Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 7

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

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Preface

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

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

Using the 1993 and 2001 NRC guidelines reports, the NAC—consisting of members from EPA, the 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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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

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

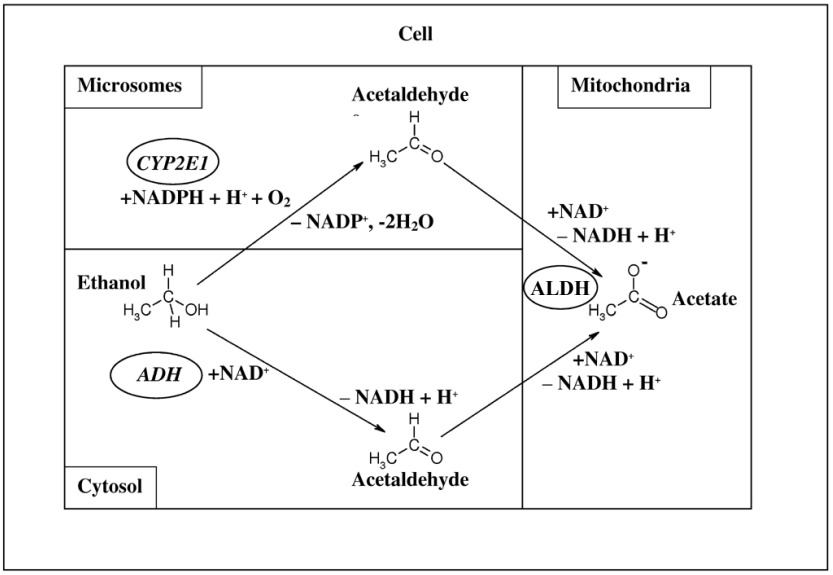

FIGURE 2-1 Oxidative pathways of ethanol metabolism. Abbreviations: ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; CYP2E1, cytochrome P-450 2 E1.

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.

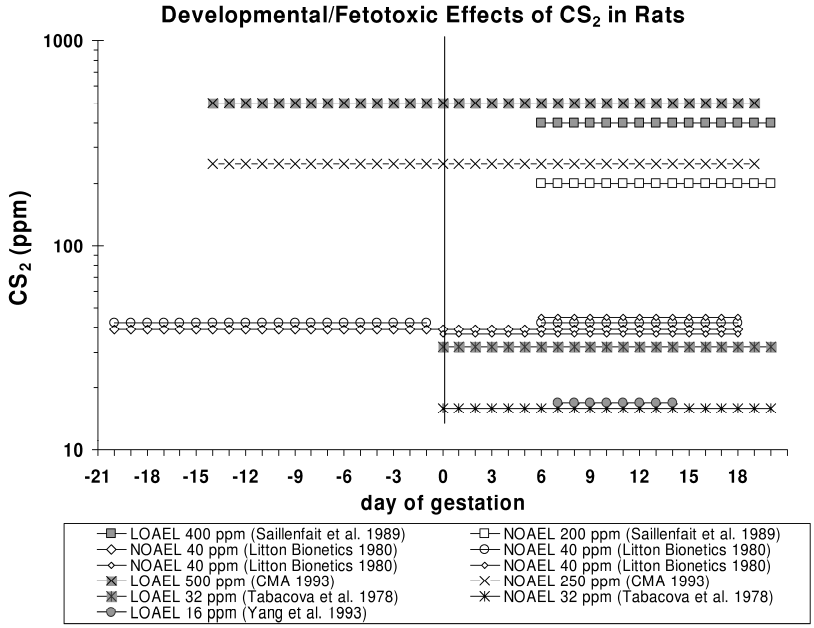

FIGURE 2-2 Overview of developmental and fetotoxicity studies with CS_2 in rats.

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

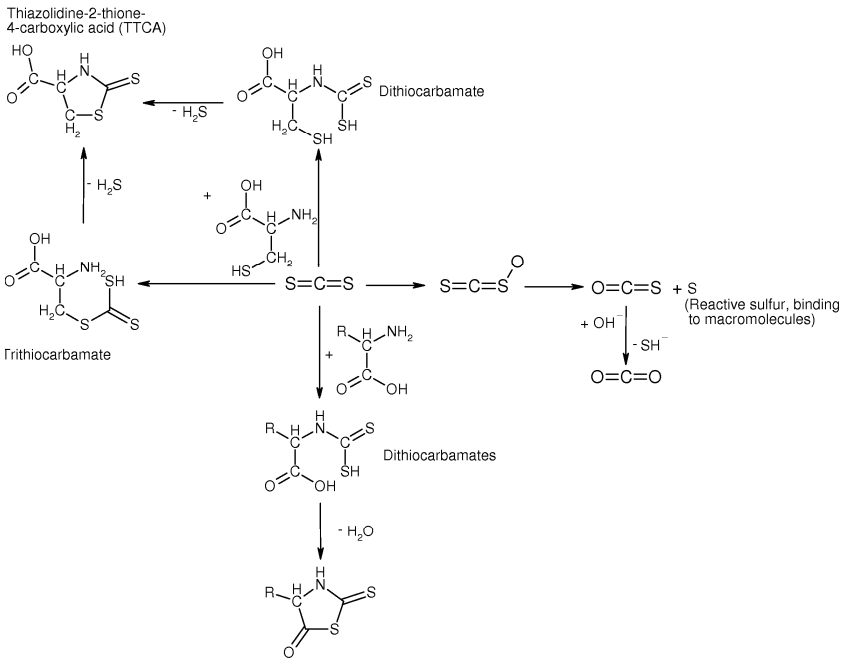

FIGURE 2-3 Principles of metabolic pathways for carbon disulfide.

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.

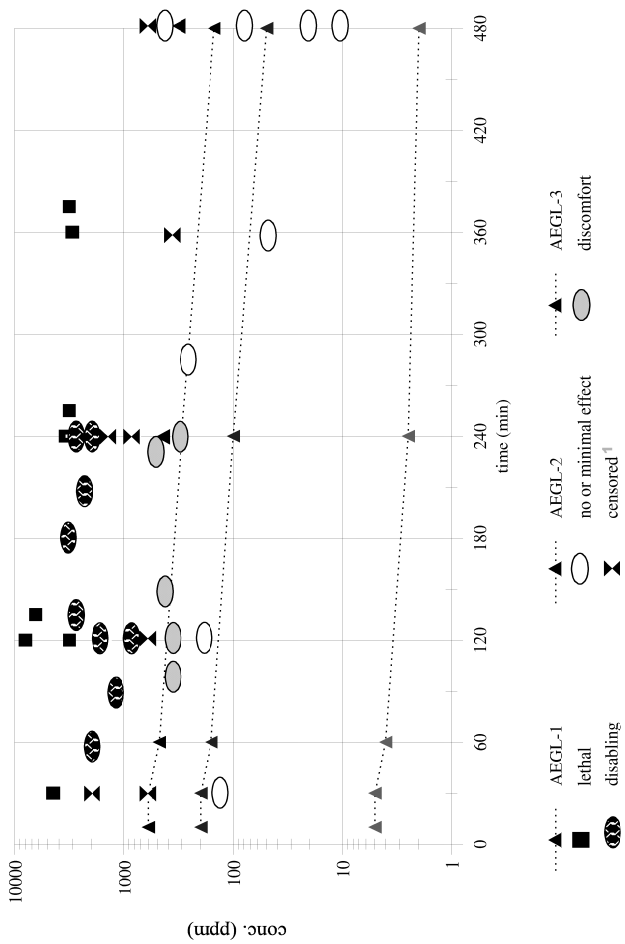

FIGURE 2-4 Categorical representation of all carbon disulfide inhalation data. Note: 1, severity category could not be established.

TABLE 2-10 Extant Standards and Guidelines for Carbon Disulfide

	Exposure duration						
Guideline	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 × 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 × 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 × 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.