min after the start of exposure. Values for kinetic parameters were calculated from the fits of a two-compartment model to the blood concentration versus time. At 50 ppm, the blood concentration of CS_2 was at the limit of quantification in males after 180 min (0.8 µg/mL) and below at all other time points and throughout in females. At 500 and 880 ppm, uptake in blood was found to be rapid with a half-time of 6-9 min. The concentration in blood at 180 min increased proportionally with dose and was significantly (about 40%) lower in females than in males. No true steady-state during the exposure was reached.

In the same study, the distribution and elimination kinetics from blood were determined following single intravenous administration of CS_2 (50 mg/kg) into the tail vein. Both parameters were modeled using a two compartment model with first order elimination from the central compartment. The apparent total volume of distribution was 4.2 L/kg, the terminal elimination half-life was 24 min, and the total clearance was 112 mL/min/kg.

Finally, in this study, experiments were conducted with rats exposed via inhalation to 50, 500, and 800 ppm, respectively, for up to 13 weeks. In males, blood concentrations of CS_2 remained relatively constant throughout but decreased in females with increasing duration of the study. Nonlinear kinetics was observed: At all time points, the CS_2 concentration in blood of the 500- and 800-ppm males and females were significantly (about 1.5-2 times) higher compared with the 50-ppm group than would be expected by linear dose proportionality. Nonlinear kinetics was also observed in the excretion of the metabolite thiazolidine-2-thione-4-carboxylic acid (TTCA) in urine of repeatedly exposed rats. The total excretion of TTCA during 18 h was not different between animals exposed to CS_2 at 500 and 800 ppm (except for males after 2 weeks). The excretion of TTCA in the 50-ppm group was lower than that in the two other groups exposed to CS_2, but the difference was less than would be predicted by dose proportionality. Taken together, these results indicate that uptake may be more efficient at higher concentrations or, more likely, metabolism and elimination pathways become saturated at the higher concentrations.

In a study with rabbits, blood equilibrium concentrations of CS_2 were reached after exposure to 20-150 ppm for 1.5-2 h. After exposure ended, 15-30% of the CS_2 absorbed was excreted through the lungs and less than 0.1% via the kidney. In rats exposed to CS_2 at 60-350 ppm, the substance was rapidly eliminated during the first 6-8 h after exposure. Low concentrations of CS_2 could still be detected in brain, liver, and kidney 20 h after exposure (Beauchamp et al. 1983).

Unmetabolized CS_2 is largely excreted via the lungs, but most of the CS_2 taken up is metabolized and eliminated in the form of various metabolites by the kidney.

The metabolism of CS_2 involves the reaction with amino (NH_2), sulfhydryl (SH), and hydroxyl (OH) groups on one hand and the reaction with the microsomal mixed-function oxidase cytochrome P-450 on the other (Figure 2-3). The reaction of CS_2 with NH_2 and SH and OH groups leads to the formation of the so-called "acid-labile" pool of bound CS_2. This pool consists of dithiocarbamates, trithiocarbamates, and related sulfur containing products. Dithiocarbamates are the first reaction products of CS_2 with the NH_2-residues of amino acids, proteins, and catecholamines. Due to the reversible reaction, it is not possible to strictly distuinguish between "free" and "acid-labile" CS_2 quantitatively (McKenna and DiStefano 1977a).

McKenna and DiStefano (1977a) studied the distribution of free and acid-labile CS_2 in rats following inhalation of 2 mg/L (640 ppm). The concentration of free CS_2 reached (liver, kidney, heart, muscle) or approached (brain) a steady-state level within 4 to 5 h of exposure in all tissues studied with the possible exception of fat. In contrast, the tissue level of acid-labile CS_2 continued to increase until the end of exposure. The highest concentration of free CS_2 was found in fat followed by adrenal glands and liver. Except for fat and blood, 40-90% of the total CS_2 in the tissues was found as acid-labile metabolites. In most tissues (adrenals, kidney, brain, muscle, heart), the concentration of acid-labile CS_2 was higher than that of free CS_2. The concentration of free CS_2 declined rapidly after exposure ended, and the acid-labile CS_2 was removed slowly. In brain, approximately one-third was detectable 16 h after exposure. In another study with rats exposed to CS_2 at 640 ppm for up to 4 h, the half-life of elimination of free and acid-labile CS_2 from blood could be described by a two-exponential, first-order process (Lam and DiStefano 1982). However, the half-times greatly differed for free CS_2 (about 9 and 55 min) and for acid-labile CS_2 (2.2 and 42.7 h). When rats were repeatedly exposed over several days at 120 mg/m^3 (40 ppm) for 8 h/d, acid-labile CS_2 in blood continuously increased with each exposure, and free CS_2 level remained relatively constant. By the sixth to seventh exposure, the acid-labile CS_2 concentration was about 2.5 times that after the first exposure and about 3 times higher than the concentration of free CS_2 (Lam and DiStefano 1983).

Studies with low-molecular-weight dithiocarbamates, such as diethylthiocarbamates, have shown that CS_2 can be released in vivo. Therefore, the

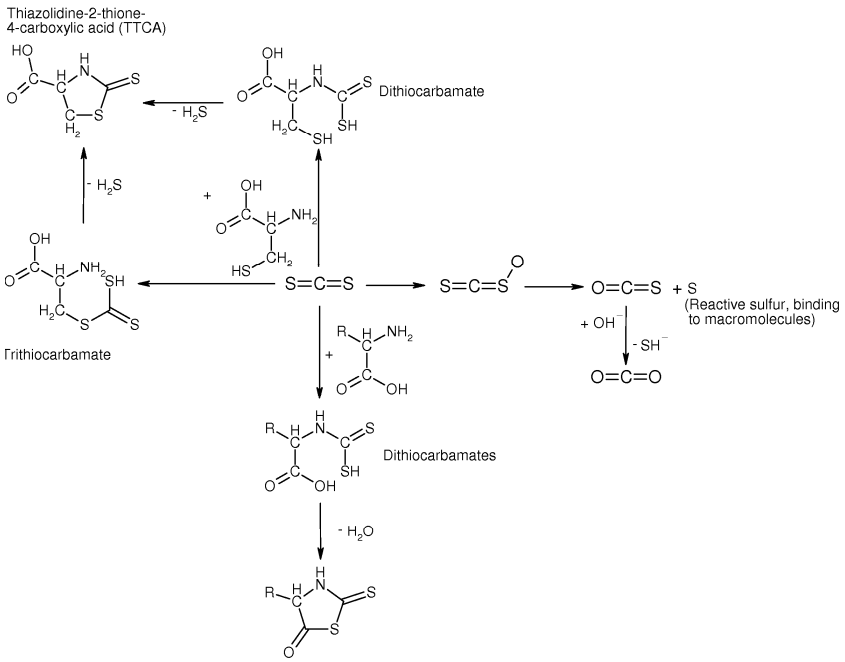

FIGURE 2-3 Principles of metabolic pathways for carbon disulfide.

formation of thiocarbamates from CS_2 and endogenous NH_2-groups probably is at least partially reversible, and that amount of CS_2 that is slowly eliminated with long half-life may be derived from this pool. On the other hand, subsequent reactions of thiocarbamates may lead to long-lived protein modifications. Cross-linking of globin and spectrin in erythrocytes and of neurofilaments in spinal cord has been demonstrated in rats after repeated exposure to CS_2 at 50 ppm by inhalation or repeated i.p. injection of 2 mmoL/kg (150 mg/kg) (Valentine et al. 1993, 1997, 1998; Erve et al. 1998a).

The cytochrome P-450 dependent oxidation of CS_2 is probably catalyzed by the cytochrome P-450 isoenzyme that can be induced by ethanol. In the first step, an active sulfur atom and carbonyl sulfide (COS) are released. COS is further metabolized mainly by carboanhydrase to carbon dioxide and hydrogen sulfide (Chengelis and Neal 1980, 1987). Sulfur and sulfide are finally oxidized to sulfate entering the endogenous sulfate pool. The reactive sulfur also binds to macromolecules, including cytochrome P-450 monoxygenases. This reaction is held responsible for P-450 monoxygenase inhibition, which has been observed in many studies after exposure to CS_2 in vivo and in vitro (e.g., Freundt et al. 1974b; Dalvi et al. 1975; Dalvi and Neal 1978), and for the hepatotoxicity of CS_2 in phenobarbital pretreated rats (Chengelis 1988).

The extent to which CS_2 is metabolized by the P-450 pathway is not clear. The sulfur-containing metabolites, which are excreted in urine of humans (see section 4.1.1) and animals, derive from reaction products of CS_2 with amino acids. In a study in rats exposed to CS_2 at 50 or 500 ppm for 6 h, pretreatment with P-450 enzyme inducers (phenobarbital, ethanol, 3-methylcholanthrene) had no effect on the excretion of TTCA. On the other hand, administration of substances that deplete the level of tissue glutathione (phorone, diethyl maleate, buthionine sulfoximine) at least initially decreased the excretion of TTCA (Kivisto et al. 1995).

4.2. Mechanism of Toxicity

The acute exposure to CS_2 primarily manifests in rapidly occurring effects on the nervous system. High exposure to CS_2 in humans results in dizziness, headaches, autonomic nervous system reactions, nausea, vertigo, vomiting, central paralysis, and finally narcosis and death. In animals, death after acute inhalation of CS_2 also occurs because of effects on the CNS with deep narcosis and finally respiratory arrest. Pulmonary congestion with hyperemia and hemorrhages were also seen in animals after lethal intoxication. Signs of toxic effects on the CNS (narcosis, stupor, ataxia, tremors, convulsions, reduced activity but also hyperexcitability) also are predominant at lower concentrations.

The formation of acid-labile CS_2, especially dithiocarbamates from the reaction of CS_2 and amino groups (e.g., of free or protein-bound amino acids), may contribute to the toxicity of CS_2. Low-molecular-weight dithiocarbamates are chelators of transition metal ions (e.g., Fe^{2+}, Cu^{2+}, Zn^{2+}), and this may lead to the inhibition of enzymes for which these ions are essential. The inhibition of acetaldehyde dehydrogenase by dimethyl- and diethyldithiocarbamates and their corresponding disulfides (thiram, disulfiram) in humans and animals in vivo is well known (Freundt and Netz 1973; 1977; Fried 1980). This inhibition seems also of relevance in the case of CS_2 because an increase in blood acetaldehyde after intake of alcohol and exposure to CS_2 was demonstrated in humans and experimental animals.

The inhibition of xenobiotic biotransformation is likely to be related to the P-450 dependent biotransformation of CS_2 by which reactive atomic sulfur is formed. It is not known whether the effects on carbohydrate metabolism (depletion of glycogen, accumulation of hepatic lactate) are also related to this reaction.

With respect to long-term toxicity, the formation of reactive thiocarbamates also seems to play a role in the development of lesions in the nervous system. It has been postulated that the axonal degeneration that underlies the neuropathy caused by CS_2 is the result of the reaction of CS_2 with protein amino groups to yield initial adducts (dithiocarbamate derivatives). Covalent binding of CS_2 with the formation of thiocarbamates and subsequent cross-linking of neurofilaments was demonstrated in rats after subacute to subchronic exposure

(Erve et al. 1998a,b; Harry et al. 1998). Progressive crosslinking of the neurofilament is postulated to occur during its transport along the axon, and covalently crosslinked masses of neurofilaments may occlude axonal transport at the nodes of Ranvier, ultimately resulting in axonal swelling and degeneration (Environment Canada/Health Canada 2000).

The mechanisms by which CS_2 may lead to arteriosclerotic changes and cardiotoxicity remain to be elucidated.

4.3. Other Relevant Information

4.3.1. Interspecies variability

The limited database with respect to lethality from CS_2 exposure does not show marked species differences. LC_{50} values for comparison are missing. The LC_{50} for mice reported by Gibson and Roberts (1972) is exceedingly low and contrasts with all other observations regarding lethal effects in this and other species in acute and in repeated exposure studies. It is likely that this value is erroneous, and no conclusions can be drawn from it.

The data for rats and rabbits indicate a steep concentration-response curve for lethality at a similar concentration:

- All rats (6/6) died at 3,500 ppm exposed for 4 h (Du Pont 1966).
- No rat (0/6) died at 3,000 ppm exposed for 4 h (Du Pont 1966).
- Several rabbits died at 3,000 ppm or more exposed for 6 h (Flury and Zernik 1931; PAI 1991).
- No rabbit died from CS_2 exposure at
  - 6,450 ppm for 2 h 15 min
  - 3,340 ppm for 3 h
  - 2,990 ppm for 3 h 30 min
  - 2,440 ppm for 3 h 30 min (Flury and Zernik 1931; Lehmann 1894).

Cats could be more sensitive than rabbits, but the database is too restricted to allow firm conclusions. Nonlethal effects on the CNS in different species are seen at similar exposure concentrations and exposure duration. In humans, such effects have also been observed in a controlled exposure study and in case of accidents. Effects on liver metabolism (inhibition of biotransformation and CS_2-induced increase of acetaldehyde blood levels after alcohol intake) without concomitant signs of liver damage have also been seen in humans and rats.

4.3.2. Intraspecies variability

Green and Hunter (1985) observed some variability with age in the acute lethal toxicity of CS_2 in rats. Following i.p. administration, CS_2 was least toxic to 20-day-old male rats (LD_{50}, 1,545 mg/kg) and most toxic to 1-day-old rats

(LD_{50}, 583 mg/kg). The toxicity to adult male rats of the same strain (Sprague-Dawley) determined in another study (de Gandarias et al. 1992) fell within this range (LD_{50} i.p., 1,060 mg/kg).

No data on humans or experimental animals were available regarding the susceptibility to CS_2 at higher age. With respect to the narcotic effect of CS_2, it seems reasonable to assume a higher susceptibility with increasing age. For volatile anesthetics, it is well known that the elderly are more susceptible. Besides the elderly, newborn and premature infants and pregnant women are more sensitive to aneshetics than older infants, toddlers, children, and adults. The total range of sensitivity is 2-3 fold (NRC 2001). The acute effects on the nervous system in humans and animals of a single exposure to CS_2 seem compatible with an anesthetic effect. This does not hold true for other acute effects and for effects after repeated exposure to CS_2.

In the studies of Freundt et al. (1976b), the effect of CS_2 exposure on the blood acetaldehyde level in ethanol-treated humans and rats was observed not only when the alcohol was taken in during CS_2 exposure but similarly when the alcohol intake only started 16 h after CS_2 exposure. In view of the rapid elimination of free CS_2, the effect is probably mediated not by CS_2 itself but by CS_2 metabolites. Animal experiments have shown that CS_2-derived thiocarbamates (acid-labile CS_2) are slowly eliminated (see 4.1.2).

The oxidative metabolism of ethanol proceeds via two pathways, one being the oxidation via cytosolic alcohol dehydrogenase, the other the oxidation by the ethanol-inducible NADPH-dependent microsomal CYP2E1 (see Figure 2-1). Oxidation via the ADH pathway represents the predominant way of ethanol metabolism. This pathway becomes saturated at low ethanol concentrations and therefore follows zero-order kinetics at blood ethanol concentrations that are reached after ingestion of even low amounts of ethanol. The second pathway is inducible by ethanol and thus becomes more important in individuals with frequent consumption of alcoholic beverages.

Acetaldehyde, the first product of both pathways, is mainly oxidized further by a mitochondrial acetaldehyde dehydrogenase (ALDH2). Different forms of this enzyme differ in their activity. A mutation in the "normal" gene for ALDH2 results in the synthesis of an enzyme ALDH2(2) which is less active. The distribution of this allele shows ethnic differences and has a high frequency in Asians. The presence of the ALDH2(2) allele results in an excessive production of acetaldehyde after ingestion of ethanol. Individuals homozygous in ALDH2(2) are very susceptible to drinking ethanol (O`Brien 2001) and show an unpleasant alcohol intolerance syndrome involving vasodilation, facial flushing, increased heart and respiration rate, lowered blood pressure, nausea, and headache. Persons heterozygous in ALDH2(2) frequently show a mild disulfiram effect ("Antabuse syndrome") with facial flushing quickly after the ingestion of alcoholic beverages. In a Japanese study, all individuals with homozygous atypical ALDH2(2)/ALDH2(2) and most of those with heterozygous normal ALDH2(1)/atypical ALDH2(2) were alcohol flushers, and all the usual ALDH2(1)/ALDH2(1) were nonflushers (Shibuya 1993).

Although persons homozygous in ALDH2(2) may be considered hypersusceptible to ethanol—many of them tend to avoid drinking alcoholic beverages at all—individuals heterozygous in ALDH are considered a sensitive subgroup within the normal population. They may drink less alcohol than "ordinary metabolizers;" however, as the metabolism of ethanol is saturated at low concentrations (zero-order kinetics), an intake of a smaller amount of ethanol may not lower the rate of acetaldehyde formation but will shorten the time span during which ethanol is metabolized and acetaldehyde produced. Hence, an increase in the blood acetaldehyde level will occur but last for a shorter period of time.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

AIHA (1997), in a critical overview of odor thresholds, reported referenced values ranging from 0.016 to 0.42 ppm. No geometric mean and no "range of acceptable values" for CS_2 were presented. The use of the 0.21-ppm threshold from Leonardos et al. (1969) was rejected in the AIHA overview because this value represents a 100% recognition concentration. Since CS_2 decomposes rapidly under the influence of air and/or light with the formation of foul-smelling decay products, it is to be expected that the odor detection and recognition threshold of CS_2 will vary widely depending on the purity of the substance and the conditions.

There is a large span between the concentration range at which the odor may be perceived and concentrations at which other effects of CS_2 become noticeable. Hence, the odor would have warning properties at concentrations that are unlikely to represent any health hazard at acute exposure. This may be more important since irritation occurs only at concentrations of CS_2 that already have depressant effects on the CNS, and therefore, irritation offers no warning.

Alcohol intolerance has repeatedly been mentioned in workers occupationally exposed to unknown (most probably higher concentrations) of CS_2, and in its guidelines, the German Society for Occupational and Environmental Medicine states alcohol intolerance as a further adverse effect induced by CS_2 (Drexler 1998).

Inhibition of ethanol metabolism was also obseved in volunteers exposed to CS_2 in combination with controlled intake of alcohol. The blood alcohol concentration was about 0.7 g/L (70 mg/dL), representing a level that may often be obtained in "lifestyle activities." Exposure to CS_2 at 20 ppm for 8 h caused a 50% increase in the concentration of acetaldehyde in blood compared with "alcohol only" values of the same subjects. A similar effect was seen when the intake of alcohol started 16 h after exposure ended to CS_2 at 20 ppm and after an 8 h/d for 5 consecutive days of exposure to CS_2 at 20 ppm with alcohol intake only the last day. Under the conditions of the study, there were no complaints about a disulfiram effect (Antabuse syndrome) or other subjective signs of in-

toxication (Freundt and Lieberwirth 1974a; Freundt et al. 1976b). However, acetaldehyde dehydrogenase is a polymorphic enzyme, and subjects with a less active form of ALDH(2)2, which is frequent in Asians but rare or absent in Caucasians, are more susceptible to developing an disulfiram effect after alcohol intake (O`Brien 2001). As explained in section 4.3.2, individuals heterozygous in ALDH are considered a sensitive subgroup within the normal population.

Other effects seen at similar concentrations (10-80 ppm) involved an inhibition of oxidative *N*-demethylation but no signs of liver damage (Freundt and Lieberwirth 1974b; Mack et al. 1974).

Occasional slight headaches but no other symptoms were reported to occur in volunteers exposed to CS_2 at 17-51 ppm for 0.5 to 4 h (Teisinger and Soucek 1949; Harashima and Masuda 1962). The volunteers were reported to be free of symptoms in two other toxicokinetic studies at exposures to CS_2 at 3-25 ppm for about 1-2 h (McKee et al. 1943; Rosier et al. 1987). In a further toxicokinetic study in which volunteers were exposed to 17-142 ppm for up to 5 h, the authors did not report any symptoms, nor did they explicitly state their absence (Demus 1964).

5.2. Summary of Animal Data Relevant to AEGL-1

Several studies in rats describe effects on hepatic metabolism similar to those observed in humans. An increase in blood acetaldehyde levels occurred in ethanol-treated rats following CS_2 exposure at 20 or 400 ppm (Freundt and Netz 1973; Freundt et al. 1976b). The same concentration range led to a temporary depletion of hepatic glycogen accompanied by an increase in hepatic lactate and oxygen consumption and to an inhibition of phase-I biotransformation reactions (Freundt and Dreher 1969; Freundt and Kuttner 1969; Kürzinger and Freundt 1969; Freundt and Kürzinger 1975). Signs of liver damage were not observed in rats eposed to CS_2 alone but were observed after pretreatment with phenobarbital (Freundt et al. 1974a; Chengelis 1988).

5.3. Derivation of AEGL-1

The AEGL-1 was based on an increase of acetaldehyde blood level in a controlled study in humans (Freundt and Lieberwirth 1974a; Freundt et al. 1976b). Exposure to CS_2 at 20 ppm for 8 h caused a 50-100% increase in the blood acetaldehyde level when the subjects had taken in moderate amounts of ethanol (0.7 g/L [70 mg/dL] blood alcohol). The observed increase of the acetaldehyde level was not accompanied by a disulfiram effect (Antabuse syndrome) in healthy subjects. An uncertainty factor of 3 was applied to account for the protection of sensitive population subgroups (see sections 4.3.2 and 5.1).

Time scaling using the equation $C^n \times t = k$ was done to derive the other exposure duration-specific values. Due to a lack of a definitive dataset, a value of n = 3 was used in the exponential function for extrapolation from the experi-

mental period of 8 h to shorter exposure periods as described in NRC (2001). For the 10-min AEGL-1, the 30-min value was applied because the derivation was based on a long experimental exposure period of 8 h, and no supporting studies using short periods were available for characterizing the concentration-time relationship. The calculated values are listed in Table 2-6.

Support for this AEGL-1 comes from observations in toxicokinetic and other studies in humans in which no symptoms or onlyslight headaches were reported in individuals exposed to CS_2 at 3-80 ppm for several hours.

The derived AEGL-1 values are above the 100% odor recognition threshold of 0.21 ppm (Leonardos 1969) and the range of odor thresholds of 0.016-0.42 ppm (AIHA (1997). Few data are available with respect to concentrations causing odor annoyance: In the study of Lehmann (1894), 180-240 ppm caused "moderate odor annoyance," and there were no complaints in a toxicokinetic study of exposure to CS_2 at 10-20 ppm (Rosier et al. 1987). Thus, the calculated AEGL-1 values are unlikely to cause moderate odor annoyance.

The database is not sufficient to calculate a level of distinct odor awareness (LOA). It must also be taken into account that strong smelling decomposition products of CS_2 are rapidly formed under the influence of light and air. Therefore, the odor threshold and the hedonic tone of CS_2 will markedly change with the presence and formation of such impurities.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Controlled exposure to 80 ppm for 8 h was reported to be well tolerated in humans (Freundt et al. 1976b). Only one controlled exposure study is known in which exposure to CS_2 reached concentrations that caused pronounced acute effects on the CNS (Lehmann 1894). In this study, CNS symptoms and irritation of eyes and throat occurred at 260-420 ppm. CNS symptoms increased in severity with exposure concentration and time. Severe CNS effects that continued after exposure ended were seen at about 2,000 ppm. Concentrations from 2,000 ppm increasing to above 3,000 ppm led to seminarcotic state and irregular respiration.

In this study, the effects were described in detail and analytic determinations of the exposure concentrations were performed. However, only two volunteers were exposed, and the author reported that there were difficulties in maintaining the exposure concentration in this set of the experiments. Therefore,

TABLE 2-6 AEGL Values for Carbon Disulfide

AEGL	10 min	30 min	1 h	4 h	8 h
AEGL-1	17 ppm (52 mg/m³)	17 ppm (52 mg/m³)	13 ppm (42 mg/m³)	8.4 ppm (26 mg/m³)	6.7 ppm (21 mg/m³)

and although previous derivations of ERPG, EEL, and IDLH values (see Table 2-10) are based on data from secondary sources that can be traced back to Lehmann (1894), the results of this study will not be used for the derivation of AEGL values.

6.2. Summary of Animal Data Relevant to AEGL-2

As in humans, at nonlethal concentrations of CS_2, acute effects on the CNS were observed. Irritation of eyes and/or mucous membranes occurs at concentrations that already have effects on the CNS.

In squirrel monkeys, limited data from one study (Weiss et al. 1979) show behavioral alterations in response to an aversive electric shock during exposure to CS_2 at 600 ppm for 2 h. In rats, alterations in a neurobehavioral study (inhibition of escape and avoidance response in a pole climbing test) were observed at exposure to 2,000 ppm for 4 h; no such effects were seen after 4-h exposure to 1,000 ppm (Goldberg et al. 1964). It is likely that this inhibition of response is related to the narcotic effects of CS_2, which are described in other studies following acute exposure at similar and lower concentrations (see below).

In rats, CS_2 at 500 ppm for 6 h reduced activity (Kivisto et al. 1995). A little higher concentration of 600 ppm but a longer exposure period of 10 h caused narcotic-like stupor (Wilmarth et al. 1993). In single exposure studies, the effect of exposure time is obvious in three studies in rats exposed at 770-800 ppm: No visible signs of toxicity were reported after 12 h; ataxia, tremors, occasional convulsions occurred after 15 h, and severe narcosis was seen after 18 h (Tarkowski and Sobczak 1971; Tarkowski and Cremer 1972; Tarkowski et al. 1980).

Developmental toxicity effects have been described in some studies with rats and rabbits following repeated exposure to CS_2 during gestation (and in some studies, also additionally pregestational). No studies were available with single exposure of animals to CS_2. The relevance of an exposure duration of about one-third to full gestation (or even additional pregestational exposure) in rats or rabbits to a less than 1 day exposure in humans is questionable. Moreover, it has to considered that CS_2 reacts with the NH_2 group of endogenous compounds (e.g., amino acids) forming dithiocarbamates. Because some dithiocarbamate chemicals are reproductive and developmental toxins in animals, dithiocarbamates formed could play a role in the occurrence of developmental effects following CS_2 exposure. Although this cannot be ruled out, it has to be taken into account that while CS_2 itself ("free" CS_2) is rapidly eliminated from the body after ceasing exposure, the so-called "acid-labile" pool of bound CS_2 containing thiocarbamates has a long half-life and increases with daily repeated exposures. Therefore, it is unclear whether developmental effects observed after repeated exposure to CS_2 are of relevance for single acute exposures. For the reasons noted above, the results from developmental toxicity studies with CS_2 will not be used for the derivation of AEGL values.

6.3. Derivation of AEGL-2

The AEGL-2 is based on the no-observed-adverse-effect level (NOAEL) of 1,000 ppm (4-h exposure) for behavioral alterations (inhibition of escape response) (Goldberg et al. 1964). At the next higher concentration, an inhibition of escape (and of avoidance) response was observed.

A total uncertainty factor of 10 was applied. An interspecies uncertainty factor of 3 was used based on the similarity of acute effects seen in rodents compared with humans produced by agents affecting the CNS. Moreover, use of a default interspecies uncertainty factor of 10 would have resulted in values that are contradicted by experimental human studies in which no serious or escape-impairing effects were reported during or following 6-8 h of exposure to CS_2 at 80 ppm. An intraspecies uncertainty factor of 3 was applied to account for sensitive individuals because the threshold for CNS impairment is not expected to vary much among individuals (NRC 2001, pp. 79-80). Time scaling was performed according to the regression equation $C^n \times t = k$ (ten Berge et al. 1986). As outlined in NRC (2001), a default of n = 3 for shorter exposure periods (30 min and 1 h) and n = 1 for longer exposure periods (8 h) was applied owing to the lack of suitable experimental data for deriving the concentration exponent. For the 10-min AEGL-2 the 30-min value was used because the derivation of AEGL-2 values was based on a long experimental exposure period, and no supporting studies using short exposure periods were available for characterizing the concentration-time-response relationship. The calculated values are listed in Table 2-7. The obtained values are supported by data from controlled studies in humans in which 8 h of exposure up to CS_2 at 80 ppm were well tolerated (Freundt et al. 1976b).

7. DATA ANALYSIS OF AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

In the study of Lehmann (1894), very high CS_2 concentrations were applied (see section 6.1). However, for the reasons mentioned in section 6.1, the study of Lehmann (1894) will not be used for the derivation of AEGL values.

7.2. Summary of Animal Data Relevant to AEGL-3

With respect to lethality, the data for rats indicate a steep concentration-reponse curve: none of six rats survived a 4-h exposure to 3,500 ppm, but all six

TABLE 2-7 AEGL Values for Carbon Disulfide

AEGL	10 min	30 min	1 h	4 h	8 h
AEGL-2	200 ppm (620 mg/m³)	200 ppm (620 mg/m³)	160 ppm (490 mg/m³)	100 ppm (310 mg/m³)	50 ppm (160 mg/m³)

rats survived at 3,000 ppm (Du Pont 1966). No rats died after a single exposure to 2,000 ppm for 4 h (Goldberg et al. 1964) and to 1,500 ppm for 2 h (Savolainen and Järvisalo 1977).

In rabbits, death ocurred in animals after single exposures to 3,000 ppm or 3,200 ppm for 6 h (Flury and Zernik 1931; Lehmann 1894; PAI 1991). Individual cats died after exposure to 6,450 ppm for 2 ¼ h or after exposure to 3,200 ppm for 4¼ h. For mice, LC_{50} values were reported of 3,210 ppm (2 h) (Izmerov et al. 1982) and of 4500 ppm (30 min) ("average lethal concentration") (Kuljak et al. 1974).

Embryotoxic and fetotoxic effects were observed in rats (WIL Research Laboratories, Inc. 1992) and rabbits (PAI 1991) following repeated exposure to CS_2 at 500 or 600 ppm, respectively, during gestation. No developmental studies were available with single exposure of animals to CS_2. As outlined above (see section 6.2), these results will not be used for the derivation of AEGL for CS_2.

7.3. Derivation of AEGL-3

The derivation of AEGL-3 values is based on a study in rats in which a 4-h exposure to CS_2 at 3,000 ppm was not lethal during exposure or within a 2-week post-observation period (Du Pont 1966).

A total uncertainty factor of 10 was applied. An interspecies uncertainty factor of 3 was used based on the similarity of acute effects seen in rodents compared with humans produced by agents affecting the CNS. Moreover, use of a default interspecies uncertainty factor of 10 would have resulted in values that are contradicted by experimental human studies in which no serious or escape-impairing effects were reported during or following 6-8 h of exposure at 80 ppm. An intraspecies uncertainty factor of 3 was applied to account for sensitive individuals because the threshold for CNS impairment is not expected to vary much among individuals (NRC 2001, pp. 79-80). Time scaling was performed according to the regression equation $C^n \times t = k$ (ten Berge et al. 1986). As outlined in NRC (2001), a default of n = 3 for shorter exposure periods (30 min and 1 h) and n = 1 for longer exposure periods (8 h) was applied owing to the lack of suitable experimental data for deriving the concentration exponent. For the 10-min AEGL-3, the 30-min value was used because the derivation of AEGL-3 values was based on a long experimental exposure period, and no supporting studies using short exposure periods were available for characterizing the concentration-time-response relationship. The calculated values are listed in Table 2-8.

TABLE 2-8 AEGL Values for Carbon Disulfide

AEGL	10 min	30 min	1 h	4 h	8 h
AEGL-3	600 ppm (1480 mg/m³)	600 ppm (1480 mg/m³)	480 ppm (990 mg/m³)	300 ppm (930 mg/m³)	150 ppm (470 mg/m³)

The obtained values are supported by data from a controlled human study in which exposure for up to 4 h to concentrations of CS_2 at 260-820 ppm caused intoxication with headaches, dizziness, anxiety, paleness, cold sweat, and palpitations but no life-threatening symptoms (Lehmann 1894, see Table 2-3).

8. SUMMARY OF AEGLs

8.1. AEGL Values, Toxicity End Points, and Comparison with Other Standards and Criteria

The AEGL values for various levels of effects and various time periods are summarized in Table 2-9. All inhalation data are summarized in Figure 2-4. Other standard and guidance levels for workplace and community are listed in Table 2-10.

8.3. Data Adequacy and Research Needs

Because CS_2 is a solvent that has been used in large quantities in industry for more than a century, its chronic effects have been extensively studied, and the database is large. Effects of acute intoxication in occupational workers who were also chronically exposed have been described. In these reports, appropriate exposure concentrations are lacking. Very few controlled studies with humans are available that could be used for the derivation of AEGL. These studies focused on toxicokinetics, inihibition of biotransformation, and other alterations of liver functions. The AEGL-1 was derived from a controlled metabolism study in subjects with moderate intake of alcohol. Studies on odor perception are also available, but the detection threshold has not been characterized. It is likely that odor perception will be markedly affected by the impurities that form in CS_2 under the influence of air and light. Only one older study with controlled exposure of two students described acute effects over a wide range of concentrations. The data from this study were used to derive AEGL-2 and AEGL-3. In view of the severe acute effects of CS_2 observed in this study and of the chronic effects

TABLE 2-9 Summary of AEGL Values for Carbon Disulfide[a]

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	17 ppm (52 mg/m³)	17 ppm (52 mg/m³)	13 ppm (42 mg/m³)	8.4 ppm (26 mg/m³)	6.7 ppm (21 mg/m³)
AEGL-2 (Disabling)	200 ppm (620 mg/m³)	200 ppm (620 mg/m³)	160 ppm (490 mg/m³)	100 ppm (310 mg/m³)	50 ppm (160 mg/m³)
AEGL-3 (Lethality)	600 ppm (1,480 mg/m³)	600 ppm (1,480 mg/m³)	480 ppm (990 mg/m³)	300 ppm (930 mg/m³)	150 ppm (470 mg/m³)

[a]Cutaneous absorption may occur. Liquid CS_2 is a severe skin irritant and vesicant. Direct skin contact with the liquid must be avoided.

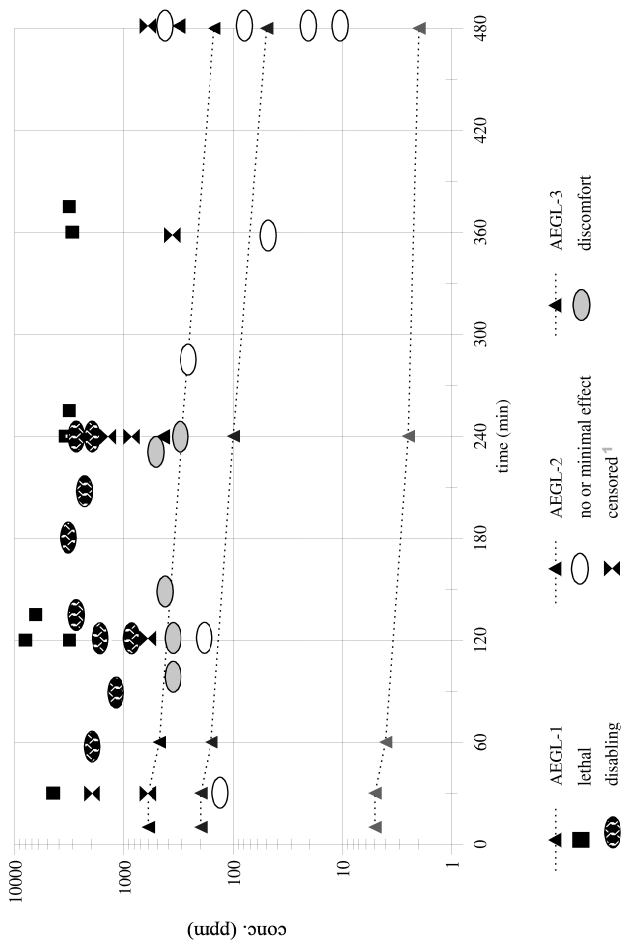

FIGURE 2-4 Categorical representation of all carbon disulfide inhalation data. Note: 1, severity category could not be established.

TABLE 2-10 Extant Standards and Guidelines for Carbon Disulfide

Guideline	Exposure duration						
	10 min	30 min	1 h	4 h	6 h	8 h	24 h
AEGL-1	17 ppm	17 ppm	13 ppm	8.4 ppm		6.7 ppm	
AEGL-2	200 ppm	200 ppm	160 ppm	100 ppm		50 ppm	
AEGL-3	600 ppm	600 ppm	480 ppm	300 ppm		150 ppm	
ERPG-1 (AIHA)[a]			1 ppm				
ERPG-2 (AIHA)			50 ppm				
ERPG-3 (AIHA)			500 ppm				
IDLH (NIOSH)[b]		500 ppm					
EEL (NRC)[c]	200 ppm	100 ppm	50 ppm				
Air MEG (USACHPPM)[d]			Minimal: 1 ppm Significant: 50 ppm Severe: 500 ppm			3 ppm	
Acute REL[e] (OEHHA)			144 ppm		2 ppm		
PEL-TWA (OSHA)[f]						20 ppm	
Acceptable peak (OSHA)[g]		30 ppm					
REL-TWA (NIOSH)[h]						1 ppm	
TLV-TWA (ACGIH)[i]						10 ppm	
MAK (DFG, Germany)[j]						5 ppm	
MAK (DFG, Germany) Kurzzeitkategorie[k]		10 ppm					
Einsatztoleranzwert[l]				10 ppm			
AQG (WHO)[m]		20 µg/m³ (.006 ppm)					100 µg/m³ (.032 ppm)
MRL (ATSDR)[n]							0.30 ppm

(Continued)

[a]ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association). The ERPG-1 is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 h without experiencing or developing effects more serious than mild irritation, other mild transient health effects, or perception of a clearly objectionable odor. The ERPG-1 for carbon disulfide is based on a reported odor threshold of 0.21 ppm, which is referenced as ASTM (1973), a compilation of odor threshold data. The original source for this odor threshold is Leonardos et al. (1969). The ERPG-1 of 1 ppm is nearly five times greater than the reported odor threshold. In a critical review of odor threshold data, AIHA (1997) rejected the use of the 0.21 ppm threshold because this value represents a 100% recognition concentration. 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 adverse health effects or symptoms that could impair an individual's ability to take protective action. The ERPG-2 for carbon disulfide is based on findings that although individuals may experience transitory effects, such as headache, confusion, and eye irritation, the effects would be reversible, and serious effects are not expected to occur. Although developmental effects were reported to occur in rats exposed 8 h/d to 32 and 64 ppm, exposure at 40 ppm did not result in maternal toxicity or developmental effects. The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects. The ERPG-3 for carbon disulfide is based upon reports of severe poisoning at 1,150 ppm for 30 min and reports of psychosis and paralysis following acute exposure at 500 ppm.

[b]IDLH (immediately dangerous to life and health, National Institute of Occupational Safety and Health). Basis for original IDLH: The IDLH is based on the statement in Patty (1963) that symptoms occur after 30 min of exposure to 420 to 510 ppm (Flury and Zernik 1931). AIHA (1956) reported that severe symptoms and unconsciousness may occur within 30 min at 1,100 ppm (Patty 1963). Patty (1963) also reported that exposure of humans to 4,800 ppm for 30 min causes coma and may be fatal (Flury and Zernik 1931). Basis for revised IDLH: Based on acute inhalation toxicity data in humans (Flury and Zernik 1931; Browning 1953; Lefaux 1968; Bittersohl et al. 1972), the original IDLH for carbon disulfide (500 ppm) is not being revised at this time (NIOSH 1996).

[c]EEL (emergence exposure limit, National Research Council, Committee on Toxicology). The EEL is defined as a ceiling limit for an unpredictable single exposure, usually lasting 60 min or less, and never more than 24 h—an occurrence expected to be rare in the lifetime of any person. It reflects an acceptance of the statistical likelihood of the occurrence of a nonincapacitating, reversible effect in an exposed population. It is designed to avoid substantial decrements in performance during emergencies and might contain no uncertainty factor. The use of uncertainty factors will depend on the specific compound in question and on the type of effect produced by the compound. The values for carbon disulfide are based on neurotoxic symptoms in humans (NRC 1984).

[d]MEG (military exposure guidelines) (USACHPPM 2002). MEGs are concentrations of chemicals in air, water, and soil that can be used during deployments to assist in the assessment of the significance of field exposures to occupational and environmental health (OEH) chemical hazards. TG 230 MEGs are designed to address a variety of scenarios, such as for a single catastrophic release of large amounts of a chemical, for temporary exposure conditions lasting hours to days, or for ambient environmental conditions, such as regional pollution, use of a continuously contaminated water supply, or persistent soil contamination where there is regular contact. For each media, there are slightly different exposure scenarios of concern. Specifically, a MEG is a chemical concentration in air, water, or soil that, after a one-time exposure of specified duration, represents an estimate of the level above which certain types of health effects may begin to occur in individuals among the exposed population.

1-h SEVERE: the airborne concentration above which continuous exposure for 1 h could begin to produce life-threatening or lethal effects in a small portion of individuals. Increas-

ing concentrations or duration of exposure will increase incidence of lethality and severity of nonlethal severe effects.

1-h SIGNIFICANT: the airborne concentration above which continuous exposure for 1 h could begin to produce irreversible, permanent, or serious health effects that may result in performance degradation and incapacitate a small portion of individuals. Increasing concentrations or duration of exposure will increase incidence and severity of effects.

1-h MINIMAL TO NONSIGNIFICANT: the airborne concentration above which continuous exposure for 1 h could begin to produce mild, nondisabling, transient, reversible effects, if any. Such effects should not impair performance. Increasing concentration or duration could result in performance degradation, especially for tasks requiring extreme mental and visual acuity or physical dexterity and strength.

8-h and 24-h MINIMAL TO NONSIGNIFICANT: the airborne concentration above which continuous exposure for 8 or 24 h could begin to produce mild, nondisabling, transient, reversible effects, if any. Such effects should not impair performance. Increasing concentration or duration could result in performance degradation, especially for tasks requiring extreme mental and visual acuity or physical dexterity and strength.

[e]Acute REL (acute reference exposure levels for airborne toxicants) (OEHHA 1999b). The concentration level at or below which no advese health effects are anticipated for a specified exposure duration is termed the reference exposure level (REL). The REL for a 6-h exposure protective against severe adverse effects of carbon disulfide is based on a developmental toxicity study in rats (Saillenfait et al. 1989). The 1-h level protective against life-threatening effects is based on CNS effects in occupationally exposed workers (Vigliani 1954; OEHHA 1999a).

[f]OSHA PEL-TWA (Occupational Health and Safety Administration, permissible exposure limits–time-weighted average) for 8 h (OSHA 1999).

[g]Acceptable peak OSHA (Occupational Health and Safety Administration, permissible exposure limits) (OSHA 1999). The maximum peak is 100 ppm.

[h]REL-TWA NIOSH (National Institute of Occupational Safety and Health, recommended exposure limits–time-weighted average) (NIOSH 1992), is defined analogous to the ACGIH TLV-TWA.

[i]ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value–time-weighted average) (ACGIH 1994). 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.

[j]MAK (maximale arbeitsplatzkonzentration [maximum workplace concentration]), (Deutsche Forschungs-gemeinschaft [German Research Association], Germany) (Greim 1999) is defined analogous to the ACGIH TLV-TWA.

[k]MAK kurzzeitkategorie (kategorie II, 2) (short-term category II, 2) (German Research Association) constitutes the maximum average concentration to which workers can be exposed for a period of up to 30 min (mean value) no more than 2 times per workshift.

[l]Einsatztoleranzwert (Buff and Greim 2000) (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 risk.

[m]AQG (air quality guidelines for Europe) (WHO 2000) provides a concentration below which no adverse effects or (in the case of odorous compounds) no nuisance or indirect health significance are expected, although it does not guarantee the absolute exclusion of effects at concentrations below the given value. The guideline value was derived from epidemiologic studies indicating an adverse effect at about 10 mg/ m³, which may be equivalent to a concentration in the general environment of 1 mg/m³. The 30-min value is based on the sensory effects (odor) of carbon disulfide.

(Continued)

[n]MRL (minimal risk level) (ATSDR 1996) is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. The MRL for carbon disulfide is based on effects on the peripheral nervous system observed in a study on workers chronically exposed to carbon disulfide (Johnson et al. 1983).

at continued exposure that have become known since that study was performed, any further studies with controlled exposure to high concentrations must be considered risky, and under ethical points of view, cannot be justified. Animals studies, largely conducted with rats, indicate a steep concentration-response curve for lethality. In animals, there is a broad database from studies on acute nonlethal effects, mostly on the nervous system and the liver. These data are in agreement with the limited data from controlled human studies, and support the AEGL values derived from human studies.

Epidemiologic studies on occupational cohorts chronically exposed to CS_2 cause suspicion of developmental or reproductive effects. The lowest level at which such effects may occur is not known. In animal experiments, embryotoxic and fetotoxic effects, malformations, and alterations of postnatal behavior in offsprings have been described when dams were repeatedly exposed over a number of days in different periods reaching from pregestation to the end of gestation. Some of these studies report that effects could be seen down to very low concentrations, but these studies are not properly described. Studies with single exposure are lacking. Thus, additional studies devoted to developmental or reproductive toxicity would be beneficial. Further studies on metabolism, toxicokinetics, and mechanism of action also would be useful.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR CARBON DISULFIDE

Derivation of AEGL-1 Values

Key study:	Freundt et al. 1976b
Toxicity end point:	Exposure to 20 ppm for 8 h in volunteers with a blood ethanol concentration of 0.75 g/L (75 mg/dL) caused a 50% increase in blood acetaldehyde level. This effect is explained by an inhibition of acetaldehyde dehydrogenase (ALDH) by CS_2 which is similarly caused by dithiocarbamates and disulfiram ("Antabuse"). The increase of blood acetaldehyde in the key study was asymptomatic, that is, no disulfiram effect ("Antabuse syndrome") was observed. However, ALDH is a polymorphic enzyme and individuals with low ALDH-activity (as frequently observed in Asians) may experience discomfort under conditions as in the experiment described. Individuals heterozygous in ALDH are considered a sensitive subgroup within the normal population.
Scaling:	$C^3 \times t = k$ for extrapolation to 8 h, 4 h, 1 h, and 30 min. The 10-min AEGL-1 was set at the same concentration as the 30-min AEGL-1. $k = 20^3$ ppm$^3 \times 8$ h = 64,000 ppm^3-h
Uncertainty/ modifying factors	3 for intraspecies variability.
Calculations:	
10-min AEGL-1	10-min AEGL-1 = 30-min AEGL-1 = 17 ppm (52 mg/m^3)
30-min AEGL-1	$C^3 \times 0.5$ h = 64,000 ppm^3-h C = 50 ppm 30-min AEGL-1 = 50 ppm/3 = 17 ppm (52 mg/m^3)
1-h AEGL-1	$C^3 \times 1$ h = 64,000 ppm^3-h C = 40 ppm 1-h AEGL-1 = 40 ppm/3 = 13 ppm (42 mg/m^3)
4-h AEGL-1	$C^3 \times 4$ h = 64,000 ppm^3-h C = 25 ppm 4-h AEGL-1 = 25 ppm/3 = 8.4 ppm (26 mg/m^3)
8-h AEGL-1	$C^3 \times 8$ h = 64,000 ppm^3-h C = 20 ppm 8-h AEGL-1 = 20 ppm/3 = 6.7 ppm (21 mg/m^3)

Derivation of AEGL-2 Values

Key study:	Goldberg et al. 1964
Toxicity end point:	Behavioral alterations (Inhibition of escape response) in rats exposed to 2,000 ppm for 4 h; NOEL: 1,000 ppm, 4 h.
Scaling:	$C^3 \times t = k$ for extrapolation to 30 min, 1 h. The 10-min AEGL-2 was set at the same concentration as the 30-min AEGL-2. $k = 1{,}000^3$ ppm$^3 \times 4$ h $= 4 \times 10^9$ ppm^3-h $C^1 \times t = k$ for extrapolation to 4 h and 8 h $k = 1{,}000$ ppm $\times 4$ h $= 4{,}000$ ppm-h
Uncertainty/ modifying factors	3 for interspecies variability. 3 for intraspecies variability. Combined uncertainty factor of 10.
Calculations:	
10-min AEGL-2	10-min AEGL-2 = 30-min AEGL-2 = 200 ppm (620 mg/m^3)
30-min AEGL-2	$C^3 \times 0.5$ h $= 4 \times 10^9$ ppm^3-h C = 2,000 ppm 30-min AEGL-2 = 2,000 ppm/10 = 200 ppm (620 mg/m^3)
1-h AEGL-2	$C^3 \times 1$ h $= 4 \times 10^9$ ppm^3-h C = 1,587 ppm 1-h AEGL-2 = 1587 ppm/10 = 160 ppm (490 mg/m^3)
4-h AEGL-2	C $\times 4$ h = 4000 ppm-h C = 1,000 ppm 4-h AEGL-2 = 1,000 ppm/10 = 100 ppm (310 mg/m^3)
8-h AEGL-2	C $\times 8$ h = 4,000 ppm-h C = 500 ppm 8-h AEGL-2 = 500 ppm/10 = 50 ppm (160 mg/m^3)

Derivation of AEGL-3 Values

Key study:	Du Pont 1966
Toxicity end point:	Acute lethality in rats following 4-h exposure: 6/6 rats died at 3,500 ppm, 0/6 rats died at 3,000 ppm.
Scaling:	$C^3 \times t = k$ for extrapolation to 30 min, 1 h. The 10-min AEGL-1 was set at the same concentration as the 30-min AEGL-1. $k = 3{,}000^3$ ppm$^3 \times 4$ h $= 1.08 \times 10^{11}$ ppm^3-h

	$C^1 \times t = k$ for extrapolation to 4 h and 8 h k = 3,000 ppm × 4 h = 12,000 ppm-h
Uncertainty/ modifying factors	3 for interspecies variability 3 for intraspecies variability Combined uncertainty factor of 10
Calculations:	
10-min AEGL-3	10-min AEGL-3 = 30-min AEGL-3 = 600 ppm (1,870 mg/m³)
30-min AEGL-3	$C^3 \times 0.5$ h = 1.08×10^{11} ppm³-h C = 6,000 ppm 30-min AEGL-3 = 6000 ppm/10 = 600 ppm (1,870 mg/m³)
1-h AEGL-3	$C^3 \times 1$ h = 1.08×10^{11} ppm³-h C = 4,762 ppm 1-h AEGL-3 = 4,762 ppm/10 = 480 ppm (1500 mg/m³)
4-h AEGL-3	C × 4 h = 12,000 ppm-h C = 3,000 ppm 4-h AEGL-3 = 3,000 ppm/10 = 300 ppm (930 mg/m³)
8-h AEGL-3	C × 8 h = 12,000 ppm-h C = 1,500 ppm 8-h AEGL-3 = 1,500 ppm/10 = 150 ppm (470 mg/m³)

APPENDIX B

ACUTE EXPOSURE GUIDELINES FOR CARBON DISULFIDE

Derivation Summary for Carbon Disulfide

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
17 ppm (52 mg/m³)	17 ppm (52 mg/m³)	13 ppm (42 mg/m³)	8.4 ppm (26 mg/m³)	6.7 ppm (21 mg/m³)

Key Reference: Freundt, K.J., K. Lieberwirth, H. Netz, and E. Pöhlmann. 1976b. Blood acetaldehyde in alcoholized rats and humans during inhalation of carbon disulphide vapor. Int. Arch. Occup. Environ. Health 37, 35-46.

Test Species/Strain/Number: Human/ Healthy young males/12.

Exposure Route/Concentrations/Durations: Inhalation/0, 20, 40, 80 ppm, 8 h.

Effects: At 20 ppm, increase in blood acetaldehyde concentration (ca. 50% above control level) in healthy human subjects with moderate intake of alcohol (blood ethanol ca. 0.7 g/L [70 mg/dL]). The effect can be explained by an inhibition of the ALDH. The rise in acetaldehyde was not accompanied by signs of a "disulfiram effect." However, alcohol intolerance has been reported in workers occupationally exposed to unknown concentrations of CS_2. In further controlled human studies, exposure to 10-80 ppm CS_2 caused a temporary reversible inhibition of xenobiotic biotransformation, but no signs of liver damage were observed.

End Point/Concentration/Rationale: Increase in blood acetaldehyde concentration at 20 ppm, 8 h.

Uncertainty Factors/Rationale:

Interspecies: 1, test subjects were humans.

Intraspecies: 3, subjects were healthy male volunteers. An uncertainty factor of 3 was applied to account for the protection of sensitive population subgroups with an acetaldehyde dehydrogenase (ALDH2[2]) less active than the typical form ALDH2. The presence of the ALDH2(2) allele (which is especially common in Asians but rare or absent in Caucasians) results in low enzyme activity and higher levels of acetaldehyde after ingestion of alcohol compared with persons in which the normal enzyme is present. Individuals heterozygous in ALDH are considered as a sensitive subgroup within the normal population. An additional increase of the acetaldehyde concentration due to exposure to CS_2 may lead to a disulfiram effect or aggravate otherwise mild symptoms.

Modifying factor: NA

Animal to Human Dosimetric Adjustment: NA

Time Scaling: Extrapolation was made to the relevant AEGL time points using the relationship $C^n \times t = k$ with the default of n = 3 (ten Berge et al. 1986) for shorter exposure periods, due to the lack of experimental data for deriving the concentration

(Continued)

AEGL-1 VALUES Continued

10 min	30 min	1 h	4 h	8 h
17 ppm (52 mg/m³)	17 ppm (52 mg/m³)	13 ppm (42 mg/m³)	8.4 ppm (26 mg/m³)	6.7 ppm (21 mg/m³)

exponent. For the AEGL-1 for 10 min, the AEGL-1 for 30 min was adopted because the derivation of AEGL values was based on a study with a long experimental exposure period of 8 h, no supporting studies using short exposure periods were available characterizing the concentration time-response relationship, and it is considered inappropriate to extrapolate back to 10 min.The derived AEGL-1 values are above the reported odor thresholds but below concentrations reported to cause moderate odor annoyance.

Confidence and Support for AEGLs: A well-conducted study with a sufficient number of human volunteers and an appropriate end point for AEGL-1 was available.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
200 ppm	200 ppm	160 ppm	100 ppm	50 ppm

Key Reference: Goldberg, M.E., H.E. Johnson, D.C. Pozzani, and H.F.Jr. Smyth. 1964. Effect of repeated inhalation of vapors of industrial solvents on animal behavior. I. Evaluation of nine solvents vapors on pole-climb performance in rats. Am. Ind. Hyg. Assoc. J. 25: 369-375.

Test Species/Strain/Number: Rats/ Carworth Farms Elias/ Groups of 8-10 females.

Exposure Route/Concentrations/Durations: Inhalation, 0, 250, 500, 1,000, 2,500 ppm, 4 h.

Effects: At 2,000 ppm, inhibition of escape reponse in 12% (and of avoidance response in 50%) of the animals was observed. No inhibition of escape (and avoidance) response was observed at 1,000 ppm.

End Point/Concentration/Rationale: Exposure to 1,000 ppm for 4 h was a NOAEL for inhibition of escape response.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, based on the similarity of acute effects seen in rodents compared with humans produced by agents affecting the CNS.
Intraspecies: 3, human data suggest that acute effects of volatile anesthetics and gases on the CNS show little intraspecies variability (about 2-3 fold).

Modifying factor: Not applicable.

Animal to Human Dosimetric Adjustment: Not applicable.

Time Scaling: Extrapolation was made to the relevant AEGL time points using the relationship $C^n \times t = k$ with the default of n = 3 for shorter exposure periods of 1 h and of 30 min and of n = 1 for longer exposure periods of 4 and 8 h (ten Berge et al. 1986; NRC 2001). The 10-min AEGL-2 was assigned the same value as that for the 30-min AEGL-2 as it was considered inapproprate to extrapolate from an experimental period of 4 h to 10 min.

(Continued)

AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
200 ppm	200 ppm	160 ppm	100 ppm	50 ppm

Confidence and Support for AEGLs: AEGL-2 values are protective of human health. The level is based on a NOEL for inhibition of escape response in a behavioral study with rats in which concentrations in the exposure chamber were monitored. The AEGL values are supported by data from human studies in which no effects meeting the AEGL-2 definition were observed at similar concentrations.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
600 ppm	600 ppm	480 ppm	300 ppm	150 ppm

Key Reference: Du Pont. 1966. Acute inhalation toxicity–progress report. Haskell Laboratory Report No. 161-66. EI Du Pont De Nemours and Company. Haskell Laboratory, Newark, DE.

Test Species/Strain/Number: Rats/CD/6 males.

Exposure Route/Concentrations/Durations: Inhalation, 3,500 ppm, 3,000 ppm/4 h.

Effects: 6/6 rats died at 3,500 ppm, none of 6 rats died at 3,000 ppm.

End Point/Concentration/Rationale: No lethality following 4 h of exposure to 3,000 ppm.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10

Interspecies: 3, based on the similarity of acute effects seen in rodents compared with humans produced by agents affecting the CNS.

Intraspecies: 3, human data suggest that acute effects of volatile anesthetics and gases on the CNS show little intraspecies variability (about 2-3 fold).

Modifying factor: Not applicable.

Animal to Human Dosimetric Adjustment: Not applicable.

Time Scaling: Extrapolation was made to the relevant AEGL time points using the relationship $C^n \times t = k$ with the default of n = 3 for shorter exposure periods of 1 h and of 30 min and of n = 1 for longer exposure periods of 4 and 8 h (ten Berge et al. 1986; NRC 2001). The 10-min AEGL-2 was assigned the same value as that for the 30-min AEGL-2 as it was considered inapproprate to extrapolate from an experimental period of 4 h to 10 min.

Confidence and Support for AEGLs: AEGL-3 values are protective of human health. The available indicate a very steep concentration-lethality response curve and the values are based on a no-observed lethality concentration in rats. Additionally, the AEGL-3 values are supported by data from a human study in which the effects noted were milder than those defined by the AEGL-3 definition.

3

Monochloroacetic Acid[1]

Acute Exposure Guideline Levels

PREFACE

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

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

AEGL-1 is the airborne concentration (expressed as parts per million [ppm] or milligrams per cubic meter [mg/m^3]) of a substance above which it is

[1]This document was prepared by the AEGL Development Team composed of Peter Griem (Forschungs- und Beratungsinstitut Gefahrstoffe GmbH) and Chemical Manager Ernest V. Falke (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guideline reports (NRC 1993, 2001).

predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m³) 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/m³) 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 odor, taste, and sensory irritation or certain asymptomatic, nonsensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including sensitive subpopulations, it is recognized that certain individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Monochloroacetic acid (MCAA) is a colorless crystalline material, which is highly soluble in water and soluble in organic solvents. Its vapor pressure at room temperature is moderate with reported values between 0.2 hectopascals (hPa) (crystalline substance) and 10 hPa (solution in water). MCAA has a pungent odor.

MCAA is produced by chlorination of acetic acid or hydrolysis of trichloroethylene (also known as trichloroethene) using sulfuric acid. The world production capacity was estimated at 362,500 metric tons/year in 1987. MCAA or its sodium salt, sodium monochloroacetate, are used primarily in the industrial production of carboxymethyl-cellulose, herbicides, and thioglycolic acid as well as in the production of plastics, pharmaceuticals, flavors, cosmetics, and other organic chemicals.

MCAA is an acid (pK_a, 2.85) and, therefore, can cause eye and skin irritation upon contact with a diluted MCAA solution and can cause skin corrosion and conjunctival burns upon contact with more concentrated solutions. The systemic toxicity of MCAA is caused by inhibition of enzymes of the glycolytic pathway and the tricarboxylic acid cycle. This metabolic blockage damages organs with a high-energy demand, such as heart, central nervous system (CNS), and muscles, and leads to metabolic acidosis due to the accumulation of lactic acid and citric acid in the body.

No studies are available reporting severe toxic effects in humans after inhalation exposure to MCAA. Mortality was reported in a child after oral uptake of 5-6 milliliters (mL) of an 80% MCAA solution (Rogers 1995). Several lethal accidents have been reported, in which workers were dermally exposed to hot liquid MCAA. An inadequately described study reported an irritation threshold of 1.48 ppm (Maksimov and Dubinina 1974); no respiratory tract irritation, effects on lung function parameters, or irritation of skin and mucous membranes were reported for more than 33 workers potentially exposed to MCAA concentrations between <0.13 ppm for 3 h and 0.31 ppm for 7 h (Clariant GmbH, unpublished material, 2000).

The only animal study reporting lethal effects after inhalation exposure was an inadequately described study in which an LC_{50} (concentration with 50% lethality) of 46.8 ppm for 4 h was reported for rats (Maksimov and Dubinina 1974). Several studies report lethal effects after oral exposure with LD_{50} values mostly between 50 and 200 mg/kg for rats, mice and guinea pigs. In a single inhalation experiment on rats, eye squint and slight lethargy were observed during exposure to an analytic concentration of 66 ppm for 1 h (Dow Chemical Co. 1987). In an inadequately reported study, an irritation threshold in rats of 6.16 ppm and a no-observed-effect level (NOEL) for histologic changes in the respiratory tract in rats and guinea pigs of 1.5 ppm after 4 months have been reported (Maksimov and Dubinina 1974).

No relevant studies of adequate quality were available for the derivation of the AEGL-1. Therefore, AEGL-1 values were not recommended because of insufficient data. Due to the lack of an adequately performed study reporting an odor threshold for MCAA, no level of distinct odor awareness (LOA) was derived.

The AEGL-2 was based on a single inhalation study of MCAA in rats (Dow Chemical Co. 1987) in which eye squint and lethargy were observed in rats exposure to 66 ppm for 1 h. A total uncertainty factor of 10 was used. An uncertainty factor of 3 was applied for interspecies variability (1) because the effect level was considered below that of an AEGL-2, (2) because the available data on acute oral lethality do not point at a large interspecies variability for more severe (lethal) effects, and (3) because of the limited toxicodynamic variability, as the enzymes inhibited by MCAA do not vary considerably within and between species. An uncertainty factor of 3 was applied for intraspecies variability because of the limited toxicokinetic variability with respect to local effects and because of the limited toxicodynamic variability with respect to systemic effects, as the enzymes inhibited by MCAA do not vary considerably within and between species. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of $n = 3$ for shorter exposure periods and $n = 1$ for longer exposure periods, due to the lack of suitable experimental data for deriving the concentration exponent.

No relevant studies of adequate quality were available for the derivation of the AEGL-3 value. Therefore, due to insufficient data and the uncertainties of a

route-to-route extrapolation, AEGL-3 values were not recommended. The AEGLs are summarized in Table 3-1.

1. INTRODUCTION

MCAA is a colorless crystalline material, which is highly soluble in water and soluble in organic solvents.

MCAA is produced by chlorination of acetic acid or hydrolysis of trichloroethylene using sulfuric acid (BUA 1994). (1) The chlorination of acetic acid is carried out in liquid phase at temperatures between 85° and 120°C. Acetic anhydride and acetylchloride may be used as catalysts. The chlorination product contains considerable amounts of acetic acid and dichloroacetic acid. Purification takes place either by selective dechlorination of dichloroacetic acid and subsequent distillation, or by recrystallization from suitable solvents (ECB 2005). (2) Trichloroethylene and sulfuric acid are heated to 130-140°C in the reactor. A mixture of trichloroethylene and sulfuric acid is continuously fed to the bottom of the reactor. The chloroacetic acid and sulfuric acid are permitted to overflow into a cascade, where the chloroacetic acid is distilled at 20 mm Hg, and the sulfuric acid is recycled. The hydrolysis of trichloroethylene yields high-purity MCAA, but has the disadvantage of utilizing a relatively more expensive starting material (ECB 2005).

The world production capacity was estimated at 362,500 metric tons/year in 1987 (KEMI 1994). Europe produced about 145,000 metric tons in 1999 (ECB 2005), and the United States produced about 39,000 metric tons in 1989 (OECD 1996). Imports into the United States comprised about 17,000 metric tons of chloroacetic acids in 2003 (USITA 2004). The TRI database (DHHS 2008) lists 17 sites in the United States where production and use of MCAA causes emissions to the air.

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

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (Nondisabling)	N.R.[b]	N.R.	N.R.	N.R.	N.R.	Insufficient data
AEGL-2 (Disabling)	12 ppm (47 mg/m³)	8.3 ppm (33 mg/m³)	6.6 ppm (26 mg/m³)	1.7 ppm (6.7 mg/m³)	0.83 ppm (3.3 mg/m³)	Eye squint and lethargy in rats (Dow Chemical Co. 1987)
AEGL-3 (Lethal)	N.R.	N.R.	N.R.	N.R.	N.R.	Insufficient data

[a]Skin contact with molten MCAA or MCAA solutions should be avoided; dermal penetration is rapid, and fatal intoxications have been observed when 10% or more of the body surface was involved.
[b]Not recommended because of insufficient data.

MCAA is pumped in molten form (about 80°C) or as 80% aqueous solution through pipes on industrial sites and is also transported in molten form in tank trucks and rail tank cars between industrial sites (ECETOC 1999; ECB 2005). Therefore, an inhalation exposure during accidental releases cannot be ruled out (ECETOC 1999), although no case of severe intoxication by inhalation has been published in the literature.

MCAA or its sodium salt, sodium monochloroacetate, are used primarily in the industrial production of carboxymethylcellulose, herbicides, thioglycolic acid as well as in the production of plastics, pharmaceuticals, flavors, cosmetics, and other organic chemicals (KEMI 1994; ECB 2005).

Haloacetic acids, including MCAA, are a group of chemicals that are formed along with other drinking-water disinfection byproducts (e.g., trihalomethanes) when chlorine or other disinfectants used to control microbial contaminants in the water react with naturally occurring organic and inorganic matter in water. Depending on the amount of bromide in the source water, varying amounts of chlorinated, brominated, and mixed bromochlorohaloacetic acids are produced. EPA (63 Fed. Reg. 69390 [1998]) published the stage 1 Disinfectants/Disinfection Byproducts Rule to regulate a group of five haloacetic acids at a maximum contaminant level of 0.06 mg/L (60 ppb) annual average. A very small inhalation exposure might result from this water contamination. Xu and Weisel (2003) measured an aerosol-bound concentration of haloacetic acids at 6.3 nanograms (ng)/m³ during showering with water containing haloacetic acids at 250 µg/L. Chemical and physical properties of MCAA are listed in Table 3-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Deaths after inhalation of MCAA have not been reported in the literature (ECETOC 1999). Lethal effects have occurred after oral intoxication and after dermal exposure to hot, liquid MCAA (BUA 1994; IUCLID 1996; ECETOC 1999). Some of these incidences are described in the following paragraphs.

Feldhaus et al. (1993) and Rogers (1995) reported a case study of a fatal acute oral exposure. A 5-year old girl was accidentally given 5-6 mL of an 80% MCAA-containing wart remover. One and one- half hours after exposure, she developed refractory ventricular tachycardia, pulmonary edema, and acidemia. The patient died 8 h after ingestion despite medical intervention. An autopsy revealed diffuse gastric erosions, fatty infiltration of the liver, and pulmonary and cerebral edema. The postmortem MCAA concentration in serum was 100 mg/L as determined by gas chromatography and mass spectroscopy. The exposure corresponds to an oral dose of about 200-240 mg/kg (see section 7.1).

Fatal cases and life-threatening poisonings in workers have been described after skin contact (BUA 1994; IUCLID 1996): Christofano et al. (1970) reported

TABLE 3-2 Chemical and Physical Data for MCAA

Parameter	Data	Reference
Molecular formula	$ClCH_2$-COOH ($C_2H_3ClO_2$)	NTP 1992
Molecular weight	94.5 g/mol	NTP 1992
CAS Registry Number	79-11-8	NTP 1992
Physical state	Solid	NTP 1992
Color	Colorless	NTP 1992
Synonyms	Chloroacetic acid; monochloroethanoic acid; chloroethanoic acid; Monochloressigsäure; Chlorethansäure	OECD 1996; Greim 1998
Vapor pressure	0.1 mm Hg (at 20°C) ca. 0.2 hPa (crystalline substance at 20°C) 1 hPa (at 20°C) 10 hPa (solution in water at 20°C) 1 mm Hg (at 43°C) 4.4 hPa (liquid at 65°C) 8.23 mm Hg (at 80°C) 10 mm Hg (at 81°C) 40 mm Hg (at 109.2°C) 100 mm Hg (at 130.7°C) 400 hPa (at 169°C)	Dow Chemical Co. 1987 Greim 1998 IUCLID 1996 IUCLID 1996 Weast 1984 IUCLID 1996 Dow Chemical Co. 1987 Weast 1984 Weast 1984 Weast 1984 Weast 1984
Density	1.58 g/cm³ (solid) 13,707 g/cm³ (liquid)	OECD 1996
Melting point	63°C (-crystalline form, common form) 56.2°C (-crystalline form) 52.5°C (-crystalline form)	Weast 1984
Boiling point	187.8°C (-crystalline form) 187.9°C (-crystalline form) 187.8°C (-crystalline form)	Weast 1984
Solubility	Very soluble in water (4,210 g/L at 20°C); soluble in methanol, ethanol, acetone, ether, dioxane, DMF, DMSO	IUCLID 1996; BG Chemie 1993; Weast 1984
Acidity, pK_a	2.85	Weast 1984
Odor	Pungent odor	ICPS & CEC 1994
Explosive limits in air	No data	
Conversion factors	1 ppm = 3.92 mg/m^3 (at 1,013 hPa, 25°C) 1 mg/m^3 = 0.26 ppm (at 1,013 hPa, 25°C)	BG Chemie 1993

a case, in which about 10% of the body surface was contaminated with warm MCAA solution. Although the contaminated skin was immediately rinsed with water for more than 1 h, first-grade burns, anxiety, restlessness, and shock developed, followed by death about 10 h after the accident. Ruty et al. (1988) re-

ported on the case of a 47-year-old worker, who had pressurized, molten (about 90°C) MCAA squirted on both legs. Although the legs were immediately rinsed with water, 6% of the body area showed first-grade burns. Four hours after the accident, nausea, vomiting, cardiovascular shock, unconsciousness, and coma developed. Arrhythmia, hypotension, and severe metabolic acidosis were found. The patient was treated with ethanol, an effective antidote for fluoroacetic acid intoxications. His symptoms ameliorated after 24 h, and the patient returned to work 3 months later. Kulling et al. (1992) reported the case of a 38-year-old man who was splashed with an 80% MCAA solution on 25-30% of his body surface. On admission to hospital 1 h after the accident, he had epidermal and dermal superficial burns and showed slight disorientation. One hour later, he developed agitation, cardiac failure and coma. He later developed severe metabolic acidosis, rhabdomyolysis, renal insufficiency, and cerebral edema and died on day 8 after the accident because of severe CNS damage.

2.2. Nonlethal Toxicity

Clariant GmbH (unpublished material, 2000) reported that routine medical examinations of workers of two plants, producing MCAA and sodium monochloroacetate, respectively, revealed no respiratory tract irritation, effects on lung-function parameters, or irritation of skin and mucous membranes. The number of potentially exposed workers was 33 in one plant and not stated for the other. Concentrations of MCAA and sodium monochloroacetate, respectively, were measured at individual workplaces about every 1 to 2 years between 1991 and 2000. Measurements were carried out either as area or personal sampling by drawing a defined volume of air through a 0.01-mol/L sodium hydroxide solution during a time period between 275 and 430 min followed by ion chromatography analysis. Results are given in Table 3-3.

Maksimov and Dubinina (1974) and Rodionova and Ivanov (1979) reported an irritation threshold for humans of 5.7 mg/m³ (1.48 ppm) (for this study, an exposure time of 1 min was stated in Izmerov et al. [1982]). The experimental details were not described by the authors.

An odor threshold of 0.01 ppm cited from an unpublished correspondence from Dow Chemical Co. was reported by AIHA (1993). Oelert and Florian (1972) cited an odor threshold of 0.045 ppm; however, the authors did not state whether this value was taken from the literature or whether and how they measured the odor threshold.

Knapp (1923) reported a case in which occupational exposure to MCAA had resulted in severe damage of the cornea (keratitis traumatica), but did not provide details of the exposure.

Morrison and Leake (1941) reported that daily oral exposure for 60 days to 300 mL of a 0.05% MCAA solution in water did not result in adverse effects in three human volunteers. The exposure corresponds to an oral dose of about 2.1 mg/kg/day (d) (see section 6.1).

TABLE 3-3 Results of Monochloroacetic Acid Measurements at Workplace

Plant	Workplace Situation	Individual MCAA Concentrations Measured Between 1991 and 2000	Number of Workers and Exposure Time Per Workshift
SMCA production	Area of rollers for production of MCAA flakes	Area sampling; 1, <1, <1, 1, 1, 1, 1 mg/m³ (MCAA measured) (0.26, <0.26, <0.26, 0.26, 0.26, 0.26, 0.26 ppm)	1 person for 1 h
SMCA production	Filling of MCAA flakes	Personal sampling; <1, 1.2, 1, <1, 1 mg/m³ (MCAA measured) (<0.26, 0.31, 0.26, <0.26, 0.26 ppm)	Max. 4 persons for 7 h
SMCA production	SMCA mixer	Area sampling; 0.81, 0.89 mg/m³ (SMCA measured) (0.21, 0.23 ppm)	1 person for 1 h
SMCA production	Filling of bags with SMCA	Personal sampling; 0.49, 0.45, <0.40 mg/m³ (SMCA measured) (0.13, 0.12, <0.10 ppm)	1 person for 6 h
MCAA production	Round and sampling men work area in five buildings	Personal sampling; <1, <1, <1,<1,<1, <1, <1, <1,<1,<1, 0.8, <0.5, <0.5, <0.5, <0.5, <0.5, <0.5 mg/m³ (MCAA measured) (<0.26, <0.26, <0.26, <0.26, <0.26, <0.26, <0.26, <0.26, <0.26, <0.26, 0.21, <0.13, <0.13, <0.13, <0.13, <0.13, <0.13 ppm)	8 persons for 3 h

Abbreviations: SMCA; sodium monochloroacetate; MCAA, monochloroacetic acid.
Source: Adapted from Clariant GmbH, upublished material, 2000.

2.3. Reproductive and Developmental Toxicity

No studies documenting developmental or reproductive effects of MCAA in humans were identified (IUCLID 1996; MEDLINE and TOXLINE search, November 2003).

2.4. Genotoxicity

No studies documenting genotoxic effects of MCAA in humans were identified (IUCLID 1996; Greim 1998; MEDLINE and TOXLINE search, November 2003).

2.5. Carcinogenicity

No studies documenting carcinogenic effects of MCAA in humans were identified (IUCLID 1996; Greim 1998; MEDLINE and TOXLINE search, November 2003).

2.6. Summary

No studies are available on severe toxic effects in humans after inhalation exposure to MCAA. An inadequately described study reported an irritation threshold of 1.48 ppm (Maksimov and Dubinina 1974; Rodionova and Ivanov 1979); no respiratory tract irritation, effects on lung-function parameters or irritation of skin and mucous membranes were reported for more than 33 workers potentially exposed to MCAA concentrations at less than 0.13 ppm for 3 h and at 0.31 ppm for 7 h (Clariant GmbH, unpublished material, 2000). Mortality of a child was reported after oral uptake of 5-6 mL of an 80% MCAA solution (Feldhaus et al. 1993; Rogers 1995). Several lethal accidents were reported in which workers were dermally exposed to hot liquid MCAA or aqueous MCAA solutions (BUA 1994; IUCLID 1996; ECETOC 1999).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Several studies are available that report oral lethal doses of MCAA in different animal species. The oral lethality data are summarized in Table 3-4. Only one study was found that reported lethal effects after inhalation exposure.

3.1.1. Nonhuman Primates

In a metabolic study, Dow Chemical Co. (1976) administered MCAA intravenously to one male rhesus monkey. The animal was given 75 mg/kg on day 1 and 200 mg/kg on day 2. It died 2 h after the second dose. No signs of toxicity other than vomiting were reported; the cause of death remained undetermined. (Note: The study would be ethically unacceptable today.)

3.1.2. Rats

Maksimov and Dubinina (1974) observed no deaths in albino rats exposed to MCAA vapor at 5 mg/m³ (1.3 ppm). (The authors stated that this was the maximum achievable vapor concentration at 20°C.) When MCAA was heated to 95°C and rats were exposed to the condensed aerosol, the authors reported an LC_{50} of 180 (146-221) mg/m³ (46.8 ppm) for 4 h (exposure duration taken from Izmerov et al. 1982). The experimental details were not described by the authors.

Hoechst AG (1979a) administered 1% (weight/volume[w/v]) solutions of MCAA in water to groups of 10 female Wistar rats that were deprived of food for 16 h before and 2 h after gavage. The post-exposure observation period was

TABLE 3-4 Summary of Acute Oral Lethal Doses in Laboratory Animals

Species	Dose (mg/kg)	Study Type/Size	Type of MCAA solution	Signs and Symptoms	Reference
Cattle	100	1 animal	No details reported	Anorexia, ruminal atony, diarrhea, fibrillar muscle twitchings, survived	Dalgaard-Mikkelsen and Rasmussen 1961
	150	1 animal		Colic, diarrhea, generalized muscle twitching, dyspnea, death after 9 h	
Rabbit	90	LD_{50} (no details reported)	Neutralized solution	Apathy	Woodard et al. 1941
Guinea pig	79.8	LD_{50} (10 animals/group)	Neutralized solution	Apathy	Woodard et al. 1941
Rat	102	LD_{50} (4 rats/group)	Non-neutralized solution in water	Central nervous system effects, death after 1-4 h	Berardi 1986
Rat	90.4	LD_{50} (10 rats/group)	1% solution in water	Restlessness, crouching, balance disturbance, prone position, passiveness, drowsiness, incomplete eyelid closure, discharge from the eyes and dyspnea	Hoechst AG 1979a
Rat	76.2	LD_{50} (5-20 rats/group)	Neutralized solution	Apathy	Woodard et al. 1941
Rat	55	LD_{50} (no details reported)	10% non-neutralized solution in water	Not reported	Maksimov and Dubinina 1974
	580	LD_{50} (no details reported)	10% neutralized solution		
Mouse	260	LD_{50} (8-10 mice/group)	Non-neutralized solution	Immobility, ataxia, slight tremors, labored respiration, death after 3-6 h	Berardi and Snyder1983
Mouse	255	LD_{50} (10 mice/group)	Neutralized solution	Apathy	Woodard et al. 1941

Mouse	165	LD_{50} (no details reported)	No details reported	Respiratory paralysis		Morrison and Leake 1941
Goose	50	2 animals	No details reported	No symptoms		Christiansen and Dalgaard-Mikkelsen 1961
	75	Same animals, 2 wk later		Incoordination, seizures, death after 4-6 h		

14 days. Mortality was 0 of 10 animals at a dose of 40 g/kg, 2 of 10 at 63 mg/kg, 5 of 10 at 100 mg/kg and 10 of 10 at 160 mg/kg. Death occurred between 128 min and 24 h after gavage. Symptoms before death included restlessness, crouching, balance disturbance, prone position, passiveness, drowsiness, incomplete eyelid closure, discharge from the eyes, and dyspnea. Gross pathologic examination revealed brownish-red livers with prominent lobular structuring and light-red to pink spotted lungs. In surviving animals, the same symptoms occurred to a lesser extent but were not observed longer than 48 h after exposure. Using Probit analysis, an oral LD_{50} of 90.4 mg/kg (95% CI [95% confidence interval] 73.6-112 mg/kg) was calculated by the study authors.

Using subcutaneous injection of a 50% solution of MCAA in saline, an LD_{50} of 97.4 (89.9-105.5) mg/kg was reported for Wistar rats (10 animals/group) (Hoechst AG 1979d). Dermal LD_{50}s were 305 (242-384) mg/kg for a 40% non-neutralized MCAA solution in water (Hoechst AG 1979d) and more than 2,000 mg/kg for sodium monochloroacetate in saline (Hoechst AG 1988c).

Berardi (1986) reported an oral LD_{50} of 102 mg/kg (95% CI 51-204 mg/kg) using groups of four Sprague-Dawley rats and gavage of a non-neutralized MCAA solution in water.

Woodard et al. (1941) reported an oral LD_{50} of 76.2 mg/kg (95% CI 70.7-82.2 mg/kg) using a neutralized MCAA solution and groups of 5 to 20 rats (strain not specified).

Maksimov and Dubinina (1974) investigated oral LD_{50} values in albino rats administered a 10% of MCAA solution. A value of 55 mg/kg was found when the acid solution was used, and a value of 580 mg/kg was determined for the neutralized solution. No experimental details were provided.

Using subcutaneous injection, Hayes et al. (1973) determined an LD_{50} in groups of 5-10 male Sprague-Dawley rats of 108 mg/kg (95% CI 88-133 mg/kg).

Using intravenous injection of a 20% MCAA solution in phosphate buffer, pH 7, Elf Atochem (1995) reported an LD_{50} of 75 (53-117) mg/kg in Sprague-Dawley rats. Clinical signs were hypokinesia, sedation, dyspnea, lateral decubitus, suffocation, coma, and death (after 1-3 h).

Mitroka (1989) reported the following 24-h mortality of Sprague-Dawley rats injected neutralized MCAA solution intravenously with 20, 40, 80 and 100 mg/kg in zero of six, one of six, four of 5, and six of six animals, respectively. Intoxication was characterized by a fixed posture, slight tremors, hyperreactivity to stimuli and a dark ruddy eye color. Death usually occurred 1-4 h after exposure. Death was usually preceded by slow, labored respiration, wheezing, gasping for breath, and unconsciousness. No consistent differences were observed in the gross appearance of organs of unexposed and exposed animals upon necropsy.

Using MCAA administration via implanted minipumps, Rozman (2000) found that the relationship between dose and time to MCAA-induced coma in male Sprague-Dawley rats followed the $C \times t = k$ relationship. The time-dose combinations were between about 125 mg/kg for about 60 min to about 50

mg/kg for about 120 min. The details of these experiments are not provided in the publication and have not been published until now.

3.1.3. Mice

Berardi (1986) reported an oral LD_{50} of 260 mg/kg (95% CI 214-316 mg/kg) using groups of 8-10 Swiss-Webster mice and gavage of a non-neutralized MCAA solution in water. Reported symptoms included immobility, head bobbing, ataxia, hyperreactivity to stimuli, slight tremors, clasping of front paws, and labored respiration. Death occurred 3-6 h after MCAA administration. Using dermal application of molten (65°C) MCAA for 2 min followed by rinsing with water, an LD_{50} of 490 (428-562) mg/kg was found. After subcutaneous injection of MCAA into Swiss-Webster mice (eight animals/group), reported LD_{50} values were 150 (129-175) mg/kg for non-neutralized MCAA solution in water and 130 (105-160) mg/kg for neutralized MCAA solution.

Woodard et al (1941) found an oral LD_{50} of 255 mg/kg (95% CI 196-334 mg/kg) using a neutralized MCAA solution and groups of 10 mice (strain not specified). Morrison and Leake (1941) published an oral LD_{50} of 165 mg/kg for MCAA in mice.

Mitroka (1989) reported the following 24-h mortality of Swiss-Webster mice injected neutralized MCAA solution intravenously with 100, 125, 160, and 200 mg/kg in zero of seven, one of four, five of seven, and four of four animals, respectively. Signs of intoxication appeared within 2 h of expsoure. Intoxication was characterized by a fixed posture, slight tremors, hyperreactivity to stimuli, and a dark ruddy eye color. Death usually occurred 3-12 h after exposure. Death was usually preceded by slow, labored respiration, wheezing, gasping for breath, and unconsciousness. No consistent differences were observed in the gross appearance of organs of unexposed and exposed animals upon necropsy.

3.1.4. Other Species

Woodard et al (1941) reported an oral LD_{50} of 79.8 mg/kg (95% CI 71.8-88.6 mg/kg) for guinea pigs (10 animals/group) and about 90 mg/kg for rabbits (1-10 animals/group) using a neutralized MCAA solution (respective strains not specified).

Dalgaard-Mikkelsen and Rasmussen (1961) evaluated oral toxicity in cattle. Doses of 0, 50, 100, and 150 mg/kg were given to one animal each by stomach tube. A dose of 50 mg/kg resulted in inappetence of 24 h duration. A dose of 100 mg/kg produced severe symptoms of intoxication with anorexia, ruminal atony, diarrhea, and fibrillar muscle twitchings. The animal recovered within 2 weeks. Administration of 150 mg/kg caused colic, diarrhea, generalized fibrillar muscle twitching, and dyspnea. The animal died 9 h after dosing.

Christiansen and Dalgaard-Mikkelsen (1961) gave doses of 50 mg/kg by oral gavage to two geese. No symptoms were observed. The same animals were

given 75 mg/kg 2 weeks later. After 3 h, incoordination and seizures were observed; the animals died after 4 to 6 h.

3.2. Nonlethal Toxicity

A small number of studies describe nonlethal effects after inhalation exposure. Signs of irritation were observed after inhalation and after oral exposure of animals to MCAA.

3.2.1. Rats

Dow Chemical Co. (1987) exposed a group of six female and six male Fischer 344 rats to MCAA vapor by inhalation for 1 h. The test material was vaporized into a stainless steel and glass 112-L Rochester-type inhalation chamber. The targeted concentration of MCAA was 1,000 ppm. The nominal chamber concentration was calculated based on the amount of test material used and the total air passed through the chamber during each exposure period. The nominal concentration was 964 ppm. The analytic concentration in the chamber was determined by taking an air sample from the chamber by pulling air through a glass tube containing silica gel during exposure and subjecting this sample to ion chromatography. The actual analytic concentration of MCAA vapor during exposure was calculated to be 66 ppm. It was stated that an analytic concentration of 1,000 ppm was not feasible due to "substantial recrystallization of MCAA in the presence of room temperature (23°C) air."

During all exposures, all rats (12/12) showed eye squint and slight lethargy. Although the expression "slight lethargy" is used in the text, "lethargy" is used in the corresponding table. "The observations [prior to and after exposure] included an evaluation of fur, eyes, mucous membranes, and respiration. Behavior pattern and nervous system activity was also assessed by specific observation for tremors, convulsions, salivation, lacrimation, and diarrhea, as well as slight lethargy and other signs of altered central nervous system function." During the 2-week observation period, MCAA-exposed rats lost weight initially (day 2) and regained weight during the remainder period (days 4-15). Gross pathologic examination of rats revealed no exposure-related effects.

Hercules (1969a) exposed groups of three rats, mice and guinea pigs by inhalation to MCAA-saturated vapor generated at 75°C (nominal concentration 27,000 mg/m^3; 7,020 ppm). No deaths occurred after exposure for 3, 5, or 10 min, although nasal discharge and lung hyperemia were observed. In a similar study involving exposure of groups of two rats, mice and guinea pigs to saturated MCAA vapor (nominal concentration 31,000 mg/m^3; 8,060 ppm) mild lacrimation, nasal discharge, and dyspnea, but no mortality, was found (Hercules 1969b). No experimental details were reported. The relevance of these studies is compromised by the fact that no information about the analytic concentrations was provided.

Maksimov and Dubinina (1974) reported an irritation threshold in rats of 23.7 mg/m³ (6.16 ppm) based on changes in the respiration rate. The exposure duration and other experimental details were not stated by the authors.

Maksimov and Dubinina (1974) exposed 75 rats and 18 guinea pigs to MCAA at 5.8 ± 3.0 and 20.8 ± 1.0 mg/m³ (1.5 ± 0.8 and 5.4 ± 0.3 ppm) over a period of 4 months (probably continuous exposure; exact exposure conditions were not stated by the authors). In the high-dose group, the following observations were made: a reduction in body weights of guinea pigs and rats during weeks 2 and 10; a reduction in oxygen uptake on days 3 and 15; a lowering of the rectal body temperature on days 2 and 15; and a reduction in the chloride concentration in urine at the end of month 2 and hemoglobinemia during month 4. The pathomorphologic investigation revealed inflammatory changes in the respiratory organs and tracheal catarrh, bronchitis, and bronchopneumonia. In the low-dose group, only very slight effects were found: a lower oxygen uptake on day 3; a lower rectal temperature on days 7 and 14, and a reduction in the chloride concentration of the urine in month 4. Morphologic examinations revealed only slight effects on the respiratory organs—effects that were not considered significant compared with the control group by the authors. The experimental details were not described by the authors.

NTP (1992) exposed groups of five male and five female Fischer 344 rats to MCAA in water by gavage at 0, 7.5, 15, 30, 60, and 120 mg/kg once daily for a total of 12-dose days over a 16-day period. One male rat of the high-dose group died on the third day of dosing (symptoms observed within 4 h after dosing were lacrimation, prostration, bradypnea, decreased limb tone, ataxia, and an impaired gasping reflex); no other deaths occurred. Lacrimation was also observed in males receiving 60 or 120 mg/kg and females receiving 15 mg/kg or higher. No gross or histologic lesions were observed.

Bryant et al. (1992), also described in NTP (1992), exposed groups of 20 male and 20 female Fischer 344 rats to oral doses of MCAA at 0, 30, 60, 90, 120, or 150 mg/kg in water by gavage once daily, 5 d/wk for up to 13 weeks. All rats receiving 120 or 150 mg/kg and all but one receiving 90 mg/kg died before the end of the exposure period. Other deaths included two male rats and one female rat receiving 60 mg/kg and one female rat receiving 30 mg/kg. A complete pathologic and histopathologic examination on all early deaths and all surviving animals at the end of the exposure period was done. The final mean body weights of rats surviving to the end of the study were similar to those of the controls. Relative heart weights of male and female rats in the 60-mg/kg groups as well as those of female rats in the 30-mg/kg group were significantly lower than controls. Relative weights of liver and kidney of male and female rats at 60 mg/kg were significantly greater than those of the controls. Blood urea nitrogen was increased in a dose-related trend in males at 90-150 mg/kg and in females at 60-150 mg/kg. Male rats at 150 mg/kg and females at 60, 120, and 150 mg/kg had a significant increase in serum alanine aminotransferase activity compared with controls. Chemical-related degenerative and inflammatory changes (including cardiomyopathy) were observed in the hearts of male and female rats receiv-

ing 60, 90, 120, or 150 mg/kg. In these dose groups, acute or subacute cardiomyopathy was observed in the rats that died before the end of the study and was considered to be the cause of death in these animals. No cardiomyopathy or other histologic effects were observed at a dose of 30 mg/kg.

Bhat et al. (1991) gave a neutralized solution of MCAA at 1.9 mmol/L of drinking water to male Sprague-Dawley rats (number not stated) for 90 days. On day 90, body weights were not significantly reduced compared with controls (426.8 ± 22.1 g vs. 448.2 ± 22.8 g); liver weights were reduced (13.25 ± 0.64 g vs. 14.68 ± 0.78 g). Minimal to mild morphologic liver alterations were observed (enlarged portal veins, increased numbers of bile ducts, areas of edema, and inflammatory cells surrounding the portal veins). Increased perivascular inflammation compared with controls was observed in the lungs. The dose tested was equivalent to about 20 mg/kg/d (BIBRA 1997).

Daniel et al. (1991) administered the sodium salt of MCAA by oral gavage for a period of 90 consecutive days to Sprague-Dawley rats. Groups of 10 male and 10 female rats received daily doses of 0, 15, 30, 60 or 120 mg/kg. At 120 mg/kg, 30% of females and 80% of the males died, 7 of the 11 deaths occurred within the first 3 days of treatment, while the other 4 deaths occurred between days 14 and 90. In the early deaths, hemorrhagic and congested lungs were observed but considered a postmortem change. In the later deaths, liver lesions were found. One male in each of the 60- and 15-mg/kg groups died. No apparent dose-response-related differences between treated and control groups in body or organ weights were found with the exception of significant increased liver and kidney weights in females at 120 mg/kg. Relative liver weights were increased in both females and males at 60 and 120 mg/kg. Histopathologic examination revealed a significant increase in chronic renal nephropathy and increased splenic pigmentation at 60 mg/kg/d (120-mg/kg/d group excluded due to mortality). In female but not in male rats, significantly increased numbers of white blood cells were found at 30, 60, and 90 mg/kg, and sporadic but not dose-related changes were found in subpopulations (lymphocytes and monocytes) at doses of 15 mg/kg or higher. Increased blood urea nitrogen levels in females at 120 mg/kg and in males at 15 and 30 mg/kg, but not 60 and 120 mg/kg, as well as increased creatinine levels in females at 15 and 30 mg/kg, but not at 60 and 120 mg/kg, and in males at all dose levels were found.

3.2.2. Mice

NTP (1992) exposed groups of five male and five female $B6C3F_1$ mice by gavage to MCAA in water once daily using doses of 0, 15, 30, 60, 120 and 240 mg/kg for males and 0, 30, 60, 120, 240, and 480 mg/kg for females for a total of 12-dose days over a 16-day period. All mice receiving 240 mg/kg or higher died within 2 days; no other deaths occurred except for one male in the 15-mg/kg group. Clinical findings in animals that died included lacrimation, ataxia, hypoactivity, bradypnea, bradycardia, hypothermia, prostration, piloerection,

decreased limb tone, and impaired gasping. Lacrimation was also observed in females receiving 120 mg/kg. No changes in organ weights and gross or histologic lesions were observed.

Bryant et al. (1992) (also described in NTP 1992) exposed groups of 20 male and 20 female B6C3F_1 mice to oral doses of MCAA in water at 0, 25, 50, 100, 150, or 200 mg/kg by gavage once daily, 5 d/wk for up to 13 weeks. All mice receiving 200 mg/kg died or were killed when moribund before the end of the exposure period (all but two died within the first week). Two males given 200 mg/kg and one female given 100 mg/kg died from gavage trauma; two male controls died from unknown causes. With the exception of females receiving 200 mg/kg, the mean body weights of dosed mice were similar to those of controls. Cholinesterase levels were significantly decreased in female mice receiving 150 or 200 mg/kg at weeks 8 and 13. No chemical related lesions were observed in mice of either sex. Hepatocellular vacuolization was seen in mice in the 200-mg/kg group that died during the study. No effects were observed at a dose of 100 mg/kg.

3.3. Reproductive and Developmental Toxicity

No studies evaluating developmental or reproductive toxic effects after inhalation exposure were located in the literature (MEDLINE and TOXLINE search, November 2003).

Smith et al. (1990) exposed pregnant Long-Evans rats to 0, 17, 35, 70, and 140 mg/kg (daily gavage) during gestational days 6 to 15. The body-weight increase was significantly reduced in the highest exposure group. No effects on the number of resorptions and birth weight were found. The rate of visceral malformations (especially of the heart and cardiovascular system) was between 1.2% in controls and 6.4% in the highest dose group, but no dose-dependency was observed. No skeletal malformations were found. This study has only been published as an abstract, and no details were reported.

Johnson et al. (1998) exposed pregnant Sprague-Dawley rats during gestational days 1-22 to MCAA at 1,570 ppm in drinking water as well as to other halogenated hydrocarbons. The authors calculated the dose for exposure to MCAA as 33 mg/kg/d. No signs of maternal toxicity were observed. No effects on the number of mean implantation sites and resorption sites were found. MCAA produced no cardiac abnormalities. Of the substances tested, only trichloroacetic acid caused a significant increase in the number of cardiac abnormalities.

Bhunya and Das (1987) injected single doses of MCAA intraperitoneally at 12.5, 25, and 50 mg/kg into groups of three male Swiss mice. After 35 days, an increased number of malformed sperm was found in the two highest dose groups.

3.4. Genotoxicity

In genetic toxicity testing in the NTP (1992) study, MCAA was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA1537, and TA98 (with and without metabolic activation using rat liver S9 mix). It induced trifluorothymidine resistance in L5178Y mouse lymphoma cells in the absence of S9 mix and induced sister chromatid exchanges in Chinese hamster ovary cells in the absence but not in the presence of S9 mix. MCAA did not induce chromosomal aberrations in Chinese hamster ovary cells (with and without activation). MCAA administered in feed was negative for the induction of sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster*; results were equivocal when MCAA was administered by injection.

Several other reports have been published on negative results in assays for mutations in bacteria and positive as well as negative results in tests for mutations and sister chromatid exchanges in eucaryotic cells in vitro (see BG Chemie 1993; IUCLID 1996; ECETOC 1999).

Bhunya and Das (1987) injected MCAA intraperitoneally at 12.5, 25, and 50 mg/kg one time or at 10 mg/kg five times into male and female Swiss mice. A significantly increased rate of chromosomal aberrations was observed for all doses after 6-120 h in the bone marrow. No effect was seen 24 h after oral gavage or subcutaneous injection of 50 mg/kg.

3.5. Carcinogenicity

In a NTP carcinogenicity study (NTP 1992) male and female Fischer 344 rats were given 0, 15, or 30 mg/kg and male and female $B6C3F_1$ mice were given 0, 50, and 100 mg/kg by gavage of a MCAA solution in water for 5 d/wk for 2 years. In both species there was no evidence of carcinogenic activity of MCAA. In mice, but not in rats, a dose-dependent increase in inflammation of the nasal mucosa and metaplasia of the olfactory epithelium was found, as well as squamous metaplasia of the forestomach.

DeAngelo et al. (1997) performed a 2-year carcinogenicity study in Fischer 344 rats. Animals were given MCAA at 50, 500, and 2,000 mg/L in drinking water. Due to severe inhibition of body-weight gain, the high dose was reduced to 1,500 mg/L at 8 weeks and further to 1,000 mg/L at 24 weeks. The authors calculated time-weighted mean daily doses of MCAA at 3.5, 26.1, and 59.9 mg/kg/d. They found no significant differences in animal survival between the control and exposed groups. No increased incidence of neoplastic lesions was found.

3.6. Summary

The only animal study reporting lethal effects after inhalation of MCAA

was an inadequately described study in which an LC_{50} of 46.8 ppm for 4 h was reported for rats (Maksimov and Dubinina 1974). Several studies report lethal effects after oral exposure. LD_{50} data presented in Table 3-4 are mostly from 50 to 200 mg/kg for rats, mice, and guinea pigs. In addition, lethal doses in other species were 200 mg/kg in a rhesus monkey (Dow Chemical Co. 1976), 150 mg/kg for a cow (Dalgaard-Mikkelsen and Rasmussen 1961), and 75 mg/kg for geese (Christiansen and Dalgaard-Mikkelsen 1961).

In a single inhalation experiment on rats, eye squint and slight lethargy were observed during MCAA exposure at 66 ppm for 1 h (Dow Chemical Co. 1987). In an inadequately reported study, an irritation threshold in rats of 6.16 ppm and a NOEL for histologic changes in the respiratory tract in rats and guinea pigs of 1.5 ppm after 4 months have been reported (Maksimov and Dubinina 1974).

After repeated oral gavage for 2 weeks, lacrimation was observed in male rats receiving MCAA at 60 or 120 mg/kg and in female rats receiving 15 mg/kg or higher (NTP 1992). In experiments performed in parallel, lacrimation was also observed in female mice receiving 120 mg/kg (NTP 1992). In subchronic studies using oral exposure by gavage or drinking water, a dose of 30 mg/kg in rats and 100 mg/kg in mice had no or only minor effects (Bhat et al. 1991; Daniel et al. 1991; Bryant et al. 1992; NTP 1992).

The study by Smith et al. (1990) suggests that high doses of MCAA (close to the LD_{50} in other rat strains) can cause maternal toxicity and malformations in the offspring. The effect on fertility upon intraperitoneal injection (Bhunya and Das 1987) requires further study using other exposure routes. There is no evidence of genotoxic potential in bacterial mutagenicity studies, in vitro chromosomal aberration tests, and in vitro and in vivo primary DNA damage assays. Gene mutation tests in mammalian cells gave contradictory results, and in one study, increased chromosomal aberrations were found after intraperitoneal injection in mice. No carcinogenic activity of MCAA was found in mice and rats after oral administration of MCAA by gavage or drinking water.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No quantitative absorption rate data are available for inhalation exposure. An oral absorption rate of 82% (^{14}C recovery in urine was 70%) was found in a rat that was given 1-^{14}C-labeled MCAA (Dow Chemical Co. 1976). A rate of 90% in 24 h for the cumulative excretion of MCAA in urine was reported in Sprague-Dawley rats after an oral dose of 1-^{14}C-labeled MCAA at 9.4 mg/kg (Kaphalia et al. 1992). Berardi (1986) reported values for cumulative excretion in urine of 51% in 24 h and 52.5% in 72 h in Sprague-Dawley rats and 32.0-59.3% in 24 h and 33.7-60.8% in 72 h in Swiss-Webster mice. Lethal effects in

humans after dermal contact with liquid MCAA indicate a considerable dermal absorption.

Yllner (1971) injected doses of 0.07, 0.09, and 0.1 g/kg 1-^{14}C-labeled MCAA subcutaneously into mice and measured radioactivity after 24, 48, and 72 h in urine, feces, and expired air. Within 72 h, 82-88% of the radioactivity was eliminated in urine, 8% was eliminated via the lungs, and 0.2-0.3% was eliminated in feces, and 2-3% remained in the body. The main metabolites found in urine were *S*-carboxymethyl-L-cysteine (33-43% in free form and 1-6% as glutathione conjugate) and thiodiacetic acid (33-42%) as well as MCAA (6-22%), glycolic acid (3-5%), and oxalic acid (0.1-0.2%). The authors suggested two metabolic pathways: (1) conjugation with glutathione resulting in formation of *S*-carboxymethyl glutathione, which can be further metabolized to *S*-carboxymethyl-L-cysteine and further to thiodiacetic acid; and (2) enzymatic hydrolysis of the chlorine-carbon bond and formation of glycolic acid that can be degraded completely to carbon dioxide.

In the urine of rats, thiodiglycolic acid, but not *S*-carboxymethyl-L-cysteine, was found. However, according to the study, *S*-carboxymethyl-L-cysteine might have been present in bile but could not be identified unequivocally (Dow Chemical Co. 1976).

Hayes et al. (1972, 1973) injected rats with 1-^{14}C-labeled MCAA subcutaneously at 162 mg/kg. After 2 h, higher radioactivity was found in kidneys and liver than in plasma, and heart and brain had similar levels to plasma. A similar distribution was found after administration of 53 mg/kg. A biphasic elimination curve was observed with half-life times of 90 min and 17 h.

The fact that rodents can be exposed for long periods of time (90 days or 2 years) (Daniel et al. 1991; Bryant et al. 1992; NTP 1992; DeAngelo et al. 1997) at daily doses close to the oral LD_{50} (see Table 3-4) argues for rapid clearance of MCAA after each exposure.

4.2. Mechanism of Toxicity

The biochemical basis of systemic MCAA toxicity is the inhibition of single enzymes of the glycolytic and tricarboxylic acid metabolic pathways. The blockage of these metabolic processes results in inhibition of energy metabolism (ATP generation) and in accumulation of lactic acid in the glycolytic pathway, causing metabolic acidosis.

Prolonged incubation of isolated rat heart mitochondria with MCAA inhibits both pyruvate dehydrogenase and α-ketoglutarate dehydrogenase (van Hinsbergh and Vermeer 1994) via an indirect inhibition through formation of oxalate from MCAA (Mitroka 1989) or a direct inhibition through slow alkylation or sulfhydryl groups (van Hinsbergh and Vermeer 1994). Since the inhibition of the enzymes of the glycolytic (pyruvate dehydrogenase) and tricarboxylic acid (α-ketoglutarate dehydrogenase) metabolic pathways has a major impact on cellular energy production, the cell would then revert to anaerobic glycolysis,

which results in lactate accumulation (van Hinsbergh and Vermeer 1994). In vitro, MCAA inhibited oxidation of radiolabeled acetate to carbon dioxide by rat liver homogenate (Hayes et al. 1973), indicating an inhibitory effect on the tricarboxylic acid cycle. Blockade of aerobic energy metabolism can be expected to especially damage organs and tissue with a high-energy demand, such as heart, CNS, and skeletal muscles (Kulling et al. 1992).

It has been suggested that in analogy to monofluoroacetic acid, MCAA could also inhibit the tricarboxylic-acid-cycle enzyme aconitase (IUCLID 1996). Experimental evidence suggests organ-specific differences with respect to aconitase inhibition by MCAA and by monofluoroacetic acid: about 1.5-2 h after oral administration of MCAA at 24, 48, or 96 mg/kg to Fischer 344 rats, an inhibition of aconitase was detected in the heart (54%, 55%, and 46% inhibition, respectively) but not in the liver (0% inhibition at all doses), while monofluoroacetic acid inhibited aconitase in both organs (4.0%, 10.5%, and 21.0% inhibition, respectively; same inhibition in both organs) (Bryant et al. 1992; NTP 1992). These findings suggest that different isoenzymes with different susceptibility to the inhibitory effect of MCAA are expressed in the two organs. In the experiments, no dose-response relationship was revealed: a 33-55% inhibition was found after doses between 4 and 150 mg/kg.

After intravenous injection of MCAA at 40 or 80 mg/kg (neutralized solution in phosphate buffer) in rats, blood and cerebrospinal fluid lactate concentrations increased progressively with time until death (1-2 h after dosing) (Mitroka 1989). In the blood, a significant increase in lactate concentrations was found for the 80-mg/kg dose starting at 60 min, and a very slight increase was seen for the 40-mg/kg dose. In the cerebrospinal fluid, significant increases were found for the 40-mg/kg dose at 120 min and for the 80-mg/kg dose at 60 min (Mitroka 1989). The accumulation of lactate in the brain can contribute to the lethal effects of MCAA, especially since the removal of lactate from the brain via the blood-brain barrier is slow. The damage of the blood-brain barrier by MCAA has also been shown by Berardi (1986) and Berardi et al. (1987): nearly lethal doses administered orally to mice (257 and 380 mg/kg) led to an increased entry of radiolabeled dopamine and inulin into all brain regions; in addition, red blood cells were found in the brain parenchyma. The associated neurologic dysfunction was characterized by front paw rigidity. At doses that caused no or little mortality (80, 118, and 174 mg/kg) the concentration of radioactive inulin did not differ from controls.

Unlike monofluoroacetate and like monoiodoacetic acid, MCAA can bind to sulfhydryl groups (Yllner 1971; Hayes et al. 1973; van Hinsbergh and Vermeer 1994). After oral administration, MCAA was shown to bind to sulfhydryl groups in the kidney and liver of rats. Direct inhibition of sulfhydryl groups in the kidney may account for the anuria present in animals receiving toxic levels of MCAA, which could contribute to enzyme inhibition and renal dysfunction (Hayes et al. 1973). Renal insufficiency was also found in humans after oral intoxication (Kulling et al. 1992), and renal nephropathy was found after subchronic oral exposure in rats (Daniel et al. 1991).

MCAA causes severe local effects on skin and eyes: after occlusive application of MCAA paste at 100 and 500 mg (solution in 0.05 mL 0.9% sodium chloride) to the skin of rabbits, corrosion (at both doses) and mortality (all animals died at the higher dose) were observed (Hoechst AG 1979e). After occlusive application for 24 h of a 10% solution to the intact rabbit skin, there was marked hyperemia and edema (Rodionova and Ivanov 1979). Sodium monochloroacetate did not produce any signs of irritation when applied for 4 h to the skin of rabbits (Hoechst AG 1988d). MCAA was extremely irritant to the rabbit eye (instillation of 100 mg MCAA as paste into conjunctival sac; Hoechst AG 1979e), and sodium monochloroacetate induced moderate irritation (instillation of 100 mg sodium monochloroacetate into conjunctival sac; Hoechst AG 1988d). From this, it can be expected that inhalation of MCAA vapor or MCAA aerosol can cause local irritation and tissue damage in the respiratory tract either by local decrease of the pH or by local enzyme inhibition.

4.3. Structure-Activity Relationships

4.3.1. Studies Using Alkyl Esters of MCAA

Hoechst AG (1988a) determined the acute inhalation toxicity of chloroacetic acid methyl ester. Groups of five female and five female Wistar rats were exposed whole body for 4 h in an exposure chamber at 90, 210, 315, and 385 ppm. The concentration in the exposure chamber was measured by infrared spectroscopy using a Miran analyzer and by gas chromatography. The post-exposure observation period was 14 days. Mortality rates were 0 of 10 animals at 90 and 210 ppm, 7 of 10 at 315 ppm, and 10 of 10 at 385 ppm. Death occurred between 270 min and 6 days after exposure.

Torkelson et al. (1971) exposed groups of four to five female rats in an exposure chamber to different concentrations of chloroacetic acid methyl ester for different exposure times. The following mortality was observed for different exposure periods: two of four animals at 1,000 ppm for 1 h; four of five at 2,000 ppm and zero of four at 500 ppm for 2 h; five of five at 2,000 ppm, five of five at 500 ppm, and zero of four at 250 ppm for 4 h; and zero of four at 100 ppm for 7 h. The authors noted severe irritation at 250-1,000 ppm and slight irritation at 100 ppm. In rabbits, 7- and 4-h exposures at 100 ppm caused delayed conjunctival and corneal irritation; 50 ppm did not cause eye irritation.

Hoechst AG (1988b) exposed groups of 10 female and 10 male Wistar rats repeatedly to chloroacetic acid methyl ester at 0, 10, 33, and 100 ppm (6 h/d, 5 d/w, total of 20 exposures). Mean concentrations measured in the exposure chamber by a Miran infrared analyzer were 10.4, 32.3, and 100.1 ppm, respectively. Gross morphologic and histologic examinations were performed in half of the animals after the last exposure and in the other half after a 14-day recovery period. At 10 ppm, narrowed palpebral fissures were observed only during the first exposure, which was interpreted as a sign of irritation. Additional signs

in the 33-ppm group were sneezing and increased hair grooming, which were observed only during individual exposures. Additional signs in the 100-ppm group were incoordination, retracted flanks, irregular respiration, passiveness, and standing hair, some of which persisted until the next morning and into the recovery period. Food-consumption decrease, body-weight increase, and significantly increased relative lung weights were found in the 100-ppm group. No histopathologic alterations or differences in hematologic and clinical chemistry parameters were observed.

Hoechst AG (1979b) determined the acute oral toxicity of chloroacetic acid ethyl ester administered to groups of 10 female Wistar rats by gavage of a 5% (w/v) solution in sesame oil. The post-exposure observation period was 14 days. Mortality was 0 of 10 animals at a dose of 80 mg/kg, 2 of 10 at 125 mg/kg, 5 of 10 at 200 mg/kg, and 10 of 10 at 315 mg/kg. Death occurred between 136 min and 24 h after gavage. Symptoms before death included crouching, balance disturbance, prone position, and passiveness. No abnormal findings were observed in gross pathologic examinations. Using Probit analysis, an LD_{50} of 180 (151-215) mg/kg was calculated by the authors.

Using the same study design, a 0.5% (w/v) solution of chloroacetic acid methyl ester in sesame oil was used (Hoechst AG, 1979c). Mortality was 0 of 10 animals at doses of 50 and 80 mg/kg, 4 of 10 at 100 mg/kg, 8 of 10 at 125 mg/kg, and 10 of 10 at 200 and 315 mg/kg. Using Probit analysis, an LD_{50} of 107 (95% CI 97.2-121) mg/kg was calculated by the authors.

4.3.2. Studies with Other Monohaloacetic Acids

Hayes et al. (1973) found that the subcutaneous LD_{50} for three haloacetic acids varied considerably in rats and that toxicity is probably caused by differing mechanisms. LD_{50} (95% CI) values were 5 (4-6) mg/kg for monofluoroacetic acid, 60 (54-67) mg/kg for monoiodoacetic acid, and 108 (88-133) mg/kg for MCAA. The mean time to death was 130 (112-151) min for MCAA, 310 (292-360) min for monofluoroacetic acid, and 480 (343-672) min for monoiodoacetic acid. MCAA and monoiodoacetic acid, but not monofluoroacetic acid, significantly reduced the total sulfhydryl concentration in rat liver at an LD_{90} dose after 5% of the time to death. In vitro, MCAA did not alkylate sulfhydryl groups of cysteine.

In mice, Morrison and Leake (1941) found oral LD_{50} values of 63 mg/kg for monoiodoacetate, 100 mg/kg for monobromoacetate, and 165 mg/kg for MCAA.

4.3.3. Conclusions from Structure-Activity Relationships

Several studies evaluated the toxicity of MCAA esters on rats. Although the LD_{50} values for oral administration are comparable to the LD_{50} values for MCAA (see Table 3-4), lethal effects after inhalation exposure to MCAA esters

occurred at considerably higher concentrations. Although Maksimov and Dubinina (1974) reported a 4-h LC_{50} of 46.8 ppm for MCAA, a 4-h exposure at 210 ppm for chloroacetic methyl ester did not result in deaths, and at 315 ppm, 7 of 10 rats died (Hoechst AG 1988a). This difference suggests toxicokinetic and toxicodynamic differences between MCAA and its alkyl esters. Compared with MCAA, local effects of its esters are less likely, because (1) the esters are not acidic and thus do not cause local effects by lowering the tissue pH value, and (2) local effects due to glutathione binding or enzyme inhibition can be expected to be smaller because the esters have to get hydrolyzed enzymatically to free MCAA first. Although quantitative data for the hydrolysis are lacking, it is likely that due to its rapid distribution in the body, much of the deposited ester will enter systemic circulation before it is hydrolyzed, and thus the concentration of MCAA in respiratory tract tissue is likely to be much smaller during inhalation exposure to MCAA esters than during MCAA exposure. In summary, the inhalation studies using MCAA esters cannot be used as supportive evidence for MCAA data.

Oral lethality data for different monohaloacetic acids found a considerable difference in LD_{50} values. These findings and the probable differences in biochemical mechanism presented in section 4.2 argue for different toxicodynamic properties of the different monohaloacetic acids and do not support the use of data on other monohaloacetic acids as supportive evidence for MCAA data.

4.4. Other Relevant Information

4.4.1. Species Variability

Lethal effects have been suggested to be mediated by damage to the blood-brain barrier and by metabolic acidosis, which is especially due to lactate accumulation in the brain; that, in turn, results from inhibition of single enzymes of the glycolysis and tricarboxylic acid cycle (pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, and aconitase). Because these enzymes are evolutionarily highly conserved, a limited interspecies variability can be assumed. The available oral lethality data support this conclusion and indicate that the variability in LD_{50} values is small: LD_{50} values for different species (mean values of LD_{50} values given in Table 3-4) were 90 mg/kg for rabbits, 79.8 mg/kg for guinea pigs, 80.9 mg/kg for rats (mean of all LD_{50}s except the 580 mg/kg value), and 227 mg/kg for mice; moreover, one of the cattle survived an oral dose of 100 mg/kg, showing only moderate toxic effects (another died at 150 mg/kg) (Dalgaard-Mikkelsen and Rasmussen 1961), and a rhesus monkey survived intravenous injection of 75 mg/kg (and died after another dose of 200 mg/kg the next day) (Dow Chemical Co. 1976). Good data are available for two of these species only, namely, rats and mice, and the difference between these two species is also in line with what can be expected on the basis of standard

scaling using (body weight)$^{0.75}$. No data are available that would suggest a large species difference for local effects in the respiratory tract.

4.4.2. Intraspecies Variability

Lethal effects have been suggested to be mediated by damage of the blood-brain barrier and by metabolic acidosis, which is especially due to lactate accumulation in the brain; that, in turn, is secondary to inhibition of single enzymes of the glycolysis and tricarboxylic acid cycle (pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, and aconitase). Because these enzymes are housekeeping enzymes, which are required for energy metabolism and show a constant expression level, a limited intraspecies variability can be assumed. The available oral lethality data support this conclusion and indicate that the variability in LD_{50} values within individual species is small because the reported LD_{50} values for different species varied within each species by less than a factor of 2 (see Table 3-4). Some variation is indicated by the finding that repeated oral exposure of rats to 120 mg/kg/d led to death in 8 of 10 males but only in 3 of 10 females (Daniel et al. 1991). The contribution to death of local effects in the respiratory tract upon inhalation is unknown.

At lower concentrations that do not lead to systemic effects, MCAA is irritating to the eye and mucosal surfaces. The mechanism for this effect may involve both local lowering of the pH value and local metabolic blockage by enzyme inhibition. A limited interindividual variability can be assumed for this local effect because it involves direct effects on the tissue (acidity) or effects on highly conserved enzymes, which are expected not to differ considerably between individuals.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Clariant GmbH (unpublished material, 2000) found no respiratory tract irritation, effects on lung function parameters, or irritation of skin and mucous membranes in more than 33 workers potentially exposed to MCAA concentrations of less than 0.13 ppm for 3 h and 0.31 ppm for 7 h.

Maksimov and Dubinina (1974) and Rodionova and Ivanov (1979) reported an irritation threshold for humans of 5.7 mg/m³ (1.48 ppm). (For this study, an exposure time of 1 min was stated in Izmerov et al. 1982.) The experimental details were not stated by the authors and, therefore, evaluation of the studies is impossible.

Reported odor thresholds are 0.01 ppm (cited from unpublished correspondence from Dow Chemical Co. in AIHA [1993]) and 0.045 ppm (Oelert and Florian 1972). (In the latter study, it was unclear if the value was cited from the literature or measured by the authors.)

5.2. Animal Data Relevant to AEGL-1

Maksimov and Dubinina (1974) reported an irritation threshold in rats of 23.7 mg/m³ (6.16 ppm) based on changes in the respiration rate.

After exposure of rats and guinea pigs to MCAA at 5.8 and 20.8 mg/m³ (1.5 and 5.4 ppm) over a period of 4 months (probably continuous exposure; exact exposure conditions were not stated by the authors), slightly reduced body weights, effects on metabolism (reduced oxygen uptake and lower rectal body temperature) and kidney function (reduced chloride concentration in urine and hemoglobinemia), and inflammatory alterations of respiratory organs were found in the high-dose group. In the low-dose group, only very slight effects (lower oxygen uptake, lower rectal temperature, and lower urine chloride concentration) were found (Maksimov and Dubinina 1974).

5.3. Derivation of AEGL-1

No definitive study was available for the derivation of AEGL-1 values (Table 3-5). The human irritation threshold reported by Maksimov and Dubinina (1974) was inadequately described and, therefore, was not considered an adequate basis for the derivation of AEGL-1 values. The report by Clariant GmbH (unpublished material 2000) was not considered an adequate basis for the derivation, because the depth of the routine medical examination was not reported and the time point of the examination was not linked to an actual exposure assessment. Moreover, the exposure assessment using about 1 to 2 measurements per year was considered insufficient. Therefore, due to insufficient data, AEGL-1 values were not recommended.

Because of the lack of an adequately performed study reporting an odor threshold for MCAA, no level of distinct odor awareness (LOA) was derived.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

Morrison and Leake (1941) reported that daily oral exposure for 60 days to 300 mL of a 0.05% MCAA solution in water did not result in adverse effects in three human volunteers. Assuming a body weight of 70 kg and 0.05% as 500 mg/L, this oral exposure corresponds to a daily dose of 500 mg/L × 0.3 L/d × 1/70 kg = 2.1 mg/kg/d.

TABLE 3-5 AEGL-1 Values for Monochloroacetic Acid

AEGL	10 min	30 min	1 h	4 h	8 h
AEGL-1	N.R.[a]	N.R.	N.R.	N.R.	N.R.

[a]Not recommended because of insufficient data.

6.2. Animal Data Relevant to AEGL-2

Dow Chemical Co. (1987) exposed a group of six female and six male Fischer 344 rats to MCAA vapor by inhalation for 1 h. The targeted concentration was 1,000 ppm, and the nominal concentration was 964 ppm; however, the analytic concentration of MCAA vapor during exposure was found to be 66 ppm. It was stated that a concentration of 1,000 ppm could not be achieved because of "substantial recrystallization of MCAA in the presence of room temperature (23°C) air." During exposure, all rats squinted and appeared "slightly lethargic" (stated in the text) or "lethargic" (stated in the tables). During the 2-week observation period, MCAA-exposed rats lost weight initially (day 2) and regained weight during the remaining period (days 4-15). Gross pathologic examination of rats revealed no exposure-related effects.

6.3. Derivation of AEGL-2

For the derivation of AEGL-2 values, the study of MCAA in rats by Dow Chemical Co. (1987) was used because it was the only relevant inhalation study available. Exposure of rats to 66 ppm for 1 h resulted in eye squint and in some lethargy, which might be interpreted as an effect on the central nervous system. No severe effects occurred. There is some uncertainty as to the exposure because of the large discrepancy between the nominal exposure concentration of 964 ppm and the analytically measured exposure concentration of 66 ppm. The authors did not discuss whether recrystallization of MCAA took place completely outside the exposure chamber (that is, before the air stream entered the chamber) or whether uptake of recrystallized MCAA might have occurred by routes other than inhalation (e.g., dermal and oral uptake after deposition on the hair). In case of an additional exposure, the measured air concentration of 66 ppm is regarded as a conservative exposure assumption. The AEGL-2 values were based on a 1-h exposure to 66 ppm.

Time scaling using the equation $C^n \times t = k$ was done to derive the other exposure duration-specific values. Due to lack of a definitive dataset, an n of 3 was used in the exponential function for extrapolation from the experimental period (1 h) to shorter exposure periods, and an n of 1 was used for extrapolation to longer exposure periods. The calculations of exposure concentrations scaled to AEGL-2 time periods are shown in Appendix A.

A total uncertainty factor of 10 was used. An uncertainty factor of 3 was applied for interspecies variability (1) because the effect level was considered below that of an AEGL-2; (2) because the available data on acute oral lethality do not point at a large interspecies variability for more severe (lethal) effects (see section 4.4.1); and (3) because of the limited toxicodynamic variability, as the enzymes inhibited by MCAA do not vary considerably within and between species. An uncertainty factor of 3 was applied for intraspecies variability because of the limited toxicokinetic variability with respect to local effects and

because of the limited toxicodynamic variability with respect to systemic effects since the enzymes inhibited by MCAA do not vary considerably within and between species. The values are listed in the Table 3-6.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No reports on deaths after inhalation of MCAA are available in the literature. Fatal cases and life-threatening poisonings in workers have been described after skin contact (Kulling et al. 1992; BUA 1994; IUCLID 1996); however, exact doses have not been reported.

Only one study reporting lethality after oral uptake was located: Feldhaus et al. (1993) and Rogers (1995) reported the case of a 5-year-old girl who was accidentally given 5-6 mL of an 80% MCAA containing wart remover, resulting in a dose of MCAA at 4.0-4.8 g (corresponding to 200-240 mg/kg), assuming a body weight of 20 kg. The girl died 8 h post-ingestion despite medical intervention. An autopsy revealed diffuse gastric erosions, fatty liver, and pulmonary and cerebral edema. The postmortem MCAA concentration in serum was 100 mg/L (this concentration corresponds to an MCAA concentration of about 75 mg in serum, assuming a serum volume of 750 mL) as determined by gas chromatography/mass spectroscopy.

Morrison and Leake (1941) reported that daily oral exposure for 60 days to 300 mL of a 0.05% MCAA solution in water did not result in adverse effects in three human volunteers. Assuming a body weight of 70 kg and 0.05% as 500 mg/L, this oral exposure corresponds to a daily dose of 500 mg/L × 0.3 L/d × 1/70 kg = 2.1 mg/kg/d.

7.2. Animal Data Relevant to AEGL-3

Maksimov and Dubinina (1974) reported an LC_{50} in rats of 180 (146-221) mg/m³ (46.8 ppm) for 4 h without providing experimental details. Assuming a body weight of 0.3 kg for rats and a pulmonary absorption rate of 100% and deriving a respiration rate using the allometric relationship published by EPA (1988),

$$\text{ventilation rate (m}^3\text{/d)} = 0.80 \times \text{body weight (kg)}^{0.8206} \text{ (EPA 1988).}$$
$$\text{ventilation rate} = 0.80 \times 0.3^{0.8206} = 0.298 \text{ m}^3\text{/d.}$$

TABLE 3-6 AEGL-2 Values for Monochloroacetic Acid

AEGL	10 min	30 min	1 h	4 h	8 h
AEGL-2	12 ppm (47 mg/m³)	8.3 ppm (33 mg/m³)	6.6 ppm (26 mg/m³)	1.7 ppm (6.7 mg/m³)	0.83 ppm (3.3 mg/m³)

The corresponding dose can be calculated as

$$\text{dose (mg/kg)} = \text{exp. conc. (mg/m}^3\text{)} \times \text{ventilation rate (m}^3\text{/d)} \times \text{exp. time (d)} \times 1/\text{body weight (kg)}.$$

$$\text{dose} = 180\ \text{mg/m}^3 \times 0.298\ \text{m}^3\text{/d} \times 4/24\ \text{d} \times 1/0.3\ \text{kg} = 29.8\ \text{mg/kg}.$$

Hercules (1969a,b) reported that exposure of rats, mice, and guinea pigs to MCAA-saturated vapor generated at 75°C (reported nominal concentrations 7,020-8,060 ppm) for up to 10 min resulted in irritation (mild lacrimation, nasal discharge), dyspnea, and lung hyperemia but did not cause lethality. Because no experimental details, especially no analytic concentrations, were reported, these studies provide little meaningful information.

Oral LD_{50} data are presented in Table 3-4. Hoechst AG (1979a) administered doses of MCAA at 0, 40, 63, 100, and 160 mg/kg to groups of 10 female Wistar rats using gavage of 1% (w/v) solutions of MCAA in water. Using Probit analysis, an LD_{50} of 90.4 (95% CI 73.6-112) mg/kg was calculated by the authors. The very high LD_{50} of 580 mg/kg for neutralized MCAA solution found in rats by Maksimov and Dubinina (1974) will not be considered further (1) because this value is much higher than other values reported for neutralized MCAA solutions (see Table 3-4), which are similar to non-neutralized MCAA solutions; and (2) due to inadequate data presentation, neutralization by addition of sodium hydroxide (solid or as solution) to the acidic MCAA solution cannot be excluded; this could give rise to high pH either locally in the solution or temporarily due to overtitration and thus cause nucleophilic substitution (hydrolysis) of the chlorine moiety in MCAA, resulting in reaction to the much less toxic glycolic acid.

7.3. Derivation of AEGL-3

For the derivation of AEGL-3 values, no relevant and well-documented LC_{50} studies were available.

Although oral lethality data in animals are available, these were not used as a basis for derivation of AEGL values because of the uncertainty regarding local effects of MCAA in the respiratory tract. Several mechanistic aspects point to a possible role of local effects: (1) MCAA has a pK_a of 2.85 and thus is a strong acid, which may cause irritation and local tissue damage by its acidity alone; (2) MCAA can bind to sulfhydryl groups (Yllner 1971; Hayes et al. 1973; van Hinsbergh and Vermeer 1994), for example, those of reduced glutathione, and may thus cause lung damage through glutathione depletion; and (3) during inhalation exposure, local concentrations of MCAA in the respiratory tract could cause local tissue damage by enzyme inhibition already in doses lower than those required for systemic effects in oral studies.

Experimental findings support a possible local effect on the respiratory tract: (1) the available inhalation studies report effects on the respiratory tract,

that is, Hercules (1969a) reported lacrimation, nasal discharge, dyspnea and lung hyperemia in rats, and Maksimov and Dubinina (1974) reported inflammation in the respiratory organs, tracheal catarrh, bronchitis, and bronchopneumonia in rats; and (2) MCAA causes severe local damage to skin and eyes (Hoechst AG 1979e, 1988d; see section 4.2).

Unfortunately, in the only LC_{50} study located in the literature (Maksimov and Dubinina 1974), data presentation is inadequate. Because pathologic findings were not reported, it remains unknown whether rats died from local lung-tissue destruction or from systemic toxicity (that is, acidosis affecting CNS or heart). With respect to systemic effects, it could be argued that the rat LC_{50} value of 46.8 ppm for 4 h (Maksimov and Dubinina, 1974), corresponding to a dose of 29.8 mg/kg (see section 7.2), is not supported by studies reporting oral LD_{50} values of about 90 mg/kg for rats (see Table 3-4 and Figure 3-1). However, as discussed above, a higher toxicity of MCAA for the inhalation route compared with the oral route cannot be ruled out. The data presented in Figure 3-1 suggest that upon inhalation exposure, lethal effects might occur at lower doses compared with oral exposure.

Inhalation studies using MCAA esters revealed no mortality after 4 h of exposure at up to 210 or 250 ppm (Torkelson et al. 1971; Hoechst AG 1988a). These data were not considered relevant for the derivation of AEGL-3 values; compared with MCAA, local effects of its esters are less likely, because (1) the esters are not acidic and thus do not cause local effects by lowering the tissue pH value; and (2) local effects due to glutathione binding or enzyme inhibition can be expected to be smaller because the esters have to get hydrolyzed enzymatically to free MCAA first. Although quantitative data for the hydrolysis are lacking, it is likely that due to its rapid distribution in the body, much of the deposited ester will enter systemic circulation before it is hydrolyzed, and thus the concentration of MCAA in respiratory tract tissue is likely to be much smaller during inhalation exposure to MCAA esters than during MCAA exposure.

Due to the inadequate presentation of the only LC_{50} available (Maksimov and Dubinina, 1974) and the uncertainties of a route-to-route extrapolation, no AEGL-3 values were derived (Table 3-7).

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

The AEGL values for various levels of effects and various time periods are summarized in Table 3-8. They were derived using the following key studies and methods.

No relevant studies of adequate quality were available for the derivation of the AEGL-1 value. Therefore, due to insufficient data, AEGL-1 values were not derived.

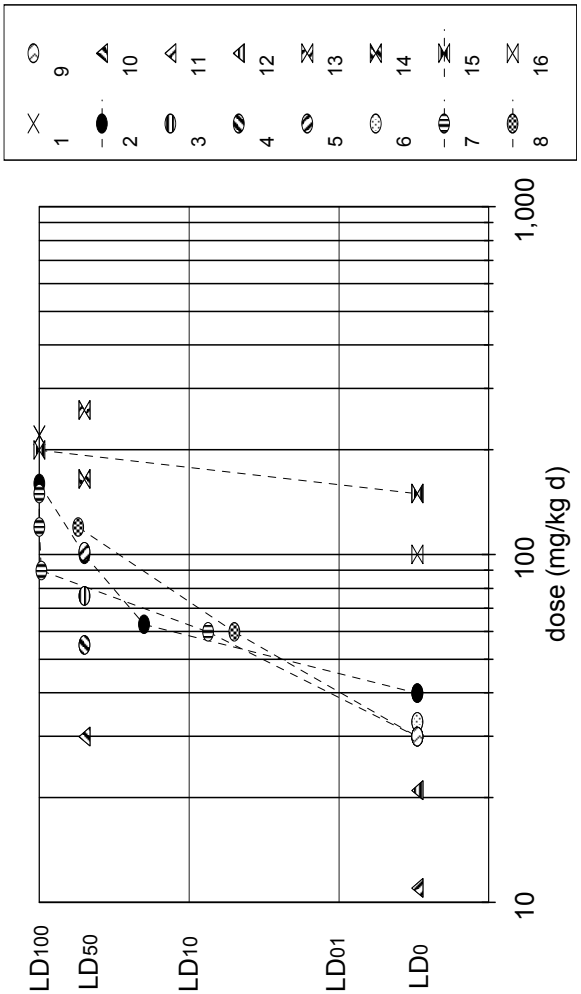

FIGURE 3-1 Relationship between MCAA dose and lethal effects. All exposures (including single and repeated inhalation exposures and single oral exposures) were converted to daily doses. LD_0 designates a NOEL for lethality. (1) Human case, single oral exposure (Feldhaus et al. 1993; Rogers 1995); (2) rat, single oral exposure (Hoechst AG 1979a); (3) rat, oral LD_{50} (Woodard et al. 1941); (4) rat, oral LD_{50} (Maksimov and Dubinina 1974); (5) rat, oral LD_{50} (Berardi 1986); (6) rat, subacute oral exposure (Johnson et al. 1998); (7) rat, subchronic oral exposure (Bryant et al. 1992; NTP 1992); (8) rat, subchronic oral exposure (Daniel et al. 1991); (9) rat, chronic oral exposure (NTP 1992); (10) rat, inhalation LC_{50} (Maksimov and Dubinina 1974); (11) rat, acute inhalation exposure (Dow Chemical Co. 1987); (12) rat, subchronic inhalation exposure (Maksimov and Dubinina 1974); (13) mouse, oral LD_{50} (Berardi 1986); (14) mouse, oral LD_{50} (Morrison and Leake 1941); (15) mouse, subchronic oral exposure (Bryant et al. 1992; NTP 1992); (16) mouse, chronic oral exposure (NTP 1992).

TABLE 3-7 AEGL-3 Values for Monochloroacetic Acid

AEGL	10 min	30 min	1 h	4 h	8 h
AEGL-3	N.R.[a]	N.R.	N.R.	N.R.	N.R.

[a]Not recommended because of insufficient data.

TABLE 3-8 Summary of AEGL Values for Monochloroacetic Acid[a]

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	N.R.[b]	N.R.	N.R.	N.R.	N.R.
AEGL-2 (Disabling)	12 ppm (47 mg/m³)	8.3 ppm (33 mg/m³)	6.6 ppm (26 mg/m³)	1.7 ppm (6.7 mg/m³)	0.83 ppm (3.3 mg/m³)
AEGL-3 (Lethal)	N.R.	N.R.	N.R.	N.R.	N.R.

[a]Skin contact with molten MCAA or MCAA solutions should be avoided; dermal penetration is rapid, and fatal intoxications have been observed when 10% or more of the body surface was involved.
[b]Not recommended because of insufficient data.

The AEGL-2 was based on a single inhalation study in rats (Dow Chemical Co. 1987) in which eye squint and lethargy were observed in rats exposed at 66 ppm for 1 h. A total uncertainty factor of 10 was used. Other exposure-duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of n = 3 for shorter exposure periods and n = 1 for longer exposure periods due to the lack of suitable experimental data for deriving the concentration exponent.

No relevant studies of adequate quality were available for the derivation of the AEGL-3 value. Therefore, due to insufficient data, AEGL-3 values were not derived.

All inhalation data are summarized in Figure 3-2. The data were classified into severity categories chosen to fit into definitions of the AEGL health effects. The category severity definitions are "no effect;" "discomfort;" "disabling;" "lethal;" and "some lethality" (animals that did not die at an experimental lethal concentration at which other animals died). Note that the AEGL-2 values are designated as triangles.

8.2. Comparison with Other Standards and Criteria

Existing limit and guideline concentrations are shown in Table 3-9. The occupational exposure limits for Sweden is 1 ppm (with skin notation) and a STEL of 2 ppm (with skin notation) (KEMI 1994). Maksimov and Dubinina (1974) recommended 1 mg/m³ (0.26 ppm) as the Russian occupational exposure limit.

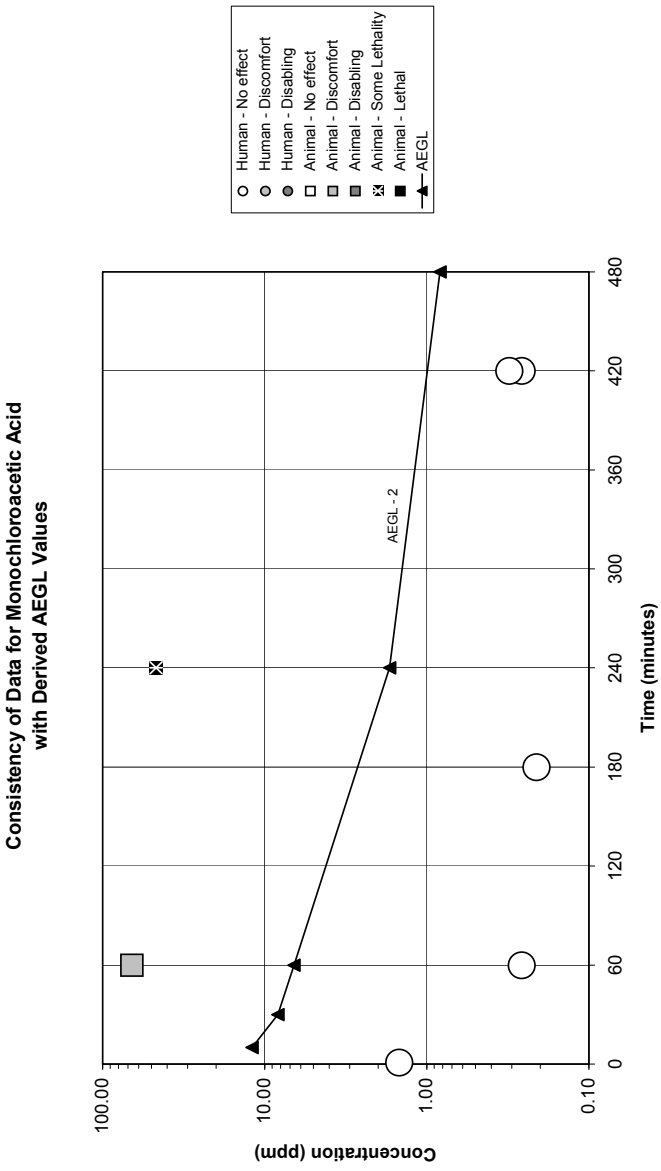

FIGURE 3-2 Categorical representation of all MCAA inhalation data.

TABLE 3-9 Extant Standards and Guidelines for Monochloroacetic Acid

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	N.R.	N.R.	N.R.	N.R.	N.R.
AEGL-2	12 ppm	8.3 ppm	6.6 ppm	1.7 ppm	0.83 ppm
AEGL-3	N.R.	N.R.	N.R.	N.R.	N.R.
REL-TWA (AIHA)[a]					0.26 ppm 1 mg/m³
STEL (AIHA)[b]	1.0 ppm (4 mg/m³) for 15 min				
MAK (Germany)[c]					1.0 ppm
MAC-Peak Category (The Netherlands)[d]					1.0 ppm (4 mg/m³)

[a]AIHA TWA (American Industrial Hygiene Association 1993) is defined as 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.
[b]AIHA STEL (American Industrial Hygiene Association 1984) (AIHA 1993) is defined as a 15-min TWA exposure that should not be exceeded at any time during the workday.
[c]MAK (maximale Arbeitsplatzkonzentration [maximum workplace concentration]) (Deutsche Forschungsgemeinschaft [German Research Association]) is defined analogous to the ACGIH Threshold Limit Value–time-weighted average (TLV-TWA). The peak category is 1; MCAA has a skin notation (BMAS 2000).
[d]MAC (maximaal aanvaarde concentratie [maximal accepted concentration–peak category]) (MSZW 2004) is defined analogous to the AIHA TWA.
Abbreviation: N.R., not recommended.

8.3. Data Adequacy and Research Needs

Definitive, high-quality studies assessing health effects of MCAA after single or repeated inhalation exposure in humans or experimental animals are not available. Due to insufficient data, AEGL-1 and AEGL-3 values were not derived.

The derivation of AEGL-2 was based on a single 1-h inhalation exposure study on rats using a single concentration.

Single inhalation exposure studies focusing on lethal effects in animals and irritative effects in animals and humans would allow for more precisely defining the thresholds for the three AEGLs.

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APPENDIX A

TIME-SCALING CALCULATIONS FOR AEGLS

AEGL-2 VALUES

Key study:	Dow Chemical Co. 1987
Toxicity end point:	Rats were exposed for 1 hat an analytic MCA concentration of 66 ppm, no other concentrations were tested. During exposure all rats squinted and appeared slightly lethargic.
Scaling:	$C^3 \times t = k$ for extrapolation to 30 min and 10 min $k = 66^3$ ppm$^3 \times 1$ h = 287,496 ppm^3-h $C \times t = k$ for extrapolation to 8 h and 4 h k = 66 ppm × 1 h = 66 ppm-h
Uncertainty factors:	Combined uncertainty factor of 10. 3 for interspecies variability 3 for intraspecies variability
Calculations:	
10-min AEGL-2	$C^3 \times 0.167$ h = 287,496 ppm^3-h C = 119.85 ppm 10-min AEGL-2 = 119.85 ppm/10 = 12 ppm (47 mg/m^3)
30-min AEGL-2	$C^3 \times 0.5$ h = 287,496 ppm^3-h C = 83.15 ppm 30-min AEGL-2 = 83.15 ppm/10 = 8.3 ppm (33 mg/m^3)
1-h AEGL-2	C = 66 ppm 1-h AEGL-2 = 66 ppm/10 = 6.6 ppm (26 mg/m^3)
4-h AEGL-2	C × 4 h = 66 ppm-h C = 16.50 ppm 4-h AEGL-2 = 16.50 ppm/10 = 1.7 ppm (6.7 mg/m^3)
8-h AEGL-2	C × 8 h = 66 ppm-h C = 8.25 ppm 8-h AEGL-2 = 8.25 ppm/10 = 0.83 ppm (3.3 mg/m^3)

APPENDIX B

ACUTE EXPOSURE GUIDELINES FOR MONOCHLOROACETIC ACID

Derivation Summary for Monochloroacetic Acid

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:
No definitive study was available for the derivation of AEGL-1 values. The human irritation threshold reported by Maksimov and Dubinina (1974) was inadequately described and, therefore, was not considered an adequate basis for the derivation of AEGL-1 values. The report by Clariant GmbH (unpublished material 2000) was not considered an adequate basis because the depth of the routine medical examination was not reported and the time point of the examination was not linked to an actual exposure assessment. Moreover, the exposure assessment using about one to two measurements per year was considered insufficient. Therefore, due to insufficient data, AEGL-1 values were not recommended.

Uncertainty Factors/Rationale: Not applicable.

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Not applicable.

Time Scaling: Not applicable.

Data Adequacy: Adequate human or animal data relevant for the derivation of AEGL-1 values are not available.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
12 ppm	8.3 ppm	6.6 ppm	1.7 ppm	0.83 ppm

Key Reference: Dow Chemical Company. 1987. Monochloroacetic acid: An acute vapor inhalation limit study with Fischer 344 rats. Unpublished report, Dow Chemical Company, Midland, USA.

Test Species/Strain/Sex/Number: Rat/Fischer 344/6 female and 6 male.

Exposure Route/Concentrations/Durations: Inhalation/66 ppm (analytic concentration)/1 h

(Continued)

AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
12 ppm	8.3 ppm	6.6 ppm	1.7 ppm	0.83 ppm

Effects: During all exposures, all rats (12/12) showed eye squint and slight lethargy. While in the text the expression "slight lethargy" is used, "lethargy" is used in the corresponding table. "The observations [prior to and after exposure] included an evaluation of fur, eyes, mucous membranes, and respiration. Behavior pattern and nervous system activity was also assessed by specific observation for tremors, convulsions, salivation, lacrimation, and diarrhea, as well as slight lethargy and other signs of altered central nervous system function." During the 2-week observation period, MCAA-exposed rats lost weight initially (day 2) and regained weight during the remainder period (days 4-15). Gross pathologic examination of rats revealed no exposure-related effects.

End Point/Concentration/Rationale: For the derivation of AEGL-2 values, the study in rats by Dow Chemical Co. (1987) was used because it was the only relevant inhalation study available. Exposure of rats to 66 ppm for 1 h resulted in eye squint and in some lethargy, which might be interpreted as an effect on the central nervous system, but no severe effects. There is some uncertainty as to the exposure because of the large discrepancy between the nominal exposure concentration of 964 ppm and the analytically measured exposure concentration of 66 ppm. The authors did not discuss whether recrystallization of MCAA took place completely outside the exposure chamber (that is, before the air stream entered the chamber) or whether uptake of recrystallized MCAA by routes other than inhalation (e.g., dermal and oral uptake after deposition on the hair) might have occurred. In case of an additional exposure, the measured air concentration of 66 ppm and be regarded as a conservative exposure assumption. The AEGL-2 values were based on a 1-h exposure to 66 ppm.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10

Interspecies: 3, because (1) the effect level was considered below that of an AEGL-2, (2) because the available data on acute oral lethality do not point at a large interspecies variability for more severe (lethal) effects, and (3) because of the limited toxicodynamic variability as the enzymes inhibited by MCAA do not vary considerably within and between species.

Intraspecies: 3, because of the limited toxicokinetic variability with respect to local effects and limited toxicodynamic variability with respect to systemic effects since the enzymes inhibited by MCAA do not vary considerably within and between species.

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Insufficient data.

Time Scaling: The exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of $n = 3$ for shorter exposure periods and $n = 1$ for longer exposure periods, due to the lack of suitable experimental data for deriving the concentration exponent.

Data Adequacy: The only available single inhalation study in animals was used for the derivation of AEGL-2 values. In this study, neither different exposure concentrations nor different exposure durations were used. The derived values are supported by an older subchronic toxicity study in humans who had daily oral exposures to MCAA.

AEGL-3 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/Sex/Number: Not applicable.

Exposure Route/Concentrations/Durations: Not applicable.

Effects: Not applicable.

End Point/Concentration/Rationale: For the derivation of AEGL-3 values, no relevant and well-documented LC_{50} studies were available.

Although oral lethality data in animals are available, they were not used as a basis for derivation of AEGL values because of the uncertainty regarding local effects of MCAA in the respiratory tract. Several mechanistic aspects point at a possible role of local effects: (1) MCAA has a pK_a of 2.85 and thus is a strong acid, which may cause irritation and local tissue damage by its acidity alone; (2) MCAA can bind to sulfhydryl groups, for example, those of reduced glutathione, and may thus cause lung damage through glutathione depletion; and (3) during inhalation exposure, local concentrations of MCAA in the respiratory tract could cause local tissue damage by enzyme inhibition already in doses lower than those required for systemic effects in oral studies. Experimental findings support a possible local effect on the respiratory tract: (1) the available inhalation studies report effects on the respiratory tract, and (2) MCAA causes severe local damage to skin and eyes.

Unfortunately, in the only LC_{50} study located in the literature (Maksimov and Dubinina, 1974), data presentation is inadequate. Because pathologic findings were not reported, it remains unknown whether rats died from local lung tissue destruction or from systemic toxicity (that is, acidosis affecting CNS or heart).

Inhalation studies using MCAA esters were not considered relevant for the derivation of AEGL-3 values; compared with MCAA, local effects of its esters are less likely, because (1) the esters are not acidic and thus do not cause local effects by lowering the tissue pH value; and (2) local effects due to glutathione binding or enzyme inhibition can be expected to be smaller because the esters have to get hydrolyzed enzymatically to free MCAA first. Although quantitative data for the hydrolysis are lacking, it is likely that due to its rapid distribution in the body, much of the deposited ester will enter systemic circulation before it is hydrolyzed, and thus the concentration of MCAA in respiratory tract tissue is likely to be much smaller during inhalation exposure to MCAA esters than during MCAA exposure.

Due to the inadequate presentation of the only LC_{50} available (Maksimov and Dubinina 1974) and the uncertainties of a route-to-route extrapolation, AEGL-3 values were not recommended.

Uncertainty Factors/Rationale: Not applicable.

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Not applicable.

Time Scaling: Not applicable.

Data Adequacy: Adequate animal data relevant for the derivation of AEGL-3 values are not available.

4

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

AEGL-1 is the airborne concentration (expressed as parts per million [ppm] or milligrams per cubic meter [mg/m^3]) of a substance above which it is

[1]This document was prepared by the AEGL Development Team composed of Peter Griem (Forschungs- und Beratungsinstitut Gefahrstoffe GmbH) and Chemical Managers Robert Snyder and Bill Bress (National Advisory Committee [NAC] on Acute Exposure Guideline s 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 s. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guideline reports (NRC 1993, 2001).

predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m³) 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/m³) 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 odor, taste, and sensory irritation, or certain asymptomatic, nonsensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including sensitive subpopulations, it is recognized that certain individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Phenol is a colorless to pink, hygroscopic solid with a characteristic, sweet, tarlike odor. Pure phenol consists of white-to-clear acicular crystals. In the molten state, it is a clear, colorless liquid with a low viscosity.

Human fatalities by phenol have been reported after ingestion and skin contact. Few studies after inhalation of phenol are available: one occupational study reported slight changes in liver and blood parameters (increased serum transaminase activity, increased hemoglobin concentration, increased numbers of basophils and neutrophils, and lower levels of monocytes) after repeated exposure to a mean time-weighted average concentration of 5.4 ppm (Shamy et al. 1994). Piotrowski (1971) did not report symptoms or complaints in a toxicokinetic study, in which subjects were exposed at 6.5 ppm for 8 h. Likewise, Ogata et al. (191986) in a toxicokinetic field study did not mention any effects on workers exposed to mean workshift concentrations of 4.95 ppm. Among persons exposed to phenol at more than 1 mg/liter (L) of contaminated drinking water for several weeks, gastrointestinal symptoms (diarrhea, nausea, and burning pain and sores in the mouth) and skin rashes occurred (Baker et al. 1978). A geometric mean odor detection threshold of 0.060 ppm (range of all critiqued odor thresholds 0.0045-1 ppm) has been reported (AIHA 1989). Don (1986) reported an odor detection threshold of 0.010 ppm in a CEN (2003) comparable study.

No studies reporting LC_{50} (concentrations with 50% lethality) values for phenol in animals are available. Oral LD_{50} values were reported as 420 mg/kg for rabbits, 400-650 mg/kg for rats, and 282-427 mg/kg for mice. In rats, exposure to a phenol aerosol concentration of 900 mg/m³ for 8 h resulted in ocular and nasal irritation, incoordination, and prostration in one of six rats (Flickinger 1976). After 4 h of exposure of phenol vapor at 211 or 156 ppm, a decrease of the number of white blood cells but no signs of toxicity were reported (Brondeau et al. 1990). After vapor exposure of rats at 0.5, 5, or 25 ppm for 6 h/d, 5 d/wk for 2 weeks, no clinical, hematologic, or histopathologic effects were found (Huntingdon Life Sciences 1998; published in Hoffman et al. 2001). Continuous exposure to phenol vapor at 5 ppm for 90 days caused no hematologic or histologic effects in rhesus monkeys, rats, and mice. A vapor concentration of 166 ppm (for 5 min) resulted in a 50% decrease of respiration (RD_{50}) in female Swiss OF_1 mice. No teratogenic effects were found in studies using repeated oral gavage and doses of up to 120 mg/kg in CD rats and 140 mg/kg in CD-1 mice. In a two-generation drinking-water study in Sprague-Dawley rats, decreased pup survival linked to decreased maternal body weight was observed at the highest dose of 5,000 ppm; the no-observed-adverse-effect level (NOAEL) was 1,000 ppm (equivalent to 70 mg/kg/d for males and 93 mg/kg/d for females). In an oral carcinogenicity study, $B6C3F_1$ mice and Fischer 344 rats received phenol at 2,500 or 5,000 mg/L of drinking water (corresponding to 281 and 412 mg/kg/d for mice and 270 and 480 mg/kg/d for rats). No increased incidence of tumors was observed in mice and female rats; a significant incidence of tumors (pheochromocytomas of the adrenal gland, leukemia, or lymphoma) occurred in male rats of the high-exposure group. Phenol had tumor promoting activity when applied repeatedly on the skin after induction using benzene. It can cause clastogenic and possibly very weak mutagenic effects. IARC evaluated the findings on carcinogenicity and concluded that there is inadequate evidence in both humans and experimental animals for the carcinogenicity of phenol. Consequently, phenol was found "not classifiable as to its carcinogenicity to humans (Group 3)" (IARC 1999, p.762). EPA concluded that "the data regarding the carcinogenicity of phenol via the oral, inhalation, and dermal exposure routes are inadequate for an assessment of human carcinogenic potential. Phenol was negative in oral carcinogenicity studies in rats and mice, but questions remain regarding increased leukemia in male rats in the bioassay as well as the positive gene mutation data and the positive results in dermal initiation/promotion studies at doses at or above the maximum tolerated dose (MTD). No inhalation studies of an appropriate duration exist. Therefore, no quantitative assessment of carcinogenic potential via any route is possible" (EPA 2002, p. 103). Therefore, carcinogenicity was not an end point in the derivation of AEGL values.

The AEGL-1 was based on a repeat inhalation study of phenol in rats (Huntingdon Life Sciences 1998; Hoffman et al. 2001), which found no clinical, hematologic or histopathologic effects after exposure to phenol at 25 ppm (highest concentration used) for 6 h/d, 5 d/wk for 2 weeks. An uncertainty factor of 1 was applied for interspecies variability: the toxicokinetic component of the un-

certainty factor was reduced to 1 because toxic effects are mostly caused by phenol itself without requirement for metabolism; moreover, possible local irritation effects depend primarily on the phenol concentration in inhaled air with little influence of toxicokinetic differences between species. The starting point for AEGL derivation was a NOAEL from a repeat exposure study, and thus the effect level was below that defined for AEGL-1. The human experimental and workplace studies (Piotrowski 1971; Ogata et al. 1986) support the derived values. For these reasons, the interspecies factor was reduced to 1. An uncertainty factor of 3 was applied for intraspecies variability because, for local effects, the toxicokinetic differences do not vary considerably within and between species. Therefore the toxicokinetic component of the uncertainty factor was reduced to 1 and the factor of 3 for the toxicodynamic component was retained, reflecting a possible variability of the target-tissue response in the human population. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of $n = 3$ for shorter exposure periods and $n = 1$ for longer exposure periods, because of the lack of suitable experimental data for deriving the concentration exponent. For the 10-min AEGL-1, the 30-min value was applied because the derivation of AEGL values was based on a long experimental exposure period, and no supporting studies using short exposure periods were available for characterizing the concentration-time-response relationship.

A level of distinct odor awareness (LOA) for phenol of 0.25 ppm was derived on the basis of the odor detection threshold from the study of Don (1986). The LOA represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity; about 10% of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception.

The AEGL-2 was based on a combination of the Flickinger (1976) and Brondeau et al. (1990) studies. Aerosol exposure to phenol at 900 mg/m³ (equivalent to phenol vapor at 234 ppm) for 8 h resulted in ocular and nasal irritation, slight loss of coordination, and spasms of the muscle groups at 4 h into the exposure. After 8 h, additional symptoms (tremor, incoordination, and prostration) were observed in one of the six animals. No deaths occurred. Because the aerosol concentration was below the saturated vapor concentration at room temperature of about 530 ppm, it was assumed that much of the phenol had evaporated from the aerosol and a mixed aerosol and vapor exposure prevailed. This study is supported by the study of Brondeau et al. (1990), who reported only slight effects after exposure to phenol vapor at 211 ppm for 4 h. Although both studies had shortcomings—that is, aerosol exposures, nominal concentrations, and no description of toxic signs in one study—taken together, they had consistent results. The derivation of AEGL-2 values was based on an exposure concentration of 234 ppm for 8 h. An uncertainty factor of 3 was applied for interspecies variability because oral lethal data did not indicate a high variability between species (cf. section 4.4.1.) and because application of a higher uncertainty factor

would have resulted in AEGL-2 values below levels that humans can stand without adverse effects (Piotrowski 1971; Ogata et al. 1986). An uncertainty factor of 3 was applied for intraspecies variability because the study of Baker et al. (1978) who investigated health effects in members of 45 families (including children and elderly) that were exposed to phenol through contaminated drinking water for several weeks did not indicate that symptom incidence or symptom severity was higher in any specific subpopulation. Moreover, newborns and infants were not considered more susceptible than adults because of their smaller metabolic capacity to form toxic phenol metabolites (cf. section 4.4.2.). Based on the small database and study shortcomings, a modifying factor of 2 was applied. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of n = 3 for shorter exposure periods, because of the lack of suitable experimental data for deriving the concentration exponent. For the 10-min AEGL-2, the 30-min value was applied because the derivation of AEGL values was based on a long experimental exposure period and no supporting studies using short exposure periods were available for characterizing the concentration-time-response relationship.

Although phenol is a high-production-volume chemical, no acute inhalation studies of adequate quality were available for the derivation of the AEGL-3 value. Therefore, due to insufficient data and the uncertainties of a route-to-route extrapolation, AEGL-3 values were not recommended. The calculated values are listed in Table 4-1.

TABLE 4-1 Summary of AEGL Values for Phenol[a]

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (Nondisabling)	19 ppm (73 mg/m³)	19 ppm (73 mg/m³)	15 ppm (58 mg/m³)	9.5 ppm (37 mg/m³)	6.3 ppm (24 mg/m³)	No effects in rats (Huntingdon Life Sciences 1998; Hoffman et al. 2001)
AEGL-2 (Disabling)	29 ppm (110 mg/m³)	29 ppm (110 mg/m³)	23 ppm (90 mg/m³)	15 ppm (57 mg/m³)	12 ppm (45 mg/m³)	Irritation and CNS depression in rats (Flickinger 1976; Brondeau et al. 1990)
AEGL-3 (Lethal)	N.R. [b]	N.R.	N.R.	N.R.	N.R.	

[a]Skin contact with molten phenol or concentrated phenol solutions should be avoided; dermal penetration is rapid, and fatal intoxications have been observed when a small part of the body surface was involved.
[b]Not recommended because of insufficient data.

1. INTRODUCTION

Phenol is a colorless to pink, hygroscopic solid with a characteristic, sweet, tarlike odor. Pure phenol consists of white-to-clear acicular crystals. In the molten state, it is a clear, colorless liquid with a low viscosity. A solution with approximately 10% water is called phenolum liquefactum, as this mixture is liquid at room temperature (WHO 1994).

Phenol is produced either by oxidation of cumene or toluene, by vapor-phase hydrolysis of chlorobenzene, or by distillation from crude petroleum (WHO 1994). Worldwide phenol production has been reported to be about 500,000 to 1,000,000 metric tons per year (IUCLID 1996). Newer data report a production of 1,800,000 metric tons per year in the European Union (ECB 2002) and about 1,500,000 metric tons for 1994 in the United States (HSDB 2003).

Phenol is pumped in molten form (about 50°C) or in liquefied form (containing 10% water) through pipes on industrial sites and is also transported in molten form in tank trucks and rail tank cars between industrial sites. Therefore, inhalation exposure during accidental release cannot be ruled out.

Phenol is principally used in production of various phenolic resins, biphenol A, caprolactam, and a wide variety of other chemicals and drugs. It is also used as a disinfectant and in germicidal paints and slimicides (ACGIH 1996). The TRI database (DHHS 2008) lists 649 sites in the United States where production and use of phenol causes emissions to the air. Chemical and physical data are provided in Table 4-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No relevant studies documenting lethal effects in humans after inhalation exposure to phenol were identified. During the second half of the nineteenth century, several hundred cases of intoxication occurred from inhalation, oral, or dermal exposure (Lewin 1992). Contemporary reports concerning fatalities after oral or dermal exposure are available; however, for dermal exposures, information about the absorbed dose is often not reported (WHO 1994). Lethality data in humans are summarized in Table 4-3.

2.1.1. Case Studies

Heuschkel and Felscher (1983) reported on the death of a newborn (weight 3 kg) that was exposed through a contaminated continuous positive airway pressure system of an incubator. Instead of distilled water, the system contained a disinfection fluid, composed of 2% formalin (30% formaldehyde), 1.5% sodium tetraborate, and 0.5% phenol. This solution was removed after 5-6 h.

TABLE 4-2 Chemical and Physical Data for Phenol

Parameter	Data	Reference
Molecular formula	C_6H_6O; C_6H_5OH	WHO 1994
Molecular weight	94.11	WHO 1994
CAS Registry Number	108-95-2	WHO 1994
Physical state	Solid A solution with approx. 10% water (phenolum liquefactum) is liquid at room temperature	ACGIH 1996 WHO 1994
Color	Colorless Assumes a pink to red discoloration on exposure to air and light	ACGIH 1996
Synonyms	Carbolic acid; hydroxybenzene; phenyl hydroxide; phenol	ACGIH 1996
Vapor pressure	0.48 hPa at 20°C 0.357 mm Hg at 20°C 1 mm Hg at 40.1°C 3.5 hPa at 25°C 2.48 mm Hg at 50°C 10 mm Hg at 73.8°C 18.39 hPa at 80.1°C 40 mm Hg at 100.1°C 100 mm Hg at 121.4°C	IUCLID 1996 WHO 1994 Weast 1984 IUCLID 1996 WHO 1994 Weast 1984 IUCLID 1996 Weast 1984 Weast 1984
Density	1.0719 g/cm³	ACGIH 1996
Melting point	43°C	Weast 1984
Boiling point	181.75°C	Weast 1984
Solubility	Very soluble in chloroform, alcohol, ether, and aqueous alkali hydroxides; 67 g/L in water at 16°C	ACGIH 1996 WHO 1994
Odor	Sweet, tarlike odor Sweet and acrid	ACGIH 1996 IARC 1999
Explosive limits in air	1.7% (lower), 8.6% (upper)	ACGIH 1996
Conversion factors	1 ppm = 3.84 mg/m³ 1 mg/m³ = 0.26 ppm	WHO 1994

However, exposure was continued since disinfection fluid was also used for filling up the reservoir for humectation of the air. The newborn developed severe symptoms after 20 h of exposure. It showed a gray-pale skin color, edema on the head and legs, and tachypnea and died on the fifth day from pro-

TABLE 4-3 Summary of Data on Lethal Effects in Humans

Subject Information	Exposure Route	Exposure Information	Estimated Dose	Effect	Reference
1-d old newborn	Inhalation	About 5.2 ppm for 5-6 h, subsequently about 1.3 ppm for 14-15 h	Unknown	Cyanosis, tachypnea, death 4 days later; additional formaldehyde exposure	Heuschkel and Felscher 1983
65-y-old female	Oral	70 mL of 42-52% phenol solution	490-606 mg/kg Assuming a density of 1 g/mL and a body weight of 60 kg	After 1 h respiratory arrest, coma, survived due to intensive care	Kamijo et al. 1999
50-y-old male	Oral	Approx. 60 mL of an 88% phenol emulsion	754 mg/kg Assuming a density of 1 g/mL and a body weight of 70 kg	After 45 min stuporous, tachycardia, stertorous breathing, rales in the lungs, survived with medical treatment	Bennett et al. 1950
19-y-old female	Oral	15 mL liquefied phenol	250 mg/kg Assuming a density of 1 g/mL and a body weight of 60 kg	90 min later nausea, vomiting, diarrhea, cyanosis, stuporous, death after 17.5 h	Bennett et al. 1950
Adult female	Oral	10-20 g phenol	166-333 mg/kg Assuming a body weight of 60 kg	Coma, absence of reflexes, tachypnea, tachycardia, death after 1 h due to cardiac and respiratory arrest	Stajduhar-Caric 1968
27-y-old male	Oral (+ dermal)	Unknown	106-874 mg/kg, Based on tissue concentration	Found dead next day; at autopsy tissue phenol concentrations between 106 and 874 mg/kg, 60 mg/kg in blood	Tanaka et al. 1998
1-d-old newborn	Dermal	2% phenol solution in umbilical bandage	125-202 mg/kg Based on tissue concentration, assuming uniform distribution and no elimination	Cyanosis, death after 11 h, at autopsy tissue phenol concentrations between 125 and 202 mg/kg	Hinkel and Kintzel 1968

gressive respiratory insufficiency. On experimental reconstitution of the exposure conditions, phenol at about 20 mg/m³ (5.2 ppm) and formaldehyde at about 30 mg/m³ (24.9 ppm) were measured in the incubator after 2 h (lower concentrations of phenol and formaldehyde after 5 h not reported) when disinfection solution was present in the evaporation container, and phenol at about 5 mg/m³ (1.3 ppm), formaldehyde at 50 mg/m³ (41.5 ppm), and methanol at 350 mg/m³ (267 ppm) were found (with decrease of the formaldehyde and methanol concentrations within the first hour) with disinfection fluid in the water reservoir. It should be noted that concentrations in the incubator were measured using simple solid sorbent test tubes. Autopsy revealed hypoxemia-caused organ alterations. The authors contributed these to two causes: (1) central respiratory depression by the intoxication and (2) congenital pulmonary adaptation disorder, expressed in an immature tissue structure of the lung.

A 65-year-old Japanese woman ingested 70 mL of 42-52% phenol in a suicide attempt. Upon hospital admission and about 1 h after ingestion, respiration had arrested, and the patient was comatose. The patient survived due to intensive medical care (Kamijo et al. 1999).

Bennett et al. (1950) reported on two suicide cases. The first case involved a 50-year-old morphine addict who swallowed approximately 60 mL of an 88% aqueous phenol emulsion. Forty-five minutes later, he was stuporous with cold and clammy skin and had a rapid and weak pulse, stertorous breathing with a phenol odor on the breath, constricted pupils that did not react to light (probably due to morphine injection prior to phenol ingestion), and rales in the lungs. An electrocardiogram showed auricular flutter with a variable auriculoventricular block. His urine was greenish with no albumin, but 12 h later there was a marked albuminuria and cylindruria. Albuminuria persisted for 10 days. The patient responded to medical treatment and recovered in 20 days. The second case involved a 19-year-old woman who had ingested 15 mL of liquefied phenol. Ninety minutes later, she complained of severe nausea and burning in the throat and epigastrium. Laryngoscopic examination revealed superficial burns and slight edema of the hypopharynx. Despite gastric lavage with olive oil and intravenous saline administration, she continued to be nauseated. One hour later, she began to vomit blood and to have diarrhea, passing copious amounts of blood with clots. She gradually became cyanotic and stuporous and died 17.5 h after ingestion.

Stajduhar-Caric (1968) described a woman who committed suicide by ingesting 10-20 g of phenol. She became comatose with partial absence of reflexes, pallor of the skin, accelerated respiration, weak and rapid pulse and dilated pupils that did not react to light. Almost 1 h after the ingestion, her heart and respiration stopped and, in spite of repeated attempts at resuscitation for 2 h, she died. Autopsy revealed marked hyperemia of the tracheal and bronchial mucous membranes. Histologic examination revealed pulmonary and liver edema as well as hyperemia of the intestine.

Tanaka et al. (1998) reported on the case of a 27-year-old male student, who died after ingestion of a DNA extraction fluid containing phenol. He was

found in the laboratory the next day lying on the floor with his trousers soaked. At autopsy on the same day, the body surface was grayish in color; the skin in the large area extending from the right arm to both legs had changed color to dark brown, and some parts of its surroundings were chemically burned. There were also blisters in the skin across the burned area. The lips, oral mucous membranes, and the walls of the orsopharynx, larynx, bronchus, esophagus, and stomach were dark brown and inflamed. Histology revealed inflammatory changes in the lungs, interstitial edema and renal tubular hemorrhage in the kidneys, and interstitial hemorrhage in the pancreas and adrenal glands. Analysis of free phenol was performed by gas chromatography/mass spectroscopy on ethyl acetate extracts of tissues. The following phenol concentrations were found: 60 mg/L in the blood, 208 mg/L in urine, 106 mg/L in the brain, 116 mg/L in the lung, and 874 mg/L in the kidney. Upon skin contact with liquefied phenol or phenol solutions, symptoms can develop rapidly leading to shock, collapse, coma, convulsions, cyanosis and death (NIOSH 1976; Lewin 1992).

Horch et al. (1994) described a healthy 22-year-old male worker who was splashed with aqueous phenol (concentration not reported) over his face, chest, one hand, and both arms (20.5% of the body surface). Extensive water showering and topical treatment with polyethylene glycol was carried out before hospital admission. Affected skin areas were swollen and reddish and looked like partial skin thickness burn wounds. Blood gas analysis revealed that oxygen saturation dropped from 99% on admission to 72% 6 h after exposure. During this period, cardiac arrhythmia and bradycardia were noted. Serum levels of phenol were 11.4 mg/L at 1 h, 17.4 mg/L at 4 h, 6.0 mg/L at 8 h, 0.37 mg/L at 22 h, and 0.07 mg/L at 28 h post-exposure. The man survived and his skin healed completely within 12 days.

Bentur et al. (1998) reported on the case of a 47-year-old male who had 90% phenol spilled over his left foot and shoe (3% of the body surface). After 4.5 h of exposure, with no attempt to remove the phenol, confusion, vertigo, faintness, hypotension, ventricular premature beats, and atrial fibrillation developed and the affected skin area showed swelling and blue-black discoloration and was diagnosed as a second degree burn. Peak serum phenol was 21.6 mg/L and was eliminated with a half-life of 13.9 h.

Lewin and Cleary (1982) described a 24-year-old male who died shortly after being painted with benzyl benzoate as a scrabicide with a brush that had been steeped in 80% phenol and not thoroughly washed before use.

Hinkel and Kintzel (1968) described two newborns having cutaneous contact with phenol-containing disinfectants. A 1-day-old newborn died 11 h after application of an umbilical bandage that was accidentally soaked with 2% phenol instead of saline. After 6 h, the baby developed severe cyanosis and died at 11 h from central respiratory depression. Autopsy revealed edematous swelling of all parenchymal organs. Phenol concentrations of 125 mg/kg in blood, 144 mg/kg in liver and 202 mg/kg in kidney were measured. Another infant, 6 days old, was treated for skin ulcer with Chlumsky's solution (phenol-camphor complex) and developed life-threatening methemoglobinemia, vomiting, cyanosis,

muscle twitchings and tremors, central circulatory collapse, mimic rigidity, muscular hypertonia, and tenderness to touch. These symptoms persisted for 3 days. The baby survived following intensive care and blood-exchange transfusion.

Schaper (1981) reported on the case of a 19-year-old woman who was accidentally splashed with molten phenol (80-90°C) on the face, left arm, and left leg (about 35-40% of the body surface). Five minutes later the patient lost consciousness, and upon hospital admission 15 min after the accident she was comatose. The patient developed bradypnea and tachycardia, brownish necrosis of the affected skin and massive intravasal hemolysis. After intensive medical care, the patient regained consciousness after 6 h; cardiac activity normalized after 8 h. No sign of organ damage was observed and the patient was discharged after 33 days. The peak phenol concentration in urine was about 600 mg/L 2 days after the accident; the urinary concentration decreased to 100-150 mg/L during the first week and second weeks.

2.2. Nonlethal Toxicity

Although some studies describe odor thresholds for phenol, no studies are available reporting adverse health effects after single inhalation exposures.

2.2.1. Experimental Studies

Piotrowski (1971) published a toxicokinetic study on phenol. Eight healthy volunteers (seven men ages 25-42 and one woman age 30) were exposed by face mask to phenol concentrations between 5 and 25 mg/m³ (1.3-6.5 ppm) for 8 h, with two breaks of 0.5 h, each after 2.5 and 5.5 h. The author did not report any complaints concerning adverse effects of phenol exposure on the subjects, nor did the report explicitly state the absence of any effects.

Don (1986) reported an odor detection threshold of 0.010 ppm for phenol in a study considered equivalent to a CEN (2003) compliant study. The study methodology has been described in TNO (1985). In this study, the odor threshold for the reference chemical *n*-butanol was determined as 0.026 ppm.

Leonardos et al. (1969) used a combination of a test room and an antechamber, which was held odor-free using an air filter system. A trained panel of four staff members of the Food and Flavor Section of Arthur D. Little, Inc., determined the odor threshold for various compounds. At least five concentrations of phenol were tested. The individual concentrations were not reported. An odor recognition threshold of phenol at 0.047 ppm was determined for all four subjects.

Mukhitov (1964) determined the odor perception threshold in 14 subjects. Each subject was tested from 33 to 43 times over a period of 2-3 days. The odor perception threshold concentration ranged from 0.022 to 0.14 mg/m³ (0.0057-

0.036 ppm); in 11/14 subjects, the odor perception threshold was 0.029 mg/m³ (0.0075 ppm) or lower.

The geometric mean of 16 air odor detection thresholds was reported by Amoore and Hautala (1983) to be 0.16 mg/m³ (0.040 ppm, with a standard error of 0.026 ppm). The American Industrial Hygiene Association reported a geometric mean odor detection threshold of 0.060 ppm (the range of all critiqued odor threshold studies was 0.0045-1 ppm) (AIHA 1989).

Ruth (1986) listed an irritation threshold of 182.4 mg/m³ (47 ppm) in humans. The author tabulated the odor and irritation threshold for a large number of chemicals but did not indicate the source for the values.

2.2.2. Case Studies

Spiller et al. (1993) reported on a 5-year retrospective review of all exposures to a high-concentration phenol disinfectant (26% phenol) that were reported to a regional poison control center. Of 96 located cases, 16 cases were lost to follow-up, leaving 80 cases for evaluation. Ages ranged from 1 to 78 years, with a mean of 10 years; 75% of the patients were less than 5 years. There were 60 oral-only exposures, 7 dermal-only exposures, 12 oral and dermal exposures and 1 inhalation exposure; 52 cases were evaluated in a hospital. Eleven patients (all oral exposures) experienced some form of central-nervous-system (CNS) depression. Nine patients experienced lethargy (the time to onset was 15 min to 1 h, with a mean time of 20 min); lethargy progressed to unresponsiveness within 1 h. Coma developed in two patients (information on the ingested dose was not available). Burns were noted in 17 patients with oral exposure and 5 patients with dermal exposure. No cardiovascular complications were noted. A distinct change in urine color to dark green and black was noted in five patients with oral exposure; oliguria or anuria was not seen. Recovery was complete in all cases. By history, the oral dose of exposure ranged from 2 to 90 mL of disinfectant (520 mg to 23.4 g of phenol). The largest ingested dose without effect was 30 mL (7.8 g of phenol), and the smallest dose with any effect was 5 mL (1.3 g of phenol). The dose was unknown in 14 exposures. No details were provided for the case involving inhalation exposure.

Baker et al. (1978) described an incidence in which residents drank contaminated well water for several weeks following an accidental spill of 37,900 L of phenol. Due to incomplete removal and flushing of the site with water, seepage into the underground water system developed. In a retrospective study, the population was divided into three groups based on residential location relative to the spill site and results of water testing: Group 1 (39 persons, mean age 26.5 years) consisted of all those living 120-310 m from the spill site and having at least one water test that revealed phenol at more than 0.1 mg/L in drinking water. Group 2 (61 persons, mean age 26.7 years) was composed of families living adjacent to group 1, that is, 210-670 m from the spill who had phenol at 0.1-0.001 mg/L in their water. Group 3 (58 persons, mean age 19.5 years) lived 1.9

km from the spill site in houses where well-water testing had detected no phenol in the water. Upon medical evaluation, no significant differences were noted in symptom rates between groups 2 and 3; therefore, the two groups were combined and symptom rates for this group were compared with rates in group 1. Diarrhea, nausea, burning pain in the mouth and sores in the mouth developed in 17 of the 39 individuals of group 1, five individuals of group 2, and two of group 3. In group 1, affected persons were slightly younger than those not affected (21.7 vs. 30.2 years) and tended to live closer to the spill site. Skin rashes were also increased in group 1. The rashes might have been caused by dermal exposure to phenol-contaminated water. Ill individuals had significantly more frequent complaints of bad tasting or smelling water during 2 months after the spill than did their neighbors who were not ill. Routine blood chemistry analyses and urinalysis performed on samples obtained half a year after the spill showed no significant abnormalities in liver function tests or other measured parameters. Mean urinary phenol levels were normal by that time because drinking water was supplied by tanks. Measured concentrations were 12 ± 12 and 12 ± 11 mg/L for group 1 and the combined control group, respectively. The phenol concentrations in drinking water for the persons in group 1 who had symptoms were more than 1 mg/L (the authors estimated an intake of phenol of 10-240 mg/d).

2.2.3. Occupational Exposure

Ogata et al. (1986) carried out a toxicokinetic study in 20 adult male employees engaged in treatment of fibers with phenol. The authors provided no information on age and health status of the employees or on time on the job. The workers were not equipped with protection masks, and the workshops were closed rooms with phenol concentrations from 1.22 to 4.95 ppm. The study investigated the correlation between workplace exposure to phenol and the concentration of phenol metabolites in urine. The number of men in each workshop exposed to phenol (time-weighted average concentrations during workshift measured by personal samplers) was two subjects at 1.22 ± 0.52 ppm, five at 1.95 ± 0.47 ppm, five at 2.52 ± 0.49 ppm, two at 2.73 ± 0.45 ppm, two at 3.81 ± 0.26 ppm, and four at 4.95 ± 0.23 ppm. The authors did not reported any adverse effects of phenol exposure on the subjects, nor did they explicitly state the absence of any effects.

Shamy et al. (1994) studied 82 male workers in an oil refining plant. Group I comprised workers (n = 20; mean duration of exposure 13.2 ± 6.6 years) exposed to phenol alone during aromatic extraction from distillates containing aromatics, wax, oil, and impurities. The time-weighted average exposure was 5.4 ppm, according to the factory. Group II (n = 32; mean duration of exposure 14.3 ± 6.1 years) represented those exposed to mixtures of phenol, benzene, toluene, and methyl ethyl ketone (4.7, 0.7, 220, or 90 ppm, respectively). Group III (n = 30) comprised employees from the administrative departments located far away from any exposure to phenol. Transaminases, total protein, prothrom-

bin time, clotting time, fasting blood sugar, serum creatinine, and trace elements were determined in blood. The mean phenol concentrations measured in urine were 11.5 ± 4.7 mg/g of creatinine in controls (group III), 54 ± 27 mg/g of creatinine in group II, and 69 ± 47 mg/g of creatinine in group I. Groups I and II showed statistically significantly higher levels of serum alanine aminotransferase and serum aspartate aminotransferase, increased clotting time, and lower levels of serum creatinine than subjects from the administrative departments. Groups I and II had statistically higher levels of hemoglobin, hematocrit, color index, mean corpuscular hemoglobin content, mean corpuscular volume, basophils, and neutrophils and lower levels of monocytes than control subjects. Groups I and II had significantly higher levels of magnesium (Mg), manganese (Mn), and calcium (Ca). The effects of combined exposure did not differ from that of exposure to phenol alone for the majority of the tested parameters. Only the platelet count, prothrombin time, eosinophils, cobalt, and iron were affected by combined exposure but were not affected after exposure to phenol only.

2.3. Reproductive and Developmental Toxicity

No studies evaluating developmental or reproductive effects of phenol in humans were identified (ATSDR 1998).

2.4. Genotoxicity

In tests using cultured human lymphocytes in vitro, phenol caused a weak increase in the frequency of micronuclei (Yager et al. 1990) and induced sister chromatid exchanges (Morimoto and Wolff 1980). For more information on genotoxicity see section 3.4.

2.5. Carcinogenicity

Kauppinen et al. (1986) reported a case-control study on respiratory cancers and chemical exposures in the wood industry. A cohort of 3,805 Finnish men who worked in the particle board, plywood, sawmill, or formaldehyde glue industries for at least 1 year between 1944 and 1965 was followed until 1981. From the cohort, 60 cases of respiratory malignant tumors were identified. The tissue locations of these tumors included tongue (1), pharynx (1), larynx or epiglottis (4), and lung or trachea (54). No cases with tumor in the mouth, nose, or sinuses were identified. Among the 60 cases, two were rejected due to a false preliminary diagnosis of cancer and one was rejected as chronic lymphocytic leukemia. The final size of the group of cases was thus 57. The control group contained three subjects for each case, selected from the cohort and matched by birth year, for a total size of 171. Individual phenol exposures were determined qualitatively as “yes” or “no” and as a function of exposure time. Phenol exposure resulted in a statistically significant odds ratio (OR) of 3.98 or 4.94 for res-

piratory tumors with or without the adjustment for smoking years, respectively. When the duration of phenol exposure was considered, both exposures of less than 5 years and more than 5 years resulted in a statistically significant OR of 5.86 or 4.03, respectively (that is, no duration response). When a provision for a 10-year latency was introduced (excluding exposure during the 10 years immediately preceding the diagnosis of cases), phenol exposure resulted in a nonsignificant OR of 2.86 adjusted for smoking years but a significant OR of 3.98 without smoking adjustment. An exclusion of workers exposed to both phenol and pesticides resulted in a change of the OR from a significant 4.9 to a nonsignificant 2.6. Thus, a confounding effect due to exposures to pesticides was very possible.

In an occupational epidemiology study, Dosemeci et al. (1991) evaluated mortality among 14,861 white male workers in five companies that used formaldehyde and phenol. Unfortunately, the phenol exposure was confounded by coexposure to other compounds, such as formaldehyde, asbestos, urea, melamine, hexamethylenediamine, wood dust, plasticizers, carbon black, ammonia, and antioxidants. On the basis of phenol concentrations obtained from historical monitoring and industrial hygiene surveys, the investigators assigned each job/department/year combination to groups with no, low, medium, or high phenol exposure and then calculated cumulative exposure. Compared with the entire U.S. population, the entire cohort, had no significant increases in standardized mortality ratios (SMRs) for all causes of death or any diseases. The phenol-exposed workers as a group had slightly elevated SMRs for cancers of the esophagus (1.6), rectum (1.4), kidney (1.3), and Hodgkin's disease (1.7); however, none of these increases were statistically significant when compared with those in general population.

2.6. Summary

Fatalities after gross phenol exposures have been reported in the literature. One neonate died after exposure at about 5.2 ppm phenol and 24.9 ppm formaldehyde (concentrations after 2 h) with a decline in chamber phenol concentrations over 5-6 h followed by about 1.3 ppm phenol and 41.5 ppm formaldehyde (measured after 1 h, with decrease over time) for 14-15 h in an incubator (Heuschkel and Felscher 1983). A newborn died from dermal phenol exposure with resulting tissue concentrations of 125-202 mg/kg (Hinkel and Kintzel 1968), lethal percutaneous exposures for which information on dose is lacking; the range of reported acute oral lethal dose in adults is 166-754 mg/kg (Kamijo et al. 1999; Bennett et al. 1950; Stajduhar-Caric 1968).

Very few studies report the consequences in humans after inhaling phenol. One study reported slight increased serum transaminase activity, increased hemoglobin concentration, increased numbers of basophils and neutrophils and lower levels of monocytes after repeat occupational exposure to a mean time-weighted average concentration of phenol at 5.4 ppm (Shamy et al. 1994).

Piotrowski (1971) did not report any complaints or adverse effects in volunteers exposed to controlled concentrations of phenol at 6.5 ppm for 8 h. Likewise, the field study of Ogata et al. (1986) did not mention the health status of workers exposed to mean workshift concentrations of 1.22-4.99 ppm. Baker et al. (1978) described an incidence in which residents drank contaminated well water for several weeks following an accidental spill of phenol. Among persons exposed to phenol at more than 1 mg/L of contaminated drinking water for several weeks (the authors' estimate of an intake of phenol at 10-240 mg/d), gastrointestinal symptoms (diarrhea, nausea, and burning pain and sores in the mouth) and skin rashes occurred (Baker et al. 1978). Odor thresholds for phenol were reported at 0.010 ppm (Don 1986), 0.047 ppm (Leonardos et al. 1969), and 0.060 ppm (mean of evaluated values from the literature) (AIHA 1989).

No studies investigating reproductive or developmental toxic effects in humans were available. In vitro, phenol induced signs of genotoxicity in human cells (Morimoto and Wolff 1980; Yager et al. 1990). Two epidemiologic studies (Kauppinen et al. 1986; Dosemeci et al. 1991) evaluating carcinogenic effects in phenol-exposed workers did not show a clear correlation between phenol exposure and increased tumor incidences, but a very weak carcinogenic effect cannot be excluded on the basis of the available data.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

No studies reporting death after a single inhalation exposure were available. One study evaluated repeated inhalation exposure in guinea pigs. For oral exposure, several studies are summarized in Table 4-4.

3.1.1. Rabbits

Deichmann and Witherup (1944) administered phenol at different concentrations by oral gavage to albino rabbits. The first muscle twitching occurred in the extrinsic eye muscles and those of the eyelids and ears, then spread to isolated bundles of muscles all over the body; the extremities were affected last. Pulse and respiration were increased in rate at first, but later became slow, irregular and weak. The pupils were contracted in the early stages of intoxication, being dilated later. There was some salivation and dyspnea was marked. Lethargy, coma and asphyxial convulsions occurred shortly before death. Death always followed an oral dose of 0.62 g/kg; some deaths were seen after a dose of 0.42 g/kg, but were not observed at a dose of 0.28 g/kg.

Flickinger (1976) applied phenol at 0.252, 0.500, 1.00 or 2.00 g/kg to the intact skin of male albino rabbits (four animals/group). The observation period was 14 days. Death was observed in zero of four, zero of four, three of four, and

TABLE 4-4 Summary of Acute Oral Lethal Data in Animals

Species	Dose (mg/kg)	Remarks on Administration	Total Number of Animals Used	Datum	Reference
Rabbit	420	Solutions with different phenol concentrations were used	35	Lowest dose that resulted in death	Deichmann and Witherup 1944
Rat	400	Gavage	Not stated	LD_{50}	Berman et al. 1995
Rat	530	Gavage, 2% solution	45	LD_{50}	Deichmann and Witherup 1944
Rat	530	Gavage, 5% solution	45	LD_{50}	Deichmann and Witherup 1944
Rat	540	Gavage, 10% solution	40	LD_{50}	Deichmann and Witherup 1944
Rat	340	Gavage, 20% solution	45	LD_{50}	Deichmann and Witherup 1944
Rat	650	Gavage	20	LD_{50}	Flickinger 1976
Mouse	282	Not stated	Not stated	LD_{50}	Horikawa and Okada 1975
Mouse	300	Not stated	Not stated	LD_{50}	Von Oettingen and Sharples 1946
Mouse	427	Not stated	Not stated	LD_{50}	Kostovetskii and Zholdakova 1971

four of four rats (all deaths occurred at the day of dosing), respectively. Necrosis of the skin was observed in all exposed rabbits. No internal gross lesions were observed upon autopsy of the killed animals. The authors calculated an LD_{50} of 0.85 g/kg (95% confidence interval [C.I.] 0.60-1.20 g/kg).

3.1.2. Rats

Berman et al. (1995) reported an oral LD_{50} of 400 mg/kg (95% C.I. 297-539 mg/kg) in female Fischer 344 rats. In a repeat gavage study (14 exposures; see Section 3.2.3), a dose of 120 mg/kg killed 8 of 10 animals (animals died between days 1 and 11). No deaths occurred at 40 mg/kg.

Deichmann and Witherup (1944) administered 2%, 5%, 10%, or 20% aqueous phenol by oral gavage to Wistar rats. The first muscle twitching occurred in the extrinsic eye muscles and those of the eyelids and ears, then spread to isolated bundles of muscles all over the body; the extremities were affected

last. Pulse and respiration were increased in rate at first, but later became slow, irregular, and weak. The pupils were contracted in the early stages of intoxication, being dilated later. There was some salivation and dyspnea was marked. Uncoordinated movements of the legs occurred shortly before death. The LD_{50} values for the different phenol concentrations were 0.53, 0.53, 0.54, and 0.34 g/kg, respectively.

Flickinger (1976) exposed groups of five male albino rats to phenol by gavage at 0.200, 0.398, 0.795, or 1.58 g/kg. The observation period was 14 days. Death was observed in zero of five, zero of five, four of five, and five of five rats (all deaths occurred at the day of dosing), respectively. All rats that died revealed hyperemia and distention of the stomach and intestines. None of the surviving rats exhibited any gross lesions. The authors calculated an LD_{50} of 0.65 g/kg (95% C.I. 0.49-0.86 g/kg).

Conning and Hayes (1970) reported a dermal LD_{50} of 0.625 mL/kg in Alderley Park rats using molten phenol (40°C).

3.1.3. Guinea Pigs

Deichmann et al. (1944) exposed 12 guinea pigs to phenol vapor at 100-200 mg/m³ (26-52 ppm), 7 h/d, 5 d/wk for 4 weeks. After three to five exposures, the animals became lethargic during exposure. Body weight either decreased or remained stationary. After about 20 exposures over a period of 28 days, some of the animals began to show respiratory difficulties and signs of paralysis affecting primarily the hind quarters. Five animals died on day 28 and the other animals were killed 1 day later. Autopsy revealed extensive coagulation necrosis of the myocardium with extensive inflammation, lobular pneumonia with occasional abscesses and vascular damage in the lungs, centrolobular degeneration and necrosis in the liver, and degenerative lesions in the kidneys.

3.1.4. Mice

For mice, oral LD_{50} values for phenol at 282 mg/kg (Horikawa and Okada 1975), 300 mg/kg (Von Oettingen and Sharples 1946), and 427 mg/kg (Kostovetskii and Zholdakova 1971) have been reported.

3.2. Nonlethal Toxicity

Studies with single and repeated inhalation exposure are available for monkey, rabbit, rat, and mouse. However, several protocols used concentrations that failed to produce any adverse effects (Table 4-5).

TABLE 4-5 Summary of Nonlethal Effects in Animals after Inhalation Exposure

Species	Concentration (ppm)	Exposure Duration	Comments	Reference
Monkey	5	24 h/d, 90 d	No or minimal hepatic histologic change	Sandage 1961
Rabbit	26-52	7 h/d, 5 d/w, 88 d	Pneumonia, histologic degeneration in heart, liver and kidney	Deichmann et al. 1944
Rat	900 mg/m^3 as aerosol (equivalent to 234 ppm)	8 h	Ocular and nasal irritation, incoordination, prostration	Flickinger 1976
Rat	111, 156, or 211	4 h	Reduced leucocyte counts after 211 or 56 ppm; no effects after 111 ppm	Brondeau et al. 1990
Rat	26	24 h/d, 15 d	After one day increased activity; during third and fourth day impaired balance, disordered gait and muscle twitchings; sluggish	Dalin and Kristofferson 1974
Rat	0.5, 5, or 25	6 h/d, 5 d/w, 2 w	No clinical, hematologic or histopathologic effects	Huntingdon Life Sciences 1998; Hoffman et al. 2001
Rat	0.0026, 0.026, or 1.3	24 h/d, 61 d	Significant motor chronaxy starting at 30 d in the two highest exposure groups	Mukhitov 1964
Rat	5	24 h/d, 90 d	No hematologic or histopathologic effects	Sandage 1961
Rat	26-52	7 h/d, 5 d/w, 74 d	No signs of gross or histopathologic change	Deichmann et al. 1944
Mouse	5	24 h/d, 90 d	No hematologic or histopathologic effects	Sandage 1961
Mouse	166	5 min	RD_{50}	De Ceaurriz et al. 1981

3.2.1. Monkeys

Sandage (1961) exposed groups of 10 male rhesus monkeys to phenol at 0 or 5 ppm 24 h/d for 90 days. The exposure chambers were aluminium-insulated rooms of 10 × 8 × 7 feet. Monkeys were exposed in individual cages of 2 × 2 × 2 feet. Exposure concentrations were determined by a colorimetric assay. (The reliability of the method could not be determined from the study.) An average phenol concentration of 4.72 ppm was measured (according to the authors, the allowed range of 4.5-5.5 ppm was not exceeded). No significant effects were found in tests assessing hematology, urine parameters, blood chemistry, and renal function. In discussion, the authors stated that "pathology ... was essentially negative." Liver and kidney pathology was observed in 30% and 20%, respectively, of the monkeys (compared with 0% of the controls). However, the authors did not consider these changes to be significant, and they noted that six of seven reports of pathology in monkeys were considered "minimal or doubtful." Although the authors concluded that there was no evidence that phenol exposure resulted in significant damage, there is some indication of liver, kidney, and lung pathology in this study, but the inadequate reporting precludes the determination of whether there was a treatment-related effect.

3.2.2. Rabbits

Deichmann et al. (1944) exposed sixrabbits to phenol vapor concentrations of 100-200 mg/m³ (26-52 ppm) for 7 h/d, 5 d/wk for a total of 63 exposures over a period of 88 days. Rabbits did not show any signs of illness or discomfort. Gross and microscopic examinations revealed widespread confluent lobular pneumonia in the lungs, myocardial degeneration with necrosis of muscle bundles and interstitial fibrosis, centrolobular degeneration and necrosis in the liver, cloudy swelling and edema of convoluted tubules, scattered tubular degeneration, atrophy, and dilatation as well as glomerular degeneration in the kidney.

3.2.3. Rats

Flickinger (1976) exposed a group of six female Harlan-Wistar rats whole body for 8 h to a phenol aerosol at 900 mg/m³. The aerosol was generated using aqueous phenol and a D18 Dautrebande aerosol generator operated at 30 pounds per square inch (psi). The author stated that at this operating pressure, the generator delivers droplet diameters of .1 µm. Nominal exposure concentrations were determined by measurement of the volume loss of solution following aerosolization. The weight of the chemical present in that volume was then calculated and related to the total volume of air used in generating the aerosol to obtain the chamber concentration. The post-exposure observation period was 14 days. The exposure to an aerosol containing phenol at 900 mg/m³ caused no deaths, but ocular and nasal irritation was observed, as well as slight loss of co-

ordination with skeletal muscle spasms within 4 h. Tremors and prostration developed in one of six rats within 8 h. Rats appeared normal the following day and continued to gain body weight normally over the next 14 days. No lesions attributable to inhalation of the aerosol were seen at gross autopsy. Because the aerosol concentration used was below the vapor pressure at room temperature, it was considered adequate to convert the aerosol concentration of 900 mg/m³ to an equivalent vapor concentration of 234 ppm for calculations and comparison with other studies.

Brondeau et al. (1990) exposed Sprague-Dawley rats whole body to phenol at 0, 111, 156, or 211 ppm for 4 h. At conclusion of exposure, rats were killed and cellular components of the blood were analyzed. No effect on erythrocyte and leukocyte differential counts could be discerned. The total white blood cell count was significantly reduced after exposure at 156 or 211 ppm. Other signs of toxicity were not evaluated. The authors interpreted this finding as a result of increased secretion of corticosteroids as a response to sensory irritation. The authors showed that for five other chemicals also causing leukopenia this effect did not occur in adrenalectomized rats.

Huntingdon Life Sciences (1998; published in Hoffman et al. 2001) exposed groups of 20 male and 20 female Fischer 344 rats via flow-past nose-only inhalation protocol to phenol vapor at 0, 0.5, 5, or 25 ppm for 6 h/d, 5 d/wk for 2 weeks. High-performance liquid chromatography (HPLC) measurement of exposure concentrations determined mean (±SD) analytic concentrations of 0.0 ± 0.0, 0.52 ± 0.078, 4.9 ± 0.57, and 25 ± 2.2 ppm, respectively; nominal concentrations for the three phenol-treated groups were 0.67 ± 0.051, 6.6 ± 0.21, and 29 ± 1.3 ppm, respectively. Physical observations were performed once during each exposure for all animals and twice daily, in-cage, for viability (prior to and 30 min after exposure). Detailed physical examinations were conducted on all animals twice pretest and weekly thereafter. Body-weight measurements were recorded twice pretest and weekly thereafter, as well as prior to the first exposure. Following 10 exposures, 10 animals of each sex in each group were killed and the remaining animals held for a recovery period of 2 weeks, after which these animals were killed. Food consumption was recorded during the week prior to exposure initiation and weekly thereafter. Hematology and clinical chemistry parameters were collected at termination (10 animals/sex/group) or during recovery (10 animals/sex/group). Complete gross evaluations were conducted on all animals. Microscopic evaluations were conducted on the liver, kidney, nasopharyngeal tissues, larynx, trachea, lungs, and gross lesions for animals in the control and high-exposure groups at termination or during recovery. For histopathology of nasopharyngeal tissues, the skull, after decalcification, was serially sectioned transversely at approximately 3-µm intervals and, routinely, four sections were examined per animal.

No differences between control and phenol-exposed animals for clinical observations, body weights, food consumption, and clinical pathology were found. The authors stated that "scattered observations of chromodacryorrhea and nasal discharge" were noted during the 2 weeks of exposure. However, the au-

thors found these changes did not appear treatment-related and mostly abated during the 2-week recovery period." While this was true for chromodacryorrhea, the summary tables of in-life physical observations reported the following incidences of red nasal discharge in the control, 0.5-ppm, 5-ppm, and 25-ppm groups: 0 of 20, 0 of 20, 3 of 20, and 4 of 20 males and 0 of 20, 0 of 20, 1 of 20, and 0 of 20 females in the first week and 0 of 20, 0 of 20, 7 of 20, and 10 of 20 males and 0 of 20, 1 of 20, 3 of 20, and 0 of 20 females in the second week. No differences between control and phenol-exposed animals for organ weights and macroscopic and microscopic postmortem examinations were reported. The authors concluded that no adverse effects were seen at phenol concentrations up to 25 ppm.

Dalin and Kristoffersson (1974) exposed rats (males and females, two experiments with 7 phenol-exposed and 12 control animals each; rat strain not stated) whole body to phenol vapor at 100 mg/m³ (26 ppm) 24 h/d for 15 days. (The authors did not state whether the exposure concentration was checked analytically.) One day after initiation of exposure, the physical activity of the phenol-exposed rats was increased. During the third and fourth days, the animals showed impaired balance and abnormal gait. Involuntary skeletal muscle twitches were observed. The authors stated that these twitches were relatively mild, and the external appearance of the animals indicated that they were in relatively good condition. These signs disappeared by day 5 and were replaced by sluggish behavior until the end of the exposure. At termination of phenol exposure, the tilting plane method was used to measure effects on the CNS, and the phenol-exposed rats showed a significantly reduced sliding angle than before exposure or compared with control.

Mukhitov (1964) exposed groups of 15 male "white rats" whole body to phenol at 0, 0.01, 0.1, or 5 mg/m³ (0.0026, 0.026, or 1.3 ppm) for 24 h/d for 61 days. Analytic concentrations were obtained once or twice daily using a colorimetric assay. Analytic concentrations were 0.0112 ± 0.0014 mg/m³ (0.0029 ± 0.00036 ppm), 0.106 ± 0.0324 mg/m³ (0.028 ± 0.0084 ppm), and 5.23 ± 0.44 mg/m³ (1.36 ± 0.11 ppm). Although behavior of the rats at the two lower exposure concentrations was not different from controls, animals were "somewhat sluggish and sleepy" in the highest exposure group. Right hind leg muscle antagonists motor chronaxy was measured once every 10 days in five rats of each exposure group. A statistically significant motor chronaxy (mostly seen as shortened extensor chronaxy) was observed in rats exposed at 0.1 or 5 mg/m³, starting after 30 days of exposure.

Sandage (1961) exposed groups of 50 male Sprague-Dawley rats whole body at 0 or 5 ppm phenol vapor for 24 h/d for 90 days. Concentrations were determined by a colorimetric assay. An average phenol concentration of 4.72 ppm was measured (the allowed range of 4.5-5.5 ppm was not exceeded, according to the authors). No significant effects were found in tests assessing hematology and urine parameters as well as in histopathologic examinations.

Deichmann et al. (1944) exposed 15 rats whole body to phenol vapor concentrations of 100-200 mg/m³ (26-52 ppm) for 7 h/d, 5 d/wk for a total of 53

exposures over 74 days. These animals failed to show any signs of illness. No macroscopic or microscopic lesions were observed.

Berman et al. (1995) gave groups of 10 female Fischer 344 rats single oral gavage doses of 0, 12, 40, 120, or 224 mg/kg or daily doses of 0, 4, 12, 40, or 120 mg/kg for 2 weeks (14 total gavage doses) phenol in corn oil. Repeated exposure to 120 mg/kg killed 8 of 10 animals (see section 3.1.1). Hepatocellular necrosis was observed after a single dose of 40 mg/kg in one of seven animals and at 120 mg/kg in two of six but not after repeated exposure at 40 mg/kg. Renal tubular necrosis, protein casts, and papillary hemorrhage developed in four of six animals exposed at 224 mg/kg (single) and in three of eight animals exposed at 40 mg/kg (repeated). Necrosis or atrophy of spleen or thymus was found in one of eight animals exposed at 12 mg/kg (single and repeated), two of eight animals at 40 mg/kg (repeated), one of seven animals at 120 mg/kg, and four of six animals at 224 mg/kg.

3.2.4. Mice

Sandage (1961) exposed groups of 100 male "general purpose albino mice" to phenol at 0 or 5 ppm 24 h/d for 90 days. Exposure concentrations were determined by a colorimetric assay. An average phenol concentration of 4.72 ppm was measured (the allowed range of 4.5-5.5 ppm was not exceeded, according to the authors). No significant effects were found in tests assessing hematology and urine parameters as well as in histopathologic examinations.

De Ceaurriz et al. (1981) determined the phenol vapor concentration associated with a 50% reduction in the respiratory rate (RD_{50}) in male Swiss OF1 mice. Analytic exposure concentration measurements were performed by pumping a defined volume of air from the exposure chamber through a glass tube packed with silica gel as a solid sorbent and analyzing the amount of phenol by gas chromatography. The authors used at least four concentrations and six mice at each concentration. For measurement of respiration rate, mice were secured in individual body plethysmographs. During phenol exposure, the plethysmographs were inserted through the wall of the exposure chamber; the head of each animal was extended into the inhalation chamber. During 10 min, a control level was established, during which time the mice were exposed to room air. The mice were then rapidly placed in the stabilized cell with a predetermined concentration of phenol and were exposed for about 5 min. The phenol vapor RD_{50} for mice was calculated as 166 ppm.

3.3. Reproductive and Developmental Toxicity

3.3.1. Rats

Jones-Price et al. (1983a) exposed groups of 20-22 pregnant CD rats by gavage to phenol at 0, 30, 60, or 120 mg/kg on gestational days 6 to 15. The

dams were evaluated after being killed (day 20) for body weight, liver weight, gravid uterine weight, and status of uterine implantation sites. Live fetuses were weighed, sexed, and examined for gross morphologic abnormalities and malformations in the viscera and skeleton. No dose-related signs of maternal toxicity were observed. Although the number of resorptions was increased in all treated groups compared with the control group, this increase was not dose-dependent and was not observed in a previous range-finding study. In the group given 120 mg/kg, fetal body weights were significantly reduced. No other signs of developmental toxicity were observed. Thus, on the basis of decreased fetal body weight, the mid dose in this study of 60 mg/kg/d was a NOAEL for developmental toxicity and the high dose of 120 mg/kg/d was an equivocal lowest-observed-adverse-effect level (LOAEL). The high dose was a maternal NOAEL.

In a screening-test validation study, Narotsky and Kavlock (1995) exposed groups of 15-20 pregnant Fischer 344 rats by gavage to doses of 0, 40, or 53.3 mg/kg on gestational days 6 to 19. In both treated groups, dams showed dyspnea and rales in the lungs. Complete resorptions were found in one litter in the low- and two litters in the high-exposure group.

Ryan et al. (2001) evaluated the potential reproductive toxicity of phenol in a rat two-generation reproduction study, which included additional study end points, such as sperm count and motility, developmental landmarks, histologic evaluation of suspect target organs (liver, kidneys, spleen, and thymus), weanling reproductive organ weights, and an immunotoxicity screening plaque assay. Phenol was administered to 30 Sprague-Dawley rats of each sex in each group in the drinking water at concentrations of 0, 200, 1,000, or 5,000 ppm corresponding to daily intake of phenol of 0, 14, 70, and 310 mg/kg/d for males and 0, 20, 93, and 350 mg/kg/d for females. Parental (P1) animals were treated for 10 weeks prior to mating, during mating, gestation, lactation, and until they were killed. The F1 generation (P1 offspring) was treated using a similar regimen, while the F2 generation was not treated. After mating, 10 P1 males per group were evaluated using standard clinical pathology parameters and an immunotoxicity screening plaque assay. Significant reductions in water and food consumption were observed in the 5,000-ppm group in both generations; corollary reductions in body weight and body-weight gain were also observed. Mating performance and fertility in both generations were similar to controls, and no adverse effects on vaginal cytology or male reproductive function were observed. Vaginal opening and preputial separation were delayed in the 5,000-ppm group and were considered to be secondary to the reduction in F1 body weight. Litter survival of both generations was reduced in the 5,000-ppm group. Absolute uterus and prostate weights were decreased in the F1 generation at all dose levels; however, no underlying pathology was observed and there was no functional deficit in reproductive performance. Therefore, these findings were not considered to be adverse. No evidence of immunotoxicity was noted in the 5,000-ppm group. The effects noted at the high concentration were presumed to be associated with flavor aversion to phenol in the drinking water. Based on a comprehensive examination of all parameters, the NOAEL for reproductive tox-

icity of phenol administered in drinking water to rats is 1,000 ppm (equivalent to 70 mg/kg/d for males and 93 mg/kg/d for females).

3.3.2. Mice

Jones-Price et al. (1983b) exposed groups of 22-29 pregnant CD-1 mice in a teratogenicity study by gavage to phenol doses of 0, 70, 140, or 280 mg/kg on gestational days 6 to 15. Maternally toxic effects, such as tremor, ataxia, reduced body-weight development and death of 4 of 36 dams were observed at 280 mg/kg. At 140 mg/kg, slight tremor was observed after the first three exposures. Reduced fetal weights were observed in the highest exposure group. An increased incidence of cleft palate was also reported at the highest dose level, although the incidence was not significantly different from that of the other groups and there was no statistically significant increase in the incidence of litters with malformations. There was no other evidence of altered prenatal viability or structural development. Thus, the high dose of 280 mg/kg/d was a maternal frank effect level and also a developmental LOAEL based on decreased fetal body weight (accompanied by a possible increase in the incidence of cleft palate) in the fetuses, an effect that was likely secondary to the severe toxicity in the dams. The study NOAEL for maternal and developmental toxicity was 140 mg/kg/d.

3.4. Genotoxicity

Genotoxicity studies have found that phenol tends not to be mutagenic in *Salmonella typhimurium* tester strains either with or without S9-mix (Haworth et al. 1983; Glatt et al. 1989), but positive or equivocal results have been obtained in gene mutation assays in mammalian cells (McGregor et al., 1988a,b; Tsutsui et al., 1997). Increases were larger in the presence of S9 activation.

Phenol tended to induce micronuclei in mice when administered intraperitoneally (LOEL 90-160 mg/kg injected intraperitoneally daily for 2 or 3 days) (Shelby et al. 1993; Marrazzini et al. 1994; Chen and Eastmond 1995), but it produced negative (or positive only at very high doses) results when administered orally (see Greim 1998; IARC 1999; EPA 2002 for review). This difference is likely due to the first-pass conjugation and inactivation of orally administered phenol in the liver.

Using cultured Syrian hamster embryo cells, phenol induced DNA synthesis (starting at 1 µmol/L), chromosomal aberrations (positive at 100 µmol/L), sister chromatid exchanges (starting at 1000 µmol/L), and cell transformation (starting at 10 µmol/L) (Tsutsui et al. 1997).

Phenol was also positive in in vitro micronucleus tests with human lymphocytes (Yager et al. 1990) and CHO cells (Miller et al. 1995), and it caused chromosome aberrations in the presence of S9 activation in CHO cells (Ivett et al. 1989).

3.5. Carcinogenicity

No valid inhalation studies evaluating the potential carcinogenic activity were located (BUA 1998; IARC 1999; EPA 2002).

In an oral bioassay (NCI 1980), groups of 50 male and female $B6C3F_1$ mice and Fischer 344 rats received phenol at 0, 2,500, or 5,000 mg/L of drinking water, leading to estimated doses of 281 or 412 mg/kg/d for mice and 270 or 480 mg/kg/d for rats. Rats showed inflammation in the kidneys. No increased incidence of tumors was observed in mice or female rats. A significant incidence of tumors (pheochromocytomas of the adrenal gland, leukemia, or lymphoma) occurred in male rats of the low-exposure group, but there was no dose-response relationship.

Topical phenol has a tumor-promoting activity and can induce skin tumors in mice after repeated dermal exposure (2.5 mg in 25 µL of benzene, 2 times/wk for 40 weeks). However, the promotion was evident only in the presence of skin lesions, which were observed during the first 6 weeks) (Boutwell and Bosch 1959).

IARC (1999) evaluated the findings on carcinogenicity and concluded that there is inadequate evidence in both humans and experimental animals for the carcinogenicity of phenol. Consequently, phenol was found "not classifiable as to its carcinogenicity to humans (Group 3)" (IARC 1999, p. 762). EPA (2002) concluded that, "the data regarding the carcinogenicity of phenol via the oral, inhalation, and dermal exposure routes are inadequate for an assessment of human carcinogenic potential. Phenol was negative in oral carcinogenicity studies in rats and mice, but questions remain regarding increased leukemia in male rats in the bioassay as well as in the positive gene mutation data and the positive results in dermal initiation/promotion studies at doses at or above the maximum tolerated dose (MTD). No inhalation studies of an appropriate duration exist. Therefore, no quantitative assessment of carcinogenic potential via any route is possible."(EPA 2002, p. 103) Therefore, carcinogenicity was not an end point in the derivation of AEGL values.

3.6. Summary

No studies reporting LC_{50} values for phenol are available. Five of 12 guinea pigs died after 20 exposures to phenol at 26-52 ppm for 7 h/d, 5 d/wk (Deichmann et al. 1944). Under the same conditions, rabbits exposed for 88 days showed no clinical signs of overt poisoning, but developed pneumonia and degeneration in heart, liver, and kidney. Rats exposed for 74 days showed neither clinical signs nor histologic alterations (Deichmann et al. 1944). Oral lethal doses of 420 mg/kg for rabbits, 400-650 mg/kg for rats (Deichmann and Witherup 1944), and 282-427 mg/kg for mice (Von Oettingen and Sharples 1946; Kostovetskii and Zholdakova 1971; Horikawa and Okada 1975) have been reported.

In 10 rhesus monkeys, exposed 24 h/d for 90 days to phenol at 5 ppm by inhalation, no significant effects were found in hematology, urine parameters, blood chemistry, or renal function or at autopsy or histologic examinations (Sandage 1961).

Rats that inhaled a phenol aerosol at 900 mg/m³ (equivalent to 234 ppm) for 8 h developed ocular and nasal irritation, incoordination, and prostration (Flickinger 1976). A reduction of the number of circulating leucocytes was observed in rats after 4-h of exposure at 211 or 156 ppm; no effect was seen for 111 ppm (Brondeau et al. 1990). After exposure of rats at 0.5, 5, or 25 ppm for 6 h/d, 5 d/wk for 2 weeks, no clinical, hematologic, or histopathologic effects were found (Huntingdon Life Sciences 1998; Hoffman et al. 2001). Continuous exposure to phenol at 5 ppm for 90 days caused no hematologic or histologic effects in rats and mice (Sandage 1961). A concentration of 166 ppm (for 5 min) resulted in a 50% decrease of respiration (RD_{50}) in mice (De Ceaurriz et al. 1981).

Reduced fetal body weights were found in studies using repeated oral gavage and doses of up to 120 mg/kg in CD rats (on gestational days 6-15) and 140 mg/kg in CD-1 mice (on gestational days 6-19) (Jones-Price et al. 1983a,b). In a two-generation drinking water study in Sprague-Dawley rats, decreased pup survival linked to decreased maternal body weight was observed at the highest dose of 5,000 ppm; the NOAEL was 1,000 ppm (equivalent to 70 mg/kg/d for males and 93 mg/kg/d for females) (Ryan et al. 2001).

Phenol has weak clastogenic and genotoxic activity both in vitro and in vivo (Shelby et al. 1993; Marrazzini et al. 1994, Chen and Eastmond 1995; Tsutsui et al. 1997). A lifetime oral bioassay of phenol in rats and mice, using exposure through drinking water, found increased numbers of male rats of the low-exposure group with pheochromocytoma, leukemia, or lymphoma but not among male rats of the high-exposure group, female rats, and mice (NCI 1980). Phenol has tumor promoting and tumorigenic activity when applied dermally (Boutwell and Bosch 1959). IARC (1999) evaluated the findings on carcinogenicity and concluded that there is inadequate evidence in both humans and experimental animals for the carcinogenicity of phenol. Consequently, phenol was found "not classifiable as to its carcinogenicity to humans (Group 3)." EPA (2002) concluded that, "the data regarding the carcinogenicity of phenol via the oral, inhalation, and dermal exposure routes are inadequate for an assessment of human carcinogenic potential."

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Phenol is a normal product of protein catabolism, and it is taken up directly from cigarette smoke and food (especially smoked products). Sittig (1980) reported phenol concentrations in human urine between 5 and 55 mg/L. Dugan

(1972) stated that humans eliminate 0.2-6.6 mg/kg/d in urine and up to 3 mg/kg/d in feces. Piotrowski (1971) reported 8.7 ± 2.0 mg/d as the daily excretion rate of total phenol (free plus conjugates) in humans with no known exposure to phenol.

Inhaled phenol is absorbed readily into systemic circulation. Piotrowski (1971) exposed eight subjects by face mask to phenol concentrations between 5 and 25 mg/m³ (1.3-6.5 ppm) for 8 h, with two breaks of 0.5 h, each after 2.5 and 5.5 h. The concentration of phenol in inhaled and exhaled air was determined and urine was analyzed for total phenol (phenol and conjugates). Steady state was achieved within 3 h. The steady-state systemic uptake and absorption was 60-88%. Urinary recovery of absorbed phenol was 99% within 24 h after initial exposure.

After a single oral dose of 0.01 mg/kg radiolabeled phenol given to three male subjects (smoker status not reported), 85-98% of the dose was excreted in the urine in 14 h (Capel et al. 1972). These data demonstrate that very small concentrations of phenol are readily absorbed by the human gastrointestinal tract. In 18 other mammalian species, mean 24-h recoveries ranged from 95% in the rat to 31% in the squirrel monkey (Capel et al. 1972).

Piotrowski (1971) also performed whole-body skin exposures in human subjects (seven men ages 25-42 and one woman age 30; smoker status not reported). The subjects were exposed to phenol vapor concentrations of 5, 10, or 25 mg/m³ (1.3, 2.6, or 6.5 ppm) for 6 h; fresh air was supplied through a face mask to preclude pulmonary absorption. The total amount of phenol excreted in urine during and after exposure was used as a measure of absorption. Percutaneous clearance was estimated to be 0.35 m³/h, that is, the amount of phenol contained in 0.35 m³ was taken up per hour.

Assuming a ventilation rate of 0.8 m³/h and a pulmonary retention of 70%, ATSDR (1998) calculated that clearance of airborne phenol through the lungs was 0.6 m³/h and concluded that percutaneous absorption was half the pulmonary uptake over the concentration range of 5-25 mg/m³ (1.3-6.5 ppm).

Topical phenol is absorbed readily. After application of phenol solutions of 2.5-10.0 g/L on the forearm skin of 12 male and female subjects (ages 20-42 not having phenol contact or taking medicines; smoker status not reported), absorption rate increased with concentration (0.079 to 0.301 mg/cm²/h). After 30-min immersion of a whole hand into the same phenol concentrations (with calculated absorbed doses between 15.2 and 62.4 mg), phenol excretion in urine within 24 h amounted to about 80% of the absorbed dose. Increasing the phenol solution temperature from 20°C to 35°C led to a 1.67-fold increase in skin absorption (Baranowska-Dutkiewicz 1981).

Seventy-two hours after intratracheal instillation of radiolabeled phenol, radioactivity (1-5% of total dose) was found in rat lungs, skin, blood, muscle, adipose tissue, and liver (Hughes and Hall 1995). Seventy-two hours after oral exposure of rats, radioactivity was distributed mainly in muscle, skin, adipose tissue, liver, and blood (Hughes and Hall 1995). Thirty minutes after oral exposure of rats, the highest concentrations of administered dose were found in liver

(29-56%); approximately 67-85% was present in the plasma, of which 41-50% was bound to proteins or other macromolecules (Liao and Oehme 1981).

Three enzymes participate in phenol metabolism. Phenol sulfotransferases catalyze transfer of inorganic sulfate from 3′-phosphoadenosine-5′-phosphosulfate to the hydroxyl group of phenol to form the sulfate conjugate. Uridine diphosphate glucuronosyltransferases (UDP-glucuronosyltransferases) catalyze the transfer of a glucuronic acid moiety to the hydroxyl group of phenol to form an *O*-glucuronide conjugate. Cytochrome P-450 2E1 catalyzes the hydroxylation of phenol to form hydroquinone and to a much lesser extent catechol, which are then conjugated mainly with sulfate and glucuronic acid (Capel et al. 1972; Cassidy and Houston 1984). In addition, other cytochrome P-450 isoenzymes, such as 2F2, may also be involved in phenol oxidation (Powley and Carlson 2001). In vivo conjugation occurs mainly in the liver, lung and gastrointestinal tract (Cassidy and Houston 1984).

Because the sulfate conjugation pathway is saturable at lower doses than the glucuronic acid conjugation, the ratio of sulfate to glucuronide conjugates in rats decreased with increasing phenol dose (Koster et al. 1981). The ration of sulfate/glucuronide conjugates shows a species dependency (Capel et al. 1972). With respect to oxidation, at a dose of 25 mg/kg, mice excreted 7-fold higher amounts of total hydroquinone than rats (Capel et al. 1972). Kenyon et al. (1995) administered 14C-phenol to B6 mice of both sexes and observed that males excreted a greater proportion of hydroquinone glucuronide than did females at all doses; the difference was roughly 2-fold at a dose of 40 µmol/kg.

Phenol, in both free and conjugated forms, is excreted rapidly in urine. Human volunteers, exposed to phenol concentrations between 5 and 25 mg/m³ (1.3-6.5 ppm) for 8 h excreted 99 ± 8% of the retained dose in the urine within 24 h after start of exposure (Piotrowski 1971). After oral exposure of humans to radiolabeled phenol, the mean 24-h recovery of radioactivity in the urine was 90% (range 85-90%) (Capel et al. 1972). In rats, elimination of radioactivity in the urine was 95% complete 24 h after intratracheal or oral administration of radiolabeled phenol (Hughes and Hall 1995).

The urinary level of total phenol (free phenol and conjugated phenol) increased linearly with phenol concentrations in air in exposed workers (Ohtsuji and Ikeda 1972).

4.2. Mechanism of Toxicity

Phenol is an irritant of eyes and nose in rats (Brondeau et al. 1990; Flickinger 1976). After acute ingestion of high doses by humans, burns, hyperemia, and inflammation of mucous membranes and edema and inflammation of the lungs have occurred (Bennett et al. 1950; Stajduhar-Caric 1968; Tanaka et al. 1998). Burns and necrosis develop in humans after skin contact (Spiller et al. 1993; Schaper 1981). From these findings, it can be concluded that phenol causes local tissue damage at the sites of contact. The mechanism of acute irrita-

tion of skin and mucous membranes is not known. However, because phenol at higher concentrations precipitates proteins from solution (Lewin 1992) and dissolves in both water and organic solvents, interference with normal protein, enzyme, and membrane function seems likely. Direct toxicity on bone marrow cells in vivo was suggested by Tunek et al. (1981) at high-exposure concentrations.

With regard to systemic it has been reported that phenol exposure results in hypotension and arrhythmias in humans and experimental animals (Deichmann and Witherup 1944; Bennett et al. 1950; Stajduhar-Caric 1968; Schaper 1981 Kamijo et al. 1999). Phenol blocks the cardiac sodium channel subtype, with little effect on sodium channels in skeletal muscle (Zamponi and French 1994). Following ingestion, typical signs in humans and animals include agitation, muscle tremors, confusion, incoordination, seizures, coma, and respiratory arrest (Deichmann and Witherup 1944; Schaper 1981; Kamijo et al. 1999). Kamijo et al. (1999) suggested that phenol causes tremors directly by inducing increased acetylcholine release both in the peripheral nervous system at motor nerve endings and within the CNS and that the resultant reduction in brain acetylcholine levels indirectly suppresses the tremor.

Because phenol is rapidly metabolized, systemic toxicity may be due to the combined actions of the parent compound and its metabolites. Eastmond et al. (1987) investigated the role of phenol in benzene-induced myelotoxicity. Exposure of male $B6C3F_1$ mice with intraperitoneal doses of phenol as high as 150 mg/kg twice daily or for 12 days caused no suppression of bone marrow cellularity. Only minimal suppression was observed in mice exposed to hydroquinone at up to 100 mg/kg. By contrast, significant dose-related suppression was seen in mice exposed to phenol at 75 mg/kg and hydroquinone at 75 mg/kg under the same conditions. In further in vitro studies, the authors showed that phenol stimulates the horseradish peroxidase-mediated metabolism of hydroquinone, and they hypothesized that similar stimulation of local myeloperoxidase occurs in the bone marrow. Corti and Snyder (1998) evaluated the effects of benzene metabolites on cultured mouse bone marrow cells by measuring colony-forming units of erythroid progenitor cells and found that the cytotoxicity of phenol was much lower than that of hydroquinone and benzoquinone.

It has been hypothesized that the genotoxicity of phenol on bone marrow results from the following chain of events: phenol is conjugated in the liver to phenylsulfate; this metabolite reaches the bone marrow via the blood stream and is cleaved there by sulfatases yielding phenol again; this can then be oxidized to hydroquinone and benzoquinone, resulting in damage of cells by direct binding to macromolecules and by formation of oxygen radicals (Greim 1998).

4.3. Structure-Activity Relationships

No clear structure-toxicity relationships between phenol and substituted phenols and benzenediols, cresols, or chlorophenols have been published. Al-

though IDLH values were based on "an analogy to cresol" (NIOSH 1996), Deichmann and Keplinger (1981) stressed the considerable differences in toxicity between phenol and other phenolic compounds, including cresols.

4.4. Other Relevant Information

4.4.1. Interspecies Variability

Deichmann et al. (1944) found species differences after repeated inhalation exposure: 5 of 12 guinea pigs died after 20 exposures to phenol at 26-52 ppm for 7 h/d, 5 d/wk; under the same conditions, rabbits exposed for 88 days showed no signs of overt poisoning but some histologic degeneration in target tissues, and rats exposed for 74 days to the same concentrations developed neither clinical signs nor histologic alterations. No definitive information on the reasons for these species differences is available.

In contrast to the 1944 inhalation data, oral lethal doses differed little between species (see Table 4-3) and were 420 mg/kg for rabbits, 400-650 mg/kg for rats (Deichmann and Witherup 1944) and 282-427 mg/kg for mice (Von Oettingen and Sharples 1946; Kostovetskii and Zholdakova 1971; Horikawa and Okada 1975).

Overall, the available data are not considered a sufficient basis in itself to reduce the default interspecies uncertainty factor.

4.4.2. Intraspecies Variability

Deichmann and Witherup (1944) found some differences in lethality following an oral dose of phenol between 10-day-old and 5-week-old or adult rats. After oral gavage of 600 mg/kg of 5% aqueous phenol, 90% of 10-day-old rats died, and 30% of 5-week-old rats and 60% of adult rats died. After dermal application of 3,000 mg/kg mortality was 65, 25 and 45%, respectively.

There are no studies indicating that newborn babies and infants are more sensitive to phenol than adults. The death of a newborn after exposure to phenol at 5.2 ppm for 5-6 h and 1.3 ppm for another 14-15 h (Heuschkel and Felscher 1983) could not be attributed to a particular susceptibility because the newborn had a congenital pulmonary disorder. Moreover, the newborn was also exposed to formaldehyde (24.9 ppm [measured at 2 h] for 5-6 h and 41.5 ppm [highest concentration, with decrease over time] for another 14-15 h). The formaldehyde may have contributed to death. For example, rat exposure to formaldehyde at 40 ppm for 6 h/d, 5 d/wk was lethal (Maronpot et al. 1986).

With respect to metabolism, both reduced and increased capacities for sulfate and glucuronic acid conjugation, depending on the chemical (no data available for phenol), have been described in newborn and young infants compared with adults (Brashear et al. 1988; Renwick 1998). Generally, cytochrome P-450

activity, which reduces the potential of toxic effects caused by oxidation and protein binding of quinone metabolites, is reduced in newborns and young infants. However, elimination via the kidney is reduced for many chemicals and drugs (low glomerular filtration rate during the first 8 months [Besunder et al. 1988; Renwick 1998]) and this could lead to an increased half-life of phenol. Nonetheless, no definitive data for phenol are available.

Overall, although the available data do not point to a large intraspecies variability, they are not considered sufficient to use as the basis for reducing the default intraspecies uncertainty factor.

4.4.3. Skin Irritation and Sensitization

Application of concentrated phenol to intact human skin resulted in inflammation and necrosis at the site of application (Spiller et al. 1993; Schaper 1981). Increased skin rash, mouth sores and throat sores have been reported in 17 of 39 humans following repeated contact with phenol (>1 ppm) in drinking water (Baker et al. 1978).

Phenol showed no sensitizing capacity in a human maximization test using 24 subjects and a 2% phenol solution (Kligman 1966), a guinea pig maximization test (Itoh 1982) and a mouse ear swelling test (Descotes 1988).

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Piotrowski (1971) exposed eight volunteers by face mask to phenol at 5-25 mg/m³ (1.3-6.5 ppm) for 8 h, with two breaks of 0.5 h, each after 2.5 and 5.5 h. The author did not report any complaints or adverse effects of phenol exposure, nor did the report explicitly state the absence of any effects. In a toxicokinetic field study (Ogata et al. 1986), 20 workers were exposed to mean workshift concentrations of 1.22-4.95 ppm. The authors did not reported any health effects of phenol exposure on the subjects, nor did they explicitly state the absence of any adverse effects.

Odor thresholds for phenol were reported as 0.0057-0.036 ppm (odor recognition threshold; Mukhitov 1964), 0.047 ppm (odor detection threshold; Leonardos et al. 1969), and 0.060 ppm (mean odor detection thresholds from the literature) (AIHA 1989). Don (1986) reported an odor detection threshold of 0.010 ppm in a CEN (2003) comparable study.

Ruth (1986) reported an irritation threshold of 182.4 mg/m³ (47 ppm) in humans. The author tabulated the odor and irritation threshold for a large number of chemicals, but did not indicate the source for the values.

5.2. Animal Data Relevant to AEGL-1

After exposure of rats to phenol at 0.5, 5, or 25 ppm for 6 h/d, 5 d/wk for 2 weeks, no clinical, hematologic or histopathologic effects were found (Huntingdon Life Sciences 1998; Hoffman et al. 2001). The authors reported the following incidences of red nasal discharge (chromadacryorrhea) in the control group and 0.5-ppm, 5-ppm, and 25-ppm groups: 0 of 20, 0 of 20, 3 of 20, and 4 of 20 males and 0 of 20, 0 of 20, 1 of 20, and 0 of 20 females in the first week (observations for individual exposures were not provided). However, histopathologic analyses revealed no alterations of the epithelium of the nasal turbinates or other respiratory tract tissues.

Sandage (1961) exposed groups of 10 male rhesus monkeys to phenol at 5 ppm continuously for 90 days. Exposure concentrations were determined by a colorimetric assay. No adverse effects were found in tests assessing hematology, urine parameters, blood chemistry, and kidney function as well as in histologic examinations.

Mukhitov (1964) reported that continuous exposure of rats to phenol at 0.026 or 1.3 ppm for 61 days resulted in significant motor chronaxy (mostly seen as shortened extensor chronaxy) starting after 30 days; no effect was found at 0.0026 ppm. The authors described the rats of the highest exposure group as "somewhat sluggish and sleepy."

5.3. Derivation of AEGL-1

Phenol is not a potent irritant. Contact with phenol causes local tissue damage in the respiratory tract (Deichmann et al. 1944). At concentrations higher than 150 ppm, phenol causes irritation in rats (Flickinger 1976) and respiratory depression in mice (De Ceaurriz et al. 1981).

The pharmacokinetic study in humans (Piotrowski 1971) was not used as a key study because it did not report on health effects. The Sandage (1961) study in monkeys was not used because, apparently, exposure chambers did not allow observation of the animals during the exposure, and histopathology was performed on the lungs but not on the upper respiratory tract so that possible upper airway irritation was not adequately evaluated. Therefore, the study by Huntingdon Life Sciences (1998; published in Hoffman et al. 2001) was the only study fulfilling the standing operating procedures (SOP) requirements for a key study and, therefore, was used for derivation of AEGL-1 values, although it was a repeated exposure study. After exposure of rats for 6 h/d, 5 d/wk for 2 weeks, no histopathologic alterations of the epithelium of the nasal turbinates or other respiratory tract tissues were found. The observation of red nasal discharge in a few male rats of the 5-ppm and 25-ppm group was not considered a relevant effect, because no clear dose-response relationship was found and because predominately males, but not females, showed this effect. Moreover, red nasal discharge occurs at the plexus antebrachii, which is very prominent in the rat, and extrava-

sation of red blood cells visible as red nasal discharge is caused easily in the rat not only by locally acting chemicals but also by stress, dry air, or upper respiratory tract infections. The derivation of AEGL-1 values was based on an exposure concentration of 25 ppm for 6 h.

Time scaling using the equation $C^n \times t = k$ was carried out to derive exposure duration-specific values. Due to lack of a definitive dataset, a default value for n of 3 was used in the exponential function for extrapolation from the experimental period (6 h) to shorter exposure periods and a default value for n of 1 was used for extrapolation to longer exposure times. For the 10-min AEGL-1 the 30-min value was applied because the derivation of AEGL values was based on a long experimental exposure period, and no supporting studies using short exposure periods were available for characterizing the concentration-time-response relationship. The calculations of exposure concentrations scaled to AEGL-1 time periods are shown in Appendix A.

A total uncertainty factor of 3 was applied in derivation of the phenol AEGL-1. An uncertainty factor of 1 was applied for interspecies variability: the toxicokinetic component of the uncertainty factor was reduced to 1 because toxic effects are mostly caused by phenol itself without requirement for metabolism. Moreover, possible local irritation effects depend primarily on the phenol concentration in inhaled air with little influence of toxicokinetic differences between species. The starting point for AEGL derivation was a NOAEL from a repeated exposure study and, thus, the effect level was below that defined for AEGL-1. The human experimental and workplace studies (Piotrowski 1971; Ogata et al. 1986) support the derived values. On the basis of these arguments, the interspecies factor was reduced to 1. An uncertainty factor of 3 was applied for intraspecies variability because, for local effects, the toxicokinetic differences do not vary considerably within and between species. Therefore the toxicokinetic component of the uncertainty factor was reduced to 1, and the factor of 3 for the toxicodynamic component was retained, reflecting a possible variability of the target-tissue response in the human population.

The derived AEGL-1 values are supported by the Sandage (1961) results, in which continuous inhalation of phenol by rhesus monkeys at 5 ppm for 90 days failed to result in any sign of phenol toxicity. Other supporting studies are the pharmacokinetic study by Piotrowski (1971) who exposed subjects at up to 6.5 ppm, and the study by Ogata et al. (1986) who reported a workplace exposure of up to 4.95 ppm. The values are listed in Table 4-6.

A level of distinct odor awareness (LOA) for phenol of 0.25 ppm was derived on the basis of the odor detection threshold from the study of Don (1986) (see Appendix B for LOA derivation). The LOA represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity; about 10% of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception.

TABLE 4-6 AEGL-1 Values for Phenol

AEGL	10 min	30 min	1 h	4 h	8 h
AEGL-1	19 ppm (73 mg/m³)	19 ppm (73 mg/m³)	15 ppm (58 mg/m³)	9.5 ppm (37 mg/m³)	6.3 ppm (24 mg/m³)

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

Inhalation data relevant for the derivation of AEGL-2 values are lacking.

Baker et al. (1978) described an incidence in which residents drank contaminated well water for several weeks following an accidental spill of phenol. Among persons exposed to phenol at more than 1 mg/L of contaminated drinking water for several weeks (the authors estimated an intake of phenol of 10-240 mg/d), gastrointestinal symptoms (diarrhea, nausea, and burning pain and sores in the mouth), and skin rashes occurred (Baker et al. 1978).

Ruth (1986) reported an irritation threshold at 182.4 mg/m³ (47 ppm) in humans. The author tabulated the odor and irritation threshold for a large number of chemicals but did not indicate the source for the values.

6.2. Animal Data Relevant to AEGL-2

Flickinger (1976) reported that exposure of six female Harlan-Wistar rats for 8 h to a nominal phenol aerosol at 900 mg/m³ caused no deaths but resulted in ocular and nasal irritation as well as slight loss of coordination with spasms of the muscle groups within 4 h and tremors and prostration (in one of six rats) within 8 h. Rats appeared normal the following day. Because the aerosol concentration was below the vapor pressure at room temperature, it is likely that the animals were actually exposed to phenol vapor (or a vapor-aerosol mixture), and it is thus considered adequate to convert the aerosol concentration of 900 mg/m³ to an equivalent vapor concentration of 234 ppm.

After exposure of rats to phenol at 211 or 156 ppm for 4 h, a decreased white blood cell count was observed (Brondeau et al. 1990). The authors did not explicitly state the absence of other effects. Deichmann et al. (1944) found that 5 of 12 guinea pigs died after 20 exposures to phenol at 26-52 ppm for 7 h/d, 5 d/wk. Rabbits exposed under the same conditions for 88 days developed degeneration and necrosis in heart, liver, and kidney. Rats exposed for 74 days showed neither clinical signs nor histologic alterations. It should be noted that these 1940s experiments did not include concurrent control groups.

In the study of Dalin and Kristoffersson (1974), rats continuously exposed at 26 ppm showed increased activity about 1 day after exposure, impaired balance, disordered walking, muscle twitches, and involuntary head movements during the third and fourth days. The symptoms disappeared during the fifth day.

6.3. Derivation of AEGL-2

Due to the lack of more adequate studies, a combination of the Flickinger (1976) and Brondeau et al. (1990) studies was used as the basis for derivation of AEGL-2 values. Aerosol exposure to phenol at 900 mg/m³ (equivalent to phenol vapor at 234 ppm) for 8 h resulted in ocular and nasal irritation, slight loss of coordination, and spasms of the muscle groups at 4 h into the exposure; after 8 h, additional symptoms (tremor, incoordination, and prostration) were observed in one of the six animals. No deaths occurred. This study is supported by the study of Brondeau et al. (1990), who reported only slight effects after exposure to phenol vapor at 211 ppm for 4 h. Although both studies had shortcomings, that is, aerosol exposures, nominal concentrations, and no description of toxic signs in one study, taken together, they had consistent results. Because the aerosol concentration was below the saturated vapor concentration at room temperature of about 530 ppm, it can be assumed that much phenol had evaporated from the aerosol so that a mixed aerosol-vapor exposure can be assumed for the Flickinger (1976) study. A significant difference between vapor and aerosol inhalation toxicity was considered unlikely because phenol causes systemic effects, that is, acute CNS depression, and has a high penetration of dermal and mucosal surfaces. Therefore, it was considered adequate to calculate and use the phenol vapor concentration corresponding to a phenol aerosol concentration of 900 mg/m³. The aerosol concentration of 900 mg/m³ is equivalent to a vapor concentration of 234 ppm. The derivation of AEGL-2 values was based on an exposure concentration of 234 ppm for 8 h.

Time scaling using the equation $C^n \times t = k$ was carried out to derive exposure duration-specific values. Due to lack of a definitive dataset, a default value for n of 3 was used in the exponential function for extrapolation from the experimental period (8 h) to shorter exposure periods. For the 10-min AEGL-2, the 30-min value was applied because the derivation of AEGL values was based on a long experimental exposure period, and no supporting studies using short exposure periods were available for characterizing the concentration-time-response relationship. The calculations of exposure concentrations scaled to AEGL-2 time periods are shown in Appendix A.

A total uncertainty factor of 10 was used. An uncertainty factor of 3 was applied for interspecies variability because oral lethal data did not indicate a high variability between species (cf. section 4.4.1.) and because application of a higher uncertainty factor would have resulted in AEGL-2 values below levels that humans can stand without adverse effects (Piotrowski 1971; Ogata et al. 1986). An uncertainty factor of 3 was applied for intraspecies variability because the study of Baker et al. (1978) who investigated health effects in members of 45 families (including children and elderly) that were exposed to phenol through contaminated drinking water for several weeks did not indicate that symptom incidence or symptom severity was higher in any specific subpopulation. Moreover, newborns and infants were not considered more susceptible than adults because of their smaller metabolic capacity to form toxic phenol metabolites (cf.

section 4.4.2.). Based on the small database and study shortcomings, a modifying factor of 2 was applied.

The calculations of AEGL-2 values are shown in Appendix A, and the values are listed in Table 4-7.

Comparison of the AEGL-2 values with the RD_{50} in mice of 166 ppm (De Ceaurriz et al. 1981) supports the derived values.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

Case reports described lethal poisonings in adults after ingestion of doses of about 166-874 mg/kg (see Table 4-3) (Bennett et al. 1950; Stajduhar-Caric 1968; Tanaka et al. 1998; Kamijo et al. 1999). In a newborn baby, tissue concentrations between 125 and 202 mg/kg were found after lethal dermal phenol exposure (Hinkel and Hintzel 1968).

The study by Heuschkel and Felscher (1983) reporting the death of a newborn baby after exposure to phenol at 5.2 ppm for 5-6 h and 1.3 ppm for another 14-15 h will not be used for derivation of AEGL-3 values because (1) use of solid sorbent test tubes for measurement did not allow accurate determination of the exposure concentration, (2) the concomitant exposure to formaldehyde at 24.9 ppm (measured at 2 h) for 5-6 h and at 41.5 ppm (highest concentration, with decrease over time; also measured using test tubes) has probably contributed to death, and (3) the newborn had a congenital pulmonary adaptation disorder, which probably rendered it vulnerable to phenol (and formaldehyde) inhalation.

7.2. Animal Data Relevant to AEGL-3

Deichmann et al. (1944) found that 5 of 12 guinea pigs died after 20 exposures to phenol at 26-52 ppm for 7 h/d, 5 d/wk; under the same conditions, rabbits exposed for 88 days showed no signs of poisoning but developed degeneration and necrosis in heart, liver, and kidney, and rats exposed for 74 days showed neither clinical signs nor histologic alterations. These experiments lacked control groups.

Oral lethal doses of phenol at 420 mg/kg for rabbits and 400-650 mg/kg for rats have been reported (Deichmann and Witherup 1944).

TABLE 4-7 AEGL-2 Values for Phenol

AEGL	10 min	30 min	1 h	4 h	8 h
AEGL-2	29 ppm (110 mg/m³)	29 ppm (110 mg/m³)	23 ppm (90 mg/m³)	15 ppm (57 mg/m³)	12 ppm (45 mg/m³)

7.3. Derivation of AEGL-3

The study by Deichmann et al. (1944) was not used as key study due to the uncertainties in the exposure concentration and because deaths were observed only after repeated exposure. Although phenol is a high-production-volume chemical, no acceptable vapor or aerosol LC_{50} studies in experimental animals or suitable reports on lethality after inhalation exposure in humans were available for the derivation of AEGL-3. Therefore, due to insufficient data and the uncertainties of a route-to-route extrapolation, AEGL-3 values were not recommended (Table 4-8).

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

The AEGL values for various levels of effects and various time periods are summarized in Table 4-9. They were derived using the following key studies and methods.

The AEGL-1 was based on a repeated inhalation exposure study in rats (Huntingdon Life Sciences 1998; Hoffman et al. 2001), which found no clinical, hematologic or histopathologic effects after exposure to phenol at 25 ppm (highest concentration used) for 6 h/d, 5 d/wk for 2 weeks. A total uncertainty factor of 3 was applied. The other exposure duration-specific values were derived by

TABLE 4-8 AEGL-3 Values for Phenol[a]

AEGL	10 min	30 min	1 h	4 h	8 h
AEGL-3	N.R. [a]	N.R.	N.R.	N.R.	N.R.

[a]Not recommended because of insufficient data.

TABLE 4-9 Summary of AEGL Values for Phenol[a]

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	19 ppm (73 mg/m³)	19 ppm (73 mg/m³)	15 ppm (58 mg/m³)	9.5 ppm (37 mg/m³)	6.3 ppm (24 mg/m³)
AEGL-2 (Disabling)	29 ppm (110 mg/m³)	29 ppm (110 mg/m³)	23 ppm (90 mg/m³)	15 ppm (57 mg/m³)	12 ppm (45 mg/m³)
AEGL-3 (Lethal)	N.R. [b]	N.R.	N.R.	N.R.	N.R.

[a]Skin contact with molten phenol or concentrated phenol solutions should be avoided; dermal penetration is rapid and fatal intoxications have been observed when a small part of the body surface was involved.
[b]Not recommended because of insufficient data.

time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of n = 3 for shorter exposure periods and n = 1 for longer exposure periods. For the 10-min AEGL-1, the 30-min value was applied.

The AEGL-2 was based on a combination of the Flickinger (1976) and Brondeau et al. (1990) studies. Aerosol exposure to phenol at 900 mg/m³ (equivalent to phenol vapor at 234 ppm) for 8 h resulted in ocular and nasal irritation, slight loss of coordination, and spasms of the muscle groups at 4 h into the exposure; after 8 h, additional symptoms (tremor, incoordination, and prostration) were observed in one of the six animals. No deaths occurred. This study is supported by the study of Brondeau et al. (1990), who reported only slight effects after exposure to phenol vapor at 211 ppm for 4 h. The derivation of AEGL-2 values was based on an exposure concentration of 234 ppm for 8 h. A total uncertainty factor of 10 was used. A modifying factor of 2 was applied. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of n = 3 for shorter exposure periods. For the 10-min AEGL-2, the 30-min value was applied.

No relevant studies of adequate quality were available for the derivation of the AEGL-3 value. Therefore, due to insufficient data, AEGL-3 values were not recommended.

All inhalation data are summarized in Figure 4-1. Data were classified into severity categories consistent with the definitions of the AEGL health effects. The category severity definitions are “no effect,” “discomfort,” “disabling,” “lethal,” and “some lethality” (animals that did not die at an experimental lethal concentration at which other animals died). Note that the AEGL values are designated as triangles without an indication to their level. AEGL-3 values were not recommended. The AEGL-2 values are higher than the AEGL-1 values.

8.2. Comparison with Other Standards and Criteria

Standards and guidance levels for workplace and community exposures are listed in Table 4-10. In addition, biologic exposure values exist: the ACGIH BEI (Biological Exposure Index) is 250 mg of phenol per gram of creatinine in urine at the end of shift (ACGIH 1996), and the German BAT (Biologischer Arbeitsstoff-Toleranz-Wert; biologic tolerance value) is 300 mg of phenol per liter post-shift urine (Henschler und Lehnert 1990).

8.3. Data Adequacy and Research Needs

Definitive studies assessing health effects of phenol in humans after a single inhalation exposure are not available. Air odor threshold determinations have been published. Older inhalation studies in animals were often compromised by uncertain quantitation of exposure concentrations. Recent studies in

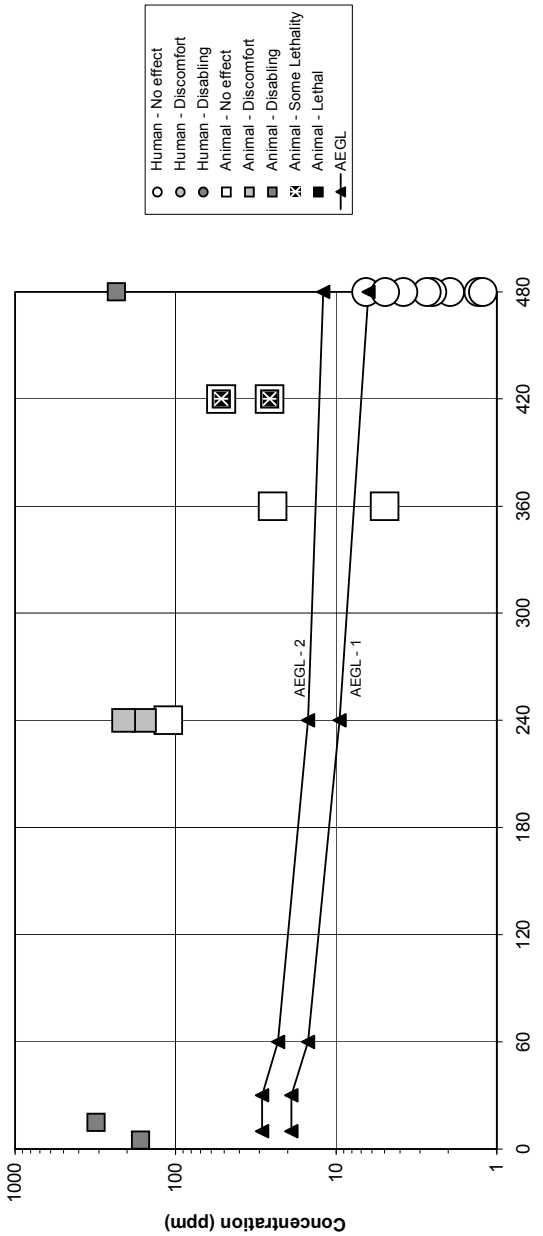

FIGURE 4-1 Categorical representation of all phenol inhalation data.

TABLE 4-10 Extant Standards and Guidelines for Phenol

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	19 ppm	19 ppm	15 ppm	9.5 ppm	6.3 ppm
AEGL-2	29 ppm	29 ppm	23 ppm	15 ppm	12 ppm
AEGL-3	N.R.	N.R.	N.R.	N.R.	N.R.
ERPG-1 (AIHA)[a]			10 ppm		
ERPG-2 (AIHA)			50 ppm		
ERPG-3 (AIHA)			200 ppm		
PEL-TWA (OSHA)[b]					5 ppm
IDLH (NIOSH)[c]		250 ppm			
REL-TWA (NIOSH)[d]					5 ppm (ceiling 15.6 ppm)
TLV-TWA (ACGIH)[e]					5 ppm
MAK (Germany)[f]	The MAK value of 5 ppm and the peak limit of 10 ppm have been withdrawn due to the genotoxic effects of phenol				
MAK Spitzen-begrenzung (Germany)[g]					
MAC (The Netherlands)[h]					2 ppm

[a]ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association) (AIHA 2007). The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. The ERPG-1 for phenol is based on human data in which no adverse effects were observed after exposure at 6.5 ppm for 8 h (Ruth 1986). Also monkeys, rats, and mice exposed at 5 ppm continuously for 90 days were not significantly affected (Sandage 1961). 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-2 for phenol is based on the observation that a 1-h exposure of rats at 312 ppm produced only signs of lacrimation (Flickinger 1976) and on an occupational study that reported eye, nose, and throat irritation after intermittent exposure at 48 ppm phenol and 8 ppm formaldehyde (ACGIH 1996). The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects. The ERPG-3 for phenol is based on the observation that exposure of rats at 235 ppm for 4 h resulted in ocular and nasal irritation, slight loss of coordination and muscular spasms, and no deaths (Flickinger 1976).

[b]OSHA PEL-TWA (Occupational Health and Safety Administration, permissible exposure limits–time-weighted average) (29 CFR 1910.1000 [1989]) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 10 h/d, 40 h/wk.

[c]IDLH (immediately dangerous to life and health, National Institute of Occupational Safety and Health) (NIOSH 1996), is based on acute inhalation toxicity data in animals (Flickinger et al. 1976) and an analogy to cresol, which has a revised IDLH of 250 ppm.

[d]NIOSH REL-TWA (National Institute of Occupational Safety and Health, recommended exposure limits–time-weighted average) (NIOSH 1996), is defined analogous to the ACGIH TLV-TWA.
[e]ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value–time-weighted average) (ACGIH 1996) The time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.
[f]MAK (maximale arbeitsplatzkonzentration [maximum workplace concentration], Deutsche Forschungs-gemeinschaft [German Research Association], Germany) (Greim 1998) is defined analogous to the ACGIH TLV-TWA.
[g]MAK Spitzenbegrenzung (kategorie I) [peak limit category I] (Greim 1998)constitutes the maximum average concentration to which workers can be exposed for a period up to 5 min, with no more than eight exposure periods per work shift; total exposure may not exceed 8-h MAK.
[h]MAC ([maximum workplace concentration], Dutch Expert Committee for Occupational Standards, The Netherlands) (MSZW 2004) is defined analogous to the ACGIH TLV-TWA.

laboratory animals, however, utilized accurate and reliable methods for characterizing exposure concentrations; however, exposure concentrations were often laboratory animals, however, utilized accurate and reliable methods for characterizing exposure concentrations; however, exposure concentrations were often used that did not lead to any adverse effects. Therefore, AEGL-1 values were based on a repeated exposure study in rats, in which no effects were found at the highest exposure concentration tested. AEGL-2 values were derived on the basis of two rat inhalation studies in which, after a single exposure, incoordination and prostration, but no death, were observed, although the number of animals used in the study was very small and data presentation was incomplete. For derivation of AEGL-3 values, studies reporting LC_{50} values in animals were lacking. Therefore, no AEGL-3 values were recommended.

Single inhalation exposure studies that measure duration and concentration-dependent lethality in animals would allow for derivation of an AEGL-3. Quantitative data on the ocular and upper respiratory tract irritant potential of phenol in air for humans are necessary to more accurately assign an AEGL-1.

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APPENDIX A

TIME-SCALING CALCULATIONS FOR AEGLS

AEGL-1 VALUES

Key study:	Huntingdon Life Sciences 1998; Hoffman et al. 2001
Toxicity end point:	Exposure of rats at 0.5, 5 or 25 ppm for 6 h/d, 5 d/wk for 2 weeks did not cause clinical, hematologic or histopathologic effects. A concentration of 25 ppm for 6 h was used as the basis for derivation of AEGL-1 values.
Scaling:	$C^3 \times t = k$ for extrapolation to 4 h, 1 h and 30 min $k = 25^3$ ppm$^3 \times 6$ h = 93,750 ppm^3-h $C^1 \times t = k$ for extrapolation to 8 h $k = 25^1$ ppm $\times 6$ h = 150 ppm-h The AEGL-1 for 10 min was set at the same concentration as the 30-min value.
Uncertainty factors:	Combined uncertainty factor of 3 1 for interspecies variability 3 for intraspecies variability
Calculations:	
10-min AEGL-1	10-min AEGL-1 = 19 ppm (73 mg/m^3)
30-min AEGL-1	$C^3 \times 0.5$ h = 93,750 ppm^3-h C = 57.24 ppm 30-min AEGL-1 = 57.24 ppm/3 = 19 ppm (73 mg/m^3)
1-h AEGL-1	$C^3 \times 1$ h = 93,750 ppm^3-h C = 45.43 ppm 1-h AEGL-1 = 45.43 ppm/3 = 15 ppm (58 mg/m^3)
4-h AEGL-1	$C^3 \times 4$ h = 93,750 ppm^3-h C = 28.62 ppm 4-h AEGL-1 = 28.62 ppm/3 = 9.5 ppm (37 mg/m^3)
8-h AEGL-1	$C^1 \times 8$ h = 150 ppm-h C = 18.75 ppm 8-h AEGL-1 = 18.75 ppm/3 = 6.3 ppm (24 mg/m^3)

AEGL-2 VALUES

Key study:	Flickinger 1976; Brondeau et al. 1990
Toxicity end point:	Aerosol exposure to phenol at 900 mg/m³ (equivalent to phenol vapor at 234 ppm) for 8 h resulted in ocular and nasal irritation, slight loss of coordination and spasms of the muscle groups at 4 h into the exposure, after 8 h additional symptoms (tremor, incoordination and prostration) were observed in one of the six animals. No deaths occurred. This study is supported by the study of Brondeau et al. (1990), which reported only slight effects after exposure to phenol vapor at 211 ppm for 4 h. The derivation of AEGL-2 values was based on an exposure concentration of 234 ppm for 8 h.
Scaling:	$C^3 \times t = k$ for extrapolation to 4 h, 1 h, and 30 min $k = 234^3$ ppm × 8 h = 1.025×10^8 ppm³-h The AEGL-2 for 10 min was set at the same concentration as the 30-min value.
Uncertainty/modifying factors:	Combined uncertainty factor: 10 3 for interspecies variability 3 for intraspecies variability Modifying factor: 2
Calculations:	
10-min AEGL-2	10-min AEGL-2 = 29 ppm (110 mg/m³)
30-min AEGL-2	$C^3 \times 0.5$ h = 1.025×10^8 ppm³-h C = 589.64 ppm 30-min AEGL-2 = 589.64 ppm/20 = 29 ppm (110 mg/m³)
1-h AEGL-2	$C^3 \times 1$ h = 1.025×10^8 ppm³-h C = 468.00 ppm 1-h AEGL-2 = 468.00 ppm/20 = 23 ppm (90 mg/m³)
4-h AEGL-2	$C^3 \times 4$ h = 1.025×10^8 ppm³-h C = 294.82 ppm 4-h AEGL-2 = 294.82 ppm/20 = 15 ppm (57 mg/m³)
8-h AEGL-2	8-h AEGL-2 = 234 ppm/20 = 12 ppm (45 mg/m³)

APPENDIX B

LEVEL OF DISTINCT ODOR AWARENESS

Derivation of the Level of Distinct Odor Awareness (LOA)

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

For derivation of the odor detection threshold (OT_{50}), a study (Don 1986) is available that is considered an equivalent to a CEN (2003) compliant study. The study methodology has been described in TNO (1985). In this study, the odor threshold for the reference chemical *n*-butanol (odor detection threshold 0.04 ppm) has also been determined (Don 1986):

Odor detection threshold for phenol: 0.0102 ppm.
Odor detection threshold for *n*-butanol: 0.026 ppm.
Corrected odor detection threshold (OT_{50}) for phenol: 0.0102 ppm
× 0.04 ppm/0.026 ppm = 0.016 ppm.

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

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

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

$3 = 2.33 \times \log (C/0.013) + 0.5$, which can be rearranged to
$\log (C/0.013) = (3\text{-}0.5)/2.33 = 1.07$ and results in
$C = (10^{1.07}) \times 0.016 = 11.8 \times 0.016 = 0.19$ ppm.

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

to adjust for peak exposure. Adjustment for distraction and peak exposure lead to a correction factor of 4/3 = 1.33.

$$LOA = C \times 1.33 = 0.19 \text{ ppm} \times 1.33 = 0.25 \text{ ppm}.$$

The LOA for phenol is 0.25 ppm.

APPENDIX C

ACUTE EXPOSURE GUIDELINES FOR PHENOL

Derivation Summary for Phenol

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
19 ppm	19 ppm	15 ppm	9.5 ppm	6.3 ppm

Reference: CMA (Chemical Manufacturers Association). 1998. Two-week (ten day) inhalation toxicity and two-week recovery study of phenol vapor in the rat. Huntingdon Life Sciences Study No. 96-6107, CMA Reference No. PHL-4.0-Inhal-HLS. Chemical Manufacturers Association, Phenol Panel, Arlington, VA; Hoffman, G.M., B.J. Dunn, C.R. Morris, J.H. Butala, S.S. Dimond, R. Gingell, and J.M. Waechter, Jr., 2001. Two-week (ten-day) inhalation toxicity and two-week recovery study of phenol vapor in the rat. International Journal of Toxicology 20:45-52.

Test Species/Strain/Number: Rats/Fischer 344/20/sex/group.

Exposure Route/Concentrations/Durations: Inhalation /0, 0.5, 5 or 25 ppm/6 h/d, 5 d/wk for 2 weeks (half of the animals were killed for analysis at the end of the exposure period and the other half after a 2-week recovery period).

Effects: No differences between controls and phenol-exposed animals for clinical observations, body weights, food consumption, and clinical pathology were found. The authors stated that "scattered observations of chromodacryorrhea and nasal discharge were noted during the 2 weeks of exposure. However, they did not appear in a clearly treatment-related pattern and mostly abated during the 2-week recovery period." While this was true for chromodacryorrhea, the summary tables of in-life physical observations reported the following incidences of red nasal discharge in the control group and 0.5-ppm, 5-ppm, and 25-ppm groups: 0/20, 0/20, 3/20, and 4/20 males and 0/20, 0/20, 1/20, and 0/20 females in the first week and 0/20, 0/20, 7/20, and 10/20 males and 0/20, 1/20, 3/20, and 0/20 females in the second week. No differences between controls and phenol-exposed animals for organ weights and macroscopic and microscopic postmortem examinations were reported. Complete macroscopic evaluations were conducted on all animals. Microscopic evaluations were conducted on the liver, kidney, respiratory tract tissues (examined organs were nasopharyngeal tissues, larynx, trachea, and lungs), and gross lesions for animals in the control and high-exposure groups at termination and recovery. For histopathology of nasopharyngeal tissues, the skull, after decalcification, was serially sectioned transversely at approximately 3-µm intervals, and routinely, four sections were examined per animal.

End Point/Concentration/Rationale: Although phenol does not seem to be a strong irritant, it causes local tissue damage in the respiratory tract as evidenced by the histopathologic findings after repeated exposure described by Deichmann et al. (1944) for guinea pigs and rabbits. At higher concentrations, phenol causes irritation in rats (Flickinger 1976) and respiratory depression in mice (De Ceaurriz et al. 1981).

(Continued)

AEGL-1 VALUES Continued

10 min	30 min	1 h	4 h	8 h
19 ppm	19 ppm	15 ppm	9.5 ppm	6.3 ppm

The pharmacokinetic study in humans (Piotrowski 1971) was not used as a key study because it did not report on health effects. The Sandage (1961) study was not used because, apparently, exposure chambers did not allow observation of monkeys during the exposure, and histopathology was performed on the lungs but not on the upper respiratory tract so that possible upper airway irritation was not adequately evaluated. Therefore, the study by Huntingdon Life Sciences 1998 (published as Hoffman et al. 2001) was the only study fulfilling the SOP requirements for a key study and was therefore used for derivation of AEGL-1 values, although it was a repeated exposure study. After exposure of rats for 6 h/d, 5 d/wk for 2 weeks, no histopathologic alterations of the epithelium of the nasal turbinates or other respiratory tract tissues were found. The observation of red nasal discharge in a few male rats of the 5-ppm and 25-ppm groups was not considered a relevant effect, because no clear dose-response relationship was found and because predominantly males, but not females, showed this effect. Moreover, red nasal discharge occurs at the plexus antebrachii, which is very prominent in the rat, and extravasation of red blood cells visible as red nasal discharge is caused easily in the rat not only by locally acting chemicals but also by stress, dry air, or upper respiratory tract infections. The derivation of AEGL-1 values was based on an exposure concentration of 25 ppm for 6 h.

Uncertainty Factors/Rationale:
Total uncertainty factor: 3

Interspecies: 1, the toxicokinetic component of the uncertainty factor was reduced to 1 because toxic effects are mostly caused by phenol itself without requirement for metabolism; moreover, possible local irritation effects depend primarily on the phenol concentration in inhaled air with little influence of toxicokinetic differences between species. The starting point for AEGL derivation was a NOAEL from a repeated exposure study and, thus, the effect level was below that defined for AEGL-1. The human experimental and workplace studies (Piotrowski 1971; Ogata et al. 1986) support the derived values. Therefore, the interspecies factor was reduced to 1.

Intraspecies: 3, because for local effects, the toxicokinetic differences do not vary considerably within and between species. Therefore the toxicokinetic component of the uncertainty factor was reduced to 1 and the factor of 3 for the toxicodynamic component was retained, reflecting a possible variability of the target-tissue response in the human population.

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Not applicable.

Time Scaling: The equation $C^n \times t = k$ was used to derive exposure duration-specific values. Due to lack of a definitive dataset, a default value for n of 3 was used in the exponential function for extrapolation from the experimental period (6 h) to shorter exposure periods and a default value for n of 1 was used for extrapolation to longer exposure times. For the 10-min AEGL-1, the 30-min value was applied because the derivation of AEGL values was based on a long experimental exposure period, and no supporting studies using short exposure periods were available for characterizing the concentration-time-response relationship.

(Continued)

AEGL-1 VALUES Continued

10 min	30 min	1 h	4 h	8 h
19 ppm	19 ppm	15 ppm	9.5 ppm	6.3 ppm

Data Adequacy: No study assessing irritative effects in humans was available. However, in two toxicokinetic studies, no statement was made on the presence or absence of effects in humans exposed experimentally at up to 6.5 ppm for 8 h (with 2 × 30 min breaks) (Piotrowski 1971) or exposed at the workplace to a mean workshift concentration of up to 4.95 ppm (Ogata et al. 1986). The derived AEGL-1 values are supported by the study of Sandage (1961), in which continuous exposure of rhesus monkeys at 5 ppm phenol for 90 days did not result in any signs of toxicity.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
29 ppm	29 ppm	23 ppm	15 ppm	12 ppm

Reference: Flickinger, C.W. 1976. The benzenediols: catechol, resorcinol, and hydroquinone—a review of the industrial toxicology and current industrial exposure limits. American Industrial Hygiene Association Journal 37:596-606.

Brondeau, M.T., P. Bonnet, J.P. Guenier, P. Simon, and J. de Ceaurriz. 1990. Adrenal-dependent leucopenia after short-term exposure to various airborne irritants in rats. Journal of Applied Toxicology 10:83-86.

Test Species/Strain/Sex/Number: (a) Rat /Wistar /6 females (b) Rat/Sprague-Dawley/ not stated.

Exposure Route/Concentrations/Durations:
Inhalation/900 mg phenol/m³ aerosol/8 h
Inhalation/111, 156 or 211 ppm/4 h

Effects: Ocular and nasal irritation were observed, as well as slight loss of coordination with spasms of the muscle groups within 4 h and tremors and prostration (in 1/6 rats) within 8 h. Rats appeared normal the following day and had normal 14-day weight gains. No deaths occurred. No lesions attributable to inhalation of the aerosol were seen at gross autopsy. The total white blood cell count was significantly decreased after exposure to 156 or 211 ppm; no effect was observed at 111 ppm. Other signs of toxicity were not evaluated. The authors interpreted this finding as a result of increased secretion of corticosteroids as a response to sensory irritation.

End Point/Concentration/Rationale: Due to the lack of more adequate studies, a combination of the Flickinger (1976) and Brondeau et al. (1990) studies was used as the basis for derivation of AEGL-2 values. Aerosol exposure at 900 mg/m³ (equivalent to phenol vapor at 234 ppm) for 8 h resulted in ocular and nasal irritation, slight loss of coordination, and spasms of the muscle groups at 4 h into the exposure; after 8 h, additional symptoms (tremor, incoordination, and prostration) were observed in 1/6 animals. No deaths occurred. This study is supported by the study of Brondeau et al. (1990), who reported only slight effects after exposure to phenol vapor at 211 ppm for 4 h. Although both studies had shortcomings, that is, aerosol exposures, nominal concentrations, and no description of toxic signs in one study, taken together, they had

(Continued)

AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
29 ppm	29 ppm	23 ppm	15 ppm	12 ppm

consistent results. It was considered adequate to calculate and use the phenol vapor concentration corresponding to a phenol aerosol concentration of 900 mg/m³. The aerosol concentration of 900 mg/m³ is equivalent to a vapor concentration of 234 ppm. The derivation of AEGL-2 values was based on an exposure concentration of 234 ppm for 8 h.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10

Interspecies: 3, because oral lethal data did not indicate a high variability between species (cf. section 4.4.1.), and because application of a higher uncertainty factor would have resulted in AEGL-2 values below levels that humans can stand without adverse effects (Piotrowski 1971; Ogata et al. 1986).

Intraspecies: 3, because the study of Baker et al. (1978) who investigated health effects in members of 45 families (including children and elderly) that were exposed to phenol through contaminated drinking water for several weeks did not indicate that symptom incidence or symptom severity was higher in any specific subpopulation. Moreover, newborns and infants were not considered more susceptible than adults because of their smaller metabolic capacity to form toxic phenol metabolites (cf. section 4.4.2.).

Modifying Factor: 2, because of the small data base and study shortcomings.

Animal to Human Dosimetric Adjustment: Not applicable, local irritative effect.

Time Scaling: The equation $C^n \times t = k$ was used to derive exposure duration-specific values. Due to lack of a definitive dataset, a default value of n of 3 was used in the exponential function for extrapolation from the experimental period (8 h) to shorter exposure periods. For the 10-min AEGL-2, the 30-min value was applied because the derivation of AEGL values was based on a long experimental exposure period and no supporting studies using short exposure periods were available for characterizing the concentration-time-response relationship.

Data Adequacy: Both studies used for the AEGL-2 derivation had shortcomings, that is, aerosol exposures, nominal concentrations, and no description of toxic signs in one study. Nevertheless, the studies had consistent results, and the derived values are supported by the overall toxicity profile of phenol.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
N.R.	N.R.	N.R.	N.R.	N.R.

Reference: Not applicable.

Test Species/Strain/Sex/Number: Not applicable.

Exposure Route/Concentrations/Durations: Not applicable.

Effects: Not applicable.

(Continued)

AEGL-3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
N.R.	N.R.	N.R.	N.R.	N.R.

End Point/Concentration/Rationale: The study by Deichmann et al. (1944) was not used as a key study because of the uncertainties in the exposure concentration and because deaths were observed only after repeated exposure. No acceptable vapor or aerosol LC_{50} studies in experimental animals or suitable reports on lethality after inhalation exposure in humans were available for the derivation of AEGL-3. Therefore, due to insufficient data and the uncertainties of a route-to-route extrapolation, AEGL-3 values were not recommended.

Uncertainty Factors/Rationale: Not applicable.

Modifying Factor: Not applicable.

Animal to Human Dosimetric Adjustment: Insufficient data.

Time Scaling: Not applicable.

Data Adequacy: Adequate animal data relevant for the derivation of AEGL-3 values are not available.