Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 17

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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Preface

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

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

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

In 1998, EPA and DOD requested that the NRC independently review the AEGLs developed by NAC. In response to that request, the NRC organized within its Committee on Toxicology (COT) the Committee on Acute Exposure Guideline Levels, which prepared this report. This report is the seventeenth vol*xiv Preface*

ume in that series. AEGL documents for acrylonitrile, carbon tetrachloride, cyanogen, epichlorohydrin, ethylene chlorohydrin, toluene, trimethylacetyl chloride, hydrogen bromide, and boron tribromide are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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

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

The interim reports of the committee that led to this report were reviewed in draft form by individuals selected for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of the committee interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for acrylonitrile (interim reports 19b, 21a, and 22), carbon tetrachloride (interim reports 13, 14, 18, and 22), cyanogen (interim report 19a), epichlorohydrin (interim reports 15, 19a, 20a, and 21a), ethylene chlorohydrin (interim reports 20a and 21a), toluene (interim reports 12, 18, and 22), trimethylacetyl chloride (interim reports 20a and 21a), hydrogen bromide (interim reports 16, 18, and 22), and boron tribromide (interim reports 19a and 22): Deepak Bhalla (Wayne State University), Harvey Clewell (The Hamner Institutes for Health Sciences), Jeffrey Fisher (U.S. Food and Drug Administration), David Gaylor (Gaylor and Associates, LLC), Sam Kacew (University of Ottawa), A. Wallace Hayes (Harvard School of Public Health), Rogene Henderson (Lovelace Respiratory Research Institute [retired]), James McDougal (Wright State University [retired]), Charles Reinhardt (DuPont Haskell Laboratory [retired]), Andrew Salmon (California Environmental Protection Agency), Joyce Tsuji (Exponent, Inc.), Bernard Wagner (New York University Medical Center [retired]), and Judith Zelikoff (New York University).

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of this volume before its re

lease. The review of interim reports was overseen by David Gaylor (Gaylor and Associates, LLC), Sidney Green, Jr., (Howard University), and Robert Goyer (University of Western Ontario [retired]). Appointed by the NRC, they were responsible for making certain that an independent examination of the interim reports was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The committee gratefully acknowledges the valuable assistance provided by Ernest Falke and Iris A. Camacho from EPA. The committee also acknowledges Susan Martel, the project director for her work this project. Other staff members who contributed to this effort are James J. Reisa (director of the Board on Environmental Studies and Toxicology), Radiah Rose (manager of editorial projects), Mirsada Karalic-Loncarevic (manager of the Technical Information Center), and Tamara Dawson (program associate). Finally, I would like to thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

Edward C. Bishop, *Chair*
Committee on Acute Exposure
Guideline Levels

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

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

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

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

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

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

but of short duration, usually less than 1 hour (h), and only once in a lifetime for the general population, which includes infants (from birth to 3 years of age), children, the elderly, and persons with diseases, such as asthma or heart disease.

The National Research Council (NRC) Committee on Toxicology (COT) has published many reports on emergency exposure guidance levels and spacecraft maximum allowable concentrations for chemicals used by the U.S. Department of Defense (DOD) and the National Aeronautics and Space Administration (NASA) (NRC 1968, 1972, 1984a,b,c,d, 1985a,b, 1986a, 1987, 1988, 1994, 1996a,b, 2000a, 2002a, 2007a, 2008a). COT has also published guidelines for developing emergency exposure guidance levels for military personnel and for astronauts (NRC 1986b, 1992, 2000b). Because of COT's experience in recommending emergency exposure levels for short-term exposures, in 1991 EPA and ATSDR requested that COT develop criteria and methods for developing emergency exposure levels for EHSs for the general population. In response to that request, the NRC assigned this project to the COT Subcommittee on Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. The report of that subcommittee, *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993), provides step-by-step guidance for setting emergency exposure levels for EHSs. Guidance is given on what data are needed, what data are available, how to evaluate the data, and how to present the results.

In November 1995, the National Advisory Committee (NAC)[3] for Acute Exposure Guideline Levels for Hazardous Substances was established to identify, review, and interpret relevant toxicologic and other scientific data and to develop acute exposure guideline levels (AEGLs) for high-priority, acutely toxic chemicals. The NRC's previous name for acute exposure levels—community emergency exposure levels (CEELs)—was replaced by the term AEGLs to reflect the broad application of these values to planning, response, and prevention in the community, the workplace, transportation, the military, and the remediation of Superfund sites.

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

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

varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

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

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

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

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

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

As described in *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993) and the NRC guidelines report *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals* (NRC 2001a), the first step in establishing AEGLs for a chemical is to collect and review all relevant published and unpublished information. Various types of evidence are assessed in establishing AEGL values for a chemical. These include information from (1) chemicalphysical 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 noobserved-adverse-effect level (NOAEL) and the mode of action of the substance in question. When available, pharmacokinetic data on tissue doses are considered for interspecies extrapolation.

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

REVIEW OF AEGL REPORTS

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

The AEGL draft reports were initially prepared by ad hoc AEGL development teams consisting of a chemical manager, chemical reviewers, and a staff scientist of the NAC contractors—Oak Ridge National Laboratory and subsequently SRC, Inc. The draft documents were then reviewed by NAC and elevated from "draft" to "proposed" status. After the AEGL documents were approved by NAC, they were published in the *Federal Register* for public comment. The reports were then revised by NAC in response to the public

comments, elevated from "proposed" to "interim" status, and sent to the NRC Committee on Acute Exposure Guideline Levels for final evaluation.

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

Because of the enormous amount of data presented in AEGL reports, the NRC committee cannot verify all of the data used by NAC. The NRC committee relies on NAC and the contractors for the accuracy and completeness of the toxicity data cited in the AEGL reports. Thus far, the committee has prepared sixteen reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009, 2010a,b, 2011, 2012a,b,c, 2013a,b, 2014). This report is the seventeenth volume in that series. AEGL documents for acrylonitrile, carbon tetrachloride, cyanogen, epichlorohydrin, ethylene chlorohydrin, toluene, trimethylacetyl chloride, hydrogen bromide, and boron tribromide are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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Appendixes

2

Carbon Tetrachloride[4]

Acute Exposure Guideline Levels

PREFACE

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

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

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

[4] This document was prepared by the AEGL Development Team composed of Robert Young (Oak Ridge National Laboratory), Gary Diamond (SRC, Inc.), Julie Klotzbach (SRC, Inc.), Chemical Manager William Bress (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (U.S. Environmental Protection Agency). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

experience notable discomfort, irritation, or certain asymptomatic, nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

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

SUMMARY

Carbon tetrachloride is a colorless, nonflammable, heavy liquid that is only slightly soluble in water. It is used as a laboratory and industrial solvent, an intermediate in the synthesis of trichlorofluoromethane and dichlorodifluoromethane, and was formerly used as a dry-cleaning agent, grain fumigant, anthelmintic (destructive to worms, especially parasitic varieties), and fire suppressant.

Numerous case reports were available on acute inhalation exposure of humans to carbon tetrachloride, but most lacked adequate exposure characterization. These reports, however, affirmed the hepatotoxic and renal toxicity of carbon tetrachloride, as well as a delayed response for serious and fatal effects. Additionally, data from controlled exposures of humans to carbon tetrachloride were also available.

Animal toxicity data on carbon tetrachloride indicate hepatotoxic and renal effects, as well as anesthetic-like effects, as primary end points. The most sensitive end point for evaluating the toxicity of carbon tetrachloride in animals appears to be measurement of serum-enzyme activities that reflect hepatic damage. Several studies provided lethality data for various concentrations and exposure durations,

but data on nonlethal effects were few or available only from long-term exposure studies.

Studies in animals have shown the metabolism and disposition of carbon tetrachloride to be complex and varied between species. Although the precise mechanism of toxicity is equivocal, the biotransformation of carbon tetrachloride by the monooxygenase enzymes (specifically CYP2E1) to reactive intermediates is critical for expression of toxicity. That activation process is critical in modifying the toxic response to carbon tetrachloride.

Data on carbon tetrachloride were inadequate to derive AEGL-1 values, so no values are recommended.

AEGL-2 values for carbon tetrachloride were derived on the basis of the highest no-effect level of 76 ppm for central nervous system (CNS) effects in humans exposed for 4 h (Davis 1934). An interspecies uncertainty factor of 1 was used because the study was conducted in humans. An intraspecies uncertainty factor of 10 was applied to account for individuals who may be more susceptible to the toxic effects of carbon tetrachloride (e.g., variability in metabolism and disposition). Temporal scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986), where an empirical value of n was determined to be 2.5 on the basis of rat lethality data.

AEGL-3 values for carbon tetrachloride were based on a 1-h LC_{01} (lethal concentration, 1% lethality) of 5,135.5 ppm on the basis of data from multiple studies in laboratory rats (Adams et al. 1952; Dow Chemical 1960). Results of a physiologically-based pharmacokinetic (PBPK) model predict that rodents will attain higher concentrations of carbon tetrachloride in venous blood and fat than would similarly exposed humans, with greater metabolism of carbon tetrachloride by rats relative to humans (Paustenbach et al. 1988; Delic et al. 2000). PBPK models predict that at equal exposure concentrations, humans will have lower rates of production of reactive metabolites of carbon tetrachloride (human ÷ rat = 0.5). On the basis of PBPK modeling, the amount of toxic metabolites produced in humans would be approximately half the amount in the rodent. Therefore, the toxicokinetic component of the interspecies uncertainty factor is 0.5. The toxicodynamic component is 3. The total interspecies uncertainty factor is 1.5 (3 × 0.5 = 1.5). An intraspecies uncertainty factor of 10 was applied to account for individuals who may be more susceptible to the toxic effects of carbon tetrachloride (e.g., variability in metabolism and disposition of carbon tetrachloride). Thus, the total uncertainty factor is 15. Temporal scaling was performed in the same manner as that for the AEGL-2 values.

The US Environmental Protection Agency (EPA 2010a, b) derived an inhalation unit risk for carbon tetrachloride of 6×10^{-6} per $\mu g/m^3$, and judged that the chemical is "likely to be carcinogenic to humans" on the basis of inadequate evidence of carcinogenicity in humans and sufficient evidence in animals by oral and inhalation exposure. Hepatic tumors were found in several species (rat, mouse, and hamster) and pheochromocytomas (adrenal gland tumors) were found

in mice. Carbon tetrachloride is classified as a Group 2B carcinogen (possibly carcinogenic to humans) by the International Agency for Research on Cancer. The National Toxicology Program has classified carbon tetrachloride as reasonably anticipated to be a human carcinogen. Extrapolation of EPA's inhalation unit risk to AEGL-specific exposure durations results in 10^{-4} cancer risk estimates at exposure concentrations that are higher than AEGL-2 values. AEGL values for carbon tetrachloride are presented in Table 2-1.

1. INTRODUCTION

Carbon tetrachloride is a colorless, nonflammable, and heavy liquid (O'Neil et al. 2006). It has been used as a laboratory and industrial solvent, as an intermediate in the synthesis of trichlorofluoromethane and dichlorodifluoromethane, and was formerly used as a dry-cleaning agent, grain fumigant, anthelmintic (destructive to worms, especially parasitic varieties), and as a fire suppressant (Walsh 1989). Carbon tetrachloride has a sweet, pungent odor that is not unpleasant. An odor threshold of 21.4-238.5 ppm has been reported (Billings and Jones 1981; Ruth 1989).

The hepatotoxicity of carbon tetrachloride is well documented and has been reviewed by Rechnagel and Glende (1973). Carbon tetrachloride is also known to affect the CNS and to induce renal toxicity. The toxicity of carbon tetrachloride has been summarized by ATSDR (2005). For derivation of AEGL values, acute exposure studies are preferentially examined in this chapter. Subchronic and chronic studies generally have not been included because of the uncertainty associated with extrapolating such data to acute exposure scenarios. Studies of subchronic or chronic exposure may be addressed when the data provided relate to effects following acute exposures, meaningful insight into understanding toxicity mechanisms, or for other special considerations. The primary physical and chemical data on carbon tetrachloride are presented in Table 2-2.

TABLE 2-1 AEGL Values for Carbon Tetrachloride

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (non-disabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Inadequate data.
AEGL-2 (disabling)	27 ppm (170 mg/m^3)	18 ppm (110 mg/m^3)	13 ppm (82 mg/m^3)	7.6 ppm (48 mg/m^3)	5.8 ppm (36 mg/m^3)	No-effect level for CNS effects in humans (Davi 1934).

AEGL-3 (lethal)	700 ppm (4,400 mg/m^3)	450 ppm (2,800 mg/m^3)	340 ppm (2,100 mg/m^3)	200 ppm (1,300 mg/m^3)	150 ppm (940 mg/m^3)	Estimated LC_{01} in rats (Adams et al. 1952; Dow chemical 1960).

[a] Not recommended. Absence of AEGL-1 values does not imply that exposures below the AEGL-2 values are without adverse effects.
Abbreviations: CNS, central nervous system; LC_{01}, lethal concentration, 1% lethality.

TABLE 2-2 Physical and Chemical Data on Carbon Tetrachloride

Parameter	Value	Reference
Synonyms	Carbon chloride; carbona; carbon tet; freon 10; methane tetrachloride; perchloromethane; tetrachloromethane; tetrachlorocarbon; tetrafinol.	Walsh 1989; HSDB 2005
CAS registry no.	56-23-5	HSDB 2005
Chemical formula	CCl_4	HSDB 2005
Molecular weight	153.82	HSDB 2005
Physical state	Liquid	HSDB 2005
Boiling point	77°C	HSDB 2005
Melting point	-23°C	HSDB 2005
Density	1.5940 at 20°C	HSDB 2005
Solubility	1,160 mg/L at 25°C in water; miscible with alcohol, benzene, chloroform, ether, petroleum ether, oils, carbon disulfide.	HSDB 2005
Vapor pressure	115 mmHg at 25°C	HSDB 2005
Conversion factors in air	1 mg/m^3 = 0.159 ppm 1 ppm = 6.29 mg/m^3	NIOSH 2011

2. HUMAN TOXICITY DATA

2.1 Acute Lethality

The acute toxicity and lethality of carbon tetrachloride in humans following inhalation exposure has been reviewed by Norwood et al. (1950), Umiker and Pearce (1953), and ATSDR (2005). Most human case reports lack reliable quantitative exposure data. The more relevant reports are summarized in the following sections. Most lethal cases involve renal failure and are characterized by oliguria or anuria prior to death.

Norwood et al (1950) reported on two fatalities involving exposure to carbon tetrachloride vapors. In one of the fatalities, a exposure concentration was

estimated on the basis of reconstruction of the incident. The case involved a 22year old male who was mopping a floor with carbon tetrachloride that was placed in an open bucket (approximately 1 gallon). The subject reported experiencing headache and dizziness after mopping for approximately 15 min. The investigators reported that "exposure conditions were duplicated to the best of our ability, and the measured concentration was 250 part carbon tetrachloride per million parts of air." The possibility of dermal contact with carbon tetrachloride was not discussed in the case report. The patient was admitted to a hospital with complaints of "generalized aches and pains, nausea and vomiting" and subsequently experienced renal failure and died 6 days after the reported exposure. Histopathologic examination conducted at autopsy confirmed centrilobular necrosis of the liver and interstitial edema and tubular (loop of Henle and distal convoluted tubule) degeneration in the kidney. The findings in the liver were consistent with, but not diagnostic of, carbon tetrachloride toxicity. The case history indicated that the patient had a history of heavy alcohol consumption. His coworkers reported that he did not work on the day previous to the exposure and did not "feel well" when he reported to work. Prior history of similar exposures to carbon tetrachloride was not reported (in this case, carbon tetrachloride was used during a night shift without the knowledge or sanction from the supervisor). Two coworkers who continued cleaning the floor for 4 h reported only mild headaches and dizziness, which subsided after the work was completed. Those symptoms are consistent with clinical studies in which exposures to carbon tetrachloride at approximately 300-2,400 ppm for periods of 3-30 min resulted in headache, nausea and dizziness, but no deaths (Davis 1934). Collectively, these observations suggest that the case may represent an example of ethanol potentiation of carbon tetrachloride toxicity; although other factors noted above may also have contributed to the severe effects observed in this case (see Section 4 for further discussion of mechanism of toxicity and interactions with ethanol).

Another fatality also reported by Norwood et al. (1950) involved an ethanol intoxicated woman with a respiratory infection who used carbon tetrachloride to clean her trailer. The patient experienced nausea and vomiting, abdominal tenderness, and anuria, and died 12 h after admission to the hospital. Histopathologic examinations revealed fatty degeneration and centrilobular necrosis of the liver and tubular degeneration of the kidneys. Exposure concentrations and duration were not reported.

2.2 Nonlethal Toxicity

2.2.1 Acute Exposure Case Reports

Although many case reports are available regarding acute exposures to carbon tetrachloride, most are deficient in exposure details. Most of the reports

do, however, describe a similar clinical picture of carbon tetrachloride poisoning that includes initial dizziness and nausea, abdominal discomfort, oliguria, anuria, and subsequent renal failure and death (Ashe and Sailer 1942; Gray 1947; Jennings 1955; Guild et al. 1958; New et al. 1962; Ruprah et al. 1985; Manno et al. 1996). The increased potential for carbon tetrachloride-induced toxicity (both renal and hepatic) associated with alcohol consumption or abuse has been documented in several of the case reports.

Davis (1934) reported the results of several experiments in which human subjects were exposed to carbon tetrachloride. The carbon tetrachloride concentrations were determined on the basis of the room volume and the amount of carbon tetrachloride necessary to achieve the desired concentration; there was no mention of air-flow rate or ventilation in the test room. In one experiment four individuals (ages 20, 28, 28, and 30 years; gender not specified) were exposed to carbon tetrachloride at158 ppm for 30 min. One subject experienced nervousness and slight nausea but the remaining three were asymptomatic. There were no physiologically significant alterations in blood pressure, heart rate, respiratory rate, blood counts, or hemoglobin content. Urinalyses at 24 h postexposure revealed no signs of toxicity.

In the second experiment, four subjects (ages 35, 48, 22, and 30; gender not specified) were exposed to a carbon tetrachloride at 76 ppm for 2.5 h. There were no symptoms or signs of toxicity in any of the subjects. In the third experiment, the same subjects used in the previous experiment were exposed 24 h later to carbon tetrachloride at 76 ppm for 4 h and did not have signs or symptoms. Urinalyses at 72 h postexposure were normal. In the fourth experiment, three additional subjects (ages 20, 45, and 36; gender not specified) were exposed at 317 ppm for 30 min. Although clinical tests (blood pressure, hemoglobin, blood count, pulse, and urinalysis) were normal, one subject experienced nausea, another nausea and vomiting, and the third complained of headache. In fifth experiment, four subjects (ages 19, 21, 28, and 40; gender not specified) were exposed for 15 min to carbon tetrachloride at 1,191 ppm. Two of the subjects (one of which could only tolerate a 9-min exposure) experienced headache, nausea, and vomiting, another experienced nausea and vomiting, and another reported nausea and headache. Pulse rate and blood pressure appeared somewhat elevated, but no baseline data were provided for comparison. Urinalyses at 48-h postexposure were negative except for slightly increased acidity and phosphates. In the six experiment, three subjects (ages 40, 26, and 19; gender not specified) were exposed to carbon tetrachloride at 2,382 ppm for 5, 3, and 7 min, respectively. The first subject became dizzy, nauseated, sleepy, and experienced a throbbing headache. The second subject became nervous, nauseated, and listless, and the third subject experienced nausea, vomiting, dizziness, and became sleepy. Clinical examination 2 weeks after exposure revealed no adverse effects.

In a less controlled experiment, Davis (1934) measured the carbon tetrachloride concentration near the faces of men asked to use the solvent in an

enclosed room. Using an alcohol potassium hydroxide and combustion method, the carbon tetrachloride concentration was found to be 0.23 % (≈2,300 ppm). None of the three subjects could work for more than 10 min without becoming nauseated and sleepy. One of the three experienced vomiting, dizziness, and a throbbing headache.

Davis (1934) also provided anecdotal data regarding compromised renal function in a worker experimentally exposed to carbon tetrachloride during an 8h work day. The concentration was estimated at 0.02% (200 ppm). Renal function was recovered 2 months after the exposure.

Smyth et al. (1936) conducted surveys in various occupational settings (e.g., dry cleaning, distillation processes) and found average concentrations of carbon tetrachloride ranging from 10-650 ppm, with peak concentrations of up to 7,860 ppm. On the basis of average working time, 8-h TWA values of 5-117 ppm were calculated for these subchronic exposure settings. The effects associated with these exposures were minimal (evidence of restricted visual field and elevated bilirubin) but indicative of carbon tetrachloride exposure. Actual daily exposures concentrations were unknown.

Elkins (1942) summarized the findings of case reports of workers in various facilities and tasks, including dry cleaning, spot cleaning, multigraphing, and coating. Reports of nausea, vomiting, and weight loss were associated with acute, albeit probably repeated, exposures to carbon tetrachloride at concentrations of 20-85 ppm. Elkins proposed that the maximum allowable concentration for carbon tetrachloride should be 25-50 ppm.

Norwood et al (1950) reported on 56 nonlethal cases of carbon tetrachloride poisoning resulting from various activities (e.g., use of a carbon tetrachloride fire extinguisher, degreasing operations). Exposures were to carbon tetrachloride vapors and possibly dermal contact with liquid carbon tetrachloride. Exposure concentrations were not reported for any of these cases. During an industrial degreasing operation in which carbon tetrachloride was used as the degreasing agent, 51 workers reported for first aid with complaints that included: nausea (21), headache (22), vomiting (15), vertigo and dizziness (12), malaise (7), gastric upset (5), rawness of throat or nasal passages (4), abdominal cramps (4), anorexia (3), nervousness (3), insomnia (2), nocturia (1), and cough (1).

Although lacking in exposure details, Stevens and Forster (1953) provided case reports with an emphasis on the neurologic signs and symptoms of carbon tetrachloride poisoning following inhalation and oral exposures. These included CNS effects (cerebellar degeneration, encephalomyelitis, cerebral hemorrhage) and peripheral neuritis.

Kazantzis and Bomford (1960) reported on the response of workers exposed to carbon tetrachloride vapors while cleaning quartz crystals used in electronic components. Although precise exposure data were not presented, the workers (14 men and four women, 16-54 years of age) were apparently exposed for about 8 h/day at concentrations of approximately 67-97 ppm. Fifteen workers complained

of gastrointestinal disturbances (nausea, anorexia, vomiting, flatulence, epigastric distention, and discomfort), headaches, and depression. The effects were first noticed on Tuesday or Wednesday afternoons and increased in severity as the week progressed. The effects were first manifested during the preceding 4 months and increased in severity a few weeks before the investigation up to the point described. The cumulative exposures were apparently aggravated by closed windows during the winter months. The effects described could not necessarily be attributed to acute exposure (a single 8-h exposure) and two subjects with prior exposures presented with no signs or symptoms. The findings, however, suggest that intermittent exposures to carbon tetrachloride at less than 100 ppm over typical occupational exposure scenarios may result in notable signs of toxicity.

Groups of six male human volunteers (30-59 years of age) were subjected to carbon tetrachloride using several different exposure protocols (Stewart et al. 1961). In the first experiment, six individuals were exposed to a time-weightedaverage (TWA) concentration of 49 ppm (31-87 ppm) for 70 min. During the exposure, all subjects noted a sweetish odor. There were no instances of ocular or soft palate irritation, no nausea, and Romberg test and heel-to-toe testing remained normal. The only changes observed in clinical chemistry parameters (serum iron, serum transaminases, urinary urobilinogen, and urinalysis) were a transient reduction in serum iron in two subjects during the first 48 h after exposure, and an elevated urinary urobilinogen in one subject 7 days postexposure. The authors suggested that the depression of serum iron and elevated urine urobilinogen might have been the result of minor changes in metabolism and could be indicative of minimal liver insult. Serum enzyme activities were monitored up to 7 days postexposure and remained within normal ranges. In experiment 2, six subjects were exposed at 10.9 ppm (TWA) for 180 min. That was followed 4 weeks later by a repeat 180-min exposure (experiment 3) to carbon tetrachloride at 10 ppm. No adverse effects were reported by any of the subjects and no changes in blood pressure or timed vital capacities were detected.

Barnes and Jones (1967) reported on three cases of carbon tetrachloride poisoning; two in an industrial setting and one involving a tank truck driver delivering carbon tetrachloride. Exposure durations ranged from several minutes to approximately 3 h. Signs and symptoms were typical of carbon tetrachloride poisoning and included dizziness, nausea, delirium, abdominal discomfort, and oliguria. In the first case, a worker was cleaning sludge from a carbon tetrachloride tank without a respirator or other protective device during the 3-h duration of the work. Soon afterward, he experienced nausea, vomiting, drowsiness, and anuria. Following medical intervention, his condition improved over several weeks. Liver biopsy revealed indications consistent with carbon tetrachloride poisoning. No exposure concentration was provided. The second case involved a worker draining a carbon tetrachloride storage tank. The incident involved an exposure of only several minutes and produced a strong odor. By evening the worker experienced

dizziness, nausea, and delirium, and medical intervention was required. Simulation of the procedure resulted in carbon tetrachloride concentrations of in excess of 600 ppm. The third case involved a truck driver exposed to carbon tetrachloride during loading of the tanker. Measurement of the carbon tetrachloride concentrations up to 30 ppm were made at various breathing zone vicinities around the truck at the discharge end of the trip but these were made during periods of high wind and unlikely to be representative of the actual accident. Concentrations of carbon tetrachloride detected during a 20-min period in the breathing zones of pipe fitters at the plan where the cases occurred ranged from 30 ppm to over 600 ppm. For one case, the "main exposure level" was estimated at 210 ppm. Although all three subjects recovered, the exposures resulted in notable toxicity.

2.2.2 Epidemiologic Studies

A cross-sectional study of hepatic function in workers occupationally exposed to carbon tetrachloride was conducted by Tomenson et al. (1995). Multivariate analysis of liver function variables and various other hematologic and biochemical parameters were compared in 135 exposed workers and 276 nonexposed controls. Exposures were categorized on the basis of mean exposures; low (≤1 ppm), medium (>1-3 ppm), and high (≥4 ppm). Four liver function variables (alanine transaminase, aspartate transaminase, alkaline phosphatase, and gamma glutamyl transferase) exhibited statistically significant differences from nonexposed controls, but no exposure-response relationship was demonstrated. The absence of an exposure-response may have been the result of imprecision in ranking worker exposures. The biologic relevance of the observed changes in serum enzyme activities was marginal and possibly of questionable clinical significance. The authors reported that there were no clinical signs concurrent with the aforementioned changes and that a 3-year follow-up study at the site with the highest exposures showed no evidence of further changes in liver function variables.

2.3 Reproductive and Developmental Toxicity

Human data on the reproductive and developmental toxicity after acute exposure to carbon tetrachloride were not available.

2.4 Genotoxicity

No information was available regarding the genotoxicity of carbon tetrachloride in humans following inhalation exposure.

2.5 Carcinogenicity

Information regarding the potential carcinogenicity of carbon tetrachloride in humans following acute inhalation exposure include two anecdotal case reports (Tracey and Sherlock 1968). In one case, a 59-year-old man (with a history of moderate alcohol usage but not to the extent of inducing cirrhosis) died of hepatocellular carcinoma 7 years after an acute exposure to carbon tetrachloride (exposure details not provided). In a second case, a 30-year-old woman died of liver cancer after 2-3 years of occupational exposure to carbon tetrachloride at concentrations sufficient to produce signs of toxicity.

EPA (2010b) states that carbon tetrachloride is "likely to be carcinogenic to humans" on the basis of inadequate evidence of carcinogenicity in humans but sufficient evidence in animals by oral and inhalation exposure. The animal evidence included hepatic tumors in three species (rat, mouse, and hamster) and pheochromocytomas (adrenal gland tumors) in mice. On the basis of the increased incidence of pheochromocytomas in male BDF1 mice (Nagano et al. 2007), EPA (2010b) derived an inhalation unit risk of 6×10^{-6} per $\mu g/m^3$. Carbon tetrachloride is classified as a Group 2B (possibly carcinogenic to humans) carcinogen by the International Agency for Research on Cancer. NTP has classified carbon tetrachloride as reasonably anticipated to be a human carcinogen.

2.6 Summary

Case reports of human fatalities resulting from acute exposure to carbon tetrachloride provide a clinical picture of dizziness, nausea, abdominal pain, oliguria, anuria, and death being attributed to renal failure and hepatotoxicity. Also well documented is the potential for greater carbon tetrachloride-induced toxicity in individuals with histories of alcohol usage, a phenomenon that is consistent with the known dispositional potentiation of carbon tetrachloride toxicity by inducers of cytochrome CYP2E1 enzymes (Plaa 2000; ATSDR 2005; EPA 2010a). Most human case reports were lack information on exposure concentrations and durations. Controlled exposure studies by Davis (1934) and Stewart et al. (1961) showed a varied response to inhaled carbon tetrachloride among the tested subjects. Cumulative exposures to carbon tetrachloride at 30-57 ppm-h resulted in odor detection but no irritation or clinical effects in most subjects, whereas cumulative exposures at 79-2,133 ppm-h produced effects ranging from nervousness and headaches to nausea and vomiting. The variability in response to carbon tetrachloride is emphasized by the fact that an estimated exposure at 63 ppm-h was fatal in a heavy drinker whereas controlled exposures at 190 ppmh were without effect.

Quantitative data pertaining to inhalation exposures of humans to carbon tetrachloride are presented in Table 2-3.

3. ANIMAL TOXICITY DATA

The discussion of animal toxicity studies on carbon tetrachloride focuses on acute exposure studies (durations of less than 24 h) or longer-term studies that provided response data for exposure periods that were of possible use in the derivation of AEGL values or as a basis for comparison with AEGL values.

3.1 Acute Lethality

Lethality following acute exposures to carbon tetrachloride has been documented in various laboratory species. Where available, histopathologic findings revealed hepatic injury. For some studies, data are presented that are not strictly from acute exposures, as some of the data may provide reference points with which to evaluate AEGL values.

3.1.1 Nonhuman Primates

In a repeated exposure study (8 h/day, 5 days/week for 6 weeks), one of three squirrel monkeys died after the seventh exposure to carbon tetrachloride at 82 ppm (Prendergast et al. 1967).

TABLE 2-3 Exposure-Response Data from Studies of Human Subjects Exposed to Carbon Tetrachloride

No. of Subjects	Exposure Concentration and Duration	Response	Reference
6	TWA of 49 ppm (31-87 ppm) for 70 min Ct = 57 ppm-h	Odor detection; transient decline in serum iron 20-68 h postexposure; elevated urinary urobilinogen in one subject; no clinically significant effects and no irritation.	Stewart et al. (1961)
6	TWA of 10.9 ppm (10-14.2 ppm) for 180 min; Ct = 33 ppm-h	Odor detection; no clinically significant effects; no irritation.	Stewart et al. (1961)
6	TWA of 10.1 (9-14 ppm) for 180 min; Ct = 30 ppm-h	Odor detection; no clinically significant effects; no irritation.	Stewart et al. (1961)
1	250 ppm (estimated) for 15 min; Ct = 63 ppm-h	Dizziness and nausea followed by renal failure and death 6 d postexposure (subject was heavy drinker).	Norwood et al. (1950)
2	250 ppm (estimated) for 4 h; Ct = 1,000 ppm-h	Mild headache and dizziness during exposure (nondrinkers).	Norwood et al. (1950)
4	158 ppm for 30 min; Ct = 79 ppm-h	Nervousness in one subject, no effect in three subjects.	Davis (1934)
4	76 ppm for 2.5 h; Ct = 190 ppm-h	No effects.	Davis (1934)
4	76 ppm for 4 h (same subjects as above, 24 h later); Ct = 304 ppm-h	No effects.	Davis (1934)
3	317 ppm for 30 min; Ct = 159 ppm-h	Slight nausea and vomiting, headache.	Davis (1934)
4	1,191 ppm for 15 min; Ct = 298 ppm-h	Nausea, vomiting, headache; intolerable for one subject (9-min exposure only).	Davis (1934)
3	2,382 ppm for 3-7 min; Ct = 640 ppm-h	Nausea, vomiting, dizziness, listlessness, headache, sleepiness.	Davis (1934)
3	2,382 ppm for ≤10 min; Ct ≤ 2,133 ppm-h	Nausea, vomiting, sleepiness, headache.	Davis (1934)
NS	5-117 ppm, 8-h TWA; Ct = 40-936 ppm-h	Elevated bilirubin, restricted visual field (imprecise assessments for both).	Smyth et al. (1936)

Abbreviation: NS, not specified; TWA, time-weighted average.

3.1.2 Rats

Rhe Mellon Institute (1947) conducted range-finding studies of chlorinated hydrocarbons in which groups of 12 albino rats (sex not specified) were exposed to carbon tetrachloride at 8,000 ppm for 6.5 h, 4,000 ppm for 8 h, 3,000 ppm for 8 h, or 1,000 ppm for five 8-h exposures. Mortality incidence after 14 days were 12/12, 2/12, 0/12, and 0/12, respectively.

In studies reported by Adams et al. (1952), albino rats (5-30 animals per group) were exposed to carbon tetrachloride at 3,000-19,000 ppm for various time periods (Table 2-4). Surviving animals "were observed for two to three weeks, or until it was certain that they had fully recovered from the effects of exposure as judged by appearance, behavior and recovery weight." Carbon tetrachloride produced drowsiness and stupor at concentrations of 4,600 ppm and lower, loss of equilibrium and coordination at 7,300 ppm, and loss of consciousness at 12,000 and 19,000 ppm. Animals surviving 16-24 h after exposure to potentially lethal or near-lethal concentrations exhibited marked hepatic injury (increased serum enzyme activity, increased liver weight, lipidosis, and fatty degeneration). The investigators estimated that exposures of 3,000 ppm for 6 min, 800 ppm for 30 min, and 50 ppm for 7 h would likely be without adverse effects in rats.

Dow Chemical (1960) reported the results of acute inhalation studies in rats (age, weight, and strain not specified) exposed to carbon tetrachloride at concentrations of 10,000 or 20,000 ppm (Table 2-5). Lethality in rats exposed at 10,000 ppm for 1, 1.5, 2.0, or 2.5 h was 0/5, 0/5, 5/10, and 5/5, respectively. In rats exposed to carbon tetrachloride at 20,000 ppm for 0.1, 0.25, or 0.5 h, lethality was 0/10, 5/10 and 8/10, respectively.

3.1.3 Mice

Svirbaly et al. (1947) exposed groups of 20 Swiss mice (20 g; gender not specified) to carbon tetrachloride vapors for 8 h. The concentrations were calculated by dividing the amount of carbon tetrachloride volatilized during the 8-h exposure by the volume of air that flowed through the chamber. The concentrations were confirmed by chemical analysis. The results are shown in Table 2-6.

Gehring (1968) reported an 11.5-h LC_{50} of 8,500 ppm for female SwissWebster mice. The lethality response appeared to be biphasic. The study also reported two LCt_{50} values (680 and 850 min) for the steep exposure-response curve.

The lethal response of mice (strain and gender not specified) to a 3.5 min exposure to carbon tetrachloride was provided by Merck and Co. in a report to the EPA Office of Toxic Substances (Merck 1983). Lethality incidence in groups of

mice exposed at 150,000, 75,000, 37,500, 18,800, or 9,400 ppm were 6/6, 2/6, 0/5, 0/5, and 0/5, respectively. No additional details were provided.

TABLE 2-4 Lethality in Rats Following Acute Inhalation Exposure to Carbon Tetrachloride

Concentration (ppm)	Duration (h)	Number Dead/Number Exposed
19,000	0.1	1/10
	0.2	1/5
	0.3	3/5
	0.5	2/5
	0.6	14/15
	0.7	5/5
	0.8	4/5
	1.0	9/19
	2.2	20/20
12,000	0.25	0/20
	0.5	1/10
	1.0	3/10
	2.0	7/10
	3.0	8/10
	4.0	20/20
7,300	1.0	0/20
	1.5	0/20
	2.0	1/10
	3.0	1/10
	4.0	4/10
	6.0	6/10
	7.0	4/10
	8.0	20/20
4,600	5.0	0/20
	6.0	1/11
	8.0	2/10
3,600	8.0	4/20
	12.0	1/10
3,000	8.0	0/20

	10.0	1/30

Source: Adapted from Adams et al. 1952.

3.1.4 Guinea Pigs

In a repeated exposure study (8 h/day, 5 days/week for 6 weeks), three of 15 guinea pigs died on the after 20, 22, and 30 days of exposure to carbon tetrachloride at 82 ppm (Prendergast et al. 1967). Histopathologic findings in the liver were consistent with carbon tetrachloride-induced hepatotoxicity. Data for time frames that would be appropriate for AEGL derivations were not provided.

3.1.5 Rabbits

A single rabbit was exposed to carbon tetrachloride at 20 mg/L (3,178.6 ppm) for 3 h/day for 3 days. The rabbit died on the fifth day; necropsy revealed pulmonary, renal, and hepatic involvement (Davis 1934).

3.1.6 Summary of Lethal Toxicity in Animals

Quantitative data regarding the lethality of carbon tetrachloride following acute inhalation exposure are available for several laboratory species (rats, mice, and guinea pigs). A smaller set of data are available on nonhuman primates and dogs.

Dow Chemical (1960) reported the results of acute inhalation studies in guinea pigs (age, weight, and strain not specified) exposed to carbon tetrachloride at concentrations of 10,000 or 20,000 ppm (Table 2-7). Lethality in guinea pigs exposed at 10,000 ppm for 1, 1.5, 2.0, 2.5, or 3.0 h was 0/5, 1/10, 4/5, 1/5, and 1/5, respectively. For exposure at 20,000 ppm for 0.25, 0.5, or 1.0 h, lethality was 0/5, 2/5 and 4/5, respectively.

TABLE 2-5 Lethality in Rats Following Acute Inhalation Exposure to Carbon Tetrachloride

Concentration (ppm)	Duration (h)	Number Dead/Number Exposed
10,000	1.0	0/5
	1.5	0/5
	2.0	5/10
	2.5	5/5
20,000	0.1	0/10

	0.25	5/10
	0.5	8/10

Source: Adapted from Dow Chemical 1960.

TABLE 2-6 o Carbon Tetrachloride for Eight Hours

Concentration (ppm)	Mortality
6,340	0/20
7,628	2/20
8,088	19/20
8,787	10/20
9,327	20/20

Source: Adapted from Svirbaly et al. 1947.

TABLE 2-7 Lethality in Guinea Pigs Following Acute Inhalation Exposure to Carbon Tetrachloride

Concentration (ppm)	Duration (h)	Number Dead/Number Exposed
10,000	1.0	0/5
	1.5	1/10
	2.0	4/5
	2.5	1/5
	3.0	1/5
	0.25	0/5
20,000	0.5	2/5
	1.0	4/5

Source: Adapted from Dow Chemical 1960.

3.2 Nonlethal Toxicity

3.2.1 Nonhuman Primates

A subchronic exposure study by Smyth et al. (1936) reported little harm to groups of four rhesus monkeys exposed to carbon tetrachloride at 50 or 200 ppm for 8 h/day, 5 days/week for 10.5 months. Liver damage (slight fatty degeneration) was detected but resolved 28 days following cessation of exposure. No data were provided that were specific to acute exposure times frames.

3.2.2 Dogs

In a study submitted to the EPA Office of Toxic Substances by Union Carbide (Mellon Institute 1947), a mongrel dog was exposed to carbon tetrachloride at 400 ppm for 7 h/day for 6months. The dog did not die but exhibited a significant decrease in body weight relative to unexposed controls.

3.2.3 Rats

In a subchronic inhalation exposure study, groups 21-25 albino rats were exposed to carbon tetrachloride at 50, 100, 200, or 400 ppm for 8 h/day, 5 days/week for 10.5 months. Hepatic and renal damage was observed; however, with the exception of two rats in the 400-ppm group, was not severe enough to compromise what the investigators termed as adequate function (Smyth et al. 1936). Data specific to acute exposure periods were not provided.

Adams et al. (1952) exposed groups of three or four male albino rats to carbon tetrachloride using various protocols (3-420 min) to determine the maximum exposure without overt signs of toxicity. Toxicity end points evaluated included changes in hepatic weight, alterations in total lipid content of the liver, and gross and microscopic evidence of fatty degeneration. The results are summarized in Table 2-8. The no-effect responses identified in this study are based on end points characteristic of notable hepatic damage; an evaluation of more sensitive end points (e.g., serum enzyme activities) probably would have detected a toxic response at lower concentrations or shorter exposure durations.

Cornish and Block (1960) exposed male and female Sprague-Dawley rats to carbon tetrachloride at 50, 100, 250, 1,000, or 1,500 ppm for 4 h. Exposure concentrations were found to be within 10% of the calculated target concentrations. Twenty-four hours after a single 4-h exposure at 1,500 ppm, activities of serum glutamatic-oxaloacetic transaminase (SGOT) and xanthine oxidase were increased by 750% and 250%, respectively, relative to controls (Table 2-9). Males and females responded similarly at 1,500 ppm. Serum enzyme activities returned to normal 5 days after the exposure. SGOT and xanthine oxidase activities increased in males exposed at 1,000 ppm; increases 24 and 48 h after exposure were by 275% and 180% respectively. Respective increases in females were by 800% and 285%. Twenty-four hours after exposure at 250 ppm, SGOT activity in males was increased 160%; xanthine oxidase was unaffected. For females, SGOT activity was increased by 250% and xanthine oxidase by 135% compared with unexposed controls. At 50 and 100 ppm, no significant changes in enzyme activities were found.

The relationship between exposure time and exposure concentration was examined by David et al. (1981) (Table 2-9). Serum glutamic-pyruvate transaminase (SGPT) activity was used to assess the toxic response of male Wistar

rats (12 per group) subjected to various exposure protocols that provided identical cumulative exposures (Ct = 300 ppm-h). The protocols included a 72-min exposure at 250 ppm, a 6-h exposure at 50 ppm, six 3-min exposures at 1,000 ppm at 1-hr intervals, and an 18-min exposure at 1,000 ppm. A control group of 12 rats were exposed to clean air. Even though the cumulative exposure was the same for all protocols, exposures at greater concentrations of short duration resulted in a greater increase in serum SGPT activity than did exposures at lower concentrations for longer durations (Table 2-8). Histologic examination of the exposed

TABLE 2-8 Nonlethal Responses of Rats Exposed to Carbon Tetrachloride

Concentration (ppm)	Exposure Duration (min)	Exposure Duration (min)
	No adverse effect[a]	Adverse effect[a]
12,000	–	3
3,000	6	9
800	30	60
400	–	60
100	–	420
50	420	–

Source: Adapted from Adams et al. 1952.

[a] Adverse effects characterized by alteration in hepatic weight, total lipid content of the liver, and gross and microscopic changes in the liver.

rats revealed mild changes (mild steatosis, mild hydropic degeneration) in the liver that were not qualitatively different between the groups. The authors concluded that the concentration of carbon tetrachloride in the blood and liver are more important than the total amount of carbon tetrachloride absorbed.

Appelman et al. (1985) conducted a series of experiments in which groups of 10 male Wistar rats were exposed 6 h/day, 5 days/week for 4 weeks to carbon tetrachloride vapor. Daily exposure regimens varied and included: 6-h exposures (63 and 80 ppm), two 3-h exposures (63 and 80 ppm, with 1.5 h between exposures), two 3-h exposures (63 and 80 ppm, at 1.5 hr intervals) with 5-min peaks equivalent to six times the base exposure. Controls were exposed to fresh air. With the exception of body weight data that were taken at weekly intervals, data were available only at the end of the 4-week period. No overt signs of toxicity were detected in the treated rats. Serum enzyme activities (SGOT, SGPT) were significantly elevated (2- to 9-fold) in all treatment groups, and microsomal protein content and some microsomal enzyme activity levels were significantly reduced following treatment. The study showed measurable evidence of reversible toxic effects following various regimens of inhalation exposure to carbon

tetrachloride at 63 or 80 ppm over a 4-week period. The available data were not appropriate for AEGL-specific time frames or for extrapolation to AEGL time frames.

TABLE 2-9 Effect of Exposure Protocol on Xanthine-Oxidase, SGPT, and SGOT Activity in Rats Exposed to Carbon Tetrachloride

Exposure	Xanthine Oxidase (% of control)	SGPT or SGOT (U/L or % of controls)
50 ppm for 4 h[a]	No effect	No effect
100 ppm for 4 h[a]	No effect	No effect
250 ppm for 4 h[a]	Males: marginal Females: 135%	Males: marginal Females: 250%
1,000 ppm for 4 h[a]	Males: 180% Females: 285%	Males: 275% Females: 800%
1,500 ppm for 4 h[a]	Males: 250% Females: 250%	Males: 750% Females: 750%
Controls[b]	NA	50
250 ppm for 72 min[b]	NA	60
50 ppm for 6 h[b]	NA	50
1,000 ppm for 18 min[b]	NA	95
1,000 ppm (six 3-min exposures at 1-h intervals)[b]	NA	40

Abbreviation: NA, not applicable (not examined); SGPT, serum glutamic-pyruvic transaminase; SGOT, serum glutamic-oxaloacetic transaminase.

[a] Cornish and Block 1960 (SGOT monitored).

[b] David et al. 1981 (SGPT monitored).

In an extensive study to evaluate the effect of exposure regimen on the distribution and toxicity of carbon tetrachloride, Paustenbach et al. (1986b) exposed groups of four male Sprague-Dawley rats to carbon tetrachloride at 100 ppm for 8 or 11.5 h/day for 1-10 days. For toxicity determination, serum sorbitol dehydrogenase (SDH) activity was measured. Results of the 1-day exposure showed that SDH was slightly higher ($p < 0.05$) in the 11.5-h group (14.8 ± 3.7 IU/ml) relative to those in the 8-h group (7.0 ± 1.5 IU/ml). SDH activity in control rats was 8.5 ± 2.0 IU/ml. SDH activity increased only about 2.5- to 3.5-fold (21.0 ± 3.3 IU/ml for 8 h/day; 29.0 ± 6.2 IU/ml for 11.5 r/day) with exposure durations

of 3 days. Histopathologic evaluation was limited to 1- and 2-week exposures and were not available for the shorter exposures.

In studies to examine the effect of route and pattern of exposure on the pharmacokinetics and acute toxicity of carbon tetrachloride, Sanzgiri et al. (1995) exposed male Sprague-Dawley rats (325-375 g) to carbon tetrachloride at 100 or 1,000 ppm for 2 h. The total internal dose (systemically absorbed dose) over the 2h exposure was 17.5 and 179 mg/kg, respectively. Relative to unexposed controls, a 2-h exposure at 100 ppm resulted in no biologically relevant alterations in SDH or serum alanine aminotransferase (ALT) activity but did significantly reduce hepatic microsomal P450 and glucose-6-phosphatase (G6Pase) levels. Following a 2-h exposure at 1,000 ppm, both serum SDH (87.9 ± 25.7 mU/ml vs 5.2 ± 1.0 mU/ml for controls; $p \leq 0.05$) and ALT activities (53.3 ± 14.7 mU/ml vs 24.4 ± 2.2 mU/ml for controls; $p \leq 0.05$) were significantly increased, microsomal P450 activity significantly decreased (0.61 ± 0.04 vs 0.81 ± 0.02 for controls), and G6Pase activity was unchanged.

Wang et al. (1997) studied the effects of dose and route of administration on the metabolism and toxicity of carbon tetrachloride. Groups of five Wistar rats were exposed to carbon tetrachloride at 50 or 500 ppm for 6 h. Chamber concentrations were monitored every 15 min by gas chromatography with a hydrogen flame ionization detector. As determined by SGOT and SGPT activity, carbon tetrachloride at 50 ppm resulted in no hepatic damage in rats, although exposure at 500 ppm resulted in statistically significant elevations indicative of minor hepatic injury (SGOT: 29, 33, and 57 IU/L for the control, 50-ppm, and 500-ppm groups, respectively; SGPT: 20, 20, and 38 IU/L for the control, 50ppm, and 500-ppm groups, respectively). Rats pretreated with ethanol (2 g/day) for 3 weeks exhibited substantially greater evidence of hepatic damage as measured by SGOT and SGPT activity (SGOT: 31, 62, and 1,720 IU/L for the ethanol-control, 50-ppm, and 500-ppm groups, respectively; SGPT: 18, 41, and 870 IU/L for the ethanol-control, 50-ppm, and 500-ppm groups, respectively).

3.2.4. Mice

Gehring (1968) examined nonlethal end points of anesthesia and SGPT activity. At an exposure concentration of 8,500 ppm, an ECt_{50} of about 0.16 min was determined for SGPT activity and about 21 min for anesthesia effects. Belyaev et al. (1992) conducted experiments to assess fibroblast growth in the livers of male A/He mice following carbon tetrachloride exposure. Centrilobular necrosis encompassing one-fifth to one-third of the lobule was observed at 24 h after a single 4-h exposure at 30 mg/L (30,000 mg/m^3 or 4,770 ppm). Continued biweekly exposures ultimately resulted in fibrosis and cirrhosis. No animal deaths were reported.

3.2.5 Rabbits

One study on the nonlethal effects of inhalation exposure of rabbits to carbon tetrachloride was available (Ugazio et al. 1995). The study involved a subchronic exposure for the development of a model for cirrhosis. Male New Zealand white rabbits were exposed to carbon tetrachloride for 2 h, twice per week, at concentrations that increase from 100 ppm to 600 ppm by week 23. Although results of daily exposure were not provided, none of the 12 rabbits died. By week 4, however, there was a 300% increase in hexobarbital sleeping time, implying a decrease in hepatic microsomal enzyme activity, and laparotomy revealed initial signs of hepatic fibrosis.

3.2.6 Cats

Wong and DiStefano (1966) conducted inhalation exposure experiments on anesthetized cats. Cats of both sexes were anesthetized with sodium pentobarbital, and were exposed by a tracheal cannula to carbon tetrachloride at 10,000 ppm for 15, 30, 60, or 240 min. Controls were treated similarly but with no carbon tetrachloride exposure. The kidney weight-to-body weight ratio was significantly increased ($p < 0.05$) following the 60- and 240-min exposures, and adrenal weightto-body weight ratios were significantly increased ($p < 0.05$) for the 30-, 60-, and 240-min exposures. Liver weight-to-body weight ratios were unaffected by the treatment. Total lipid content in the renal cortex increased after 15 min of exposure but was not further increased with longer exposures. The elevated total lipids were still evident 12-h postexposure but were lower than baseline values at 24 h. Lipid content in the adrenal glands and liver were unaffected. With the exception of lipid accumulation, there were no significant histologic findings in the kidneys, and there were no histologic changes in the adrenal glands. Central necrosis was observed in the liver 12 h after the 240-min exposure; it became more prevalent 24-h postexposure. The results of the study affirm the liver and kidneys as target organs for carbon tetrachloride toxicity but also suggest that the kidneys may be affected earlier than the liver. It is uncertain whether the effects observed would have progressed to cause death.

3.2.7 Summary of Nonlethal Toxicity in Animals

Table 2-10 summarizes the nonlethal effects in animals following inhalation exposure to carbon tetrachloride. Although data pertaining to acute exposures is the primary focus, longer-term exposures with observations at 24 h or less are included as well as longer-term exposures that may provide useful perspective in assessing the effects of inhalation exposure to carbon tetrachloride. Generally, the concentration of carbon tetrachloride appears to be the driver for severity of effects. The liver and kidneys appear to be primary targets for toxicity. Serum

enzyme activity levels are routinely employed as biochemical indices of toxicity and serve as reliable indicators of hepatic damage, although a progression of injury may occur after cessation of exposure. The toxic response to carbon tetrachloride among the various species tested appears to vary.

3.3 Developmental and Reproductive Toxicity

In a study by Schwetz et al. (1974), groups of pregnant Sprague-Dawley rats were exposed for 7 h/day on days 6-15 of gestation to carbon tetrachloride at nominal concentrations of 300 or 1,000 ppm (analytic concentration were 334 and 1,004 ppm, respectively). The two doses were tested in separate experiments, each with its own concurrent controls. Rats exhibited no overt signs of toxicity, but reduced food consumption (and consequent decreased body-weight gain) and signs of hepatotoxicity (increased SGPT activity, pale and mottled livers, and increased relative liver weight) were evidence of maternal toxicity in both exposure groups. Signs of maternal toxicity were resolved 6 days after exposure. Carbon tetrachloride had no effect on conception rate, number of implantations, or litter size. A summary of fetal anomalies is presented in Table 211. Relative to unexposed controls, the only statistically significant findings were total skeletal anomalies (300 ppm), sternebral anomalies (1,000 ppm), and subcutaneous edema (300 ppm). The investigators concluded that carbon tetrachloride was not teratogenic to the developing embryo under the conditions of the study. The authors stated that evidence of fetotoxicity (decreased crownrump length and fetal body weight) was observed in the 300- and 1,000-ppm groups compared with the control groups. However, the experimental variability over the 3-fold dose range rendered these results inconclusive for identifying any fetal end points relevant to deriving AEGL values. For example, when compared with concurrent controls, the incidence of delayed sternebral ossification was statistically significant only at 1,000 ppm, with a substantially lower incidence in the concurrent control group; however, when the control data were combined, total skeletal abnormalities (predominantly delayed ossification) was significant only at 300 ppm. Similarly, compared with the combined controls, fetal subcutaneous edema (potentially pertinent to acute exposure scenarios) was only significant at 300 ppm; however, no significant increase in total soft-tissue

TABLE 2-10 Nonlethal Effects of Carbon Tetrachloride in Laboratory Species Following Inhalation Exposure

Species	Exposure	Effect	Reference
Rhesus monkey	200 ppm, 8 h/d, 5 d/wk for 10.5 mos	Transient hepatic injury.	Smyth et al. 1936
Dog	400 ppm, 7 h/d for 6 mos	Decreased body weight.	Mellon Institute 1947
Rat	1,500 ppm, varying exposure profiles all with Ct = 4,500 ppm-h	Hepatic vacuolation and individual cell necrosis which varied with exposure profile.	Van Stee et al. 1982
Rat	200 ppm, 8 h/d, 5 d/wk for 10.5 mos	No significant effects.	Smyth et al. 1936
Rat	50 ppm, 6 h for 13-18 d	Minor increase in SGPT, minor histologic changes in the liver.	David et al. 1981
	250 ppm, 72 min for 13-18 d	Minor increase in SGPT, minor histologic changes in the liver.	
	1,000 ppm, 18 min for 13-18 d	Minor increase in SGPT, minor histologic changes in the liver.	
	1,000 ppm (six 3-min exposures with 1-hr intervals)	Minor increase in SGPT, minor histologic changes in the liver.	
Rat	63 ppm, 6 h/d, 5 d/wk for 4 wk	Transient hepatic effects; 2- to 9-fold increase in SGOT, SGPT.	Appelman et al. 1985
	80 ppm 6 h/d, 5 d/wk for 4 wk	Transient hepatic effects; 2- to 9-fold increase in SGOT, SGPT.	
	63 ppm (two 3-h exposures, 1.5 h intervals)	Transient hepatic effects; 2- to 9-fold increase in SGOT, SGPT	
	80 ppm (two 3-h exposures, 1.5 h intervals)	Transient hepatic effects; 2- to 9-fold increase in SGOT, SGPT.	
	63 ppm (two 3-h exposures, 1.5 h intervals, 5-min peaks of 6-fold baseline)	Transient hepatic effects; 2- to 9-fold increase in SGOT, SGPT.	
	80 ppm (two 3-h exposures, 1.5 h intervals, 5-min peaks of 6-fold baseline)	Transient hepatic effects; 2- to 9-fold increase in SGOT, SGPT.	
Rat	100 ppm, 8 h	No significant effect on SDH.	Paustenbach et al. 1998b
	100 ppm, 11.5 h	Marginally increased SDH.	
Rat	180 ppm, 15 min	"Comatose"; increased ALT at 24 h postexposure.	Sakata et al. 1987
Rat	100 ppm, 2 h	No biologically relevant effect.	Sanzgiri et al. 1995
	1,000 ppm, 2 h	Increased ALT and SDH, decreased P-450.	

(Continued)

TABLE 2-10 Continued

Species	Exposure	Effect	Reference
Rat	50 ppm, 6 h	No effect.	Wang et al. 1997
	500 ppm, 6 hr	Minor increase in SGOT and SGOT.	
Rat	12,000 ppm, 3 min	Altered hepatic weight, total lipid content and/or gross or microscopic changes in the liver.	Adams et al. 1952
	3,000 ppm, 6 min	No effect.	
	3,000 ppm, 9 min	Altered hepatic weight, total lipid content, and/or gross or microscopic changes in the liver.	
	800 ppm, 30 min	No effect.	
	800 ppm, 60 min	Altered hepatic weight, total lipid content, and/or gross or microscopic changes in the liver	
	400 ppm, 60 min	Altered liver weight, total lipid content and/or gross or microscopic changes in the liver	
	100 ppm, 420 min	Altered hepatic weight, total lipid content, and/or gross or microscopic changes in the liver.	
	50 ppm, 420 min	No effect.	
Mouse	8,500 ppm, 0.16 min	ECt_{50} for SGPT activity.	Gehring 1968
	8,500 ppm, 21 min	ECt_{50} for anesthesia.	
Rabbit	100 ppm, 2 h/wk for 23 wk (increased to 600 ppm by 23 weeks)	Increased hexobarbital sleeping time; hepatic fibrosis.	Ugazio et al. 1995
Cat	10,000 ppm (via tracheal cannulation) for 15, 30, 60, or 240 min	Increased total lipids in renal cortex at 15 min; increased relative adrenal weight after 15 to 30 min; central necrosis in liver at 240 min.	Wong and DiStefano 1966

Abbreviations: ALT, alanine aminotransferase; ECt_{50}, effective concentration at which 50% of individuals exhibit a specific biologic effect; SDH, sorbitol dehydrogenase; SGPT, serum glutamic-pyruvic transaminase; SGOT, serum glutamic-oxaloacetic transaminase.

TABLE 2-11 Effects of Carbon Tetrachloride During Gestation in Rats[a]

	Control	300 ppm	1,000 ppm
Maternal body weight, g (mean ± SD)			
Number of dams examined	43	22	23
Gestation day 6	283 ± 17	290 ± 21	275 ± 19
Gestation day 13	317 ± 18	281 ± 25[b]	253 ± 24[b]
Gestation day 21	397 ± 24	368 ± 33[b]	336 ± 57[b]
Fetal anomalies, % litters affected (number of litters)			
Number of litters examined	43	22	22
Gross anomalies	0 (0)	0 (0)	0 (0)
Skull anomalies (delayed ossification)	12 (5)	9 (2)	9 (2)
Lumbar ribs or spurs	24 (10)	41 (9)	27 (6)
Vertebral anomalies (bipartite centra)	21 (9)	27 (6)	14 (3)
Sternebral anomalies (bipartite, delayed ossification)	61 (14)	68 (15)	–
	11 (2)	–	59 (13)[c]
Subcutaneous edema	33 (14)	59 (13)[c]	50 (1)
Dilated ureters	12 (5)	14 (3)	5 (1)
Total soft tissue anomalies	51 (22)	68 (15)	59 (13)
Fetal growth			
Fetal body weight, g (mean ± SD)	5.64 ± 0.34	5.29 ± 0.34[d]	4.96 ± 0.68[d]
Fetal crown-rump length, mm (mean ± SD)	43.7 ± 1.0	42.2 ± 1.0[d]	41.8 ± 2.2[d]

[a] Carbon tetrachloride was administered by inhalation for 7 h/day on days 6-15 of gestation.
[b] Significantly different from control group ($p \leq 0.05$, by Dunnett's test).
[c] Significantly different from control group ($p < 0.05$, Fisher exact probability test)
[d] Significantly different from control group ($p < 0.05$, ANOVA and Dunnett's test).
Source: Adapted from Schwetz et al. 1974.

abnormalities was detected at either dose. Data on each set of concurrent controls and for individual litters were unavailable for further analysis. Furthermore, no gross abnormalities at either test concentration were found, and a clear doseresponse relationship in skeletal and soft-tissue anomalies was lacking. Findings of lower fetal body weight and shorter crown-rump length are likely to be associated with the sustained lower maternal weight over gestation days 6-15.

3.4. Genotoxicity

Data on the genotoxicity of carbon tetrachloride are equivocal. Although DNA adducts have been identified in a variety of studies, no specific adducts were characterized (McGregor and Lang 1996). Using Chinese hamster ovary cells, carbon tetrachloride at 1,270 µg/ml was negative in sister-chromatid exchange and chromosomal-aberration tests both with and without activation (Loveday et al. 1990). Recombination effects have been reported in *Saccharomyces cerevisiae* and *Aspergillus nidulans* (reviewed in McGregor and Lang 1996). Reverse mutation tests using several strains of *Salmonella typhimurium* were negative (McGregor and Lang 1996).

Mirsalis and Butterworth (1980) reported no unscheduled DNA synthesis in hepatocytes from rats treated with carbon tetrachloride.

Studies of radiolabeled carbon tetrachloride indicated binding to DNA and rRNA in the liver of rats treated with 3-methylcholanthrene (Rocchi et al. 1973), and Sawada et al. (1989) reported that carbon tetrachloride (200 mg/kg) caused a 23-fold increase in replicative DNA synthesis at 48 h.

3.5 Carcinogenicity

Data on tumorigenic responses to carbon tetrachloride following inhalation exposure were limited. Costa et al. (1963) reported the occurrence of hepatic tumors in 30 rats (age, sex, strain not specified) after repeated inhalation exposure to carbon tetrachloride (concentration and daily exposure protocol not specified). The exposure duration was 7 months followed by a 3-9 month observation period. Ten of the rats exhibited lesions of the liver characterized histologically as adenocarcinomas, trabecular carcinomas, and anaplastic carcinomas accompanied by cirrhosis. The malignant nature of the tumors was affirmed by the invasion of hepatic veins by hepatoma cellular elements.

Liver tumors have been reported in rats and mice following subcutaneous injection (Reuber and Glover 1970) and gavage administration (Edwards 1941; Edwards and Dalton 1942; Edwards et al. 1942; Andervont 1958; Weisburger 1977). Because of the possible differences in metabolism and disposition for different routes of administration, and the resulting differences in target organ and

tissue doses, the data are inappropriate for assessing carcinogenic potential from acute inhalation exposures.

In studies with rat liver microsomal preparations, Castro et al. (1997) reported that free radicals ($\cdot CCl_3$, $CCl_3O_2\cdot$, $\cdot OH$) were capable of altering the DNA bases, guanine, cytosine, and thymine. The authors contended that if these altered bases were formed and not adequately repaired before cell replication, liver DNA could be adversely affected and that such processes may be involved in carbon tetrachloride-induced carcinogenicity.

In a study by Nagano et al. (2007), groups of F344/DuCrj rats (50/sex/group) were exposed (whole-body) to carbon tetrachloride (99.8%) vapor at 0, 5, 25, or 125 ppm (0, 31.5, 157, or 786 mg/m^3) for 6 h/day, 5 days/week for 104 weeks. The incidence of hepatocellular adenomas and carcinomas was statistically significantly increased in both sexes at 125 ppm. The study also examined the toxic responses of Crj:BDF1 mice (50/sex/group) exposed to carbon tetrachloride (99%) at 0, 5, 25, or 125 ppm (0, 31.5, 157, or 786 mg/m^3) for 6 h/day, 5 days/week for 104 weeks. The incidences of hepatocellular adenomas and carcinomas were significantly increased in both sexes at concentrations of 25 ppm and greater. The incidence of liver adenomas in female mice (8/49 or 16%) in the 5ppm group was statistically significantly higher than that of the concurrent control group and exceeded the historical control range (2-10%). The incidences of adrenal pheochromocytomaas were significantly increased in males at 25 ppm and in females at 125 ppm.

3.6 Summary

Animal toxicity data for inhaled carbon tetrachloride affirm hepatotoxic and renal effects, as well as anesthetic-like effects, as primary end points. The findings are consistent with those associated with human exposures, although carbon tetrachloride-induced nephrotoxicity appears to be more prevalent in humans than in laboratory species. The most sensitive end point for evaluating the hepatic toxicity of carbon tetrachloride in animals appears to be serum enzyme activities that reflect tissue damage. Results of a developmental-toxicity study were equivocal. Several studies have provided lethality data for various concentrations and exposure durations. Data on nonlethal effects are also available but are much more limited or come from studies that reported effects only after long-term exposures at low concentrations (generally less than 200 ppm).

4. SPECIAL CONSIDERATIONS

4.1 Metabolism and Disposition

Carbon tetrachloride is metabolized by the mixed function oxidases of the liver (Sipes et al. 1977) and other organs, such as the adrenal glands (Colby et al. 1994). Known metabolites include carbon dioxide, chloroform, free radicals, and possibly hexachloroethane (Recknagel 1967; Glende 1972; Paustenbach et al. 1988). Additional, unidentified metabolites are excreted in the feces and urine (McCollister et al. 1951; Paustenbach et al. 1986a).

On the basis of limited data on human subjects, Stewart et al. (1961) found that the elimination of carbon tetrachloride via expired air is inversely related to the duration of exposure.

The absorption, distribution, and excretion of [^{14}C]-carbon tetrachloride was studied in female Rhesus monkeys (McCollister et al. 1951). The monkeys breathed from bags containing [^{14}C]-carbon tetrachloride at 50 ppm and exhaled via a valve system into exhale bags; both types of bags were impermeable to air and carbon tetrachloride for the duration of the experiments. Exposure was for 139, 300, or 344 min. The average rate of absorption was 0.022 mg/kg/min, and the average absorption was 30% of the amount inhaled. Tissue analysis revealed that most of the carbon tetrachloride was in adipose tissue (tissue:blood ratio = 7.94). Radioactivity was found in the blood, exhaled carbon dioxide, urinary urea and carbonate, and feces. At least 51% of the absorbed radioactivity had been eliminated within 180 min of exposure. Test of dermal exposure to vapors of carbon tetrachloride (485 ppm for 240 min and 1,150 ppm for 270 min) revealed negligible absorption, as determined by radioactivity in the blood and expired air.

On the basis of limited data from humans, Lehmann and Schmidt-Kehl (1936) estimated pulmonary absorption to be about 60% for exposures at 50 ppm, or about twice that observed from nonhuman primates (McCollister et al. 1951).

Paustenbach et al. (1986a) reported differences in the distribution and elimination of inhaled carbon tetrachloride relative to exposure regimen. Sprague-Dawley rats were exposed to carbon tetrachloride at 100 ppm for either 8 h/day or 11.5 h/day. The daily exposure regimens were adjusted such that cumulative exposures were identical. Following the 2-week exposure using the 11.5h/day regimen, ^{14}C-activity in expired air and feces represented 32% and 62% of the total dose, respectively. For the 8-h/day exposure regimen, ^{14}C-activity in expired air and feces represented 45% and 48% of the total dose, respectively, demonstrating that fecal excretion was greater after the 11.5-h exposure regimen. Regardless of the exposure schedule, urinary excretion and ventilatory elimination of $^{14}CO_2$ was minimal (8% and 2%, respectively). Results of the study indicated that over 60% of the inhaled dose was metabolized and that the 11.5-h/day schedule resulted in greater accumulation of carbon tetrachloride in the poorly perfused lipophilic depots, such as adipose tissue. Overall, the results suggest that relatively small changes in exposure regimens may influence the rate and route of elimination of carbon tetrachloride.

A physiologically-based pharmacokinetic (PBPK) model for inhaled carbon tetrachloride was developed by Paustenbach et al. (1988). Values for V_{max} (0.65

mg/kg/h) and K_m (0.25 mg/L) were determined on the basis of data from Sprague-Dawley rats exposed to carbon tetrachloride at 100 ppm. Metabolites were partitioned into three compartments: those excreted in the breath (CO_2 and possibly hexachloroethane), urine, and feces. Results of simulations with the model were consistent with the human data of Stewart et al. (1961) and the monkey data reported by McCollister et al. (1951).

Although McCollister et al. (1951) reported measurable amounts of radioactivity in the feces of monkeys exposed to [^{14}C]-carbon tetrachloride via inhalation and Paustenbach et al. (1986a) reported fecal excretion in rats, Page and Carlson (1994) found that fecal elimination of carbon tetrachloride (as parent compound) by Sprague-Dawley rats did not significantly contribute to overall elimination of carbon tetrachloride following single or repeated inhalation exposure. The authors contended it was more likely that the minimal fecal elimination represents a very slow elimination of a metabolite or catabolic product of a carbon tetrachloride-macromolecular adduct.

Kinetic parameters were estimated for rats exposed to carbon tetrachloride at 100 or 1,000 ppm for 2 h (Sanzgiri et al. 1995). There were no significant differences in the t_2 (162 and 166 min, respectively), or the apparent clearance (148 and 100 ml/min/kg, respectively). However, as would be expected, the area under the curve (AUC) was proportionately greater at 1,000 ppm (1,885 µgmin/ml) compared with that at 100 ppm (124 µg-min/ml), as was the C_{max} (1.0 and 12.8 µg/ml, respectively).

The effect of exposure route on the disposition of carbon tetrachloride in rats was examined by Sanzgiri et al. (1997). A comparison of uptake, distribution, and elimination of carbon tetrachloride following inhalation (1,000 ppm for 2 h) or oral exposure (179 mg/kg, single bolus or 2-h oral infusion) was conducted in male Sprague-Dawley rats. Carbon tetrachloride tissue concentrations were lower in the gastric infusion groups than in the oral bolus or inhalation exposure group. In fact, AUC data (0-24 h) indicated that liver accumulation (and accumulation in most tissues) of carbon tetrachloride was higher after inhalation (2,823 µg·min/ml) than after oral bolus (1,023 µg-min/ml) or oral infusion (149 µg-min/ml). As would be expected for a lipid-soluble chemical, the tissuespecific time courses for uptake and elimination were determined largely by the perfusion rate and lipid content of the tissue. The authors concluded that the most appropriate measure of internal dose for carbon tetrachloride-induced acute hepatotoxicity is the tissue-concentration versus time curve from 0 to 30 min.

4.2 Mechanism of Toxicity

Pulmonary, hepatic, cardiovascular, hematologic, and CNS effects have been documented in humans and laboratory animals exposed to carbon tetrachloride. However, the liver and kidneys appear to be the primary targets for

carbon tetrachloride toxicity. The majority of research on mechanism of action has focused on hepatotoxic processes.

The mechanism of carbon tetrachloride hepatotoxicity has been extensively studied (e.g., reviews by Zimmerman 1978; Clawson, 1989). Because of the great volume of data available on this topic, an indepth discussion is beyond the scope of this chapter. Briefly, the metabolism of carbon tetrachloride is mediated by ethanol-inducible CYP2E1. The hepatotoxicity of carbon tetrachloride appears to be mediated by reactive metabolites. Several reactive metabolites have been implicated in the mechanism(s) and include the trichloromethyl and chlorine free radicals (Rechnagel and Glende 1973), the trichloromethylperoxy free radical (Slater 1982), carbenes (Reiner and Uehleke 1971), and the carbon dioxide anion radical (LaCagnin et al. 1988). The trichloromethyl free radical, resulting from homolytic cleavage of the carbon-chlorine bond, is thought to react with fatty acids in the endoplasmic reticulum membranes which form secondary free radicals resulting in lipid peroxidation. The process rapidly becomes autocatalytic and results in further peroxidation thereby explaining the toxic potency of carbon tetrachloride. Rao and Recknagel (1969) showed that incorporation of ^{14}C from [^{14}C]-carbon tetrachloride into rat liver microsomal and mitochondrial lipids was rapid (about 5 min) following oral administration of carbon tetrachloride. Slater (1982) hypothesizes that the trichloromethylperoxy free radical, which is even more reactive, interacts with unsaturated membrane lipids resulting in lipid peroxidation. Ultimately, the lipid peroxidation from either of these mechanisms leads to cellular degeneration. Alternatively, the involvement of carbenes and their mediation of covalent binding of macromolecules has also been proposed, as has been involvement of the carbon dioxide anion radical. These processes ultimately result in centrilobular necrosis and fatty degeneration of the liver. Glende and Recknagel (1991) reported on the involvement of carbon tetrachloride-activated phospholipase A2 and the role of increased intracellular calcium in hepatocyte injury.

In addition to hepatotoxicity, carbon tetrachloride is also known to affect the CNS (Stevens and Forster 1953; Cohen 1957). The narcotic properties of carbon tetrachloride are well documented (ATSDR 2005) but the precise mechanism of action is unknown.

4.3 Structure-Activity Relationships

Assessment of structure-activity relationships were not instrumental is deriving AEGL values for carbon tetrachloride.

4.4 Other Relevant Information

4.4.1 Species and Individual Variability

Johnson and Simmons (1994) reported on the variable susceptibility to carbon tetrachloride-induced hepatotoxicity between Fischer-344 and SpragueDawley rats. Following gavage administration of carbon tetrachloride at 0.1 or 0.4 ml/kg, Sprague-Dawley rats appeared to be more resistant to carbon tetrachloride-induced hepatic necrosis than Fischer-344 rats.

It has also been reported that rats eliminate carbon tetrachloride faster than larger species (Andersen 1981), such as monkeys (McCollister et al. 1951) and humans (Stewart et al. 1961), and that rat studies may underestimate the accumulation of carbon tetrachlorie in tissues of humans.

One toxic end point that occurs consistently among species is hepatotoxicity. Mild signs of hepatotoxicity, such as elevated serum enzyme activities, have been reported in both humans and rodents. Interspecies comparisons of this end point can be made by examining the exposure associated with producing the effect in each species. The study by Stewart et al. (1961) reported minor enzymatic changes in two of six human subjects exposed at 49 ppm for 70 min. In contrast, rats exhibited mild elevations in serum enzyme activities following exposures at 250 ppm for 4 h (Cornish and Block 1960) and at 250 ppm for 70 min (David et al. 1981). Using these similar responses among species as a reference point, one can compare the relative susceptibility using exposures on a ppm-min or $ppm^{2.5}$-min basis (Table 2-12). For carbon tetrachloride, the appropriate exposure metric appears to be $ppm^{2.5}$-min. The range of human-to-rat variability is 5- to 200-fold for serum enzyme activity. That end point, however, is known to exhibit inherent variability.

As discussed earlier, the metabolism of carbon tetrachloride is mediated primarily by the mixed function oxidase, CYP2E1. Hepatotoxicity of carbon tetrachloride is mediated by reactive intermediates resulting from metabolism. Genetic polymorphisms in CYP enzymes have been proposed as a biomarker of susceptibility to environmental toxicants (Hong and Yang 1997). Substantial variation in human hepatic levels of CYP2E1 has been found, which may contribute to population variability in sensitivity to carbon tetrachloride. A 7-fold range in activity of CYP2E1 in liver samples collected from 23 subjects, and a 12-fold range in CYP2E1 protein content of liver samples from 40 liver donors has been reported (Lipscomb et al. 1997; Snawder and Lipscomb 2000). Furthermore, coexposure with CYP2E1 inducers, such as ethanol, isopropanol, and ketones, may increase susceptibility to carbon tetrachloride. In addition to genetic polymorphisms and exposure to CYP2E1 inducers, sensitive populations also include individuals with ketosis (diabetics, obese individuals, and people who are fasting). Bruckner et al. (2002) showed a circadian rhythmicity in carbon tetrachloride-induced hepatotoxicity in rats due to increased lipolysis and subsequent acetone production during overnight fasting associated with sleep cycles. Age-related variations in cytochrome-oxidase activity levels may also

impact susceptibility to carbon tetrachloride. The reduction of cytochrome-oxidase activity associated with young age and older ages implies a decreased production

TABLE 2-12 Comparison of Exposures to Carbon Tetrachloride

Species	Exposure	C × t (ppm-min)	C × t ($ppm^{2.5}$-min)	Reference
Human	49 ppm, 70 min	3,430	1,176,490	Stewart et al. 1961
Rat	250 ppm, 4 h	60,000	237,170,824	Cornish and Block 1960
Rat	250 ppm, 70 min	17,500	10,249,085	David et al. 1981
Interspecies variability	–	5-17 fold	9-200 fold	

reactive intermediates and subsequent decrease in susceptibility of children and elderly individuals. Although age-related variations in cytochrome oxidsae activity imply decreased susceptibility to carbon tetrachloride toxicity, other agerelated factors such as alterations in antioxidant activity are important in assessing overall susceptibility. Further, pathologic conditions such as cirrhosis and hepatitis may compromise hepatic function and reserve thereby increasing susceptibility to carbon tetrachloride. Although it is difficult to quantify the range of susceptibility, as indicated earlier in this report, human subjects have exhibited a wide range of response severity. More extensive discussion of factors affecting susceptibility to carbon tetrachloride are available in the reviews by Bruckner et al. (2008) and EPA (2010a).

Species variability in the metabolism and disposition of carbon tetrachloride has been addressed in several PBPK models and application of the models. The PBPK model of Paustenbach et al. (1988) predicted fat and venous-blood concentrations of carbon tetrachloride to be notably higher in rats than in humans at exposure concentrations of 5 ppm. Gargas et al. (1989) reported higher blood:air partition coefficients in rats than in humans. The greater respiratory rates and greater cardiac output/tissue perfusion rates in rodents in conjunction with the higher blood:air partition coefficients argues for a greater tissue dose in rodents than in humans when exposed at equivalent concentrations. Based on PBPK model predictions, Delic et al. (2000) showed that the ratio of rate and extent of metabolism in rats was greater than that in humans exposed at low concentrations (5 ppm [NOAEL] for rats and 2 ppm for humans [occupational exposure limit in the United Kingdom).

4.4.2 Concurrent Exposure Issues

The potentiation of carbon tetrachloride-induced hepatotoxicity by ethanol, aliphatic alcohols, and ketones has been well documented in animals and humans

(Folland et al. 1976; reviewed by ATSDR2005; EPA 2010a; Plaa 2000; see also Section 2.2.1). Folland et al. (1976) reported on an individual who exhibited only a modest, transient increase in serum transaminase activity, but experienced renal failure following acute exposure to carbon tetrachloride. The individual was thought to have been preexposed to isopropanol, which induces CYP2E1 and thereby markedly potentiates acute carbon tetrachloride-induced cytotoxicity. Potentiation of carbon tetrachloride-induced toxicity in humans by ethanol has also been documented (Markham 1967; Manno and Rezzadore 1994; Manno et al. 1996). Although the precise mechanism of potentiation has not been elucidated for all interactions, the enhancement of metabolic processes resulting in increased production of reactive metabolites has been demonstrated. Because the toxicity of carbon tetrachloride is mediated by CYP2E1, it may be assumed that modulation of CYP2E1 expression by other chemicals (see reviews by Raucy 1995; EPA, 2010a) may alter the impact of carbon tetrachloride-initiated toxicity. In a study by Wang et al. (1997), it was shown that prior exposure of rats to ethanol (2 g/day) for 3 weeks resulted in an increase in the hepatotoxicity (determined by serum enzyme activities) from carbon tetrachloride. The increase was 2-fold following a 6-h exposure at 50 ppm, and 20- to 30fold after a 6-h exposure at 500 ppm.

Cornish and Adefuin (1967) reported on the effects of aliphatic alcohol pretreatment on the toxicity of carbon tetrachloride (1,000 ppm for 2 or 2.5 h) in male albino rats. Carbon tetrachloride had little effect on SGOT activity relative to unexposed controls (246 ± 20 vs 238 ± 8 units), but most of the alcohols studied resulted in notable increases in SGOT activity in combination with carbon tetrachloride relative to carbon tetrachloride alone (1,941 ± 558 vs 217 ± 17 units).

A remarkable potentiation of carbon tetrachloride-induced lethality by nontoxic concentrations of chlordecone has been documented in animal models (Mehendale 1994). Although such synergistic responses are often the result of altered metabolism, the chlordecone-potentiated carbon tetrachloride lethality appears to be the result of alterations in tissue-repair processes resulting in an amplification of the toxic insult rather than altered biotransformation (Mehendale 1990).

5. DATA ANALYSIS FOR AEGL-1

5.1 Human Data Relevant to AEGL-1

Tomenson at al. (1995) affirmed that occupational exposure to carbon tetrachloride at mean concentrations of up to 4 ppm resulted in only minor alterations in serum enzyme activity. On the basis of estimated exposure concentrations and the responses of four individuals exposed under controlled conditions, Davis (1934) reported that no signs or symptoms of toxicity were observed at 158 ppm for 30 min or at 76 ppm for 2.5 or 4 h. At higher

concentrations, CNS effects were observed. Six subjects exposed to a time-weighted average (TWA) concentration of 49 ppm for 70 min reported only odor detection and no irritation or symptoms of toxicity. Minor transient changes in serum iron, serum transaminases, and urinary urobilinogen were detected in two subjects exposed for 70 min (Stewart et al. 1961). In the same study, six subjects were exposed at a TWA concentration of 10.9 ppm for 180 min; no adverse effects were detected. In a report of an occupational exposure study, Smyth et al. (1936) concluded that exposure to carbon tetrachloride at 5-117 ppm (8-h TWA) resulted in minimal effects (restricted visual field and slightly elevated bilirubin), although actual daily exposures concentrations were unknown. However, Elkins (1942) noted that exposures to carbon tetrachloride at 20-85 ppm produced notable signs of toxicity (nausea, vomiting, and weight loss).

5.2 Animal Data Relevant to AEGL-1

Animal data defining no effect or minimal effects that are consistent with the derivation of AEGL-1 values are few and equivocal. Smyth et al. (1936) found no significant signs of toxicity in rats exposed to carbon tetrachloride at 200 ppm for 8 h/day, 5 days/week for 10.5 months. In contrast, Appelman et al. (1985), using a similar exposure protocol (6 h/day, 5 days/week), reported transient hepatic effects and elevated serum enzyme activities in rats exposed at 63 ppm for 4 weeks. Although Adams et al. (1952) reported no adverse effects in rats exposed at 3,000 ppm (6 min), 800 ppm (30 min), and 50 ppm (420 min), serum enzyme activities were not measured and, therefore, hepatotoxic effects may have been overlooked. Paustenbach et al. (1986b) reported no significant changes in SDH activity in rats exposed at 100 ppm for 8 h. David et al. (1981) noted minor changes in SGPT activity and minor histopathologic findings in rats exposed at 1,000 ppm for 18 min, 250 ppm for 72 min, 50 ppm for 6 h, or following six 3-min exposures (at 1-h intervals) at 1,000 ppm. Minor increases in activities of some serum enzymes were reported by Cornish and Block (1960) for rats exposed to carbon tetrachloride at 250, 1,000, or 1,500 ppm for 4 h, but not for rats exposed at 50 or 100 ppm for 4 h. Although several lethality studies (Mellon Institute 1947; Adams et al. 1952; Dow Chemical 1960) provided data showing no lethalities, those investigations did not assess other toxicity end points and, therefore, it cannot be assumed that the animals surviving the exposures were devoid of toxic effects above and beyond what would be considered for AEGL-1 assessments.

5.3 Derivation of AEGL-1 Values

Although the available data set of human studies on carbon tetrachloride was not robust, the data were considered for derivation of AEGL-1 values to eliminate the uncertainties inherent in extrapolating from animal data. Furthermore, the

animal data on effects consistent with the definition of AEGL-1 are equivocal. Data reported by Tomenson at al. (1995) affirmed that occupational exposure to carbon tetrachloride at mean exposures of up to 4 ppm resulted in only minor alterations in serum enzyme activity. However, the study involved long-term and repeated exposures to carbon tetrachloride, a regimen that was inappropriate for derivation of AEGL values. Reports by Davis (1934) and Stewart et al. (1961) also provided human exposure data, but they are not appropriate for derivation of AEGL-1 values. The Davis (1934) study was not used because the concentrations of carbon tetrachloride that produced no effects were also the no-effect levels for CNS effect (AEGL-2 level effects). The Stewart et al. (1961) study did not identify any irritation or clinically significant adverse effects; therefore, the study does not provide suitable data to derive AEGLvalues. Therefore, AEGL-1 values are not recommended.

6. DATA ANALYSIS FOR AEGL-2

6.1 Human Data Relevant to AEGL-2

Several reports provided data describing nonlethal effects of acute exposure of humans to carbon tetrachloride. Davis (1934) conducted experiments in which three human subjects were exposed to carbon tetrachloride at 317 ppm (concentration calculated on the basis of room volume and amount of carbon tetrachloride) for 30 min. CNS effects, including nausea, vomiting, dizziness, and headaches, were reported by the subjects but clinical assessments (urinalysis, blood count, hemoglobin levels, blood pressure, and heart rate) remained normal for up to 48 h postexposure. Similar effects were reported by subjects exposed at 1,191 ppm for 15 min, with the exception that one of the four subjects found the exposure to be intolerable after 9 min. Exposures at 2,382 ppm for 3-7 min produced these effects in addition to dizziness and signs of anesthesia. The observed effects were apparently not long-lasting but may be considered severe enough to impair escape or normal function and, therefore, can be considered as a conservative end point for deriving AEGL-2 values. No effects were observed following exposure to carbon tetrachloride at 76 ppm for 2.5 or 4 h. Davis (1934) also reported notable renal effects in a worker experimentally exposed to carbon tetrachloride at 200 ppm for 8 h; renal function returned to near normal 2 months after exposure.

6.2 Animal Data Relevant to AEGL-2

Animal studies of carbon tetrachloride described effects indicative of hepatotoxicity following highly varied exposure regimens (Adams et al. 1952; David et al. 1981; Appleman et al. 1985; Belyaev et al. 1992). One report noted a

"comatose" condition in rats following a 15-min exposure to carbon tetrachloride at 180 ppm (Sakata et al. 1987). Adams et al. (1952) characterized the severity of response of rats to various inhalation exposure protocols. Because the end points considered were responses characteristic of notable hepatic insult (change in hepatic weight, increased lipid content, and gross and microscopic changes), the adverse effects are considered to be consistent with AEGL-2 effects. Adverse effects were detected after exposures to carbon tetrachloride at 12,000 ppm for 3 min, 3,000 ppm for 9 min, 800 ppm for 60 min, and 400 ppm for 420 min. Minor changes in SGPT activity were reported by David et al. (1981) for rats exposed at 300 ppm-h under different exposure regimens; 1,000 ppm for 18 min; 250 ppm for 72 min; 50 ppm for 6 h; or after six 3-min exposures (at 1-h intervals) at 1,000 ppm. Four-week exposure of rats to carbon tetrachloride at 63 or 80 ppm for 6 h/day, 5 days/week, resulted in transient hepatic effects and 2- to 9-fold increases in serum enzyme concentrations. However, no data were provided relative to acute exposures. Mice exposed at 4,770 ppm for 4 h exhibited centrilobular necrosis in the liver (Belyaev et al. 1992). With the exception of the hepatic necrosis (Belyaev et al. 1992), the "comatose" effects reported in rats (Sakata et al. 1987), and the hepatic damage noted in rats (Adams et al. 1952), the available animal data do not suggest effects of a severity consistent with AEGL-2 effects. Furthermore, the liver is primarily affected by carbon tetrachloride in rodents, whereas hepatic injury is often relatively minor human poisoning cases, where renal damage predominates.

Schwetz et al. (1974) reported fetal toxicity (decreased fetal body weight and crown-rump length and) following exposures to carbon tetrachloride at 300 ppm (lowest concentration tested) or 1,000 ppm for 7 h/day on gestation days 615. Other reported effects included significant increases (relative to controls) in incidences of total skeletal anomalies (300 ppm), sternebral anomalies (1,000 ppm), and subcutaneous edema (300 ppm). Maternal toxicity (e.g., heptaotoxicity) was evident at both exposure concentrations. However, methodology issues compromised interpretation of the results. The tests of the two doses were conducted in separate experiments, each with its own concurrent controls. The experimental variability over the 3-fold dose range rendered these results inconclusive for identifying any fetal end points for deriving AEGL values. For example, when compared with concurrent controls, the incidence of delayed sternebral ossification was statistically significant only at 1,000 ppm, with a substantially lower incidence in the concurrent control group; however, when the control data were combined, total skeletal abnormalities (predominantly delayed ossification) was significant only at 300 ppm. Similarly, compared with the combined controls, fetal subcutaneous edema (potentially pertinent to acute exposure scenarios) was only significant at 300 ppm; however, no significant increase in total soft tissue abnormalities was detected at either dose. Data on each set of concurrent controls and for individual litters were unavailable for further analysis. Furthermore, no gross abnormalities at either test concentration were

found, and a clear dose-response relationship in skeletal and soft-tissue anomalies was lacking. Findings of lower fetal body weight and shorter crown-rump length are likely to be associated with the sustained lower maternal weight over gestation days 6-15. Due to these uncertainties, the Schwetz et al. (1974) study is not suitable to serve as the basis for the AEGL-2 values.

6.3 Derivation of AEGL-2 Values

AEGL-2 values were derived on the basis of the highest no-effect level of 76 ppm for CNS effects in humans exposed carbon tetrachloride for 4 h (Davis 1934). An interspecies uncertainty factor of 1 was used because the study was conducted in humans. An intraspecies uncertainty factor of 10 was applied to account for individuals who may be more susceptible to the toxic effects of carbon tetrachloride (e.g., variability in metabolism and disposition). Temporal scaling was based on the equation $C^n \times t = k$ (ten Berge et al. (1986), where an empirical value for n of 2.5 was derived from rat lethality data. AEGL-2 values for carbon tetrachloride are presented in Table 2-13 and their derivations are presented in Appendix A.

TABLE 2-13 AEGL-2 Values for Carbon Tetrachloride

10 min	30 min	1 h	4 h	8 h
27 ppm (170 mg/m^3)	18 ppm (110 mg/m^3)	13 ppm (82 mg/m^3)	7.6 ppm (48 mg/m^3)	5.8 ppm (36 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1 Human Data Relevant to AEGL-3

Although data on lethality in humans following acute exposures to carbon tetrachloride are available, exposure concentration and duration information are lacking. Norwood et al. (1950) provided the only quantitative exposure data regarding a human fatality in a heavy drinker following acute exposure to carbon tetrachloride. An exposure duration of 15 min was estimated in the study, but how it was estimated was not described in the report. Other uncertainties about the case included that the exposure concentration was estimated and may not have been an accurate estimate of the actual exposure of the individual; prior history of exposure to carbon tetrachloride could not be ruled out; dermal exposure to carbon tetrachloride could not be ruled out; the patient reported to work feeling unwell, so illness which may have contributed to higher vulnerability to carbon tetrachloride; and the patient was a heavy consumer of ethanol, which is known to potentiate the toxicity of carbon tetrachloride. Any or all of those factors could explain why the single fatality occurred, while two co-workers experienced minor

symptoms of toxicity in association with exposures to carbon tetrachloride that were 16 times longer (4 h vs. 15 min).

Other studies have reported data that suggest that higher exposures to carbon tetrachloride are not lethal. As noted above, two co-workers of the worker that died continued mopping for 4 h and experienced mild headache and dizziness, which cleared after they stopped mopping. Davis (1934) reported that exposure of three individuals to carbon tetrachloride at 317 ppm for 30 min resulted in headache in one, nausea in two, and vomiting in one. Exposure at 1,191 ppm for up to 15 min resulted in headache, nausea, and vomiting in four adult subjects. Davis (1934) also reported that exposure to carbon tetrachloride at 2,382 ppm for up to 7 min resulted in headache, nausea, vomiting, dizziness, and "sleepiness" in three adult subjects. Given thse considerations, the Norwood et al. (1950) lethality case is considered to be an unreliable basis for deriving AEGL-3 values.

7.2 Animal Data Relevant to AEGL-3

Lethality data are available from studies of squirrel monkeys, dogs, rats, mice, and guinea pigs. The squirrel monkey and guinea pig data did not involve acute exposures, and the dog study involved only one animal. The most complete data sets are those of the Mellon Institute (1947), Adams et al. (1952), and Dow Chemical (1960) for rats exposed to carbon tetrachloride at concentrations of 1,000-20,000 ppm for durations of 0.1-10 h (these durations were not for all concentrations).

7.3 Derivation of AEGL-3 Values

Rat lethality data from the Adams et al. (1952) and Dow Chemical (1960) reports were used to derive AEGL-3 values for carbon tetrachloride. The method of Litchfield and Wilcoxon (1949) was used to obtain an estimate of a lethality threshold (LC_{01}) on the basis of 1-h lethality data. For durations other than 1 h, time scaling was performed using the equation $C^n \times t = k$, where $n = 2.5$. The value of the exponent n was determined empirically from rat lethality data (see Appendix B). With the exception of a 5-h exposure at 4,600 ppm (Adams et al. 1952), scaling was performed for durations of 0.5-2.2 h used in the study by Adams et al. The resulting 1-h LC_{01} of 5,153.5 ppm (see Appendix B) was used as the basis for scaling to other AEGL durations. PBPK model results predict that rodents will attain higher concentrations of carbon tetrachloride in venous blood and fat than would similarly exposed humans (Paustenbach et al. 1988). Delic et al. (2000) used PBPK model predictions to emphasize the greater metabolism of carbon tetrachloride by rats relative to humans. Overall, PBPK models affirm greater sensitivity of rodent species to carbon tetrachloride on the basis of metabolism and disposition considerations for carbon tetrachloride. PBPK models predict that at equal exposure concentrations, humans will have lower rates of

production of reactive metabolites of carbon tetrachloride (human/rat = 0.5). O the basis of PBPK modeling, the amount of toxic metabolites produced in humans would be approximately half the amount in the rodent. Therefore, the toxicokinetic component of the interspecies uncertainty factor is 0.5. The toxicodynamic component is 3. The total intraspecies uncertainty factor is 1.5 (3 × 0.5 = 1.5). An intraspecies uncertainty factor of 10 was applied to account for individuals who may be more susceptible to the toxic effects of carbon tetrachloride (e.g., variability in metabolism and disposition). Due to the known variability in the metabolic disposition of carbon tetrachloride that may result in an altered toxic response, an uncertainty factor of 10 was retained for protection of susceptible individuals (see Section 4.4.1 for further discussion of variation in metabolism of carbon tetrachloride). Thus, the total uncertainty factor is 15.

Regression analysis of concentration-time relationships for rat lethality data (Mellon Institute 1947; Adams et al. 1952; Dow Chemical 1960), using the method of ten Berge et al. (1986), resulted in an n value of 2.5 (see Appendix B). That value is slightly lower than the n of 2.8 reported by ten Berge et al. (1986). The current analysis, however, used two additional data sets in addition to that of Adams et al. (1952), which was the study used by ten Berge. The AEGL-3 values for carbon tetrachloride are presented in Table 2-14, and their derivations are presented in Appendix A.

TABLE 2-14 AEGL-3 Values for Carbon Tetrachloride

10 min	30 min	1 h	4 h	8 h
700 ppm (4,400 mg/m^3)	450 ppm (2,800 mg/m^3)	340 ppm (2,100 mg/m^3)	200 ppm (1,300 mg/m^3)	150 ppm (940 mg/m^3)

8. SUMMARY OF AEGL VALUES

8.1 AEGL Values and Toxicity End Points

AEGL values for carbon tetrachloride are shown in Table 2-15. AEGL-1 values are not recommended, as available data relevant to AEGL-1 end points yield values that exceed the AEGL-2 values. AEGL-2 values are based on a noeffect level for CNS effects in humans (Davis 1934). The AEGL-3 values are based on an estimate lethality threshold in rats. Data from nonhuman primates indicate that chronic exposures to carbon tetrachloride at concentrations greater than the 8-h AEGL-3 value were not lethal.

Extrapolation of EPA's inhalation unit risk to AEGL-specific exposure durations yield 10^{-4} cancer risk estimates at exposure concentrations that are higher than AEGL-2 values (see Appendix C).

8.2 Standards and Guidelines for Carbon Tetrachloride

Exposure standards and guidelines for carbon tetrachloride have been established by several organizations (Table 2-16). The 8-h AEGL-2 of 5.8 ppm is similar to the threshold limit value–time-weighted average (TLV-TWA) concentration of the American Conference of Governmental Industrial Hygienists (ACGIH) of 5 ppm. The 10-min and 30-min AEGL-2 values of 27 ppm and 18 ppm, respectively, and are approximately 3-fold and 2-fold higher than the ACGIH short-term exposure limit (STEL) of 10 ppm. The AEGL-2 values are based on fetal toxicity in rats, whereas the TLV-TWA and STEL are based on hepatotoxicity observed in rats after repeated exposures. The STEL was based on the TLV-TWA; a PBPK model was used to adjust for duration.

8.3 Data Quality and Research Needs

The overall database on carbon tetrachloride was sufficient for developing AEGL-2 and AEGL-3 values. Although human data were considered for developing AEGL-1 values, the resulting values were higher than AEGL-2 values; therefore, AEGL-1 values are not recommended. AEGL-2 values are based on a no-effect level for CNS effects in humans. AEGL-3 values are based on animal lethality data sufficient to estimate a threshold. Metabolism and disposition data suggesting that rodents are more sensitive than humans to carbon tetrachloride was considered in the derivation of the AEGL-3 values. Metabolism data on carbon tetrachloride and the consequent ramifications of metabolism on the toxic response allowed for the identification of an important sensitive population (those with enhanced cytochrome P450 activity) and relevant adjustments to the AEGL values to account for this more sensitive group.

TABLE 2-15 AEGL Values for Carbon Tetrachloride

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2 (disabling)	27 ppm (170 mg/m^3)	18 ppm (110 mg/m^3)	13 ppm (82 mg/m^3)	7.6 ppm (48 mg/m^3)	5.8 ppm (36 mg/m^3)
AEGL-3 (lethal)	700 ppm (4,400 mg/m^3)	450 ppm (2,800 mg/m^3)	340 ppm (2,100 mg/m^3)	200 ppm (1,300 mg/m^3)	150 ppm (940 mg/m^3)

[a] absence of AEG

below the AEGL-2 values are without adverse effects.

TABLE 2-16 Standards and Guidelines for Carbon Tetrachloride

Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]

AEGL-2	27 ppm	18 ppm	13 ppm	7.6 ppm	5.8 ppm
AEGL-3	700 ppm	450 ppm	340 ppm	200 ppm	150 ppm
ERPG-1(AIHA)[b]	–	–	20 ppm	–	–
ERPG-2	–	–	100 ppm	–	–
ERPG-3	–	–	750 ppm	–	–
IDLH (NIOSH)[c]	–	200 ppm	–	–	–
TLV-TWA (ACGIH)[d]	–	–	–	–	5ppm
PEL-TWA (OSHA)[e]	–	–	–	–	10ppm
TLV-STEL (ACGIH)[f]	10ppm (15min)				
REL-STEL (NIOSH)[g]	–	–	2ppm	–	–
PEL-C (OSHA)[h]	25ppm	25ppm	25ppm	25ppm	25ppm
MAK (Germany)[i]	–	0.5 ppm	–	–	–

[a] NR: not recommended. However, absence of AEGL-1 values does not imply that exposures below the AEGL-2 values are without adverse effects.

[b] ERPG (emergency response planning guidelines, American Industrial Hygiene Association) (AIHA 2013).

ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protection action.

ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing lifethreatening health effects.

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

[d] TLV-TWA (threshold limit value–time-weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 2012) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[e] PEL-TWA (permissible exposure limit–time-weighted average, Occupational Health and Safety Administration) (29CFR 1910.1045[2008]) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week.

[f] TLV-STEL (threshold limit value - short term exposure limit, American Conference of Governmental Industrial Hygienists) (ACGIH 2012) is defined as a 15-min TWA exposure which should not be exceeded at any time during the workday even if the 8-h TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 min and should not occur more than four times per day. There should be at least 60 min between successive exposures in this range. [g] REL-STEL (recommended exposure limits - short term exposure limit, National Institute for Occupational Safety and Health) (NIOSH 2011) is defined analogous to the ACGIH TLV-TWA.

[h] PEL-C (permissible exposure limit – ceiling, Occupational Health and Safety Administration) (29CFR 1910.1045[2008]) is defined analogous to the ACGIH TLV-ceiling. Exposure to concentrations in excess of this value should not be permitted regardless of duration. For carbon tetrachloride, the acceptable maximum peak above the acceptable ceiling concentration for an 8-h shift is 200 ppm for 5 min in any 3-h period.

[i] MAK (maximale arbeitsplatzkonzentration [maximum workplace concentration], Deutsche Forschungsgemeinschaft [German Research Association]) (DFG 2000) is defined analogous to the ACGIH TLV-TWA.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR CARBON TETRACHLORIDE

Derivation of AEGL-1 Values

Data were inadequate for deriving AEGL-1 values for carbon tetrachloride. Attempts to use data from studies of human exposures to the chemical resulted in AEGL-1 values that exceeded AEGL-2 values. Thus, not values are recommended.

Derivation of AEGL-2 Values

Key study:	Davis 1934
Toxicity end point:	No-effect level for CNS effects in human volunteers, 76 ppm for 4 h
Scaling:	$C^{2.5} \times t = k$; n = 2.5 (see Appendix B for how the value for n was determined) $(76 \text{ ppm})^{2.5} \times 4 \text{ h} = 201{,}416 \text{ ppm-h}$
Uncertainty factors:	1 for interspecies differences 10 for intraspecies variability (e.g., variation in cytochrome P-450)
Modifying factors:	None
Calculations:	
10-min AEGL-2	$C^{2.5} \times 0.167 \text{ h} = 201{,}416 \text{ppm-h}$ C = 270 ppm 270 ppm ÷ 10 = 27 ppm (170 mg/m^3)
30-min AEGL-2:	$C^{2.5} \times 0.5 \text{ h} = 201{,}416 \text{ ppm-h}$ C = 175 ppm 175 ppm ÷ 10 = 18 ppm (110 mg/m^3)
1-h AEGL-2:	$C^{2.5} \times 1 \text{ h} = 201{,}416 \text{ ppm-h}$ C = 132 ppm 132 ppm ÷ 10 = 13 ppm (82 mg/m^3)
4-h AEGL-2:	$C^{2.5} \times 4.0 \text{ h} = 201{,}416 \text{ ppm-h}$ C = 76 ppm

76 ppm ÷ 10 = 7,6 ppm (48 mg/m^3)

8-h AEGL-2: $C^{2.5} \times 8.0$ h = 201,416 ppm-h
C = 58 ppm
58 ppm ÷ 10 = 5.8 ppm (36 mg/m^3)

Carbon Tetrachloride

Derivation of AEGL-3 Values

Key study: Adams et al. 1952; Dow Chemical 1960

Toxicity end point: Lethality in rats; estimated 1-h LC_{01} of 5,153.5 ppm (see Appendix B)

Time scaling: $C^{2.5} \times t = k$ (ten Berge et al.1986)
$(5,153.5 \text{ ppm})^{2.5} \times 1$ h = 1,906,582,933 ppm-h

Uncertainty factors: 1.5 for interspecies variability; results of PBPK models clearly indicate that the kinetics of carbon tetrachloride in rodents are markedly different from that in humans; rodents exhibit greater sensitivity in toxic responses. On the basis of PBPK modeling, the amount of toxic metabolites produced in humans would be approximately half the amount produced in rodents. Therefore, the toxicokinetic component of the interspecies uncertainty factor is 0.5. The toxicodynamic component is 3. The total intraspecies uncertainty factor is 1.5 (3 × 0.5 = 1.5).
10 for intraspecies variability (e.g., ethanol-induced P-450)

Calculations:

10-min AEGL-3: $C^{2.5} \times 0.167$ h = 1,906,582,933 ppm-h
C = 10,544 ppm
10,544 ppm ÷ 15 = 702.95 ppm, rounded to 700 ppm (4,400 mg/m^3)

30-min AEGL-3: $C^{2.5} \times 0.5$ h = 1,906,582,933 ppm-h
C = 6,800 ppm
6,800 ppm ÷ 15 = 453.3 ppm, rounded to 450 ppm (2,800 mg/m^3)

1-h AEGL-3:	$C^{2.5} \times 1$ h = 1,906,582,933 ppm-h C = 5,153.5 ppm 5,153.5 ppm ÷ 15 = 343.6 ppm, rounded to 340 ppm (2,100 mg/m^3)
4-h AEGL-3:	$C^{2.5} \times 4$ h = 1,906,582,933 ppm-h C = 2959.9 ppm 2,959.9 ppm ÷ 15 = 197.3 ppm, rounded to 200 ppm (1,300 mg/m^3)
8-h AEGL-3:	$C^{2.5} \times 8$ h = 1,906,582,933 ppm-h C = 2,243 ppm 2,243 ppm ÷ 15 = 149.5 ppm, rounded to 150 ppm (940 mg/m^3)

APPENDIX B

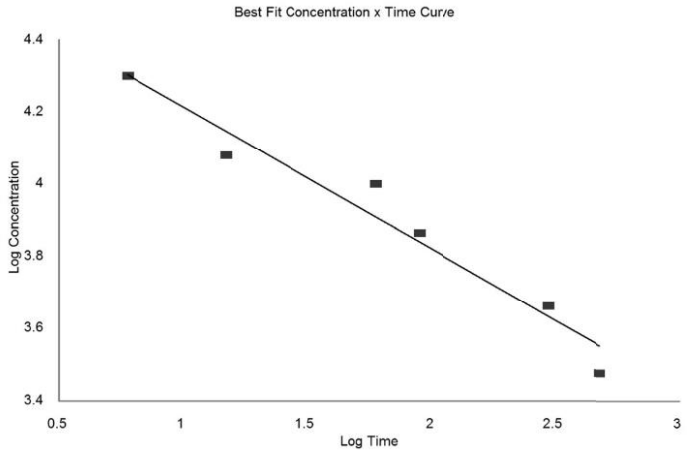
DERIVATION OF EXPONENTIAL FUNCTION FOR TEMPORAL SCALING AND DERIVATION OF LETHALITY THRESHOLD VALUE

Concentration-Time Mortality Response Relationship for Rats

Time	Concentration	Log Time	Log Concentration
6	20,000	0.7782	4.3010
15	12,000	1.1761	4.0792
60	10,000	1.7782	4.0000
90	7,300	1.9542	3.8633
300	4,600	2.4771	3.6628
480	3,000	2.6812	3.4771

Regression Output	
Intercept	4.6106
Slope	-0.3947
R Squared	0.9545
Correlation	-0.9770
Degrees of Freedom	4
Observation	6

n = 2.53 k = 4.813E+11



Data Sources: Adams et al. 1952; Dow Chemical 1960.

Estimation of Lethal Response by Rats to Carbon Tetrachloride

Dose	Mortality	Observed %	Expected %	Observed-Expected	Chi-Square
7,300.000	0/20	0 (7.20)	4.43	2.77	0.0181
8,750.000	0/20	0 (8.60)	9.30	-0.70	0.0006
10,000.000	0/5	0 (9.4)	15.54	-6.14	0.0287
11,760.000	0/5	0 (10.30)	27.23	-16.93	0.1446
12,000.000	3/10	30.00	29.02	0.98	0.0005
13,200.000	5/10	50.00	38.29	11.71	0.0580
15,150.000	8/10	80.00	53.14	26.85	0.2897
15,800.000	7/10	70.00	57.68	12.32	0.0621
19,000.000	9/19	47.37	75.35	-27.98	0.4215
26,000.000	20/20	100 (93.80)	92.35	1.45	0.0030

Values in parentheses are corrected for 0 or 100 percent Total = 1.0268

LD_{50} = 14,720.510 (12,841.527 – 16,874.428)*
Slope = 1.46 (1.26 - 1.69)*
*Values are 95 percent confidence limits

Total animals = 129
Total doses = 10
Animals/dose = 12.90
Chi-square = total chi-square × animals/dose = 13.2454
Table value for Chi-square with 8 Degrees of Freedom = 15.5100

Expected Lethal Dose Values:

$LD_{0.1}$	3,039.445
$LD_{1.0}$	5,153.488
$LD_{5.0}$	7,513.524
LD_{10}	8,911.792
LD_{25}	11,453.651
LD_{50}	14,720.510
LD_{75}	18,919.156
LD_{90}	24,315.358
LD_{99}	42,047.909

Data sources: Adams et al. 1952; Dow Chemical 1960.

APPENDIX C

CARCINOGENICITY ASSESSMENT FOR CARBON TETRACHLORIDE

Cancer Assessment of Carbon Tetrachloride

An inhalation unit risk of 6E-6 per μg/m^3 was derived by EPA (2010a, b) on the basis of pheochromocytomas in male mice. Carbon tetrachloride at a concentration of 17 μg/m^3 is associated with a risk level of 1 in 10,000 (EPA 2010b).

To convert a 70-year exposure to a 24-h exposure:

24-h exposure = d × 25,600; where d = 16.7 μg/m^3
16.7 μg/m^3 × 25,600 days
426,667 μg/m^3 (426.67 mg/m^3)

To account for uncertainty regarding the variability in the stage of the cancer process at which carbon tetrachloride or its metabolites may act, a multistage factor of 2.8 is applied (Crump and Howe 1984):

426.67mg/m^3 ÷ 2.8 = 152 mg/m^3

Therefore, on the basis of the potential carcinogenicity of carbon tetrachloride, an acceptable 24-h exposure would be 152 mg/m^3 (24.2 ppm) for a 10^{-4} risk.

If the exposure is limited to a fraction (f) of a 24-h period, the fractional exposure becomes 1/f × 24 h (NRC 1985). For a 10^{-4} risk:

24 h = 152mg/m^3 (24.2ppm) 8
h = 457mg/m^3 (72.6ppm)
4 h = 914mg/m^3 (145.3ppm)
1 h = 3,657mg/m^3 (581.2ppm)
0.5 h = 7,314mg/m^3 (1162 ppm)

Exposures relating to risk levels of 10^{-4}, 10^{-5}, and 10^{-6} are presented in Table C-1.

A comparison of the AEGL-2 and AEGL-3 values with the estimated concentration of carbon tetrachloride associated with a 10^{-4} cancer risk is presented in Table C-2. Estimated cancer risks for AEGL-2 and AEGL-3 values are also provided, obtained by assuming a linear relationship between exposure concentration and cancer

risk. The cancer assessment is based on the EPA (1983) carcinogenicity assessment of carbon tetrachloride.

TABLE C-1 Potential Cancer Risk Associated with Acute Inhalation of Carbon Tetrachloride

	Exposure Duration				
Risk Level	0.5 h	1 h	4 h	8 h	24 h
1 in 10,000 (10^{-4})	1,200 ppm (7,500 mg/m^3)	580 ppm (3,600 mg/m^3)	140 ppm (880 mg/m^3)	73 ppm (460 mg/m^3)	24 ppm (150 mg/m^3)
1 in 100,000 (10^{-5})	120 ppm (750 mg/m^3)	58 ppm (360 mg/m^3)	14 ppm (88 mg/m^3)	7.3 ppm (46 mg/m^3)	2.4 ppm (15 mg/m^3)
1 in 1,000,000 (10^{-6})	12 ppm (75 mg/m^3)	5.8 ppm (36 mg/m^3)	1.5 ppm (9.4 mg/m^3)	0.73 ppm (4.6 mg/m^3)	0.24 ppm (1.5 mg/m^3)

TABLE C-2 Comparison of AEGL Values and Potential Cancer Risk Associated with Acute Inhalation of Carbon Tetrachloride

	Exposure Duration					
Value	10 min	30 min	1 h	4 h	8 h	24 h
Cancer risk (10^{-4})	–	1,200 ppm	580 ppm	140 ppm	73 ppm	24 ppm
AEGL-1 value:	NR	NR	NR	NR	NR	–
Estimated cancer risk:	–	–	–	–	–	–
AEGL-2 value:	27 ppm	18 ppm	13 ppm	7.6 ppm	5.8 ppm	–
Estimated cancer risk:	–	1.5×10^{-6}	2.2×10^{-6}	5.4×10^{-6}	7.9×10^{-6}	–
AEGL-3 value:	700 ppm	450 ppm	340 ppm	200 ppm	150 ppm	–
Estimated cancer risk:	–	3.8×10^{-5}	5.9×10^{-5}	1.4×10^{-4}	2.1×0^{-4}	–

Abbreviation: NR, not recommended. However, absence of AEGL-1 values does not imply that exposures below the AEGL-2 values are without adverse effects.

APPENDIX D

ACUTE EXPOSURE GUIDELINE LEVELS FOR CARBON TETRACHLORIDE

Derivation Summary

AEGL-1 VALUES

Although human data on AEGL-1 effects from carbon tetrachloride are available, values derived on the basis of the data greater than the corresponding AEGL-2 values. Therefore, AEGL-1 values for carbon tetrachloride are not recommended.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
27 ppm	18 ppm	13 ppm	7.6 ppm	5.8 ppm

Reference: Davis, P.A. 1934. Carbon tetrachloride as an industrial hazard. JAMA 103(13):962-966.

Test species/Strain/Number: Humans (gender not specified); ages 20-48 years; 3-4 per exposure group

Exposure route/Concentrations/Durations: Inhalation: 76 ppm for 2.5 or 4 h; 158 or 317 ppm for 30 min; 1,191 ppm for 15 min; 2,382 ppm for 3-7 min or ≤10 min; 5-117 ppm for 8 h.

Effects: CNS effects at concentrations >76 ppm
76 ppm for 2.5 h: no effects
76 ppm for 4 h: no effects
158 ppm for 0.5 h: nervousness in one subject; no effect in three subjects.
317 ppm for 0.5 h: slight nausea and vomiting, headache.
1,191 ppm for 0.25 h: nausea, vomiting, headache; intolerable for one subject (9-min exposure only)
2,382 ppm for 3-7 min: nausea, vomiting, dizziness, listlessness, headache, sleepiness.
2,382 ppm for ≤10 min: nausea, vomiting, headache, sleepiness.

Time scaling: $C^n \times t = k$; n = 2.5, on the basis of regression analysis of lethality data from Adams et al. (1952).

Concentration/Time Selection/Rationale: 76 ppm for 4 h; the highest no-effect level for CNS effects

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies:1, because the critical study was conducted in humans
Intraspecies:10, to protect sensitive individuals (e.g., variation in cytochrome P-450)
Modifying factor: none
Animal-to-human dosimetric adjustment: None
Data adequacy: Data are adequate to derive AEGL-2 values.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
700 ppm	450 ppm	340 ppm	200 ppm	150 ppm

References: Adams, E.M., H.C. Spencer, V.K. Rowe, D.D. McCollister, and D.D. Irish. 1952. Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. AMA Arch. Ind. Hyg. Occup. Med. 6(1):50-66.
Dow Chemical. 1960. Comparison of the Result of Exposure of Rats and Cavies to the Vapors of Carbon Tetrachloride and Bromochloromethane, June 11, 1960. Submitted to EPA by Dow Chemical with cover letter dated September 4, 1987. EPA Document No. 86870002363. Microfiche No. OTS0515887.

Test Species/Strain/Number: Rats; albino or not specified; 5-30 per group Exposure route/Concentrations/Durations: Inhalation ; 3,000-20,000 ppm for 0.1-12 h.

Effects: Lethality in rats; estimated 1-h LC_{01} of 5,135.5 ppm.

Time scaling: $C^n \times t = k$; n = 2.5 on the basis of regression analysis of lethality data from Adams et al. (1952).

Concentration/Time selection/Rationale: Estimated 1-h LC_{01} of 5,153.5 ppm

Uncertainty factors/Rationale:
Total uncertainty factor: 15
Interspecies: 1.5, PBPK model results predict that rodents will attain higher concentrations of carbon tetrachloride in venous blood and fat than would similarly exposed humans, with greater metabolism of carbon tetrachloride by rats relative to humans (Paustenbach et al. 1988; Delic et al. 2000). PBPK models predict that, at equal exposure concentrations, humans will have lower rates of production of reactive CCl_4 metabolites (human/rat = 0.5). On the basis of PBPK modeling, the amount of toxic metabolites produced in humans would be expected to be approximately half the amount in the rodent. Therefore, the toxicokinetic component of the interspecies uncertainty factor is 0.5. The toxicodynamic component is 3. The total intraspecies uncertainty factor is 1.5 ($3 \times 0.5 = 1.5$).
Intraspecies:10, to account for individual variability in the sensitivity to carbon tetrachloride-induced toxicity (e.g., alcohol-potentiated hepatotoxicity).

Modifying factor: None

Animal-to-human dosimetric adjustment: Insufficient data.

Data adequacy: The AEGL-3 values are supported by subchronic exposure studies in animals showing that exposures above the AEGL-3 values did not result in lethality. Potential dermal absorption of carbon tetrachloride is not addressed by the AEGL values.

APPENDIX E

CATEGORY PLOTS FOR CARBON TETRACHLORIDE

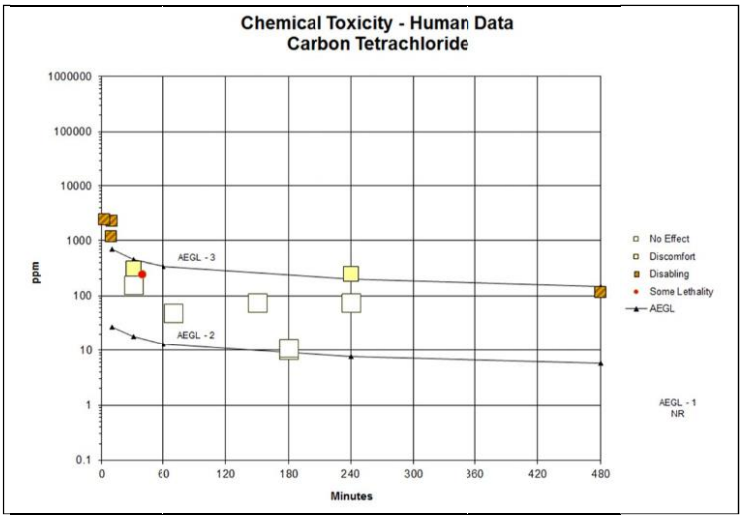


FIGURE E-1 Category plot of human toxicity data and AEGL values for carbon tetrachloride.

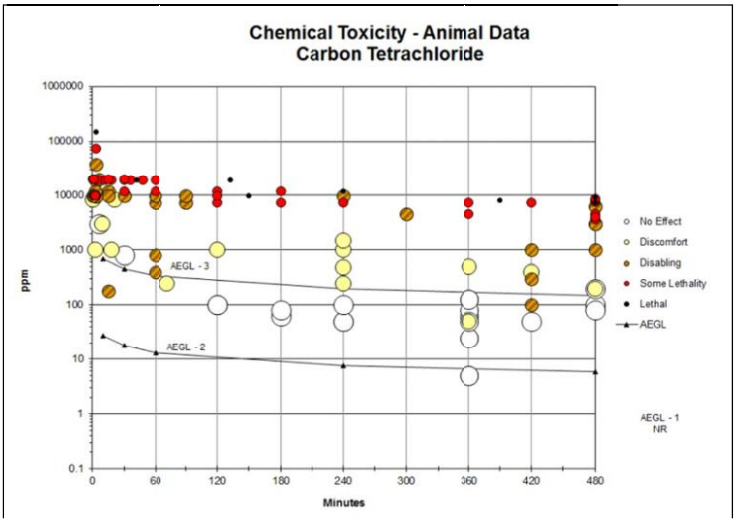


FIGURE E-2 Category plot of animal toxicity data and AEGL values for carbon tetrachloride.

TABLE E-1 Date Used in the Category Plots for Carbon Tetrachloride

Source	Species	Sex	# Exposures	ppm	Min.	Category	Comments
AEGL-1				NR	10	AEGL	
AEGL-1				NR	30	AEGL	
AEGL-1				NR	60	AEGL	
AEGL-1				NR	240	AEGL	
AEGL-1				NR	480	AEGL	
AEGL-2				27	10	AEGL	
AEGL-2				18	30	AEGL	
AEGL-2				13	60	AEGL	
AEGL-2				7.6	240	AEGL	
AEGL-2				5.8	480	AEGL	
AEGL-3				700	10	AEGL	
AEGL-3				450	30	AEGL	
AEGL-3				340	60	AEGL	
AEGL-3				200	240	AEGL	
AEGL-3				150	480	AEGL	
Davis 1934	Human		1	76	150	0	4 subjects, no adverse effects.
Davis 1934	Human		2	76	240	0	4 subjects, no adverse effects.
Davis 1934	Human		1	158	30	0	4 subjects, no adverse effects.
Davis 1934	Human		1	317	30	1	3 subjects: one experienced nausea, one had nausea and vomiting, and one complained of headache.
Davis 1934	Human		1	1,191	9	2	4/4 subjects experienced headache, nausea, vomiting, and tolerated exposures of 9 - 15 min.

TABLE E-1 Continued

Source	Species	Sex	# Exposures	ppm	Min.	Category	Comments
Davis 1934	Human			2,300	10	2	3/3 subjects could not tolerate more than 10 min without becoming nauseated and sleepy. One experienced vomiting, dizziness, and a throbbing headache.
Davis 1934	Human		1	2,382	3	2	3/3 subjects experienced nausea, vomiting, dizziness, and listlessness or sleepiness and tolerated exposure for 3 - 7 min.
Norwood et al 1950	Human	M	1	250	15	SL	1/3 subjects experienced headache and dizziness, aches and pains, nausea and vomiting, renal failure and death, centrilobular necrosis of the liver and interstitial edema and tubular (loop of Henle and distal convoluted tubule) degeneration in the kidney.
Norwood et al 1950	Human		1	250	240	1	2/3 workers experienced mild headache and dizziness during exposure.
Smyth et al 1936	Human			117	480	2	Elevated bilirubin, restricted visual field (imprecise assessments for both).
Stewart et al. 1961	Human			10.1	180	0	6 subjects; no adverse effects.
Stewart et al. 1961	Human			10.9	180	0	6 subjects; no adverse effects.
Stewart et al. 1961	Human			49	70	0	6 subjects; no clinically significant effects; no irritation; odor detection; transient decline in serum iron 20-68 h postexposure; elevated urinary urobilinogen in one subject.
McCollister et al. 1951	Monkey		1	485	240	1	Negligible absorption as determined by radioactivity in the blood and expired air.
Dow Chemical 1960	Mouse	F	1	8,500	680	SL	LCt50
Gehring 1968	Mouse		1	8,500	0.16	1	ECt50 for SGPT activity
Gehring 1968	Mouse		1	8,500	21	1	ECt50 for anesthesia

(Continued)

Merck 1983	Mouse		1	9,400	3.5	2	Mortality (0/5)

Merck 1983	Mouse		1	18,800	3.5	2	Mortality (0/5)
Merck 1983	Mouse		1	37,500	3.5	2	Mortality (0/5)
Merck 1983	Mouse		1	75,000	3.5	SL	Mortality (2/6)
Merck 1983	Mouse		1	150,000	3.5	3	Mortality (6/6)
Nagano et al. 2007	Mouse	B	520	5	360		
Nagano et al. 2007	Mouse	B	520	25	360		
Nagano et al. 2007	Mouse	B	520	125	360		
Svirbaly et al. 1947	Mouse		1	6,340	480	2	Mortality (0/20)
Svirbaly et al. 1947	Mouse		1	7,628	480	SL	Mortality (2/20)
Svirbaly et al. 1947	Mouse		1	8,088	480	SL	Mortality (19/20)
Svirbaly et al. 1947	Mouse		1	8,787	480	SL	Mortality (10/20)
Svirbaly et al. 1947	Mouse		1	9,327	480	3	Mortality (20/20)
Ugazio et al. 1995	Rabbit		23	100	120	0	Increased hexobarbital sleeping time; hepatic fibrosis.
Adams et al. 1952	Rat		1	50	420	0	No effects.
Adams et al. 1952	Rat		1	100	420	2	Altered hepatic weight, total lipid content, and/or gross or microscopic changes in the liver.
Adams et al. 1952	Rat		1	400	60	2	Altered hepatic weight, total lipid content, and/or gross or microscopic changes in the liver.
Adams et al. 1952	Rat		1	800	30	0	No effects.
Adams et al. 1952	Rat		1	800	60	2	Altered hepatic weight, total lipid content, and/or gross or microscopic changes in the liver.
Adams et al. 1952	Rat		1	3,000	6	0	No effects.
Adams et al 1952	Rat		1	3,000	9	1	Altered hepatic weight, total lipid content, and/or gross or microscopic changes in the liver.
Adams et al. 1952	Rat		1	3,000	480	2	Mortality (0/20)
Adams et al. 1952	Rat		1	3,000	600	SL	Mortality (1/30)
Adams et al. 1952	Rat		1	3600	480	SL	Mortality (4/10)
Adams et al. 1952	Rat		1	3,600	720	SL	Mortality (1/10)

TABLE E-1 Continued

Source	Species	Sex	# Exposures	ppm	Min.	Category	Comments
Adams et al. 1952	Rat		1	4,600	300	2	Mortality (0/20)
Adams et al. 1952	Rat		1	4,600	360	SL	Mortality (1/11)
Adams et al. 1952	Rat		1	4,600	480	SL	Mortality (2/10)
Adams et al. 1952	Rat		1	7,300	60	2	Mortality (0/20)
Adams et al. 1952	Rat		1	7,300	90	2	Mortality (0/20)
Adams et al. 1952	Rat		1	7,300	120	SL	Mortality (1/10)
Adams et al. 1952	Rat		1	7,300	180	SL	Mortality (1/10)
Adams et al. 1952	Rat		1	7,300	240	SL	Mortality (4/10)
Adams et al. 1952	Rat		1	7,300	360	SL	Mortality (6/10)
Adams et al. 1952	Rat		1	7,300	420	SL	Mortality (4/10)
Adams et al. 1952	Rat		1	7,300	480	3	Mortality (20/20)
Adams et al. 1952	Rat		1	12,000	3	2	Altered hepatic weight, total lipid content, and/or gross or microscopic changes in the liver.
Adams et al. 1952	Rat		1	12,000	15	2	Mortality (0/20)
Adams et al. 1952	Rat		1	12,000	30	SL	Mortality (1/10)

(Continued)

Adams et al. 1952	Rat		1	12,000	60	SL	Mortality (3/10)
Adams et al. 1952	Rat		1	12,000	120	SL	Mortality (7/10)
Adams et al. 1952	Rat		1	12,000	180	SL	Mortality (8/10)
Adams et al. 1952	Rat		1	12,000	240	3	Mortality (20/20)
Adams et al. 1952	Rat		1	19,000	6	SL	Mortality (1/10)
Adams et al. 1952	Rat		1	19,000	12	SL	Mortality (1/5)
Adams et al. 1952	Rat		1	19,000	18	SL	Mortality (3/5)
Adams et al. 1952	Rat		1	19,000	30	SL	Mortality (2/5)
Adams et al. 1952	Rat		1	19,000	36	SL	Mortality (14/15)

Adams et al. 1952	Rat		1	19,000	42	3	Mortality (5/5)
Adams et al. 1952	Rat		1	19,000	48	SL	Mortality (4/5)
Adams et al. 1952	Rat		1	19,000	60	SL	Morality (9/19)
Adams et al. 1952	Rat		1	19,000	132	3	Mortality (20/20)
Appelman et al. 1985	Rat		2	63	180	0	Transient hepatic effects; 2- to 9-fold increase in SGOT, SGPT.
Appelman et al. 1985	Rat		20	63	360	0	Transient hepatic effects; 2- to 9-fold increase in SGOT, SGPT.
Appelman et al. 1985	Rat		2	80	180	0	Transient hepatic effects; 2- to 9-fold increase in SGOT, SGPT.
Appelman et al. 1985	Rat		20	80	360	0	Transient hepatic effects; 2- to 9-fold increase in SGOT, SGPT.
Cornish and Block 1960	Rat	B	1	50	240	0	
Cornish and Block 1960	Rat	B	1	50	240	0	
Cornish and Block 1960	Rat	B	1	100	240	0	
Cornish and Block 1960	Rat	B	1	250	240	1	
Cornish and Block 1960	Rat	B	1	1,000	240	1	
Cornish and Block 1960	Rat	B	1	1,500	240	1	
David et al. 1981	Rat		13-18	50	360	1	Minor increase in SGPT, minor histologic changes in the liver.
David et al. 1981	Rat		13-18	250	72	1	Minor increase in SGPT, minor histologic changes in the liver.
David et al. 1981	Rat		13-18	1,000	3	1	Minor increase in SGPT, minor histologic changes in the liver.
David et al. 1981	Rat		13-18	1,000	18	1	Minor increase in SGPT, minor histologic changes in the liver.
Dow Chemical 1960	Rat		1	10,000	60	2	Mortality (0/5)
Dow Chemical 1960	Rat		1	10,000	90	2	Mortality (0/5)
Dow Chemical 1960	Rat		1	10,000	120	SL	Mortality (5/10)
Dow Chemical 1960	Rat		1	10,000	150	3	Mortality (5/5)
Dow Chemical 1960	Rat		1	20,000	6	2	Mortality (0/10)

TABLE E-1 Continued

Source	Species	Sex	# Exposures	ppm	Min.	Category	Comments
Dow Chemical 1960	Rat		1	20,000	15	SL	Mortality (5/10)
Dow Chemical 1960	Rat		1	20,000	30	SL	Mortality (8/10)
Nagano et al. 2007	Rat	B	520	5	360		
Nagano et al. 2007	Rat	B	520	25	360		
Nagano et al. 2007	Rat	B	520	125	360		Increased hepatocellular adenomas and carcinomas.
Paustenbach et al. 1986b	Rat		1	100	480	0	No significant effect on SDH.
							(Continued)
Paustenbach et al. 1986b	Rat		1	100	690	1	Marginally increased SDH.
Sakata et al. 1987	Rat		1	180	15	2	"Comatose"; increased ALT at 24-h postexposure.
Sanzgini et al. 1995	Rat		1	100	120	0	No effects.
Sanzgini et al. 1995	Rat		1	1,000	120	1	Increased ALT and SDH, decreased P-450.
Schwetz et al. 1974	Rat	F	10	300	420	2	Fetoxicity.
Schwetz et al. 1974	Rat	F	10	1,000	420	2	Fetoxicity.
Smyth et al. 1936	Rat		210	200	480	0	No significant effects.
Mellon Institute 1947	Rat		1	1,000	480	2	Mortality (0/12)
Mellon Institute 1947	Rat		1	3,000	480	2	Mortality (0/12)
Mellon Institute 1947	Rat		1	4,000	480	SL	Mortality (2/12)
Mellon Institute 1947	Rat		1	8,000	390	3	Mortality (12/12)
Van Stee et al. 1982	Rat		1				Hepatic vacuolation and individual cell necrosis which varied with exposure profile.
Wang et al. 1997	Rat		1	50	360	0	No effects.
Wang et al. 1997	Rat		1	500	360	1	Minor increase in SGOT and SGPT.
Smyth et al. 1936	Rhesus monkey		210	200	480	1	Transient hepatic injury.

Prendergast et al. 1967	Squirrel monkey	1	82	480	0	One of three monkeys died after the 7th exposure at 82 ppm (8h/day; 5d/wk for 6 wk).
Wong and DiStefano 1966	Cat	1	10,000	15	2	Increased total lipids in renal cortex.
Wong and DiStefano 1966	Cat	1	10,000	30	2	Increased relative adrenal weight.
Wong and DiStefano 1966	Cat	1	10,000	60	2	
Wong and DiStefano 1966	Cat	1	10,000	240	2	Central necrosis in liver.
Mellon Institute 1947	Dog	168	400	420	1	Decreased body weight.
Dow Chemical 1960	Guinea pig	1	10,000	0.25	2	Mortality (0/5)
Dow Chemical 1960	Guinea pig	1	10,000	1	2	Mortality (0/5)
Dow Chemical 1960	Guinea pig	1	10,000	1.5	SL	Mortality (1/10)
Dow Chemical 1960	Guinea pig	1	10,000	2	SL	Mortality (4/5)
Dow Chemical 1960	Guinea pig	1	10,000	2.5	SL	Mortality (1/5)
Dow Chemical 1960	Guinea pig	1	10,000	3	SL	Mortality (1/5)
Dow Chemical 1960	Guinea pig	1	20,000	0.5	SL	Mortality (2/5)
Dow Chemical 1960	Guinea pig	1	20,000	1	SL	Mortality (4/5)

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