# Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 11

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# Acute Exposure Guideline Levels for Selected Airborne Chemicals

**VOLUME 11**

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 eleventh volume in that series. AEGL documents for bis-chloromethyl ether, chloromethyl

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

methyl ether, chlorosilanes, nitrogen oxides, and vinyl chloride are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

The committee's review of the AEGL documents involved both oral and written presentations to the committee by the 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 five 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 five committee interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for bis-chloromethyl ether (interim reports 18 and 19a), chloromethyl methyl ether (interim reports 11, 18, and 19a), chlorosilanes (interim reports 18 and 19a), nitrogen oxides (interim reports 15, 18, and 19a), and vinyl chloride (interim reports 16, 18, and 19a): Deepak Bhalla (Wayne State University), Harvey Clewell (The Hamner Institutes for Health Sciences), Sidney Green, Jr. (Howard University), A. Wallace Hayes (Harvard School of Public Health), Rogene Henderson (Lovelace Respiratory Research Institute [retired]), Sam Kacew (University of Ottawa), James McDougal (Wright State University [retired]), Charles Reinhardt (DuPont Haskell Laboratory [retired]), Andrew Salmon (California Environmental Protection Agency), Joyce Tsuji (Exponent, Inc.), and Judith Zelikoff (New York University).

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of this volume before its release. The review of interim report 11 was overseen by Rakesh Dixit (MedImmune/AstraZeneca Biologics, Inc.), and interim reports 15, 16, 18, and 19a were overseen by Robert Goyer (University of Western Ontario [retired]). Appointed by the NRC, they were responsible for making certain that an independent examination of the interim reports was carried out in accordance with institutional

procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

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

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

# Contents

# Acute Exposure Guideline Levels for Selected Airborne Chemicals

**VOLUME 11**

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

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

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

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

As a first step in assisting the LEPCs, EPA identified approximately 400 EHSs largely on the basis of their immediately dangerous to life and health values, developed by the National Institute for Occupational Safety or Health. Although several public and private groups, such as the Occupational Safety and Health Administration and the American Conference of Governmental Industrial

Hygienists, have established exposure limits for some substances and some exposures (e.g., workplace or ambient air quality), these limits are not easily or directly translated into emergency exposure limits for exposures at high levels but of short duration, usually less than 1 hour (h), and only once in a lifetime for the general population, which includes infants (from birth to 3 years of age), children, the elderly, and persons with diseases, such as asthma or heart disease.

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

In November 1995, the National Advisory Committee (NAC)[1] for Acute Exposure Guideline Levels for Hazardous Substances was established to identify, review, and interpret relevant toxicologic and other scientific data and to develop acute exposure guideline levels (AEGLs) for high-priority, acutely toxic chemicals. The NRC's previous name for acute exposure levels—community emergency exposure levels (CEELs)—was replaced by the term AEGLs to reflect the broad application of these values to planning, response, and prevention in the community, the workplace, transportation, the military, and the remediation of Superfund sites.

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

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

sure periods (10 min, 30 min, 1 h, 4 h, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

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

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

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

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

## SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

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

inhalation exposures are most useful for setting AEGLs for airborne chemicals because inhalation is the most likely route of exposure and because extrapolation of data from other routes would lead to additional uncertainty in the AEGL estimate.

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

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

## REVIEW OF AEGL REPORTS

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

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

The NRC committee's review of the AEGL reports prepared by NAC and its contractors involves oral and written presentations to the committee by the authors of the reports. The NRC committee provides advice and 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 for the accuracy and completeness of the toxicity data cited in the AEGL reports. Thus far, the committee has prepared ten reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009, 2010a,b, 2011). This report is the eleventh volume in that series. AEGL documents for bis-chloromethyl ether, chloromethyl methyl ether, chlorosilanes, nitrogen oxides, and vinyl chloride are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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# Appendixes

# 5

# Vinyl Chloride[1]

## Acute Exposure Guideline Levels

### PREFACE

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

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

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

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

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

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

Airborne concentrations below the AEGL-1 represent exposure concentrations that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, nonsensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold 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

Vinyl chloride (VC) is a colorless, flammable gas with a slightly sweet odor. It is heavier than air and accumulates at the bottom of rooms and tanks. Worldwide production of VC is approximately 27,000,000 tons. Most VC is polymerized to polyvinyl chloride. Combustion of VC in air produces carbon dioxide and hydrogen chloride. Odor thresholds of VC range from 10 to 25,000 ppm. Validated studies that provide quantitative data on odor recognition and detection are not available; therefore, a level of odor awareness (LOA) could not be derived.

VC is an anesthetic compound. After a 5-min exposure to VC at 16,000 ppm, volunteers experienced dizziness, lightheadedness, nausea, and visual and auditory dulling (Lester et al. 1963). Mild headache and some dryness of the eyes and nose were the only complaints of volunteers exposed at 491 ppm for several hours (Baretta et al. 1969). No data on the developmental or reproductive toxicity of VC in humans after acute exposure are available. Chromosomal aberrations in human lymphocytes were associated with accidental exposure to VC. After chronic occupational exposure, VC is a known human carcinogen that induces liver angiosarcoma, possibly hepatocellular carcinoma, and brain tumors. Evidence of tumors at other sites is contradictory. Two epidemiologic studies (Mundt et al. 2000; Ward et al. 2001) found no increase in standardized mortality ratios (SMRs) after 5 years of occupational exposure to VC, whereas a third study suggested an increase after 1-5 years of exposure (Boffetta et al. 2003).

Acute exposure to VC results in narcotic effects (Mastromatteo et al. 1960), cardiac sensitization (Clark and Tinston 1973, 1982), and hepatotoxicity (Jaeger et al. 1974) in laboratory animals. Prodan et al. (1975) reported 2-h $LC_{50}$ values (lethal concentration, 50% lethality) for mice, rats, rabbits, and guinea pigs of 117,500, 150,000, 240,000, and 240,000 ppm, respectively. No studies of reproductive or developmental toxicity after a single exposure are available. In repeated-exposure studies, developmental toxicity (e.g., delayed ossification) in mice, rats, and rabbits was observed only at maternally toxic concentrations. Embryo-fetal development of rats was not affected by VC at concentrations up to 1,100 ppm for 2 weeks (6 h/day) (Thornton et al. 2002). Positive results for genotoxicity after in vitro and single and repeated in vivo treatment have been reported for VC. Elevated etheno-adducts were observed after single and short-term exposure and were associated with mutational events (Barbin 2000; Swenberg et al. 2000). Adduct levels in young animals were greater than in adult animals after identical treatment (Laib et al. 1989; Ciroussel et al. 1990; Fedtke et al. 1990; Morinello et al. 2002). A study of adult rats exposed to VC at 45 ppm for 6 h found no increase in relevant etheno-adducts above background (Watson et al. 1991).

Induction of liver tumors has been reported in rats after short-term (5 weeks and 33 days) exposure (Maltoni et al. 1981, 1984; Froment et al. 1994). VC induces lung tumors in mice after a single exposure to high concentrations of VC (Hehir et al. 1981). Short-term exposure experiments by Drew et al. (1983), Maltoni et al. (1981), and Froment et al. (1994) indicated newborn and young animals are more susceptible to tumor formation than adult animals.

The cancer risk from exposure to VC for 30 min to 8 h was estimated on the basis of laboratory animal data. However, there is great uncertainty in those estimates, and they conflict with epidemiologic data on occupational exposure to VC.

AEGL-1 values are based on a study of four to seven volunteers exposed to VC (Baretta et al. 1969). Two individuals experienced mild headache when exposed to VC at 491 ppm for 3.5 h and 7.5 h (two exposures for 3.5 h, with a 0.5 h break between exposures). The time of onset of headaches was not specified, so it was assumed to be after 3.5 h. A total uncertainty factor of 3 was used. Because the AEGL-1 values are based on human data no interspecies uncertainty factor was used. The effects are probably from VC in the blood and not a metabolite. Only small interindividual differences in the pharmacokinetics of VC are expected, as the concentration of VC required to elicit the AEGL-1 effect is greater than that required for saturation of the metabolic pathways. An intraspecies uncertainty factor of 3 is used to account for toxicodynamic differences among individuals. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of n = 3 for shorter exposure periods and n = 1 for longer exposure periods; there were no suitable experimental data for deriving the value of n. The default values were used because the mechanism for the induction of headache is unknown, but is unlikely to be a simple function of VC in the

blood. The extrapolation from a 3.5 h exposure to 10 min is justified because humans exposed at 4,000 ppm for 5 min did not experience headaches (Lester et al. 1963).

The AEGL-2 values are based on prenarcotic effects observed in human volunteers. After exposure to VC at 16,000 ppm for 5 min, five of six persons experienced dizziness, lightheadedness, nausea, and visual and auditory dulling. At 12,000 ppm, one of six persons experienced dizziness and "swimming head, reeling." No effects were reported at 4,000 ppm. A single person reported slight effects ("slightly heady") of questionable meaning at 8,000 ppm (this volunteer also felt slightly heady when given a sham exposure and reported no response when exposed at 12,000 ppm) (Lester et al. 1963). VC at 12,000 ppm was considered the no-effect level for impaired ability to escape. An intraspecies uncertainty factor of 3 was used to account for toxicodynamic differences among individuals. The effects are probably from VC in the blood and not a metabolite. Only small interindividual differences in pharmacokinetics of VC are expected, as the concentration of VC required to elicit AEGL-2 effects is greater than that required for saturation of the metabolic pathways. By analogy with other anesthetics, the effects are assumed to be solely concentration dependent. Thus, after reaching steady state after about 2 h, no increase in effect is expected. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, with $n = 2$, based on a study by Mastromatteo et al. (1960). This study reported various time-dependent prenarcotic effects in mice and guinea pigs after less than steady-state exposure conditions. Time extrapolation was performed from 5 min to 10-min, 30-min, 60-min, and 2-h exposures. The steady state concentration at 2 h is used for the 4- and 8-h values.

The AEGL-3 values are based on cardiac sensitization and the no-effect level for lethality. Short-term exposure (5 min) to VC induced cardiac sensitization in dogs (effective concentration producing 50% response [$EC_{50}$] was 50,000 and 71,000 ppm in two independent experiments) (Clark and Tinston 1973, 1982). Severe cardiac sensitization is a life-threatening effect, but at 50,000 ppm no animals died. The cardiac-sensitization model with the dog is considered an appropriate model for humans and is highly sensitive because the response is optimized by the exogenous administration of epinephrine (Brock et al. 2003; ECETOC 2009). This protocol is conservative and has built-in safety factors; thus, no additional uncertainty factors were considered necessary (ECETOC 2009). Accordingly, an interspecies uncertainty factor of 1 was applied. Only small interindividual differences in pharmacokinetics of VC are expected, as the concentration of VC required to elicit the effect is greater than that required for saturation of the metabolic pathways. An intraspecies uncertainty factor of 3 is used to account for toxicodynamic differences among individuals. By analogy with other halocarbons (e.g., Halon 1211, HFC 134a) that are cardiac sensitizer, the effects are assumed to be solely dependent on the concentration of VC in the blood. Thus, after reaching steady state after about 2 h, no increase in effect is expected. The other exposure duration-specific values were derived by time

scaling according to the dose-response regression equation $C^n \times t = k$, with n = 2, based on data from Mastromatteo et al. (1960). Time extrapolation was performed from 5 min to 10-min, 30-min, 60-min, and 2-h exposures. The steady state concentration at 2 h is used for the 4- and 8-h values.

The AEGLs values for VC are presented in Table 5-1.

## 1. INTRODUCTION

VC is a colorless, flammable gas with a slightly sweet odor. It is heavier than air and accumulates at the bottom of rooms and tanks. Its worldwide production is approximately 27,000,000 tons. Most VC is polymerized to polyvinyl chloride, which subsequently is used to produce packaging materials, building materials, electric appliances, medical-care equipment, toys, agricultural piping and tubing, and automobile parts. The largest single use of polyvinyl chloride is in the building sector (WHO 1999). About 10,000 tons are used in the production of 1,1,1-trichloroethane and other chlorinated solvents on an annual basis (Kielhorn et al. 2000).

**TABLE 5-1** Summary of AEGL Values for Vinyl Chloride[a]

| Classification | 10 min | 30 min | 1 h | 4 h | 8 h | End Point (Reference) |
|---|---|---|---|---|---|---|
| AEGL-1 (nondisabling) | 450 ppm (1,200 mg/m$^3$) | 310 ppm (800 mg/m$^3$) | 250 ppm (650 mg/m$^3$) | 140 ppm (360 mg/m$^3$) | 70 ppm (180 mg/m$^3$) | Mild headaches in 2/7 humans (Baretta et al. 1969); no-effect level for notable discomfort. |
| AEGL-2 (disabling) | 2,800 ppm (7,300 mg/m$^3$) | 1,600 ppm (4,100 mg/m$^3$) | 1,200 ppm (3,100 mg/m$^3$) | 820 ppm (2,100 mg/m$^3$) | 820 ppm (2,100 mg/m$^3$) | Mild dizziness in 1/6 humans (Lester et al. 1963); no-effect level for impaired ability to escape. |
| AEGL-3 (lethal) | 12,000 ppm[b] (31,000 mg/m$^3$) | 6,800 ppm[b] (18,000 mg/m$^3$) | 4,800 ppm[b] (12,000 mg/m$^3$) | 3,400 ppm (8,800 mg/m$^3$) | 3,400 ppm (8,800 mg/m$^3$) | Cardiac sensitization (Clark and Tinston 1973, 1982); no-effect level for lethality. |

[a]Derivation of the AEGL values excludes potential mutagenic or carcinogenic effects after a single exposure, which might occur at lower concentrations based on laboratory animal data (see Appendix C).

[b]The explosion limits for VC in air range from 38,000 ppm to 293,000 ppm. The 10-min, 30-min, and 1-h AEGL-3 values exceed 10% of the lower explosion limit. Therefore, safety considerations against explosion should be taken into account.

Most VC is produced either by hydrochlorination of acetylene, mainly in Eastern European countries, or by thermal cracking of 1,2-dichloroethane. VC is stored either under pressure at ambient temperature or refrigerated at atmospheric pressure (WHO 1999). Since it does not polymerize readily, VC is stored without additives. Combustion of VC in air produces carbon dioxide and hydrogen chloride (WHO 1999).

The chemical and physical properties of VC are presented in Table 5-2.

## 2. HUMAN TOXICITY DATA

### 2.1. Acute Lethality

Danziger (1960) describes two worker deaths from accidental exposure to VC. The concentration and exposure duration were not specified, but circumstances suggest inhalation of very high concentrations of VC. Autopsy results show cyanosis, congestion of lung and kidneys, and failure of blood coagulation. Citing results from Schaumann (1934), 12% VC (120,000 ppm) is reported as "dangerous concentrations" (Danziger 1960; Oster et al. 1947).

At very high concentrations, VC causes asphyxia, probably from narcosis-induced respiratory failure (HSDB 2005).

**TABLE 5-2** Chemical and Physical Properties of Vinyl Chloride

| Parameter | Value | Reference |
|---|---|---|
| Synonyms | Vinyl chloride monomer, monochlorethene, monochlorethylene, 1-chloroethylene, chlorethylene, chloroethene | WHO 1999 |
| CAS Reg. No. | 75-01-4 | WHO 1999 |
| Chemical formula | $C_2H_3Cl$ | WHO 1999 |
| Molecular weight | 62.5 g/mol | WHO 1999 |
| Physical state | Gaseous (at room temperature) | WHO 1999 |
| Color | Colorless | WHO 1999 |
| Melting point | -153.8°C | WHO 1999 |
| Boiling point | -13.4°C | WHO 1999 |
| Density | 0.910 g/cm$^3$ at 20°C | WHO 1999 |
| Solubility in water | Soluble in almost all organic solvents, slightly soluble in water | WHO 1999 |
| Vapor pressure | 78 kPa at -20°C<br>165 kPa at 0°C<br>333 kPa at 20°C | WHO 1999 |
| Odor | Slightly sweet | WHO 1999 |
| Explosion limits in air | 3.8-29.3 vol% in air at 20°C;<br>4-22 vol% | WHO 1999 |
| Conversion factors | 1 ppm = 2.59 mg/m$^3$ at 20°C, 101.3 kPa<br>1 mg/m$^3$ =0.386 ppm | WHO 1999 |

### 2.2. Nonlethal Toxicity

A summary of the acute effects in humans after exposure to VC is presented in Table 5-3.

**TABLE 5-3** Summary of Acute Effects in Humans after Inhalation of Vinyl Chloride

| Concentration | Duration | Effects | Reference |
|---|---|---|---|
| Very high | Unknown | Ocular irritation | Danziger 1960 |
| 25,000 ppm | 3 min | Dizziness, disorientation with regard to space and size, burning sensation in feet, persistent headache. | Patty et al. 1930 |
| 20,000 ppm | 5 min | 6/6 dizziness, lightheadedness, nausea, visual and auditory dulling, 1/6 persistent headache. | Lester et al. 1963 |
| 16,000 ppm | 5 min | 5/6 dizziness, lightheadedness, nausea, visual and auditory dulling; no effects in one volunteer. | Lester et al. 1963 |
| 12,000 ppm | 5 min | 1/6 "swimming head, reeling," 1/6 "unsure" of effects (somewhat dizzy in the middle of exposure). | Lester et al. 1963 |
| 8,000 ppm | 5 min | 1/6 "slightly heady" (volunteer also felt slightly heady at sham exposure and reported no effects at 12,000 ppm). | Lester et al. 1963 |
| 4,000 ppm | 5 min | No effects. | Lester et al. 1963 |
| 3,000 ppm | Unknown | Odor threshold (geometric averages of three studies, omitting extreme points and duplicate quotations). | Amoore and Hautala 1983 |
| High, not specified | Unknown | Prenarcotic and narcotic effects; repeated exposure caused headaches, asthenovegetative syndrome, cardiovascular effects, hepatomegaly. | Suciu et al. 1975 |
| 491 or 459 ppm | 3.5 h | 2/7 reported mild headache and dryness of the eyes and nose. | Baretta et al. 1969 |
| 261 ppm | Unknown | Detection of VC odor by 4/4 subjects. | Baretta et al. 1969 |
| 20 ppm | Unknown | Odor threshold in polyvinyl chloride production workers. | Hori et al.1972 |
| 10 ppm | Unknown | Odor threshold in workers from a polyvinyl chloride facility not working in polyvinyl chloride production. | Hori et al. 1972 |

### 2.2.1. Neurotoxicity

VC was considered a potential anesthetic. A narcotic limit concentration for man is 7-10% (70,000-100,000 ppm) (Lehmann and Flury 1938; Oster et al. 1947; Danziger 1960). Schauman (1934) reported narcosis at somewhat higher concentrations. Exposure to unknown, high concentrations of VC (e.g., during cleaning of autoclaves) also resulted in narcotic effects (Suciu et al. 1975).

*Acute Exposure*

Lester et al. (1963) exposed six volunteers (three men and three women) to VC at 0, 0.4, 0.8, 1.2, 1.6, or 2% (0, 4,000, 8,000, 12,000, 16,000, or 20,000 ppm, nominal concentration) for 5 min using a plastic breathing mask that covered the mouth and nose. The total gas flow was 50 liters per minute (L/min). The desired concentrations were obtained by metering air and VC (gas chromatography of the liquid phase indicated more than 99% VC) through flow meters and passing the appropriate flows through a 2-L mixing chamber. The concentration was continuously monitored by a thermal conductivity meter (less than 5% deviation from the desired concentration). All volunteers were exposed to every concentration in a randomized fashion, separated by a 6-h interval. Dizziness ("slightly heady") was experienced by one volunteer at 8,000 ppm (the subject also reported slight dizziness at sham exposure and reported no response at 12,000 ppm). At 12,000 ppm, four people reported no response, one subject reported reeling and swimming head, and another subject was unsure of some effects. The latter person had a somewhat dizzy feeling in the middle of exposure. Dizziness, nausea, headache, and dulling of visual and auditory cues were reported by five people exposed to VC at 16,000 ppm and by all subjects exposed at 20,000 ppm. All symptoms disappeared shortly after termination of exposure; headache persisted for 30 min in one subject after exposure at 20,000 ppm.

Two experimenters were exposed to VC at 25,000 ppm (nominal concentration) for 3 min by entering an exposure chamber. They reported dizziness, slight disorientation with regard space and size of surrounding objects, and a burning sensation in the feet. The subjects immediately recovered on leaving the chamber and complained only of a slight headache that persisted for 30 min. No further details were presented (Patty et al. 1930).

Baretta et al. (1969) exposed four to six volunteers to VC at 59, 261, and 491 ppm (analytic concentrations) for 7.5 h (including a 0.5 h lunch period). The corresponding time-weighted average concentrations were 48, 248, and 459 ppm over 7.5 h. Seven people were exposed at 491 ppm for only 3.5 h. The subjects were exposed in an exposure chamber (41 feet × 6 feet, 7.5 feet high) with a continuous positive air supply and exhaust system. Air was recirculated with a squirrel cage fan through a series of inlet and outlet ducts spanning the length of the chamber. VC concentration was monitored by an infrared spectrophotometer. The vapors were introduced from a pressurized storage cylinder through 6 feet of 1/8 inch in diameter stainless-steel tubing into a rotometer prior to enter-

ing the circulating air duct. A heating tape wrapped around the stainless-steel tubing prevented condensation of VC. Subjective and neurologic responses of the volunteers, as well as clinical parameters, were measured. Two subjects reported mild headache and some dryness of their eyes and nose after exposure to the highest concentration. The time of onset of headaches is not clearly stated, so it was assumed that headaches occurred in both experiments after 3.5 h and during or after 7.5 h.

According to a literature review, acute human exposure to VC at 1,000 ppm for 1 h leads to fatigue and vision disturbances (Lefaux 1966). Exposure at 5,000 ppm for 60 min has lead to nausea and disorientation (Oettel 1954), with similar effects reported at 6,000 ppm for 30 min (Patty et al. 1930). VC concentrations of 6,000 to 8,000 ppm are reported to result in prenarcotic symptoms (von Oettingen 1964). Examination of the primary literature did not show how those values were derived. No experimental background or observational data were provided. Thus, the referred results might not be used for risk assessment.

*Occupational Exposure*

Suciu et al. (1975) reported acute effects after 1,684 workers from two factories were exposed to VC. When air concentrations of VC were high (1963-1964), acute and subacute poisonings occurred. After the first breaths of "a high concentration of VC," pleasant taste in the mouth, euphoric conditions, slow movements, giddiness, and inebriety-like condition were reported. Continued exposure caused more pronounced symptoms of somnolence and complete narcosis. After repeated exposures to unknown high concentrations, workers complained of headaches, irritability, diminution of memory, insomnia, general asthenia, paresthesia, tingling, and loss of weight. In addition to an "onset of an asthenovegetative syndrome," other systemic and local effects included cardiovascular effects, hepatomegaly, digestive responses, and respiratory changes. Workplace concentrations of VC in the factory were 2,300 mg/m$^3$ (about 890 ppm) in 1963 and decreased in subsequent years. This VC concentration may have been an average exposure (not specified in the report). No information on peak concentrations and duration of episodes with short-term high concentrations of VC exposure was provided. Some of the reported activities, such as cleaning autoclaves, are associated with very high exposures.

Several authors have reported headache in workers chronically exposed to VC. Exposure concentration and duration were not specified, but always were characterized as "high" (Lilis et al. 1975; Suciu et al. 1975; EPA 1987).

### 2.2.2. Odor

A wide range of odor thresholds (10-25,000 ppm [26-65,000 mg/m$^3$]) have been reported in the literature. Hori et al. (1972) reported a threshold of 20 ppm in production workers and 10 ppm in workers from other departments of

polyvinyl-chloride facilities (number of workers not specified). VC odor was perceived by 50% of the "non-production" workers at 200 ppm and by 50% of the "production" workers at 350 ppm. Odor threshold was tested by two methods. Polyvinyl chloride was diluted with air at fixed concentrations and was supplied from a glass injector to the subject's nostrils at a rate of 100 mL over 5 to 10 seconds. This procedure was repeated using gradually higher concentrations of VC until the subject perceived an odor. The second method involved measuring atmospheric concentrations of VC. Production workers were less sensitive to VC than workers from other departments. When workers from different facilities were compared, even greater ranges on odor threshold were observed. However, interindividual differences and measurement techniques were not strictly controlled. The odor thresholds reported by Hori et al. (1972) were reviewed by the American Industrial Hygiene Association and were rejected because there was no calibration of panel odor sensitivity, it was not clear whether the limit was based on recognition or detection, and the number of trials was not stated in the study (AIHA 1997).

Baretta et al. (1969) reported that none of six subjects perceived odor after entering an exposure chamber with VC at 59 ppm, whereas at 261 ppm all four subjects detected a very slight odor. Five of seven subjects were able to detect the odor of VC at 491 ppm, but after 5 min the odor was no longer perceived (study details described earlier).

Two people exposed to VC at 25,000 ppm (nominal concentration) for 3 min in an experimental exposure chamber reported a "fairly pleasant odor" (Patty et al. 1930).

Amoore and Hautala (1983) reported an odor threshold for VC of 3,000 ppm. This value reportedly represents the geometric average of three literature studies (individual studies not mentioned); studies reporting extreme points and duplicate quotations were omitted. It was not stated whether the value was a detection or recognition threshold.

### 2.2.3. Irritation

*Acute Exposure*

Irritating effects of VC are only observed after exposure to very high concentrations. Lesions of the eyes (wedge-shaped brown discoloration of the bulbar conjunctiva, palpebral slits, and conjunctiva and cornea appeared dry) were observed at autopsy in a worker who died from inhalation of very high concentrations of VC. Intensely hyperemic lungs, with desquamation of the alveolar epithelium also were observed (Danziger 1960).

*Chronic Exposure*

Tribukh et al. (1949) reported mucous irritation of the upper respiratory tract and chronic bronchitis in polyvinyl-chloride workers; however, Lilis et al. (1975) and Marsteller et al. (1975) did not mention these effects.

Suciu et al. (1975) describe coughing and sneezing after exposure of workers to VC during one shift; no other acute pulmonary effects or irritation were mentioned. These workers had been regularly exposed to VC for an extended duration.

In chronically exposed VC workers, evidence for adverse respiratory disease is conflicting. Lung function (respiratory volume, vital capacity, and oxygen and carbon dioxide transfer) deteriorates over time. Emphysema, chronic obstructive pulmonary disease (COPD), respiratory insufficiency, dyspnea, and pulmonary fibrosis have been described (Suciu et al. 1975; Walker 1976; Lloyd et al. 1984). Some of these observations have been attributed to smoking as a possible confounder.

### 2.2.4. Cardiovascular Effects

A slight decrease in blood pressure in VC workers has been attributed to the narcotic effects of VC (Suciu et al. 1975). In older experiments in human volunteers, no cardiovascular parameters have been measured (Lester et al. 1963).

Raynaud's disease has been correlated with extended occupational exposure to high concentrations of VC (ATSDR 1997), with histologic alterations of small vessels (Veltman et al. 1975). Other symptoms observed in VC workers are splenomegaly, hypertension, portal hypertension, generally increased cardiovascular mortality, and vasospastic symptoms (Suciu et al. 1975; Byron et al. 1976; ATSDR 1997). According to Kotseva, elevated occupational exposure to VC increases the incidence of arterial hypertension, but there is no conclusive evidence that it is associated on its own with an increased risk of coronary heart disease (Beck et al. 1973).

### 2.2.5. Other End Points

*Hematology and Immunology*

Blood tests of two workers that died from exposure to VC indicated failure of blood coagulation (Danziger et al. 1960).

*Hepatotoxicity*

More or less pronounced hepatitis and enlargement of the liver have been reported in chronically exposed workers (Marsteller et al. 1975; ECB 2000). In another study, impaired liver function and periportal liver fibrosis was found in workers at a polyvinyl chloride producing plant (no further details presented) (Lange et al. 1974). Liver function disturbances have been reported in workers from polyvinyl chloride producing factories (Fleig and Thiess 1978). Focal

hepatocellular hyperplasia and focal mixed hyperplasia has been observed in VC exposed workers; some of the individuals with focal mixed hyperplasia developed liver angiosarcoma (Tamburro et al. 1984). No data on liver effects after acute exposure are available.

### 2.3. Developmental and Reproductive Toxicity

No data on developmental or reproductive toxicity in humans after single exposure to VC were found.

### 2.4. Genotoxicity

Huettner and Nikolova (1998) investigated chromosomal aberrations in the lymphocytes of 29 people exposed to VC its combustion byproducts after a train accident in Schoenebeck, Germany, and 29 unexposed people. Blood samples were drawn 2-4 months after the accident. The authors found increased incidences of chromosomal aberrations (gaps, chromatid breaks, and acentric chromosomes). The health complaints of 60% of the exposed individuals were ascribed to the pollutants. More than 15 h after the accident, atmospheric VC concentrations were 1-8 ppm (Huettner and Nikolova 1998). Hahn et al. (1998) reported a maximum VC concentration of 30 ppm near the center of the accident. The personal exposure to VC and its combustion products experienced by individuals is highly uncertain. In a follow-up study of the same cohort of people 2 years later, Becker et al. (2001) found enhanced chromosome aberrations in peripheral lymphocytes as an indicator of clastogenic activity of VC, while no increased mutagenic activity (as measured by mutations in the hypoxanthine-guanine-phosphoribosyl-transferase was observed in exposed persons.

Clastogenic DNA damage has been detected by various tests in workers exposed chronically to VC. Chromosomal defects (inversions, translocations, rings) and micronuclei have been detected at exposure concentrations around 1 ppm (Fucic et al. 1995; short exposure spikes up to 300 ppm were reported) and 5 ppm (Graj-Vrhovac et al. 1990). Also increased frequencies of sister-chromatid exchanges were reported (Sinués et al. 1991; Fucic et al. 1992). Awara et al. (1998) observed an increased incidence of DNA damage (detected by single-cell gel electrophoresis) in workers exposed to VC. The amount of DNA-damage increased with exposure duration. Average VC concentrations were highest in the production area (about 3 ppm).

Covalent binding of VC to macromolecules in humans has not been directly assessed. However, gene mutations were found in human tumors associated with exposure to etheno-adduct-forming chemicals such as VC. Specifically, in angiosarcoma of the human liver, G→A transitions of the Ki-*ras* gene were found in five of six cases and A→T transitions of *p53* were observed in three of six cases, which may be attributed to the formation of ethenobases in DNA (Barbin 2000).

### 2.5. Carcinogenicity

No data about cancer induction in humans after a single exposure to VC have been reported. Two large epidemiologic studies of occupational exposure of adult workers (Mundt et al. 1999; Ward et al. 2000) show some evidence that risk for liver cancer or biliary-tract cancer was only increased after extended exposure duration. However, some studies have provided conflicting results (Weber et al. 1981), demonstrating a steep increase of in the SMR after very limited exposure duration (for details, see Appendix D). No epidemiologic studies have included newborn children as specific risk group.

There are sufficient epidemiologic data demonstrating a statistically significant elevated risk of liver cancer, specifically angiosarcomas, from chronic exposure to VC (summarized in WHO 1999; EPA 2000a,b; Boffetta et al. 2003). The possible association of brain, soft-tissue, and nervous-system cancer with VC exposure also has been reported. However, the evidence supporting a causal link between brain cancer and VC exposure is limited (EPA 2000a,b). Other studies have found an association between VC exposure and cancer of the hematopoetic and lymphatic systems (Greiser and Weber 1982; Simonato et al. 1991). Lung cancer also has been associated with VC, but the increased risk of lung cancer observed in some cohorts could be from exposure to polyvinyl chloride dust rather than VC monomer (Mastrangelo et al. 2003). In angiosarcoma of the human liver, mutations were observed which might be attributed to the formation of ethenobases in DNA (Barbin 2000).

Cancer risk estimates (unit risk) for VC based on epidemiologic studies have been estimated at $1 \times 10^{-6}$ per $\mu g/m^3$ by the Netherlands (Anonymous 1987), $1 \times 10^{-6}$ per $\mu g/m^3$ by the World Health Organization (WHO 1987, 2000), and $0.2\text{-}1.7 \times 10^{-6}$ by Clewell et al. (2001).

### 2.6. Summary

Odor thresholds of VC were reported in the range of 10 to 25,000 ppm (Patty et al. 1930; Baretta et al. 1969; Hori et al. 1972; AIHA 1997). Amoore and Hautala (1983) reported an odor threshold for VC of 3,000 ppm. This value represents the geometric average of three studies. Validated studies for determining the recognition and detection limit for VC were not available. VC is an anesthetic compound. Effects observed in acutely exposed VC workers and human volunteers indicate a characteristic sequence of symptoms starting with euphoria and dizziness, followed by drowsiness and loss of consciousness. After a 5-min exposure, health effects have been described at concentrations ≥8,000 ppm, and no effects were observed at 4,000 ppm (Lester et al. 1963). At 25,000 ppm, a 3-min exposure to VC caused dizziness, slight disorientation, and a burning sensation in the feet in two people (Patty et al. 1930). Mild headache and some dryness of the eyes and nose were the only complaints of volunteers exposed to VC at 491 ppm (the onset of headaches was not specified but was as-

sumed to have occurred after 3.5 h of exposure) (Baretta et al. 1969). Irritation of the eyes was reported in the context of an accidental exposure to lethal concentrations of VC (exposure concentration unknown) (Danziger et al. 1960).

No data on developmental or reproductive toxicity of VC in humans after acute exposure were found.

Huettner and Nikolova (1998) reported chromosomal aberrations in lymphocytes of humans accidentally exposed to VC more than 15 h after the accident. Atmospheric concentrations of VC were 1-8 ppm. Clastogenic changes were still detected 2 years later (Becker et al. 2001).

VC is a known human carcinogen that induces liver angiosarcomas and possibly brain tumors. Evidence for other tumors, including hepatocellular carcinoma, is contradictory (EPA 2000a,b). Mutations were found in human angiosarcomas of the liver, which might be attributed to the formation of ethenobases in DNA (Barbin 2000). Unit risk estimates based on epidemiologic studies have been published (Anonymous 1987; WHO 1987, 2000; Clewell et al. 2001).

## 3. ANIMAL TOXICITY DATA

### 3.1. Acute Lethality

Acute inhalation toxicity tests were performed in rats, mice, rabbits, and guinea pigs. However, none of $LC_{50}$ studies would comply with modern testing standards. The lethality data are summarized in Table 5-4.

#### 3.1.1. Rats

Mastromatteo et al. (1960) exposed rats (five per group) to VC (purity 99.5% maximum) at 10, 20, 30, or 40% (100,000 to 400,000 ppm) for up to 30 min. The animals were exposed in a 56.6-L inhalation chamber. The VC concentrations were adjusted by mixing it and air in a flow meter outside of the exposure chamber. The mixture was passed into to the animal chamber inlet to deliver a continuing stream (flow not given, VC concentrations not determined in the test chamber). Observations were made continuously and are summarized in Table 5-4. No animals died after exposure at 100,000 and 200,000 ppm. All animals exposed to VC at 300,000 ppm died after 15 min; their lungs, liver, and kidneys were congested and the lungs also had hemorrhagic areas.

Prodan et al. (1975) exposed rats (strain not specified) to VC for 2 h in exposure chambers (Pravdin type, with 580 L capacity). A total of 70 rats were used, with at least 10 animals per group. The animals were exposed (using Krakov's method) to variable concentrations of VC. Gas was first introduced at the lower part of the exposure chamber, without any ventilation. The gas was stirred by an inside pellet and was measured volumetrically with a Zimmermann-type spirometer. At VC concentrations of 15, 16, 17, 20, and 21% (150,000 to 210,000 ppm, nominal concentration), lethality was 23, 80, 90, 90, and 100%, respectively. The authors calculated an $LC_{50}$ of 15% (about 150,000 ppm) and an

$LC_{100}$ of 21% (about 210,000 ppm). All of the $LC_{50}$s and $LC_{100}$s reported in this study were 2-h values irrespective of the time of death. Findings shortly before death were general convulsions, respiratory failure, exopthalmia, and deflection of the head on the abdomen. Surviving animals rapidly recovered after exposure ended. Autopsy of the animals that died showed general congestion of the internal organs (lungs, liver, kidney, brain, and spleen); some animals (number not given) had pulmonary edema, marmorated liver, and kidney swelling.

**TABLE 5-4** Summary of Acute Lethality Data on Vinyl Chloride in Laboratory Animals

| Species | Concentration (ppm) | Duration | Number of Animals | Effect | Reference |
|---|---|---|---|---|---|
| Mouse | 500 | 7 h/day, several days | 29 | $LC_{17}$ | John et al. 1977, 1981 |
| Mouse | 1,000 | At least 3 × 6 h | 72 | $LC_{low}$ | Lee et al. 1977 |
| Mouse | 1,500 | 8 h | 20 | $LC_0$ | Tátrai and Ungváry 1981 |
| Mouse | 1,500 | 12 h | 60 | $LC_{90}$ | Tátrai und Ungváry 1981 |
| Mouse | 1,500 | 24 h | 20 | $LC_{100}$ | Tátrai und Ungváry 1981 |
| Mouse | 100,000 | 2 h | 40 | $LC_0$ | Prodan et al. 1975 |
| Mouse | 117,500 | 2 h | 39 | $LC_{50}$ | Prodan et al. 1975 |
| Mouse | 150,000 | 2 h | 61 | $LC_{100}$ | Prodan et al. 1975 |
| Mouse | 300,000 | 10 min | 5 | $LC_{100}$ | Mastromatteo et al. 1960 |
| Rat | 100,000 | 8 h | 18 | $LC_0$ | Lester et al. 1963 |
| Rat | 150,000 | 2 h | 10 | $LC_{50}$ | Prodan et al. 1975 |
| Rat | 150,000 | 2 h | 2 | $LC_{50}$ | Lester et al. 1963 |
| Rat | 200,000 | 30 min | 5 | $LC_0$ | Mastromatteo et al. 1960 |
| Rat | 210,000 | 2 h | 10 | $LC_{100}$ | Prodan et al. 1975 |
| Rat | 300,000 | 15 min | 5 | $LC_{100}$ | Mastromatteo et al. 1960 |
| Rabbit | 200,000 | 2 h | 4 | $LC_0$ | Prodan et al. 1975 |
| Rabbit | 240,000 | 2 h | 4 | $LC_{50}$ | Prodan et al. 1975 |
| Rabbit | 280,000 | 2 h | 4 | $LC_{100}$ | Prodan et al. 1975 |
| Guinea pig | 100,000 | 6 h | NR | $LC_0$ | Patty et al. 1930 |
| Guinea pig | 200,000 | 2 h | 4 | $LC_0$ | Prodan et al. 1975 |
| Guinea pig | 240,000 | 2 h | 12 | $LC_{50}$ | Prodan et al. 1975 |
| Guinea pig | 150,000 to 250,000 | 18-55 min | NR | $LC_{100}$[a] | Patty et al. 1930 |
| Guinea pig | 280,000 | 2 h | 4 | $LC_{100}$ | Prodan et al. 1975 |
| Guinea pig | 300,000 | 30 min | 5 | $LC_{20}$ | Mastromatteo et al. 1960 |
| Guinea pig | 400,000 | 10-20 min | NR | $LC_{100}$[a] | Patty et al. 1930 |
| Guinea pig | 400,000 | 30 min | 5 | $LC_{40}$ | Mastromatteo et al. 1960 |

[a]Number of animals per group and animals that died not specified.
Abbreviations: $LC_x$, lethal concentration with x% mortality; $LC_{low}$, lowest lethal concentration; NR, not reported.

In the context of a teratology study, John et al. (1981) exposed Sprague-Dawley rats intermittently with VC at 500 or 2,500 ppm for 7 days. At 2,500 ppm, 1/17 rats died, but the day of death was not specified by the authors (for study details see Section 3.3.).

Exposure of 18 Sherman rats (nine of each sex) to VC at 100,000 ppm for 8 h resulted in deep anesthesia, with consciousness regained 5 to 10 min after exposure ended. One female rat died after two exposures, and the remaining rats showed signs of chronic toxicity (not specified) prompting the authors to lower the VC concentration to 80,000 ppm to minimize mortality. Despite the lower concentration, mortality was considerable, especially in male rats exposed for more than 8 days. The animals were exposed in a 1,100-L steel chamber. The concentration in the chamber was initially raised rapidly to the desired level by admitting VC alone into the chamber until the effluent in the mixing chamber attained the desired level, as noted on the thermal conductivity meter. A fan mixed the VC with the air within the mixing chamber. Thereafter, the effluent from the 2-L mixing vessel was admitted to the chamber, the throughput was 20 L/min (Lester et al. 1963).

Exposure of two Sherman rats in a 10-L glass exposure chamber to VC at 150,000 ppm resulted in deep anesthesia within 5 min. One of two animals died from respiratory failure after 42 min (Lester et al. 1963) (for study details see earlier description).

### 3.1.2. Mice

Five mice were exposed to VC at 10, 20, 30, or 40% (100,000 to 400,000 ppm, nominal concentration) for up to 30 min (for study details see Section 3.1.1.) (Mastromatteo et al. 1960). One mouse exposed at 200,000 ppm died after 25 min, and all mice exposed at 300,000 ppm died after 10 min. No death occurred at 100,000 ppm. At 300,000 ppm, the lungs of the animals that died exhibited congestion of the lungs with hemorrhagic areas. Congestion of the liver and the kidney also were observed.

In ventilated exposure chambers of the Pravdin type, VC at 100,000 ppm for 2 h was not lethal to mice. VC at 150,000 ppm killed 46/61 mice within 1 h, and all animals died within 2 h. The authors calculated a 2-h $LC_{50}$ of 117,500 ppm and a 2-h $LC_{100}$ of 150,000 ppm (for study details and symptoms before death see Section 3.1.1.). When VC was administered to mice unmixed at 42,900 ppm, 70% (13 of 20) died less than an hour after exposure (Prodan et al. 1975).

Tátrai and Ungváry (1981) exposed CFLP mice to VC at 1,500 ppm for 2, 4, 8, 12, or 24 h (n = 20). Animals were observed for 24 h after exposure. An additional 40 animals were exposed for 12 h and survivors were evaluated 2 months after the exposure. Animals were exposed in dynamic exposure chambers with vertical airflow. The volume of the exposure chambers was 0.3 $m^3$; the vertical flow rate of the air was 3 $m^3$/h, at 20-23°C and 50-55% relative humid-

ity. Mortality was 100% in animals exposed for 24 h, and 90% in those exposed for 12 h. No deaths were reported in animals exposed for shorter durations. Exposure caused hemorrhages and vasodilatation characteristic of shock in the lungs. Additionally, shock-liver developed. The authors did not comment on the concentration difference between their experiment and earlier reports indicating much higher total VC concentrations as lethal. However, asphyxia is given as the cause of death in this study, which was not seen in other studies.

In a study designed to investigate long-term hepatic effects of VC, Lee et al. (1977) exposed CD-1 mice at 1,000 ppm for 6 h/day. Three of 72 mice died between day 3 and 9; all other mice, as well as replacement mice, appeared healthy throughout 12 months of exposure to VC. Autopsy showed acute toxic hepatitis with diffuse coagulation-type necrosis of hepatocytes, as well as tubular necrosis in the renal cortex.

In the context of a teratology study, John et al. (1981) exposed mice to VC at 50 or 500 ppm for 7 h/day on gestation days 6-15. At 500 ppm, 5/29 mice died, but the day of death was not specified by the authors.

### 3.1.3. Guinea Pigs

Patty et al. (1930) found VC at 15-25% (150,000-250,000 ppm) was lethal to guinea pigs within 1 h, and 40% (400,000 ppm) was lethal within 10-20 min. Gross pathology examinations revealed intense congestion and edema of the lungs, and hyperaemia of the kidneys and liver. The lungs were light pink, the cut section was uniformly light red, and bled freely. The authors concluded that VC is irritating to the lungs. No ocular or nasal irritation was described. However, it was unclear whether the atmosphere had been sufficiently mixed, and the number of animals per group was not specified.

Prodan et al. (1975) reported a 2-h $LC_{50}$ for VC of 238,000 ppm and a 2-h $LC_{100}$ of 280,000 ppm for guinea pigs exposed in a exposure chamber of the Pravdin type (the gas was permanently stirred by an inside pellet; study details are described in Section 3.1.1.). No animals died within 2 h at 200,000 ppm.

Yant (cited by Prodan et al. 1975) determined a 10-min lethal concentration for VC of 400,000 ppm in guinea pigs.

Exposure of guinea pigs to VC at 10, 20, or 30% (100,000-300,000 ppm) (5/group) did not result in death within 30 min, but one animal in the 300,000-ppm group died within 24 h after exposure. A 30-min exposure to VC at 40% (400,000 ppm) resulted in the death of one guinea pig, another animal died within 24 h, and the remaining three animals recovered (Mastromatteo et al. 1960; for study details see Section 3.1.1.). The liver of the animal from the 300,000-ppm group that died had severe fatty degeneration, was distended and very friable. In guinea pigs exposed at 400,000 ppm, liver effects were less pronounced. There was marked congestion of the lungs with hemorrhages in the dead animals.

### 3.1.4. Rabbits

Rabbits (n = 4) were exposed to VC at various concentrations for 2 h in exposure chambers (Pravdin type). No deaths occurred at 200,000 ppm, 50% mortality occurred at 240,000 ppm within the first hour of exposure, and all animals died when exposed at 280,000 ppm (Prodan et al. 1975) (for details see Section 3.1.1.).

In the context of a teratology study, John et al. (1981) exposed rabbits intermittently to VA at 500 or 2,500 ppm for 7 days. At 2,500 ppm, one of seven rabbits died, but the authors did not specify the day of death. For study details see Section 3-3.

## 3.2. Nonlethal Toxicity

Inhalation toxicity tests of VC were performed in dogs, mice, rats, guinea pigs, rabbits, and monkeys. A summary of the nonlethal effects of VC are summarized in Table 5-5.

### 3.2.1. Dogs

Oster et al. (1947) exposed two beagle dogs to VC at 50% in oxygen for induction of anesthesia (no duration given) and subsequently with 7% VC (70,000 ppm) in oxygen to maintain narcosis (no further study details described). Narcosis induction was rapid, and all animals showed salivation. Muscle relaxation was incomplete; good relaxation of the abdomen was found, but rigidity and uncoordinated movements of the legs was observed. The recovery period was quick but accompanied by violent excitation. In four dogs anesthetized with VC at 10% (100,000 ppm), no effects on blood pressure were observed, but cardiac irregularities (intermittent tachycardia, extraventricular systoles, and vagal beats) occurred. All symptoms disappeared rapidly when the dogs were exposed ethyl ether, as well as after termination of narcosis.

The cardiac-sensitizing potential of VC was tested in beagle dogs (Clark and Tinston 1973, 1982). Only summary data were presented in the publications. Conscious dogs (four to seven per dose group) were exposed to VC by a face mask for 5 min. Oxygen was added when high concentrations were used. During the last 10 seconds of exposure, a bolus injection of epinephrine (5 μg/kg) was given via a cephalic vein and electrocardiograph changes were recorded. Another injection of adrenaline was given 10 min after the end of exposure. Cardiac sensitization was deemed to have occurred when ventricular tachycardia or ventricular fibrillation resulted from the challenge injection of epinephrine. An increased number of ventricular ectopic beats was not considered evidence of sensitization because such effects could often be produced by a challenge injection of epinephrine during control air exposures. The $EC_{50}$ for cardiac sensitization was 50,000 ppm (95% confidence interval [CI]: 37,000-68,000 ppm). The postexposure injection of epinephrine did not result in arrhythmias (Clark and Tinston 1973).

**TABLE 5-5** Summary of Nonlethal Effects of Vinyl Chloride in Laboratory Animals

| Species | Concentration (ppm) | Duration | Effect | Reference |
|---|---|---|---|---|
| Dog | 50,000 | 5 min | $EC_{50}$, cardiac sensitization in response to epinephrine. | Clark and Tinston 1973 |
| Dog | 71,000 | 5 min | $EC_{50}$, cardiac sensitization in response to epinephrine. | Clark and Tinston 1982 |
| Dog | 100,000 | Not specified | Anesthesia and cardiac arrhythmia. | Oster et al. 1947 |
| Mouse | 1,500 | 2 h | Stasis of blood flow, decreasing enzyme activities in liver, subcellular liver damage, centrilobular necrosis. | Tátrai and Ungváry 1981 |
| Mouse | 5,000 | 1 h | No clinical signs of toxicity. | Hehir et al. 1981 |
| Mouse | 50,000 | 40 min | Twitching, ataxia, hyperventilation, hyperactivity. | Hehir et al. 1981 |
| Mouse | 100,000 | 6 min | No cardiac arrhythmia. | Aviado and Belej 1974 |
| Mouse | 100,000 | 6 min | Cardiac sensitization in response to adrenaline. | Aviado and Belej 1974 |
| Mouse | 100,000 | 15 min | Pronounced tremor, unsteady gait, and muscular incoordination. | Mastromatteo et al. 1960 |
| Mouse | 100,000 | 30 min | Unconsciousness, side position after 20 min, lung hyperemia persisting for >2 wk. | Mastromatteo et al. 1960 |
| Mouse | 100,000 | 2 h | Intense salivation and lacrimation immediately after onset of exposure, narcosis within 1 h. | Prodan et al. 1975 |
| Mouse | 200,000 | 6 min | Cardiac arrhythmia (second-degree block, ventricular ectopics). | Aviado and Belej 1974 |
| Mouse | 200,000 | 30 min | Deep narcosis, side position after 5 min, pulmonary congestion for >2 wk. | Mastromatteo et al. 1960 |
| Rat | 500 | 10 × 7 h | No effects on liver weight in rats exposed on days 6-15 of gestation (LOAEL: 2,500 ppm) | John et al. 1977 |
| Rat | 1,500 | 24 h | No acute toxicity. | Tátrai and Ungváry 1981 |
| Rat | 1,500 | 9 × 24 h | Increased relative and absolute liver weight, increased number of resorbed fetuses and fetal losses in rats exposed on days 1-9 of gestation. | Ungváry et al. 1978 |
| Rat | 30,000 | 4 h | Slightly soporific. | Viola 1970 |
| Rat | 50,000 | 1 h | No clinical signs of toxicity. | Viola et al. 1971; Hehir et al. 1981 |
| Rat | 50,000 | 2 h | Moderate intoxication (not further specified), loss of righting reflex. | Lester et al. 1963 |

*(Continued)*

**TABLE 5-5** Coninued

| Species | Concentration (ppm) | Duration | Effect | Reference |
|---|---|---|---|---|
| Rat | 50,000 | 6 h | No clinical or histologic signs of hepatic toxicity. | Jaeger et al. 1974 |
| Rat | 60,000 | 2 h | Intense intoxication, righting reflex still present. | Lester et al. 1963 |
| Rat | 100,000 | 15 min | Tremor, ataxia. | Mastromatteo et al. 1960 |
| Rat | 100,000 | 30 min | Deep narcosis, lung hyperemia persisting for >2 wk. | Mastromatteo et al. 1960; Jaeger et al. 1974 |
| Rat | 100,000 | 2 h | Deep anesthesia, loss of corneal reflex, no gross pathology changes. | Lester et al. 1963 |
| Rat | 100,000 | 6 h | Anesthesia, liver centrilobular vacuolization, slight increase in AKT and SDH activity in serum. | Jaeger et al. 1974 |
| Rat | 100,000 | 8 h | Deep anesthesia. | Lester et al. 1963 |
| Rat | 200,000 | 2 min | Muscular incoordination. | Mastromatteo et al. 1960 |
| Rat | 200,000 | 30 min | Deep narcosis, fatty liver infiltration, pulmonary congestion for >2 wk. | Mastromatteo et al. 1960 |
| Guinea pig | 10,000 | 8 h | No visible effects. | Patty et al. 1930 |
| Guinea pig | 25,000 | 5 min | Ataxia, unsteadiness. | Patty et al. 1930 |
| Guinea pig | 25,000 | 90 min | Quiet, apparent unconsciousness. | Patty et al. 1930 |
| Guinea pig | 25,000 | 6-8 h | Narcosis, slow and shallow respiration, unsteadiness. | Patty et al. 1930 |
| Guinea pig | 100,000 | 15 min | Unsteady gait and muscular incoordination. | Mastromatteo et al. 1960 |
| Guinea pig | 100,000 | 30 min | Unconsciousness, slightly hyperemic lungs for 2 wk after exposure. | Mastromatteo et al. 1960 |
| Guinea pig | 200,000 | 30 min | Pulmonary congestion persisting 2 wk after exposure. | Mastromatteo et al. 1960 |
| Guinea pig | 200,000 | 2 h | Deep narcosis. | Prodan et al. 1975 |
| Rabbit | 200,000 | 2 h | Deep narcosis. | Prodan et al. 1975 |
| Monkey | 25,000-100,000 | 5 min | Myocardial depression. | Belej et al. 1974 |

Abbreviations: AKT, alanine-α-ketoglutarate transaminase; $ED_{50}$, effective concentration eliciting 50% response; LOAEL, lowest-observed-adverse-effect level; SDH, sorbitol dehydrogenase.

Clark and Tinston (1982) conducted a second study on cardiac sensitization to epinephrine in beagle dogs (six male or female, not further specified) after 5 min of exposure to VC. Methods were appeared identical to the study published in 1973 (Beck et al. 1973). The $EC_{50}$ for cardiac sensitization was 71,000 ppm (95% CI: 61,000-83,000 ppm). The effect concentrations were above the concentration that caused effects on the central nervous system in rats ($EC_{50}$: 38,000 ppm after 10 min). The authors did not comment on their earlier findings, which indicated a lower $EC_{50}$ for cardiac sensitization. The authors discussed that cardiac sensitization is unlikely to occur in man in the absence of effects on the central nervous system and that dizziness should act as an early warning that a dangerous concentration was reached.

### 3.2.2. Rats

*Effects after Single Exposure*

In rats exposed to VC at 100,000 ppm, increased motor activity occurred after 5 min; pronounced tremor, unsteady gait, and muscular incoordination occurred after 15 min; side position occurred at 20 min; and deep narcosis occurred after 30 min. When the concentration was increased, deep narcosis occurred at 200,000 ppm after 15 min and at 300,000 ppm after 5 min, and muscular incoordination was observed after 2 or 1 min, respectively. At autopsy, the lungs of the animals in the 100,000-ppm group showed a very slight hyperemia even 2 weeks after exposure; in the 200,000-ppm group, congestion of the lungs in all animal and some fatty infiltration in the liver of one rat were observed. Irritation (not further explained) was reported to occur immediately after onset of exposure to VC at 10, 20, or 30% (Mastromatteo et al. 1960).

Lester et al. (1963) exposed Sherman rats for up to 2 h to VC at 50,000-150,000 ppm. The total gas flow was 50 L/min. The desired concentrations were obtained by metering air and VC (gas chromatography of the liquid phase indicated more than 99% VC) through flow meters and passing the appropriate flows through a 2-L mixing chamber. The desired concentration was passed through a 10-L all-glass exposure chamber containing two rats. The concentration was continuously monitored by a thermal conductivity meter (less than 5% deviation from the desired concentration). At a VC concentration of 50,000 ppm for 2 h, moderate intoxication was observed and the righting reflex was lost. At 60,000 ppm for 2 h, intoxication was more intense but the righting reflex was still present (lost at 70,000 ppm). The corneal reflex was lost at 100,000 ppm. On removal from the chamber, the animals returned to the pre-exposure state rapidly. Exposure to VC at 150,000 resulted in deep anesthesia within 5 min, and one of two animals died from respiratory failure after 42 min. Autopsy revealed edema and congestion of the lungs. The second rat recovered quickly after removal from the exposure chamber.

Exposure of 18 Sherman rats to VC at 100,000 for 8 h resulted in deep anesthesia, with consciousness regained 5 to 10 min after removal from the exposure chamber. One female rat died after two exposures, and the remaining rats showed signs of toxicity (not specified) (Lester et al. 1963; study details presented in Section 3.1.1.).

Male Holtzman rats were exposed once to VC at 0.5, 5, or 10% (5,000, 50,000, or 100,000 ppm, respectively) for 6 h in a dynamic inhalation chamber. Animals were killed 24 h after the exposure (no further details described). Exposure at 0.5 or 5% for a single 6-h period did not cause a substantial rise in serum alanine-α-ketoglutarate transaminase or sorbitol dehydrogenase, two cytoplasmic liver enzymes that correlate with liver injury. A slight increase in these parameters of hepatoxic response and centrilobular hepatocellular vacuolization were found only after exposure to VC at 10%. At the lower concentrations, the livers were histologically normal. Exposure to VC at 10% appeared anesthetize the animals (Jaeger et al. 1974).

Rats exposed to VC at 30,000 ppm for 4 h were slightly soporific (Viola 1970). No other acute toxicity data were reported; animals were exposed for total of 12 months.

Tátrai and Ungváry (1981) exposed CFY rats to VC at 1,500 ppm VC for 24 h (n = 20; study details are presented in Section 3.1.2.). No morphologic changes of the liver were observed.

F344 and Sprague-Dawley rats were treated for 1 h with VC at 50, 500, 5,000, or 50,000 ppm (about 90 rats/group). The chambers were Rochester-type, stainless steel, 1,000 L, and constructed to provide laminar airflow to ensure uniform exposure of test animals. The concentration of gas in the inhalation chamber was monitored by a gas chromatograph. No remarkable signs of toxicity were observed. When removed from the test atmosphere, all animals recovered to normal appearance within 24 h (Hehir et al. 1981). Viola et al. (1971) also reported no toxicity in rat exposed to VC at 50,000 ppm for 1 h.

*Effects after Repeated Exposure*

Pregnant rats exposed to VC at 1,500 ppm for 7 or 9 days (day 1-9 or 8-14 of gestation) had increased absolute and relative liver weights, but no visible changes when examined by light microscopy. The liver-to-body-weight ratio of rats exposed on days 1-9 of gestation was 4.25% compared with 3.71% in the controls, but such an increase was not observed in animals treated on days 14-21 of gestation. Additionally, an increased number of resorbed fetuses and fetal losses were observed in animals exposed during the first 9 days of pregnancy (Ungváry et al. 1978, for study details see Section 3.3.).

Intermittent exposure of rats to VC at 500 or 2,500 ppm on days 6-15 of pregnancy resulted in increased relative and absolute liver weights and an increased number of resorbed fetuses and fetal losses at 2,500 ppm (the no-observed-adverse-effect level [NOAEL] was 500 ppm). The absolute liver

weight was 15.55 grams (g) in the 2,500-ppm group and 14.27 g in the control group, and the relative liver weight was 37.8 mg/g in the 2,500-ppm group and 34.4 mg/g in the control group. One dam died at 2,500 ppm (John et al. 1977, 1981; see Section 3.3 for details).

After repeated inhalation exposure to VC at 5,000 ppm (7 h/day, 5 days/week) for 4 weeks, vacuolized hepatocytes with swollen mitochondria were found in male and female rats (Feron et al. 1979). After 13 weeks of inhalation exposure, an increase in relative liver weight was seen in male rats and centrilobular hypertrophy in females even at the lowest VC concentration of 10 ppm (Thornton et al. 2002).

### 3.2.3. Mice

Mice exposed to VC at 100,000 ppm for 30 min showed increased motor activity after 5 min; twitching of extremities after 10 min; pronounced tremor, unsteady gait, and muscular incoordination occurred after 15 min; side position at 20 min; and deep narcosis occurred after 30 min. When the VC concentration was increased, deep narcosis occurred at 200,000 ppm after 15 min (side position after 5 min) and at 300,000 ppm after 5 min (lethal after 10 min). The 100,000-ppm group had slight hyperemia of the lungs. One of five animals showed degenerative changes in the tubular epithelium of the kidney with hydropic swelling. Exposure to VC at 200,000 ppm for 30 min resulted in congestion of the lungs that persisted for 2 weeks. Irritation (no further details) occurred immediately after onset of exposure to VC at 10, 20, or 30% (Mastromatteo et al. 1960).

Prodan et al. (1975) exposed white mice (strain not specified) for 2 h to VC at 90,000 to 200,000 ppm with ventilation in an exposure chamber (for study details see Section 3.1.1.). Salivation and lacrimation appeared shortly after onset of exposure, with narcosis reached within less than 1 h in the majority of the animals. Typical narcosis stages of excitement with tonic-clonic convulsions and muscular contractions, tranquility and relaxation were described. Other symptoms were accelerated respiration, proceeding to bradypnea, Cheyne-Stokes type of respiration, and respiratory failure. No differentiation of the symptoms according to VC concentration was made. Concentrations of 110,000 ppm and greater were lethal. All symptoms were rapidly reversible in surviving mice.

Male mice exposed to VC at 50,000 ppm for 1 h exhibited hyperventilation after 45 min, with twitching and ataxia. Female mice became hyperactive after 40 min of exposure. Respiratory difficulty and ataxia were observed in approximately 25% of female mice after 55 min. At 5,000 ppm, no mice were visibly affected. Study details are presented in Section 3.2.2 (Hehir et al. 1981).

Tátrai and Ungváry (1981) exposed CFLP-mice to VC at 1,500 ppm for 2-24 h. Histology examination found circulation stasis in the liver, with concomitant decreases in enzyme activities (succinic dehydrogenase and acid phos-

phatase), subcellular damage, and centrilobular necrosis were found after 2 h. After 24 h, shock liver developed. Severity of changes increased with exposure duration. After 12 h, signs of circulatory disturbances included pulmonary hemorrhages and vasodilatation. No changes were observed in brain or kidney. Ninety percent of the animals died after 12 h and 100% died after 24 h.

Kudo et al. (1990) exposed male ICR mice (4-5/group) to VC for 4 h at 5,000 and 10,000 ppm on 5 and 6 successive days, respectively. Basophilic stippled erythrocytes (indicating disturbances in erythropoiesis) appeared in peripheral blood smears on the second day, indicating possible bone marrow damage after a single exposure; no difference was observed between the test concentrations. Reticulocyte numbers also were increased, but were not statistically significant. The authors discuss that the increase was partly from repeated blood sampling and was not entirely from exposure to VC. Exposure at lower concentrations (30-40 ppm) induced basophilic stippled erythrocytes after 3 days.

Lee et al. (1977) exposed CD-1 mice to VC at 1,000 ppm for 6 h/day in the context of a long-term hepatotoxicity and carcinogenicity study. Five percent of the mice died within the first days from acute toxic hepatitis, but no signs of toxicity were observed in the other animals.

Aviado and Belej (1974) reported that exposure of male Swiss mice to VC at 100,000 ppm for 6 min did not cause arrhythmia, but 200,000 ppm induced a second-degree block and ventricular ectopics (animals were anesthetized with sodium pentobarbital). Cardiac sensitization was observed after 6-min exposure to VC at 100,000 ppm (animals were anesthetized with sodium pentobarbital). Mice were exposed by face mask which was in contact with a 6-L flaccid bag. The inhalation gas was balanced with oxygen to prevent asphyxia. The number of animals tested was not specified. For testing cardiac sensitization, the animals received were injected intravenously with adrenaline hydrochloride (6 μg/kg).

### 3.2.4. Guinea Pigs

Guinea pigs exposed to VC at 100,000 ppm for 30 min showed increased motor activity after 5 min, unsteady gait and muscular incoordination occurred after 15 min, tremors and twitching of extremities after 20 min, and side position with tremors after 30 min and unconsciousness in one animal. When the VC concentration was increased deep narcosis occurred at 200,000 and 300,000 ppm after 30 min and at 400,000 ppm after 5 min. Guinea pigs in the 100,000-ppm group showed only slightly hyperemic lungs 2 weeks after exposure. At 200,000 ppm, congestion of the lungs was observed. At 300,000 and 400,000 ppm, survivors showed marked pulmonary congestion with hemorrhagic areas and edema. In one animal in the 400,000-ppm group, the tracheal epithelium was completely absent and the animal was unable to clot. Irritation (no further details) occurred immediately after onset of exposure to VC at 400,000 ppm, but irritation was not reported at lower dose levels (Mastromatteo et al. 1960).

Prodan et al. (1975) exposed guinea pigs (strain not specified) to VC at 20-28% (200,000-280,000 ppm) for 2 h. Symptoms of progressing anesthesia as described for mice were observed in a time-dependent manner; muscular contractions were more pronounced in guinea pigs than in mice. Lethality increased with VC concentration, and all symptoms were rapidly reversible in surviving animals. VC at 200,000 ppm were not lethal within 2 h (n = 4). Observation of the animals did not exceed 2 h.

Guinea pigs exposed to VC at 5,000 or 10,000 ppm for up to 8 h did not show any visible symptoms. Unconsciousness and deep narcosis occurred at 25,000 ppm after 90 min, and slow, shallow respiration was observed within 6-8 h. No deaths were observed within 8 h. Similar symptoms were observed at 50,000 ppm (unconsciousness within 50 min; slow, shallow respiration within 360 min; no death within 6 h). At 100,000 ppm, there was incomplete narcosis 2 min after onset of exposure, and none of the animals died within the 6-h exposure period (Patty et al. 1930).

#### 3.2.5. Rabbits

Prodan et al. (1975) exposed rabbits (strain not specified) to VC at 20-28% (200,000-280,000 ppm) for 2 h. Symptoms of progressing anesthesia as described for mice were observed in a time-dependent manner; rabbits showed heavy respiration, salivation, and muscular contractions. Lethality increased with VC concentration, and all symptoms were rapidly reversed in survivors. No death was observed within 2 h (n = 4).

Tátrai and Ungváry (1981) exposed 20 New Zealand rabbits to VC at 1,500 ppm for 24 h. No acute clinical effects or pathologic changes of the liver were found 24 h after exposure.

#### 3.2.6. Monkeys

Rhesus monkeys were anesthetized by intravenous injection of sodium pentobarbital (30 mg/kg). An electrocardiograph was implanted for continuous monitoring. Three monkeys were exposed to VC at 2.5, 5, or 10% for 5 min, and the exposure was alternated with room air for 10 min. Myocardial force was reduced by 2.3, 9.1, and 28.5%, respectively. The effect was significant with VC at 10%. There was no effect on the heart rate in comparison with controls. It was unclear whether an additional challenge with epinephrine was applied (Belej et al. 1974).

### 3.3. Developmental and Reproductive Toxicity

John et al. (1977, 1981) exposed pregnant CF-1 mice to VC at 50 or 500 ppm and Sprague-Dawley rats and New-Zealand rabbits at 500 or 2,500 ppm

during organogenesis (days 6-15 of gestation for mice and rats and days 6-18 in rabbits, 7 h/day). Exposure was conducted in 3.7 $m^3$ stainless-steel chambers of under dynamic conditions. The atmosphere of VC was generated by diluting gaseous VC with filtered room air at a rate calculated to give the desired concentration. The actual atmosphere was measured with an infrared spectrophotometer (no further details presented). Animals were sacrificed on day 18 (mice), 21 (rats), or 29 (rabbits) and a variety of parameters assessed.

VC at 500 ppm was maternally toxic to mice (five of 29 bred females died); weight gain, food consumption, and the absolute liver weight were decreased. Maternal toxicity was not evident in mice exposed at 50 ppm. In mice exposed at 500 ppm, the number of live fetuses per litter and fetal weight were decreased, probably from increased maternal toxicity, and fetal resorptions were increased. Moreover, fetal resorptions were within the range of historical control values. Fetal crown-rump length was significantly increased in mice exposed to VC at 50 ppm, but not those at 500 ppm. Delayed ossifications in the skull and sternum bones and unfused sternebrae were observed in the fetuses of the 500-ppm group.

Rats exposed at 500 ppm gained less weight than controls, but body weight was not significantly different from the controls. At 2,500 ppm, one maternal death occurred among 17 females and decreased food consumption and an increase in absolute and relative liver weight were observed. No significant changes were observed in rat fetuses, except for reduced fetal body weight and increased crown-crump length at 500 ppm (neither effect observed at 2,500 ppm). The incidence of dilated ureter was significantly increased in the 2,500-ppm group compared with the control group, and the number of lumbar spurs was increased at 500 ppm but not at 2,500 ppm.

One of seven bred female rabbits exposed to VC at 2,500 ppm died. Rabbits exposed at 500 ppm had decreased food consumption, but body weight was not significantly affected. The number of live fetuses per litter was slightly decreased in the 500-ppm group compared with controls (7 vs. 8 fetuses/litter), but no effect on litter size resulted from exposure at 2,500 ppm. Ossification of the sternebrae was delayed at 500 ppm, but not at 2,500 ppm.

Most of the observed effects were exaggerated when 15% ethanol was added to the drinking water, indicating an additive fetotoxic effect of ethanol and VC. The difference between species should be correlated with the concentrations that in rats and rabbits exceed the threshold for metabolic saturation whereas, in mice, this threshold probably has not been reached. The authors attribute the observed developmental changes to maternal toxicity: "exposure to VC did not cause significant embryonal or fetal toxicity and was not teratogenic."

CFY rats were exposed to VC at 1,500 ppm for 24 h/day during the first (days 1-9), second (days 8-14), or third trimester (days 14 to 21) of gestation. The volume of the inhalation chambers was 0.13 $m^3$, the vertical flow rate was 2 $m^3$/h at a regulated temperature of 24-25°C and 50-55% relative humidity. The concentration of VC in the inhalation chamber was determined by a gas chro-

matograph. Section was performed on the day 21 of gestation. Treatment resulted in significantly increased frequency of resorptions in the group exposed during the first trimester (two fetuses resorbed in the control group vs. 12 fetuses in the exposed group; fetal loss was 1.7% in the control group and 5.5% in the exposed group). Two cases of central-nervous-system malformations were recorded in treated animals (not significant), and no increase in other malformations were detected. The absolute and relative maternal liver weights were increased in animals treated during the first and second week of pregnancy, but not in animals exposed during the third week, and there were no visible changes when examined by light microscopy (Ungváry et al. 1978).

Thornton et al. (2002) conducted a study investigating developmental toxicity and reproduction (two generation). In the developmental toxicity study, Sprague-Dawley rats were exposed during days 6-19 of gestation to VC at 0, 10, 100, or 1,100 ppm for 6 h/day. The animals were exposed in stainless-steel, wire-mesh cages within a 6,000-L stainless-steel and glass exposure chamber. Placement of the animals was rotated at each exposure. No feed was provided during exposure, but water was available ad libitum. The temperature was 16-28°C, the relative humidity was 29-79%, and the air-flow rate was 1,200 L/min. VC was delivered from a compressed gas cylinder to a Scott Specialty Gases regulator equipped with inlet and outlet back pressure gauges, and gas test atmosphere was analyzed hourly with an ambient-air analyzer equipped with a strip chart recorder. Maternal body-weight gains were slightly, but statistically significantly, suppressed at all concentration during gestation days 15-20 and 6-20. Statistically significant increases in relative kidney weight were found in dams exposed to VC at 100 ppm, and in relative kidney and liver weights at 1,100 ppm. No other adverse effects were observed in this study.

In the two-generation study, exposure to VC started 10 weeks before mating. Other experimental details are provided above. One male rat in the 10-ppm group and one female rat in the control group died. Mating indices and pregnancy rates for the $F_0$ generation were comparable between the control and exposed groups. The live-birth index was significantly decreased whereas the number of stillborn pups was significantly increased in the $F_0$ generation exposed to VC at 1,100 ppm. These effects were regarded by the authors to be unrelated to exposure, because they were not dose dependent and were in the range of the historical control values. In male rats of the $F_0$-generation, absolute and relative liver weights were significantly increased in all exposure groups. Absolute epididymis and kidney weights were increased in male rats exposed at 100 ppm group. Although there were no changes in the liver weight of female $F_0$ rats, there were histologic alterations in the liver at all concentrations (hepatocytes were enlarged with increased acidophilic cytoplasm within the centrilobular areas of the liver). Centrilobular hypertrophy was observed in male and female rats exposed at 100 and 1,100 ppm and in two females of the 10-ppm group (Thornton et al. 2002).

One male rat in the $F_1$ control group died from unknown reasons. In the $F_2$ litters, there was a statistically significant decrease in the mean number of pups

delivered in the 1,100-ppm group. The authors considered this effect to be unrelated to exposure, because the values were lower than those of the $F_1$ control-group values but comparable to those of the $F_0$ control group. In the $F_1$ generation, there was a statistically significant increase in the absolute and relative liver weights of male rats exposed at 100 and 1,100 ppm (absolute liver weight also was increased in female rats, but was not statistically significant). Absolute and relative spleen weights were increased in male rats exposed at the highest concentration. Male (100 and 1,100 ppm) and female (all concentrations) rats had centrilobular hypertrophy. Additionally, altered foci (acidophilic, basophilic, and clear-cell foci) were observed in male and female $F_1$ rats exposed at 1,100 ppm, and sometimes at 100 ppm (foci also were observed in two $F_0$ male rats at 1,100 ppm).

### 3.4. Genotoxicity

The mutagenic properties of VC have been tested in a variety of bacteria with the Ames test. Positive results were obtained with *Salmonella typhimurium* TA100 and TA1535 when VC was tested at high concentrations and long exposure durations, especially with metabolic activation. VC is genotoxic only after metabolic activation in other tests, such as forward-mutation assays, gene-conversion assays in yeast, cell-transformation assays, unscheduled DNA synthesis, and sister-chromatid exchange assays in mammalian cells (summarized in WHO 1999). Tests were performed with VC at 5-100% in the atmosphere or at 0.025-50 mM in culture medium.

In vivo assays of VC for genotoxicity were performed with mice, rats, and hamsters. VC also has been tested in *Drosophila melanogaster*. Increased host-mediated forward mutations were observed after oral exposure to VC, whereas negative results were obtained in dominant-lethal assays with mice exposed by inhalation and in rat and mouse spot tests. Micronucleus formation in mice (VC at 50,000 ppm for 4-6 h; 1,000 ppm for 4 h, two exposures), cytogenetic aberrations in rats (1,500 ppm for 1-12 weeks) and hamsters (25,000 ppm for 6-24 h), and loss of sex chromosomes in *D. melanogaster* (50,000 ppm for 48 h) indicated dose-related chromosomal abnormalities. Also, increased DNA damage was demonstrated by alkaline elution assays in mice and sister-chromatid exchange formation in hamsters (summarized in WHO 1999). Further experiments with known metabolites of VC indicate that genotoxic effects are probably mediated by reactive intermediates with chloroethylene oxide being most effective.

DNA adducts of VC metabolites with miscoding properties have been directly detected after incubation of bacterial or phage DNA in vitro or in *Escherichia-coli* cells with DNA-adduct indicator systems in vivo with activated VC (summarized in WHO 1999). Covalent binding has been frequently observed after single- and short-term exposure.

Bolt et al. (1980) detected irreversible attachment of radioactive [1,2-$^{14}$C]VC to hepatic macromolecules in the rat. After a single exposure of adult

rats to [$^{14}$C]VC at 250 ppm for 5 h, the total amount metabolized per individual rat was 37 µmol. VC metabolites at 23 pmol/100 mg of liver wet weight were irreversibly bound to DNA. Alkylation products of d-guanosine amounted to 0.35 pmol.

Laib et al. (1989) exposed adult Wistar rats to [1,2-$^{14}$C]VC at 700 ppm. The animals received either a single 6-h exposure or two 6-h exposures separated by a treatment-free interval of 15 h. The following amounts of [$^{14}$C]VC-derived radioactivity in liver DNA was observed: 3.6 ± 0.2 pmol 7-(2'-oxoethyl)guanine (OEG)/mg DNA in male rats after a single exposure and 5.2 ± 0.5 pmol OEG/mg DNA in female rats after two exposures.

Watson et al. (1991) exposed adult male F344 rats (nose only) for 6 h to atmospheres containing [1,2-$^{14}$C]VC at nominal concentrations of 1, 10, or 45 ppm. The alkylation frequencies of OEG in liver DNA were 0.026, 0.28, and 1.28 residues OEG per $10^6$ nucleotides, respectively. These data indicate a linear relationship between exposure and DNA adducts in rats. There was no evidence to indicate the formation of the cyclic adducts 1,$N^6$-ethenoadenine (εA) or 3,$N^4$-ethenocytosine (εC). The threshold for detecting these adducts were about 1 adduct per $1 \times 10^8$ nucleotides.

Swenberg et al. (2000) reported dose-dependent data on etheno-adducts using a combination of immunoaffinity and gas-chromatography high-resolution mass spectrometry. Adult F344-rats were exposed to VC at 0, 10, 100, or 1,100 ppm for 6 h/day, 5 days/week for 1 or 4 weeks. The mean for $N^2$,3-ethenoguanine (εG) in a mixed liver cell suspension from unexposed control rats was 90 ± 40 fmol/µmol guanine. Exposure to VC at 10 ppm for 1 or 4 weeks resulted in εG concentrations of 200 ± 50 and 530 ± 11 fmol/µmol guanine, while exposure at 100 ppm resulted in 680 ± 90 and 2,280 ± 180 fmol/µmol guanine at 1 or 4 weeks, respectively. A much lesser effect was evident for the 11-fold greater exposure of 1,100 ppm because of metabolic activation was saturated, with 1,250 ± 200 and 3,750 ± 550 fmol/µmol guanine present in liver.

In addition to these studies, there are several investigations of the differences in sensitivity of young (preweaned) vs. adult animals. Laib et al. (1989) tested 11-day-old and adult Wistar rats by with [1,2-$^{14}$C]VC at 700 ppm. Adult rats received either a single 6-h exposure or two 6-h exposures separated by a treatment-free interval of 15 h. Pups received two 6 h exposures, according to the same treatment schedule. The following amounts of [$^{14}$C]VC in liver DNA were found after two exposures (female adults, male and female pups): 5.2 ± 0.5 pmol OEG/mg DNA (adults) and 25.5 ± 3.0 pmol OEG/mg DNA (pups). After a single exposure of adult male rats, the activity (3.6 ± 0.2 pmol OEG/mg DNA) was close to that found after two exposures.

After a 5-day exposure of F344 rats to VC at 600 ppm (4 h/day), the adduct levels in the liver were 162 ± 36 pmol OEG/µmol guanine and 1.81 ± 0.25 pmol εG/µmol guanine for the pups and 43 ± 7 pmol OEG/µmol guanine and 0.47 ± 0.14 pmol εG/µmol guanine for the adult animals (Swenberg et al. 1999).

Ciroussel et al. (1990) compared the concentrations of 1,$N^6$-ethenodeoxyadenosine (εdAdo) and 3,$N^4$-ethenodeoxycytidine (εdCyd) in BD

VI rats (7 day old pups and 13-week-old adults) treated with VC. The rats were exposed to VC at 500 ppm for 2 weeks (7 h/day, 7 days/week). Analyses (two for the pups, one for adults) of the liver adducts indicated molar ratios ($\times 10^{-7}$) of 1.30 and 1.31 (εdAdo/dAdo) and 4.92 and 4.67 (εdCyd/dCyd) in pups compared with 0.19 (εdAdo/dAdo) and 0.8 (εdCyd/dCyd) in adult rat.

Fedtke et al. (1990) measured the εG content in the liver of lactating Sprague-Dawley rats and their 10-day-old pups exposed to VC (600 ppm, 4 h/day for 5 days). εG concentrations found in liver DNA were 470 ± 140 fmol/μmol (dams) compared with 1,810 ± 250 fmol/μmol (pups). The mean background concentration of the control DNA was 60 ± 40 fmol/μmol (background subtracted from εG concentration). Similarly, Morinello et al. (2002) demonstrated higher εG-adduct concentrations in hepatocytes after weanling rats were exposed to VC at 10 ppm for 1 week (6 h/day) compared with adult animals. Control animals had εG concentrations of 0.55 ± 0.14 (adults) and 0.16 ± 0.01 (pups) mol/$10^7$ mol guanine; VC-treated animals had 1.4 ± 0.4 (adult) and 4.1 ± 0.8 (pups) mol/$10^7$ mol guanine. Adducts largely persisted over the 5-week recovery period.

Etheno adducts may be repaired by DNA glycolases. However, the incidence of these adducts did not fully return to background levels after an exposure-free period of 14 days (εG was 1.8 pmol/μmol immediately after exposure, 0.47 pmol/μmol after 14 days, and 90 fmol/μmol for controls). Etheno adducts also have a miscoding potential in vitro and in vivo (Swenberg et al. 1999).

Gene mutations were found in animal tumors associated with exposure to etheno-adduct-forming chemicals such as VC. Specifically, A→T mutations of the Ha-*ras* gene were found in seven of eight rat hepatocellular carcinomas, and various base-pair substitutions as mutations of *p53* were observed in 10 of 25 cases of angiosarcoma in the rat liver, which may be attributed to the formation of ethenobases in DNA (Barbin 2000).

### 3.5. Carcinogenicity

Inhalation exposure to VC causes liver tumors, especially angiosarcomas, hepatocellular carcinoma, and neoplastic liver nodules, in rats. Angiosarcomas at other sites also have been reported. Additionally, tumors at other locations have been found, such as Zymbal-gland tumors, neuroblastoma, and nephroblastoma in rats; lung tumors in mice; mammary-gland tumors in rats, mice, and hamsters; and skin tumors in rabbits and hamsters (summarized in ATSDR 1997; WHO 1999). Similar tumor types and sites also are observed after oral exposure. There is evidence that liver tumors are induced in female rats at lower doses than in males. There is also evidence that animals are more susceptible to tumor induction early in life (WHO 1999).

Short-term exposure experiments indicate increased susceptibility of newborn and young animals to VC (Maltoni et al. 1981; Drew et al. 1983). Drew et

al. (1983) found increased incidences of tumors in rats, mice, and hamsters exposed to VC during the first 6 month of life but when exposed later in life. For example, the incidence of liver hemangiosarcomas was 5.3% in rats exposed at ages 0-6 months and 3.8% in rats exposed at 6-12 months, but no tumors occurred in when rats were exposed at ages of 12-18 months or 18-24 months.

Maltoni et al. (1981, 1984) exposed newborn Sprague-Dawley rats to VC at 6,000 ppm or 10,000 ppm by inhalation (4 h/day, 5 days/week) from 1-day to 5-weeks of age. Forty-two rats (18 male, 24 female) were exposed at 6,000 ppm, and 44 (24 male, 20 female) were exposed at 10,000 ppm. Six dams were tested at each concentration. No direct control group was used; however, data from dams and newborn animals not exposed to VC in parallel experiments were included. Newborn animals were simultaneously exposed to milk from exposed dams (D. Soffritti, Laboratory of Prof. Maltoni, personal commun., August 2003). The authors found liver angiosarcomas in 17/42 and 15/44 newborn rats exposed to VC at 6,000 ppm or 10,000 ppm, respectively, but no tumors were found in the dams that had identical treatment. No angiosarcomas were found in a control group of 304 rats (parallel experiment). Additionally, hepatoma incidence was increased in newborn rats (20/42 and 20/44 in the 6,000-ppm and 10,000-ppm groups, respectively), but no hepatomas were not observed in their mothers. Only 1 hepatoma was found in a control group of 304 rats (parallel experiment). Results were determined after 124 weeks of observation. The internal dose of VC might have been influenced by oral uptake from milk of exposed dams. However, because of the very high inhalation exposure and saturation of metabolism, oral uptake of VC via contaminated milk might have contributed only a limited amount to the overall organ concentration of VC metabolites.

Maltoni et al. (1981, 1984) also exposed pregnant rats (30/concentration) to VC at 6,000 or 10,000 ppm for 1 week (4 h/day, days 12-18 of pregnancy). Thirty-two (13 male, 19 female) and 51 (22 male, 29 female) offspring were evaluated after exposure at the lower or the higher concentration, respectively. The incidence of hepatic angiosarcomas and hepatomas was not increased in transplacentally-exposed offspring. However, the incidence of Zymbal-gland carcinoma and nephroblastoma were increased after transplacental exposure.

Differences between pre- and post-natal exposure and carcinogenic outcome might be explained by hepatic CYP2E1 activity, which is lower prenatally than postnatally in rats (Carpenter et al. 1997) and humans (Cresteil 1998).

Froment et al. (1994) exposed four female Sprague-Dawley rats and their pups (22 males, 22 females) to VC at 500 ppm for 8 h/day, 6 days/week, from day 3 of gestation until 28 days after birth. At day 28 postpartum, the animals were weaned, and the males and females were separated and exposed for another 2 weeks (total exposure was 33 days). Surviving animals were killed at 19 month of age. In the VC-exposed rats, 66 hepatic lesions were identified, including nodular hyperplasia, endothelial-cell hyperplasia, peliosis, adenomas, benign cholangiomas, angiosarcoma of the liver, and hepatocellular carcinoma. Liver

tumors included eight hepatocellular carcinomas, 15 angiosarcomas of the liver, and two benign cholangioma. No further details were provided. It was assumed that oral exposure via mother's milk and inhalation exposure occurred simultaneously.

Hehir et al. (1981) found an increased incidence in lung tumors in ICR mice exposed once to VC for 1 h (age of mice not specified). Animals were exposed in an inhalation chamber to VC at concentrations of 50-50,000 ppm (Rochester-type inhalation chambers, 1,000 L with laminar air flow), and were observed for their lifetime. Tumor response was dose related: adenomas of the lung were found in 12/120, 14/139, 18/139, 24/143, and 45/137 mice exposed to VC at 0, 50, 500, 5,000, and 50,000 ppm, respectively. For carcinomas of the lung, the incidence was 0/120, 0/139, 1/143, and 3/137 (data from both sexes), respectively. A slight increase in hepatic-cell carcinoma occurred in male mice, but without a dose response (2/50, 2/64, 9/67, 6/68, and 4/63). No increase in tumor incidence was observed in the liver or lungs of rats treated in an identical fashion. Additional studies in A/J mice exposed to VC for 1 h/day at 500 ppm for 10 days or at 50 ppm VC for 100 days showed that for short-term exposure the concentration might be the most critical factor. In both experiments, primarily pulmonary adenomas were observed. However, the incidence of adenomas and progression to carcinoma were considered only marginal and not statistically significant in mice exposed at 50 ppm for 100 days (44.1% in exposed, 34.5% in control) whereas a significant increase of pulmonary adenomas was observed in animals exposed at 500 ppm for 10 days (about 74% in exposed, 34.4% in control).

Suzuki (1983) also reported that short-term exposure to VC (6 h/day, 5 days/week for 4 weeks) resulted in tumor formation in young CD1 mice (5-6 weeks old at first exposure). When the animals were killed after 12 weeks, pulmonary tumors were observed in the group exposed to the two highest concentrations (300 and 600 ppm). Forty or 41 weeks after exposure, pulmonary tumors were observed in all exposed animals (1-600 ppm) but not in control mice. In addition, subcutaneous and hepatic hemangiosarcoma were found. Angiosarcoma of the liver was found at necropsy (56 weeks after exposure) in one animal exposed to VC at 600 ppm for 4 weeks (Suzuki 1981).

**TABLE 5-6** Carcinogenic Potency of Vinyl Chloride Based on Animal Experiments

| Unit Risk, per $\mu g/m^3$ | Reference |
|---|---|
| $6.5 \times 10^{-7}$ to $1.4 \times 10^{-6}$ | Chen und Blancato 1989 |
| $8.8 \times 10^{-6}$ | EPA 2000a,b |
| $6 \times 10^{-7}$ to $2 \times 10^{-6}$ | Clewell et al. 1995 |
| $1.1 \times 10^{-6}$ | Clewell et al. 2001 |
| $5.7 \times 10^{-7}$ | Reitz et al. 1996 |

A hepatocellular adenoma developed after a single 12-h exposure of rats to VC at 1,500 ppm. That concentration was lethal to most of the animals (Tátrai and Ungváry 1981). However, the observed effect (asphyxiation) was not observed in other studies with similar concentrations.

In addition to angiosarcoma of the liver, several studies with limited exposure duration to VC confirm the occurrence of hepatocellular carcinomas and other preneoplastic parenchymal changes in adult animals (Feron et al. 1979; Thornton et al. 2002). However, these changes were seen to a much lesser extent than angiosarcoma in adult animals or hepatocellular changes in young animals (see below).

In accordance with these investigations in newborn rats, Laib et al. (1985a,b) reported that hepatocellular ATPase-deficient foci (premalignant stages) were observed in rats exposed to VC early in life. The exposure regimens were: (1) Wistar rats exposed at 10-2,000 ppm for 8 h/day, 5 days/week for 10 weeks, starting 1 day after birth (Laib et al. 1985a); (2) Wistar and Sprague-Dawley rats exposed at 2.5-80 ppm for 8 h/day for 3 weeks, starting 3 days after birth (Laib et al. 1985a); and (3) Wistar rats exposed at 2,000 ppm immediately after birth for 8 h/day, 7 days/week for 5, 11, 17, 47, or 83 days. The animals were exposed immediately after birth or starting at 7 or 21 days of age (Laib et al. 1985b). Exposure at 2,000 ppm did not result in ATPase deficient foci in very young (1-5 days of age) or in adult animals (90-160 days of age). However, relevant foci areas were found when animals were exposed to VC for short periods during growth (e.g., at 1-11 or 7-28 days of age). The foci persisted until evaluation at the age of 4 months (Laib et al. 1985b). After 10 weeks, induction of ATPase-deficient foci was dose dependent (nearly linear) at concentrations of 10-500 ppm in both Wistar and Sprague-Dawley rats. This finding is consistent with the findings that VC-metabolism follows first-order kinetics until saturation occurs at high concentrations (Laib et al. 1985a).

Quantitative cancer risk assessments based on animal experiments have been published by several authors and are summarized in Table 5-6. These estimates are based on experimental studies in adult animals exposed for a lifetime by Maltoni et al. (1981, 1984). There are only slight differences in the cancer risk estimated by Clewell et al. (1995, 2001) and Reitz et al. (1996), who both used physiologically-based pharmacokinetic models to extrapolate animal data to the humans. These data are in agreement with the unit risk estimates derived from epidemiologic data, confirming the order of magnitude. However, these risk estimates were only validated with data from adult animals and epidemiologic data from the workplace. A higher sensitivity of children was not incorporated into quantification (see data from Maltoni et al. 1981; Drew et al. 1983).

The estimates from Chen and Blancato (1989) were based on pharmacokinetic models and a modified multistage model of liver tumors. Additionally, increased sensitivity in early life stages was considered. Data from female and male animals were evaluated separately.

The most recently published risk estimate by EPA (2000a,b) is based on the animal experiments by Maltoni et al. (1981, 1984). Differences in the me-

tabolism between animals and humans were taken into consideration by use of a pharmacokinetic model. The increased sensitivity of children was taken into consideration. Additionally, tumors in sites other than the liver were considered. Unit-risk estimates based on epidemiologic studies were considered uncertain because of shortcomings in the epidemiologic studies. Besides the unit-risk estimate for full lifetime exposure (birth through death) of $8.8 \times 10^{-6}$ per $\mu g/m^3$, EPA provided an estimate of risk for early life exposure of $4.4 \times 10^{-6}$ per $\mu g/m^3$ and for adult exposure of $4.4 \times 10^{-6}$ per $\mu g/m^3$. The unit risk for adults is based on the physiologically-based pharmacokinetic modeling of Clewell et al. (2001), with slight modifications of some parameters.

### 3.6. Summary

Acute exposure of experimental animals to VC results in narcotic effects, cardiac sensitization, and hepatotoxicity. Narcotic effects are characterized by a typical sequence of symptoms starting with euphoria and dizziness, followed by drowsiness and loss of consciousness. Finally, animals died from respiratory failure. Prodan et al. (1975) reported 2-h $LC_{50}$ values for mice, rats, rabbits, and guinea pigs of 117,500, 150,000, 240,000, and 240,000 ppm, respectively. Dead animals had congested internal organs (especially the lungs, liver, and kidneys), pulmonary edema, and hemorrhagia (Mastromatteo et al. 1960; Prodan et al. 1975). No lethality was seen in mice after exposure to VC at 100,000 ppm for 2 h (Prodan et al. 1975). However, Tátrai and Ungváry (1981) reported that 90% and 100% of mice exposed to VC at 1,500 ppm died after 12 and 24 h of exposure, respectively. These results are not consistent with other lethality data.

Short-term exposure (up to 30 min) to VC at concentrations of 100,000-300,000 ppm resulted mainly in ataxia, increased motor activity, side position and unconsciousness, and slow and shallow respiration in laboratory aniamls (Mastromatteo et al. 1960). These are typical reactions before the onset of narcosis. Narcosis was observed in rats and mice after a 30-min exposure to VC at 200,000 ppm (Mastromatteo et al. 1960). Short-term exposure (5 min) to VC induced cardiac sensitization towards epinephrine in dogs ($EC_{50}$: 50,000 and 71,000 ppm in two independent experiments) (Clark and Tinston 1973, 1982). Similar effects also were seen in mice at higher concentrations of VC (Aviado and Belej 1974). In monkeys, only myocardial depression was observed with VC at 2.5-10%. It was unclear whether an addition challenge with epinephrine was administered (Belej et al. 1974). Histopathologic changes of the liver (vacuolization) were observed in rats after a single inhalation exposure to VC at 100,000 ppm for 6 h, but not at 50,000 ppm (Jaeger et al. 1974). In mice, however, Tátrai and Ungváry (1981) reported that stasis of the liver developed 2 and 4 h after exposure began. The authors observed decreasing enzyme activities in the liver and subcellular liver damage in mice exposed to VC at 1,500 ppm for 2 h; after 24 h, shock liver developed. Repeated exposure of rats to VC at 1,500 ppm for up to 9 days during pregnancy caused increased relative and absolute

liver weights, but no changes were found by light microscopy (Ungváry et al. 1978). In another developmental study, increased absolute and relative liver weights were observed in rats exposed intermittently to VC at 2,500 ppm on days 6-15 of pregnancy; the NOAEL was 500 ppm (John et al. 1977, 1981). In rats exposed at 5,000 ppm for 7 h/day, 5 days/week for 4 weeks, vacuolized liver cells were observed (Feron et al. 1979).

No studies of reproductive or developmental toxicity after single exposure to VC were found. John et al. (1977, 1981) investigated developmental effects in mice, rats, and rabbits after repeated exposure to VC. Developmental toxicity (e.g., delayed ossification) only occurred at maternally toxic concentrations. Ungváry et al. (1978) reported maternal liver toxicity in rats exposed to VC at 1,500 ppm for 24 h/day during the first or second trimester of gestation. Resorptions were significantly increased in the group exposed during the first trimester. A developmental-toxicity study in rats (exposed to VC at 10, 100, or 1,100 ppm, 6 h/day on days 6-19 of gestation) indicated that embryo-fetal development was not affected by VC at concentrations up to 1,100 ppm. The only toxic effects observed were an increased relative organ-to-body weight ratio for the kidney and liver at 1,100 ppm and for the kidney at 100 ppm in dams (Thornton et al. 2002). In a two-generation study in rats, no adverse effects on embryo-fetal development or reproductive capability were observed at concentrations up to 1,100 ppm. The primary target organ of VC, the liver, was increased in weight and had cellular alterations, such as centrilobular hypertrophy and altered hepatocellular foci, at VC concentrations of 100 and 1,000 ppm, with increased incidence in the $F_1$ generation (Thornton et al. 2002).

Positive results for genotoxicity after in vitro and single and repeated in vivo treatment have been reported for VC (e.g., induction of micronuclei at 50,000 ppm for 4-6 h; chromosomal aberrations at 25,000 ppm for 6-24 h) (WHO 1999). An increase in DNA adducts was seen in adult rats after a single 5-h exposure to VC at 250 ppm (Bolt et al. 1976). Watson et al. (1991) exposed adult male F344 rats for 6 h to atmospheres containing VC at 1, 10, and 45 ppm. The alkylation frequencies of OEG in liver DNA were 0.026, 0.28, and 1.28 residues per $1 \times 10^6$ nucleotides, respectively. There was no evidence of the formation of the cyclic adducts εA or εC. The threshold for detecting these adducts were about 1 adduct per $1 \times 10^8$ nucleotides. Adult rats repeatedly exposed to VC at 10 ppm for 6 h/day for 5 days showed slightly elevated etheno-adducts for εG compared with controls (200 ± 50 vs. 90 ± 40 fmol/μmol guanine) (Swenberg et al. 2000). Adduct levels were greater in young animals than in adult animals after identical treatment (Laib et al. 1989; Ciroussel et al. 1990; Fedtke et al. 1990). OEG residues are unlikely to cause mutations, however, the cyclic adducts εA, εC, and εG have miscoding potential; respective mutations (e.g., G→A transitions, A→T transitions) were observed in VC-induced tumors (Barbin 2000). Despite repair, adducts were not reduced to background levels 2 weeks after a 5-day exposure to VC at 600 ppm for 4 h/day (Swenberg et al. 2000).

Induction of liver tumors has been reported in rats after subacute (5 weeks and 33 days) exposure (Maltoni et al. 1981, 1984; Froment et al. 1994). The liver is the primary site of tumors after chronic exposure (for review see EPA 2000a,b). VC induced lung tumors in mice after a single 1-h exposure to VC at 5,000 ppm or 50,000 ppm (Hehir et al. 1981). After mice were exposed to VC at 1,500 ppm for 12 h, most of the animals died and a hepatocellular adenoma developed (Tátrai and Ungváry 1981). Suzuki (1983) reported that short-term exposure to VC (6 h/day, 5 days/week for 4 weeks) resulted in lung-tumor formation in young CD1-mice (5-6 weeks of age). Additionally, subcutaneous and hepatic hemangiosarcoma were found. Short-term exposure experiments by Drew et al. (1983), Maltoni et al. (1981), and Froment et al. (1994) also indicated increased susceptibility of newborn and young animals to tumor formation. Hepatoma (Maltoni et al. 1981) or hepatocellular carcinoma (Froment et al. 1994) developed to a greater extent in young animals compared with adults. Laib et al. (1985a,b) reported that hepatocellular ATPase-deficient foci (premalignant stages) were observed in rats exposed to VC. Relevant foci areas were found when animals were exposed to VC at 2,000 ppm for short periods during growth (e.g., at 1-11 or 7-28 days of age). The foci persisted until histologic examination at 4 months of age (Laib et al. 1985b).

## 4. SPECIAL CONSIDERATIONS

### 4.1. Metabolism and Disposition

Krajewski et al. (1980) estimated the retention of VC after inhalation through a gas mask in five male volunteers by measuring the difference between inhaled and exhaled concentrations. At VC concentrations of 3-24 ppm for 6 h, the average retention was 42%, independent of the VC concentration. The higher retention values (maximum 46% on average) dropped and remained relatively constant after 30 min. Interindividual retention rates varied from 20.2 to 79% at 12 ppm. Immediately after exposure was ceased, VC concentrations in expired air dropped rapidly. After 30 min, less than 5% of the initial chamber concentration could be measured. Buchter et al. (1978) determined a retention rate of 26-28% after 3-5 min of exposure to VC at 2.5 ppm in two individuals. Given the variability of VC retention found by Krajewski et al., these values might be attributed to interindividual differences. WHO (1999) reported that the average absorption of VC after inhalation exposure was 30-40%, without citing the relevant studies.

Absorption of inspired VC was calculated to be about 40% in rats (calculation based on the decline of $^{14}$C-VC in a closed system) (Bolt et al. 1976). In Rhesus monkeys, VC also is efficiently absorbed after inhalation, as deduced from data on its metabolic elimination (no further quantification) (Buchter et al. 1980).

Whole-body exposure (excluding the head) of Rhesus monkeys to radioactive VC indicated that very little VC is absorbed through the skin (about 0.031 and 0.023% at 800 and 7,000 ppm, respectively, after 2-2.5 h) (ATSDR 1997). No additional data on dermal absorption of VC are available.

The percentage of VC remaining in the carcass of rats 72 h after oral exposure at 0.05, 1, and 1 00 mg/kg was 10, 11, and 2%, respectively. The data suggest almost complete elimination of VC (Watanabe et al. 1976b). In rats exposed to radioactive VC at 10 and 1,000 ppm, 14 and 15% of $^{14}C$-activity, respectively, remained in the carcasses 72 h after exposure. Radioactivity was detected in the liver, skin, plasma, muscle, lung, fat, and kidneys, representing nonvolatile metabolites of VC (Watanabe et al. 1976a) or incorporation into $C_1$-pool (Laib et al. 1989).

Data on serum concentrations of VC are scarce. Ungváry et al. (1978) exposed pregnant rats to VC at 2,000-12,000 ppm. They determined that blood concentrations ranged from 19 µg/mL at 2,000 ppm to 48.4 µg/mL at 12,000 ppm, indicating no direct proportional relationship between VC air and blood concentrations. Feron et al. (1975) reported that blood concentrations of VC peaked at 1.9 µg/mL, 10 min after rats were administered VC by gavage at 300 mg/kg. The blood concentration of VC after oral exposure is much smaller than after inhalation; the difference might be from the effective hepatic clearance of VC after oral uptake.

Similar to other anesthetics, maximal blood concentration of VC after inhalation depends on the partial pressure of VC in the air. Blood concentrations of VC in the brain, which directly correlate with depth of narcosis (see below) and, presumably, cardiac sensitization, can be controlled by changing the concentration of VC in the air (by changing the partial pressure of VC). If equilibrium is reached between the partial pressure of VC in the air and in the blood (steady state), no further increase of VC in the blood is possible, even if the exposure duration is prolonged (Forth et al. 1987). The time necessary to establish a steady state mainly depends on the blood:air partition coefficient of the substance. The blood:air partition coefficient of VC in humans is 1.2 (Csanády and Filser 2001), similar to the partition coefficient for the anesthetic isoflurane of 1.4 (Forth et al. 1987). For isoflurane, equilibrium is reached in about 2 h, as derived by graphical extrapolation of the data on isoflurane (Goodman and Gilman 1975). For VC at much lower concentrations, the elimination half time of VC is estimated at 20.5 min (Buchter 1979; Bolt et al. 1981). Using that value, a steady state concentration for VC in blood of about 102.5 min can be calculated by standard estimation rules (5 × 20.5 min). Thus, at high or low concentrations, a relevant increase in internal concentrations of VC is not expected after more than 2 h of exposure. However, for shorter exposure durations, the relevant influence of time on the build-up of VC on internal concentrations should be taken into account.

VC is oxidized by cytochrome-P450 2E1 (CYP2E1) to the highly reactive epoxide 2-chloroethylene oxide. The epoxide can directly interact with DNA

and proteins or spontaneously rearrange to 2-chloroacetaldehyde, which might bind to proteins and DNA. 2-Chloroethylene oxide can also be transformed to glycol aldehyde by epoxide hydrolase or react with glutathione, leading to the formation *N*-acetyl-S-(2-hydroxyethyl)-cysteine. Chloroacetaldehyde is oxidized by aldehyde dehydrogenase to 2-chloroacetic acid that reacts with glutathione to form thiodiglycolic acid (which leads to the liberation of carbon dioxide). Comparison of in vitro metabolism with rat liver microsomes and in vivo experiments in rats shows that virtually all the metabolic activation of VC in vivo occurs in the liver (WHO 1999). At low concentrations, VC is metabolically eliminated and nonvolatile metabolites are excreted mainly in the urine. At doses that saturate metabolism, the major route of excretion is exhalation of unchanged VC. Excretion of metabolites via feces is only a minor route, independent of applied dose (WHO 1999).

Buchter et al. (1980) exposed Rhesus monkeys to VC at 100-800 ppm and measured the time-dependent disappearance of VC from the atmosphere. The maximum metabolic rate was 45 μmol/kg-h, which was obtained with VC at 400 ppm; no attempt was made to identify the metabolites formed. Metabolic clearance rates were calculated from the decrease in atmospheric VC. Clearance rates for monkeys, rabbit, and humans were 2.0-3.55 L/h/kg, for gerbils and rats were 11.0-12.5 L/h/kg, and for mice were 25.6 L/h/kg, indicating major species differences, which are in accordance with allometric scaling.

After oral exposure to VC at 0.05, 1.0, or 100 mg/kg, male rats metabolized VC to the epoxide, which was further metabolized (e.g., to thiodiglycolic acid; about 25% of the $^{14}C$-containing urinary metabolites). Approximately 9, 13.3, or 2.5% of the total dose was excreted as $CO_2$ and 1.4, 2.1, or 66.6% as VC in the low-, mid-, and high-dose groups, respectively (Watanabe et al. 1976b). At 100 mg/kg, pulmonary elimination showed a biphasic clearance with an initial half-life of 15 min and a terminal half-life of 41 min. At 0.05 and 1 mg/kg, only monophasic pulmonary clearance could be observed with half-life values of 53-58 min (Watanabe et al. 1976b). Initial urinary excretion of metabolites followed first-order kinetics with half-life values of 4.5-4.6 h, followed by a slow terminal phase (Watanabe et al. 1976b). Thus, the equilibrium concentration for metabolites will not be reached within 8 h. The ratio of the metabolites excreted in the urine did not vary in dependence on dose.

VC metabolism in Rhesus monkeys is saturated at concentrations greater than 380 ppm (Buchter et al. 1980). In humans, VC at 24 ppm appears to be below the threshold of saturation (Krajewski et al. 1980) because no difference in pulmonary retention was observed at concentrations of 3, 6, 12, and 24 ppm. When exposing rats in a closed system to VC at 50-1,000 ppm, metabolic clearance was slowed at concentrations greater than 220 ppm, as evidenced by longer half-lives (Hefner et al. 1975). Bolt et al. (1977) exposed rats in a similar system and found metabolic saturation occurred at 250 ppm. These data are in accordance with the findings of Watanabe et al. (1976a); metabolism was saturated in the rat after inhalation of VC at 1,000 ppm but not at 100 ppm VC (no intermediate concentration was tested).

Saturation of metabolism also has been observed after oral exposure to VC at high doses. Watanabe et al. (1976b) reported saturation was evidenced by an increase in expired VC from 2.1% at 1 mg/kg to 66.6% at 100 mg/kg (Watanabe et al. 1976b).

VC metabolites are assumed to destroy CYP enzymes responsible for its epoxidation (Pessayre et al. 1979; Du et al. 1982). On the other hand, activity of glutathione-*S*-transferase and glutathione reductase is elevated after VC exposure in rats (glutathione content is reduced), representing an early hepatocellular adaption to VC exposure (Du et al. 1982).

### 4.2. Mechanism of Toxicity

Acute neurotoxicity from high concentrations of VC is probably dependent on VC concentration and independent of VC metabolism. This assumption is supported by the finding that narcotic concentrations of VC are similar in four species, including the guinea pig, mouse, rabbit, and rat (Mastromatteo et al. 1960; Prodan et al. 1975). VC has been investigated as a possible human anesthetic (Peoples and Leake 1933; Oster et al. 1947), but was abandoned because of its induction of cardiac arrhythmia.

Acute toxicity and lethality are mainly accompanied by congestion of all internal organs, pulmonary edema, and liver and kidney changes (up to necrosis) (Prodan et al. 1975). The mechanism of action has not been established; toxic effects are possibly mediated by reactive metabolites.

The genotoxicity and carcinogenicity of VC has been attributed to the formation of reactive metabolites, especially 2-chloroethylene oxide and 2-chloroacetaldehyde (see WHO 1999). 2-Chloroethylene oxide interacts directly with DNA and produces alkylation products (Fedtke et al. 1990). This alkylation results in a highly efficient base-pair substitution that leads to neoplastic transformation (ATSDR 1997). VC-DNA ethenobases have been shown to lead to miscoding and are found in VC-induced tumors in animals and humans (Barbin 2000). Despite relevant repair, no full reduction in adducts to background levels was observed 2 weeks after a 5 day exposure to VC at 600 ppm for 4 h/day (Swenberg et al. 1999). For vinyl fluoride, when all of the data on εG and hemangiosarcomas in rats and mice were compared by regression analysis, a high correlation was seen ($r^2 = 0.88$) (Swenberg et al. 1999). However, in the case of VC, there was a close correlation in the occurrence of εA, εC, and εG, and there were indications that εA also might be related to tumor formation (Barbin 1999, 2000). In adults, nonparenchymal cells have a greater rate of proliferation than hepatocytes. Thus, this cell population is more likely to convert promutagenic DNA adducts into mutations (Swenberg et al. 1999). This relationship might be changed when exposure occurs during rapid growth of the liver; young animals have a high rate of etheno-adducts and of preneoplastic foci in the liver. These foci persisted over several months even after short durations of exposure (Laib et al. 1989). In young animals, a high rate of hepatoma and hepatocellular carci-

noma have been found after short-term exposure to VC (Maltoni et al. 1981, 1984; Froment et al. 1994).

"Vinyl chloride disease" (characterized by Raynaud's phenomena and scleroderma) is a common finding after prolonged occupational exposure to VC. No similar observations have been made in experimental animals in single-exposure experiments. The effects in humans are probably from immunologic abnormalities caused by interaction of reactive VC metabolites with proteins, as has been proposed by Grainger et al. (1980) and Ward et al. (1976); however, no definitive mechanism has been elucidated to date.

## 4.3. Other Relevant Information

### 4.3.1. Physiology-based Pharmacokinetic Modeling

Physiology-based pharmacokinetic models have been proposed to predict VC metabolism and cancer risk (Clewell et al. 1995, 2001; Reitz et al. 1996). Such models have been developed to account for physiologic differences between species relevant to VC uptake, distribution, metabolism, and excretion, and should allow better comparison across species.

Current models use four compartments (liver, fat, slowly-perfused tissues, and richly-perfused tissues) and partition coefficients determined in vitro. Metabolism is modeled by one (Reitz et al. 1996) or two (Clewell et al. 1995) saturable pathways. The model of Clewell et al. (1995, 2001) uses one high-affinity, low-capacity pathway likely pertaining to CYP2E1, and one low-affinity, high-capacity pathway tentatively assigned to CYP2C11/6 and CYP1A1/2. Because VC readily reacts with glutathione and is known to deplete hepatic glutathione stores, description of the glutathione kinetics also was included.

### 4.3.2. Interspecies Variability

A comparison of the metabolic activity across species indicates that mice are the most metabolically active, having a first-order metabolic clearance rate of 25.6 L/h/kg at VC concentrations below metabolic saturation (Buchter et al. 1980). Clearance in rats, Rhesus monkey, rabbits, and humans is lower (11.0, 3.55, 2.74, and 2.02 L/h/kg, respectively). Because the metabolism of VC is perfusion limited (Filser and Bolt 1979), comparison of clearance rates on a body-weight basis is not appropriate. If clearance is compared on a body-surface-area basis, these mammalian species exhibit similar clearance rates (WHO 1999).

Comparison of lethal concentrations of VC (lethality occurring in the context of narcosis) in mice, rats, rabbits, and guinea pigs indicate certain interspecies variations (see Table 5-7). The guinea pig and rabbit are less sensitive to VC than mice and rats. Comparing the most sensitive species (mouse) with the least sensitive species (rabbit and guinea pig) suggest a difference of a factor of 2.

**TABLE 5-7** Lethal Concentrations of Vinyl Chloride in Laboratory Animals

| Species | $LC_{50}$ | Reference |
|---|---|---|
| Mouse | 117,500 ppm | Prodan et al. 1975 |
| Rat | 150,000 ppm | Lester et al. 1963; Prodan et al. 1975 |
| Rabbit | 240,000 ppm | Prodan et al. 1975 |
| Guinea pig | 240,000 ppm | Prodan et al. 1975 |

Marginal interspecies differences are observed with nonlethal, prenarcotic effects. Rats and mice are a little more sensitive than guinea pigs. For example, exposure to VC at 100,000 ppm for 30 min resulted in similar symptoms in mice, rats, and guinea pigs: unconsciousness (in all rats and mice but only in 1/5 guinea pigs), pulmonary hyperaemia persisting for more than 2 weeks, and side position in rats and mice after 20 min and in guinea pigs after 30 min (Mastromatteo et al. 1960). No comparable data in humans are available. Mice appear to be more sensitive than rats and rabbits to hepatic effects. Exposure of mice to VC at 1,500 ppm for 2 h caused severe liver effects, resulting in shock liver and death of the mice, but no hepatic or lethal effects were observed in rats and rabbits treated identically for 24 h (Tátrai and Ungvary 1981). The reason for these interspecies differences is not known. Data on acute hepatic effects of VC in humans are not available.

With respect to lethality and VC induced prenarcotic symptoms, there appear to be only minimal interspecies differences. An extrapolation factor of 3 is recommended in this context.

### 4.3.3. Intraspecies Variability

CYP2E1 is the key enzyme converting VC to 2-chloroethylene oxide. CYP2E1 activity in human liver microsomes (substrate: *p*-nitrophenol) may vary up to 12-fold between individuals (Seaton et al. 1994). These data indicate a potential interindividual variability in VC metabolism.

Investigation of VC retention in the lung of human volunteers revealed large interindividual differences; the minimum retention was 20.2% and the maximum was 79% (Krajewski et al. 1980). Lester et al. (1963) reported that VC at 8,000 ppm did not cause any response in five individuals, but one person felt "slightly heady." Other subjects complained of adverse health effects at a concentration of 12,000 ppm, indicating only small interindividual differences in neurotoxic effects from VC.

Relevant interindividual differences were not described in animal experiments.

On the basis of these observations, a factor of 3 was used to characterize intraspecies variability in the context of neurotoxic effects or cardiac sensitization.

### 4.3.4. Concurrent Exposure Issues

Concurrent administration of ethanol and VC in rats resulted in an increase in liver angiosarcoma, compared with data from animals exposed only to VC. This difference might be from the interaction of ethanol (a known inducer of CYP2E1) with VC metabolism (WHO 1999).

Induction of certain enzymes of the mixed-function oxidase system by pretreatment with phenobarbital or a mixture of polychlorinated biphenyls enhanced acute hepatotoxicity in rats, as measured by increased activity of hepatic enzymes and focal hepatic necrosis. On the other hand, inhibitors of the mixed-function oxidase system like SKF-525A have an opposite effect (WHO 1999).

## 5. DATA ANALYSIS FOR AEGL-1

### 5.1. Summary of Human Data Relevant to AEGL-1

Odor detection of VC at 261 ppm after entering an exposure chamber was reported by Baretta et al. (1969). The authors also described that five of seven persons detected the odor at 491 ppm, but could no longer detect it after 5 min of exposure.

Amoore and Hautala (1983) reported an odor threshold for VC of 3,000 ppm. This value represents the geometric average of three studies, but the authors did not specify whether the threshold was for detection or recognition of VC.

A “fairly pleasant odor” was reported by two persons exposed to VC at 25,000 ppm for 3 min. Dizziness and slight disorientation occurred (Patty et al. 1930).

Hori et al. (1972) reported an odor threshold for VC of 10-20 ppm (20 ppm in production workers and 10 ppm in workers from other sites). These data were rejected because there was no calibration of panel odor sensitivity, it was not clear whether the limit was based on recognition or detection, and the number of trials was not stated in the study (AIHA 1997).

Irritating effects of VC are observed only at very high concentrations. Danziger (1960) reported that accidental exposure to lethal concentrations of VC was accompanied by ocular lesions.

Baretta et al. (1969) exposed four to six volunteers to VC at 59, 261, and 491 ppm (analytic concentrations) for 7.5 h (including a 0.5 h lunch period). The corresponding time-weighted average concentrations were 48, 248, and 459 ppm over 7.5 h. Seven people were exposed at 491 ppm for only 3.5 h. The only complaints were those of two subjects who reported mild headache and some dryness of their eyes and nose during exposure at the highest concentration. The time of onset of headaches was not specified but was assumed to have occurred after 3.5 h of exposure.

### 5.2. Summary of Animal Data Relevant to AEGL-1

Lacrimation occurred shortly after mice, rats, guinea pigs, and rabbits were exposed to VC (42,900-280,000 ppm). Lethal effects have been observed in mice and rats even at the lowest exposure concentrations (42,900 ppm without ventilation in mice and 150,000 ppm with ventilation in rats) (Prodan et al. 1975). Mastromatteo et al. (1960) described that irritation (no further details) occurred immediately after onset of exposure to VC at 100,000, 200,000, or 300,000 ppm in rats and mice. In guinea pigs, irritation was not described at concentrations below 400,000 ppm, but the animals exhibited unconsciousness at all concentrations. No other data on irritation in animals exposed to VC were found.

### 5.3. Derivation of AEGL-1

VC is a compound with poor odor-warning properties. Reports on odor threshold vary over a wide range (10-25,000 ppm). There are no validated studies of the detection or recognition threshold for VC. According to Baretta et al. (1969), people seem to get used to the odor of VC. In humans and animals, irritation is found at very high concentrations that are lethal or cause unconsciousness. Thus, it was not possible to derive AEGL-1 values on basis of odor detection or irritation.

Occurrence of headache has been reported by Baretta et al. (1969) in two subjects after acute exposure. These findings are supported by data from occupationally-exposed persons who developed headache after VC exposure (Lilis et al. 1975; Suciu et al. 1975). The no-effect level for notable discomfort ("mild headache") in the Baretta et al. (1969) study is 491 ppm for 3.5 h. The effects are probably from VC in the blood and not a metabolite. Only small interindividual differences in pharmacokinetics of VC are expected, as the concentration of VC required to elicit the effect is greater than that required for saturation of the metabolic pathways. An intraspecies uncertainty factor of 3 is used to account for toxicodynamic differences among individuals.

Time scaling was conducted using the default values for n = 3 for extrapolation from longer to shorter durations or n = 1 for extrapolation from shorter to longer durations (NRC 2001, see Section 2.7), as the mechanism of inducing headaches is not well understood and is unlikely to be simply due to the concentration of VC in the blood. The extrapolation to a 10-min exposure from a 3.5-h exposure is justified because people exposed at 4,000 ppm for 5 min did experience headaches (Lester et al. 1963). The AEGL-1 values for VC are presented in Table 5-8.

**TABLE 5-8** AEGL-1 Values for Vinyl Chloride

| 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|
| 450 ppm ($1,200 mg/m^3$) | 310 ppm ($800 mg/m^3$) | 250 ppm ($650 mg/m^3$) | 140 ppm ($360 mg/m^3$) | 70 ppm ($180 mg/m^3$) |

## 6. DATA ANALYSIS FOR AEGL-2

### 6.1. Summary of Human Data Relevant to AEGL-2

Lester et al. (1963) reported that a 5-min exposure to VC at 8,000 ppm caused dizziness in one of six subjects. (The same subject reported slight dizziness with sham exposure and no effect at 12,000 ppm.) No complaints were made by any volunteer at 4,000 ppm. At 12,000 ppm, one subject reported clear signs of discomfort (reeling, swimming head) and another subject was unsure of some effect (a "somewhat dizzy" feeling in the middle of exposure). Five of six subjects exposed at 16,000 ppm and all six subjects exposed at 20,000 ppm complained of dizziness, nausea, headache, and dulling of visual and auditory cues. All symptoms disappeared shortly after exposure was ceased; headache persisted for 30 min in one subject after exposure at 20,000 ppm.

Exposure to VC at 25,000 ppm for 3 min resulted in dizziness, slight disorientation with regard to space and size of surrounding objects, and a burning sensation in the feet in two people. They immediately recovered after leaving the exposure chamber and complained only of a slight headache that persisted for 30 min (Patty et al. 1930).

Baretta et al. (1969) exposed four to six volunteers to VC at 59, 261, and 491 ppm (analytic concentrations) for 7.5 h (including a 0.5 h lunch period). The corresponding time-weighted average concentrations were 48, 248, and 459 ppm over 7.5 h. Seven people were exposed at 491 ppm for only 3.5 h. The only complaints were those of two subjects who reported mild headache and some dryness of their eyes and nose during exposure to the highest concentration. The time of onset of headaches was not specified but was assumed to have occurred after 3.5 h of exposure.

### 6.2. Summary of Animal Data Relevant to AEGL-2

Animal toxicity after short-term exposure is characterized by cardiac sensitization and by prenarcotic and hepatic effects. Short-term exposure (5 min) of dogs to VC induced cardiac sensitization towards epinephrine ($EC_{50}$ was 50,000 and 71,000 ppm in two independent experiments) (Clark and Tinston 1973, 1982). This effect was confirmed by additional experimental data on higher concentrations with VC.

Hehir et al. (1981) reported that single exposure of mice to VC at 50,000 ppm caused twitching, ataxia, hyperventilation, and hyperactivity, beginning 40 min after exposure began. Consistent with these data, Mastromatteo et al. (1960) reported that VC at 100,000 ppm induced pronounced tremor, unsteady gait, and muscular incoordination in mice 15 min after onset of exposure. Exposure of mice to VC at 1,500 ppm for 2 h resulted in stasis of blood flow, decreased enzyme activities in the liver, subcellular liver damage, and shock liver after 24 h of exposure (Tátrai and Ungváry 1981).

Viola (1970) reported that rats exposed to VC at 30,000 ppm for 4 h/day were slightly soporific (no further details). Moderate intoxication and loss of righting reflex was observed in rats exposed to VC at 50,000 ppm for 2 h, and intense intoxication was seen at 60,000 ppm (but righting reflex was still present) (Lester et al. 1963). Intoxication was not further characterized. Exposure to VC at 100,000 ppm for 2 h resulted in a loss of the corneal reflex (Lester et al. 1963). In another study, tremor and ataxia were observed 15 min after onset of exposure to VC at 100,000 ppm (Mastromatteo et al. 1960). Guinea pigs exposed at 25,000 ppm for 5 min showed motor ataxia, unsteadiness on feet, and the animals were unconscious after 90 min (the NOAEL was 10,000 ppm) (Patty et al. 1930). Mastromatteo et al. (1960) reported unsteady gait and muscular incoordination in guinea pigs exposed to VC for 15 min at 100,000 ppm.

A single inhalation exposure to VC at 100,000 ppm for 6 h resulted in histopathologic changes of the liver (vacuolization) in rats, but was not observed at 50,000 ppm (Jaeger et al. 1974). However, in mice, Tátrai and Ungváry (1981) reported that stasis of the liver developed 2 and 4 h after exposure began. The authors observed decreasing enzyme activities in the liver and subcellular liver damage at a concentration of 1,500 ppm for 2 h; after 24 h, shock liver developed and all animals died. Repeated exposure of rats to VC at 1,500 ppm for up to 9 days during pregnancy caused increased relative and absolute liver weights, but no changes in the liver were found when examined by light microscopy. Also, no histopathologic effects were observed in rabbits treated identically (Ungváry et al. 1978). In another developmental study, increased absolute and relative liver weights were found in rats exposed intermittently to VC at 2,500 ppm on days 6-15 of pregnancy; the NOAEL was 500 ppm (John et al. 1977, 1981). The results in mice (Tátrai and Ungváry 1981) suggest that this species is unusually sensitive to VC, so the results were not used to derive AEGL-2 values.

### 6.3. Derivation of AEGL-2

Short-term exposure (5 min) of dogs to VC induced cardiac sensitization towards epinephrine ($EC_{50}$ was 50,000 or 71,000 ppm in two independent experiments) (Clark and Tinston 1973, 1982). A no-effect level cardiac sensitization can be reasonably estimated by using a factor of 3 with the $EC_{50}$ of 50,000 ppm, resulting in a concentration of about 17,000 ppm. This concentration leads to effects on the central nervous system in humans after 5 min of exposure (Lester et al. 1963). Thus, cardiac sensitization would not be the critical effect for AEGL-2 derivation, but can be used to support the AEGL-2 values derived below.

Liver toxicity is a major end point after long-term exposure to VC and might possibly be linked to tumor development in young animals (see Section 4.2. for further discussion). The no-effect level for irreversible effects on the liver in rats after a single 6-h exposure to VC is 50,000 ppm. The effects seen at lower concentrations (liver weight changes) were not considered key effects for AEGL-2 derivation.

Narcotic effects seem to predominate in rats, mice, and guinea pigs acutely exposed to high concentrations of VC. These effects are relevant AEGL-2 effects because they have the potential to impair escape. Although guinea pigs appear to be less sensitive than rats and mice with regard to lethality (see Section 7.2), they are more sensitive than rats and mice with regard to early signs of narcotic effects. Guinea pigs exposed to VC at 25,000 ppm showed motor ataxia and unsteadiness on feet after 5 min, and become unconscious after 90 min (no-effect level was 10,000 ppm) (Patty et al. 1930). Rats exposed to VC at 30,000 ppm for 4 h were only slightly soporific (Viola 1970), and a single exposure of mice to 50,000 ppm caused twitching, ataxia, hyperventilation, and hyperactivity after 40 min (Hehir et al. 1981).

The observations in animals are consistent with the effects observed in humans. Dizziness, reeling, swimming head, and nausea, which can be regarded as early signs of narcosis, have been reported in humans exposed to VC in concentrations ≥12,000 ppm for 5 min. No effects were reported at 4,000 ppm (Lester et al. 1963). The effects observed at 12,000 ppm (dizziness, reeling, swimming head) were seen only in one or two of six persons (one person was unsure of an effect) and do not yet impair the ability to escape. On the other hand, effects observed at concentrations ≥16,000 ppm (dizziness, nausea, headache, and dulling of visual and auditory cues) could impair escape. Therefore, 12,000 ppm was selected as the no-effect level for impaired ability to escape and was used to derive the AEGL-2 values. The effects are from VC in the blood and not a metabolite. Only small interindividual differences in pharmacokinetics of VC are expected, as the concentration of VC required to elicit the effect is greater than that required for saturation of the metabolic pathways. An intraspecies uncertainty factor of 3 is used to account for toxicodynamic differences among individuals.

By analogy with other anesthetics, the effects of VC are assumed to be solely concentration dependent. Thus, after reaching steady state (at about 2 h of exposure), no increase in effect is expected. See Section 4.1 and Appendix B for a discussion of the duration needed for VC to reach a steady-state concentration. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using n = 2, based on data from Mastromatteo et al. (1960). Mastromatteo et al. (1960) observed various time-dependent prenarcotic effects in mice and guinea pigs after less than steady-state exposure conditions (Appendix B for details). Time extrapolations were performed from 5 min to 10-min, 30-min, 60-min, and 2-h exposures. The calculations are shown in Appendix A, and AEGL-2 values for VC are presented in Table 5-9.

**TABLE 5-9** AEGL-2 Values for Vinyl Chloride

| 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|
| 2,800 ppm (7,300 mg/m$^3$) | 1,600 ppm (4,100 mg/m$^3$) | 1,200 ppm (3,100 mg/m$^3$) | 820 ppm (2,100 mg/m$^3$) | 820 ppm (2,100 mg/m$^3$) |

## 7. DATA ANALYSIS FOR AEGL-3

### 7.1. Summary of Human Data Relevant to AEGL-3

Only two cases of accidental death from exposure to VC are described in literature. Exposure concentrations and duration were unknown, but circumstances suggest inhalation of very high concentrations. At autopsy, cyanosis, congestion of lung and kidneys, and blood-coagulation failure were observed (Danziger 1960).

### 7.2. Summary of Animal Data Relevant to AEGL-3

$LC_{50}$ values for mice, rats, rabbits, and guinea pigs indicate similar sensitivity of mice and rats and of rabbits and guinea pigs. The following $LC_{50}$ values were obtained from the data of Prodan et al. (1975): 117,500 ppm for mice, 150,000 ppm for rats, 240,000 ppm for rabbits, and 240,000 ppm for guinea pigs. The findings in rats are supported by data from Lester et al. (1963), who reported that one of two rats died after exposure to VC at 150,000 ppm for 2 h, and the remaining rat recovered after exposure ended. No lethality was observed rats exposed to VC at 100,000 ppm for 2 h (Prodan et al. 1975), rats exposed at 100,000 ppm for 8 h (Lester et al. 1963) or at 200,000 ppm for 20 min (Mastromatteo et al. 1960), and rabbits exposed at 200,000 ppm for 2 h (Prodan et al. 1975).

In addition, relevant data on cardiac sensitization exist. $EC_{50}$s of 50,000 and 71,000 ppm in dogs were found in two independent experiments following 5-min exposures to VC (Clark and Tinston 1973, 1982). These effects also were seen in mice at higher concentrations (Aviado and Belej 1974). In monkeys, only myocardial depression was observed after inhalation of VC at 2.5-10% (Belej et al. 1974). It was unclear whether an addition challenge with epinephrine was applied.

### 7.3. Derivation of AEGL-3

Lethality data provide AEGL-3 values that are marginally higher than those derived on the basis of cardiac sensitization. Thus, animal data (Clark and Tinston 1973, 1982) on cardiac sensitization after exposure for 5 min were used to derive AEGL-3 values. Severe cardiac sensitization is a life-threatening effect, but no animals died at 50,000 ppm, so that concentration was used at the point-of-departure. The cardiac sensitization model with the dog is considered an appropriate model for humans and is highly sensitive because the response is optimized by the exogenous administration of epinephrine (Brock et al. 2003; ECETOC 2009). The protocol is designed conservatively with built-in safety factors and, thus, no additional uncertainty factors are needed to calculate AEGL-3 values (ECETOC 2009). Accordingly, an interspecies uncertainty fac-

tor of 1 was applied. Only small interindividual differences in pharmacokinetics of VC are expected, as the concentration of VC required to elicit the effect is greater than that required for saturation of the metabolic pathways. An intraspecies uncertainty factor of 3 is used to account for toxicodynamic differences among individuals.

By analogy with other halocarbons (e.g., Halon-1211, HFC-134a) that cause cardiac sensitization, the effects are assumed to be solely concentration dependent (Brock et al. 2003; ECETOC 2009). Thus, after reaching steady state in about 2 h, no increase in effect is expected. See Section 4.1 and Appendix B for a discussion of the time needed for VC to reach a steady-state concentration. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using n = 2, based on data from Mastromatteo et al. (1960). Mastromatteo et al. observed various time-dependent prenarcotic effects (muscular incoordination, side position, and unconsciousness, effects that occur immediately before death) in mice and guinea pigs after less than steady-state exposure conditions. Time extrapolation was performed from 5 min to 10-min, 30-min, 60-min, and 2-h exposures.

AEGL-3 values for VC are presented in Table 5-10.

## 8. SUMMARY OF PROPOSED AEGLs

### 8.1. AEGL Values and Toxicity End Points

The AEGL values for VC are presented in Table 5-11. AEGL-1 values were based on mild headaches observed in volunteers (Baretta et al. 1969). Odor threshold was not determined in a validated manner, and seems to vary over a wide range. AEGL-2 values are based on effects on the central nervous system, which could impair ability to escape (Lester et al. 1963). Data on cardiac sensitization (Clark and Tinston 1973, 1982) are supported by lethality data (Prodan et al. 1975) and are used for AEGL-3 derivation.

A category plot of toxicity data and AEGLs values is presented in Figure 5-1. The data were classified into severity categories chosen to fit definitions of the AEGL health effects. The category severity definitions are no effect, disabling, lethal, and AEGL.

### 8.2. Comparison with Other Standards and Guidelines

Other standards and guidance levels for workplace and community exposures of VC are presented in Table 5-12.

**TABLE 5-10** AEGL-3 Values for Vinyl Chloride

| 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|
| 12,000 ppm (31,000 mg/m$^3$) | 6,800 ppm (18,000 mg/m$^3$) | 4,800 ppm (12,000 mg/m$^3$) | 3,400 ppm (8,800 mg/m$^3$) | 3,400 ppm (8,800 mg/m$^3$) |

**TABLE 5-11** Summary of AEGL Values for Vinyl Chloride

| Classification | 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|---|
| AEGL-1 (nondisabling) | 450 ppm (1,200 mg/m$^3$) | 310 ppm (800 mg/m$^3$) | 250 ppm (650 mg/m$^3$) | 140 ppm (360 mg/m$^3$) | 70 ppm (180 mg/m$^3$) |
| AEGL-2 (disabling) | 2,800 ppm (7,300 mg/m$^3$) | 1,600 ppm (4,100 mg/m$^3$) | 1,200 ppm (3,100 mg/m$^3$) | 820 ppm (2,100 mg/m$^3$) | 820 ppm (2,100 mg/m$^3$) |
| AEGL-3 (lethal) | 12,000 ppm (31,000 mg/m$^3$) | 6,800 ppm (18,000 mg/m$^3$) | 4,800 ppm (12,000 mg/m$^3$) | 3,400 ppm (8,800 mg/m$^3$) | 3,400 ppm (8,800 mg/m$^3$) |

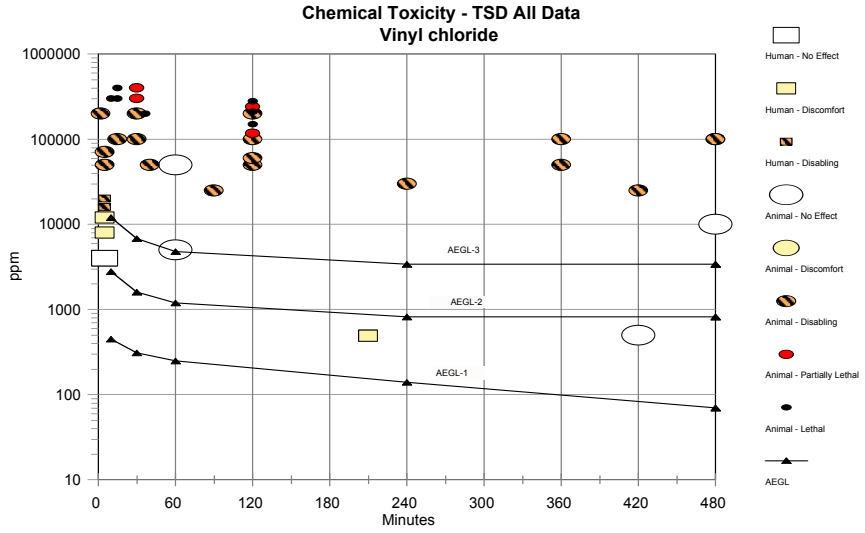


**FIGURE 5-1** Category plot of animal toxicity data on vinyl chloride compared with AEGLs values. Data from studies were exposure durations exceeded 500 min were excluded.

### 8.3. Data Adequacy and Research Needs

Because VC has poor warning properties, the database is poor from which to derive AEGL-1 values. Additional studies with volunteers may not be performed because of ethical reasons. AEGL-2 values are based on central nervous system effects observed in human studies. The concentration range is well-established but excludes potential mutagenic or carcinogenic effects after short-term exposure, which might occur at lower concentrations. However, quantitative estimates of respective risks are highly uncertain. For derivation of AEGL-3 values, the dog studies on cardiac sensitization consistent with lethality data observed at slightly higher concentrations.

**TABLE 5-12** Extant Standards and Guidelines for Vinyl Chloride

| | Exposure Duration | | | | |
|---|---|---|---|---|---|
| Guideline | 10 min | 30 min | 1 h | 4 h | 8 h |
| AEGL-1 | 450 ppm | 310 ppm | 250 ppm | 140 ppm | 70 ppm |
| AEGL-2 | 2,800 ppm | 1,600 ppm | 1,200 ppm | 820 ppm | 820 ppm |
| AEGL-3 | 12,000 ppm | 6,800 ppm | 4,800 ppm | 3,400 ppm | 3,400 ppm |
| PEL-TWA (OSHA)[a] | | | | | 1 ppm |
| TLV-TWA (ACGIH)[b] | | | | | 1 ppm |
| STEL (OSHA)[c] | 5 ppm (for 5 min) | | | | |
| TEEL-0 (DOE)[d] | | | 1 ppm | | |
| TRK (Germany)[e] | | | | | 2 or 3 ppm |
| Einsatztoleranzwerte (Greim, Germany)[f] | | | | 100 ppm | |
| Störfallbeurteilungswert (VCI)[j] | | | 1,000 ppm | | |

[a]PEL-TWA (permissible exposure limit-time-weighted average, Occupational Safety and Health Administration, [CFR 29, Part 1910.1017 [ 2002]) is the time-weighted average concentration for a normal 8-h workday and a 40-h work week, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[b] TLV-TWA (Threshold Limit Value-time-weighted average, American Conference of Governmental Industrial Hygienists [ACGIH 2010]). Is the TWA concentration for a normal 8-h workday and a 40-h work week, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. VC was classified as carcinogenicity category A1 ("confirmed human carcinogen").

[c]PEL-STEL (permissible exposure limit-short-term exposure limit, Occupational Safety and Health Administration) [CFR 29, Part 1910.1017 [2002]) 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 PEL-TWA. Exposures above the PEL-TWA and 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.

[d]TEEL-0 (temporary emergency exposure limit,U.S. Department of Energy [DOE 2010]) is the threshold concentration below which most people will experience no adverse health effects.

[e]TRK (technische richtkonzentrationen [technical guidance concentration], Deutsche Forschungsgemeinschaft [German Research Association], Germany) (DFG 2001). TRK is defined as the air concentration of a substance which can be achieved with current technical standards. TRK values are given for those substances for which no maximum workplace concentration can be established. Compliance with the TRK should minimize the risk of health effects, but health effects cannot be excluded even at this concentration. (A value of 3 ppm is given for existing plants and the production of VC and polyvinyl chloride, in all other cases 2 ppm should not be exceeded.)

[f]Einsatztoleranzwert [action tolerance levels] (Vereinigung zur Förderung des deutschen Brandschutzes e.V. [Federation for the Advancement of German Fire Prevention]) (Buff and Greim 1997 ) constitutes a concentration to which unprotected firemen and the gen-

eral population can be exposed to for up to 4 h without any health risks. The value is based on the observation that no acute toxic effects or irritating effects have been observed during exposure to 500 ppm for 4 h.

[g]Störfallbeurteilungswert [emergency assessment value] (VCI, Verband der Chemischen Industrie, Deutschland [Association of the Chemical Industry in Germany]) (VCI 1990) are values that have been set for an exposure duration of up to 1 h. Because VC leads to anesthesia at concentrations of 7%, to prenarcotic syndromes at 0.5%, and to respiratory arrest, the emergency assessment value has been set at 1,000 ppm.

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## APPENDIX A

## DERIVATION OF AEGL VALUES FOR VINYL CHLORIDE

### Derivation of AEGL-1 Values

| | |
|---|---|
| Key study: | Baretta, E.D., R.D. Stewart, and J.E. Mutchler. 1969. Monitoring exposures to vinyl chloride vapor: Breath analysis and continuous air sampling. Am. Ind. Hyg. Assoc. J. 30(6):537-544. |
| Toxicity end point: | Mild headache in two subjects exposed at highest concentration. The no-effect level for notable discomfort was 491 ppm for 3.5 h. |
| Uncertainty factors: | 3 for intraspecies variability. |
| Modifying factor: | Not applied |
| Time scaling: | $C^3 \times t = k$ for extrapolation to 10 min, 30 min, and 1 h<br>$C^1 \times t = k$ for extrapolation to 4 and 8 h<br>$k = (491\ ppm)^3 \times 210\ min = 2.49 \times 10^{10}$ $ppm^3$-min<br>$k = (491\ ppm)^1 \times 210\ min = 103{,}110$ ppm-min |
| Calculations: | |
| 10-min AEGL-1: | $C^3 \times 10\ min = 2.49 \times 10^{10}$ $ppm^3$-min<br>C = 1,355 ppm<br>1,355 ppm ÷ 3 = 450 ppm [1,200 $mg/m^3$] |
| 30-min AEGL-1: | $C^3 \times 30\ min = 2.49 \times 10^{10}$ $ppm^3$-min<br>C = 939.25 ppm<br>939 ppm ÷ 3 = 310 ppm [800 $mg/m^3$] |
| 1-h AEGL-1: | $C^3 \times 60\ min = 2.49 \times 10^{10}$ $ppm^3$-min<br>C = 745.48 ppm<br>745 ppm ÷ 3 = 250 ppm [650 $mg/m^3$] |

| | |
|---|---|
| 4-h AEGL-1: | $C \times 240$ min = 103,110 ppm-min<br>C = 429.63 ppm<br>430 ppm ÷ 3 = 140 ppm [360 mg/m$^3$] |
| 8-h AEGL-1: | $C \times 480$ min = 103,110 ppm-min<br>C = 214.81<br>215 ÷ 3 = 70 ppm [180 mg/m$^3$)] |

**Derivation of AEGL-2 Values**

| | |
|---|---|
| Key study: | Lester, D., L.A. Greenberg, and W.R. Adams. 1963. Effects of single and repeated exposures of humans and rats to vinyl chloride. Am. Ind. Hyg. Assoc. J. 24(3):265-275. |
| Toxicity end point: | Prenarcotic effects were observed in human volunteers. After exposure to VC at 16,000 ppm for 5 min, five of six persons experienced dizziness, lightheadedness, nausea, and visual and auditory dulling. At 12,000 ppm, one of six persons had "swimming head, reeling." Another individual was unsure of some effect and was somewhat dizzy. One person reported slight effects ("slightly heady") of questionable meaning at 8,000 ppm (this subject also felt slightly heady at sham exposure and reported no response at 12,000 ppm). No effects were observed at 4,000 ppm. The no-effect level for inability to escape was 12,000 ppm. |
| Uncertainty factors: | 3 for intraspecies variability. |
| Modifying factor: | Not applied |
| Time scaling: | $C^2 \times t = k$ for extrapolation to 10 min, 30 min, 1 h, and 2 h<br>Steady-state concentration occurs after 2 h, so flat-line response assumed for extrapolation to 4 and 8 h<br>$k = (12{,}000 \text{ ppm})^2 \times 5 \text{ min} = 7.2 \times 10^8$ ppm$^2$-min |

Calculations:

| | |
|---|---|
| 10-min AEGL-2: | $C^2 \times 10$ min = $7.2 \times 10^8$ ppm$^2$-min<br>C = 8,485.28 ppm<br>8,485 ppm ÷ 3 = 2,800 ppm [7,300 mg/m$^3$] |
| 30-min AEGL-2: | $C^2 \times 30$ min = $7.2 \times 10^8$ ppm$^2$-min<br>C = 4,898.98 ppm<br>4,899 ppm ÷ 3 = 1,600 ppm [4,100 mg/m$^3$] |
| 1-h AEGL-2: | $C^2 \times 60$ min = $7.2 \times 10^8$ ppm$^2$-min<br>C = 3,464.11 ppm<br>3,464 ppm ÷ 3 = 1,200 ppm [3,100 mg/m$^3$] |
| 4- and 8 -h AEGL-2: | 2-h steady state = $C^2 \times 120$ min = $7.2 \times 10^8$ ppm$^2$-min<br>C = 2,449.49 ppm<br>2,450 ppm ÷ 3 = 820 ppm [2,100 mg/m$^3$] |

**Derivation of AEGL-3 Values**

| | |
|---|---|
| Key studies: | Clark, D.G., and D.J. Tinston. 1973. Correlation of the cardiac sensitizing potential of halogenated hydrocarbons with their physicochemical properties. Br. J. Pharmacol. 49(2):355-357.<br><br>Clark, D.G., and D.J. Tinston. 1982. Acute inhalation toxicity of some halogenated and nonhalogenated hydrocarbons. Hum. Toxicol. 1(3):239-247. |
| Toxicity end point: | Short-term exposure (5 min) of dogs induced cardiac sensitization towards epinephrine ($EC_{50}$: 50,000 or 71,000 ppm in two independent experiments). These effects also observed in mice at higher concentrations (Aviado and Belej 1974). The no-effect level for lethality was 50,000 ppm. |
| Uncertainty factors: | 1 for interspecies variability<br>3 for intraspecies variability |

| | |
|---|---|
| Time scaling: | $C^2 \times t = k$ for extrapolation to 10 min, 30 min, 1 h, and 2 h<br>Steady-state concentration occurs after 2 h, so flat-line response assumed for extrapolation to 4 and 8 h<br>$k = (50{,}000 \text{ ppm})^2 \times 5 \text{ min} = 1.25 \times 10^{10}$ $\text{ppm}^2\text{-min}$ |
| Calculations: | |
| 10-min AEGL-3: | $C^2 \times 10 \text{ min} = 1.25 \times 10^{10}$ $\text{ppm}^2\text{-min}$<br>C = 35,355.34 ppm<br>35,355 ppm ÷ 3 = 12,000 ppm [31,000 $\text{mg/m}^3$] |
| 30-min AEGL-3: | $C^2 \times 30 \text{ min} = 1.25 \times 10^{10}$ $\text{ppm}^2\text{-min}$<br>C = 20,412.41 ppm<br>20,412 ppm ÷ 3 = 6,800 ppm [18,000 $\text{mg/m}^3$] |
| 1-h AEGL-3: | $C^2 \times 60 \text{ min} = 1.25 \times 10^{10}$ $\text{ppm}^2\text{-min}$<br>C = 14,433.76 ppm<br>14,434 ppm ÷ 3 = 4,800 ppm [12,000 $\text{mg/m}^3$] |
| 4- and 8-h AEGL-3: | 2-h steady state = $C^2 \times 120 \text{ min} = 1.25 \times 10^{10}$ $\text{ppm}^2\text{-min}$<br>C = 10,206.21 ppm<br>10,206 ppm ÷ 3 = 3,400 ppm [8,800 $\text{mg/m}^3$] |

## APPENDIX B

## TIME-SCALING CALCULATIONS

The relationship between dose and exposure duration to produce a toxic effect for any given chemical is a function of the physical and chemical properties of the substance and the toxicologic and pharmacologic properties of the individual substance. Historically, the relationship according to Haber (1924), commonly called Haber's rule ($C \times t = k$, where C = exposure concentration, t = exposure duration, and k = a constant), has been used to relate exposure concentration and duration to a toxic effect (Rinehart and Hatch 1964). This concept states that exposure concentration and exposure duration may be reciprocally adjusted to maintain a cumulative exposure constant (k) and that this cumulative exposure constant will always reflect a specific quantitative and qualitative response. This inverse relationship of concentration and time may be valid when the toxic response to a chemical is equally dependent on the concentration and the exposure duration. However, an assessment by ten Berge et al. (1986) determined that $LC_{50}$ data for certain chemicals revealed chemical-specific relationships between exposure concentration and exposure duration that were often exponential. This relationship can be expressed by the equation $C^n \times t = k$, where n represents a chemical-specific and even a toxic end-point-specific exponent. The relationship described by this equation is basically the form of a linear regression analysis of the log-log transformation of a plot of C vs. t (NRC 2001).

Acute central-nervous-system toxicity and lethality of VC are dominated by its narcotic effects characterized by a typical sequence of effects (increased motor activity, tremor, muscular incoordination, side position, and unconsciousness, resulting in deep narcosis). The occurrence and time sequence of these effects in rats, mice, and guinea pigs has been described by Mastromatteo et al. (1960). These experimental data are used for the derivation of values of n by linear regression analysis of the log-log transformed plot of C vs. t.

Three data sets of toxic effects in mice, rats, or guinea pigs described by Mastromatteo et al. (1960) were analyzed. The time-concentration relationships for mice and rats were identical, so the following evaluation concentrates on the data obtained from mice and guinea pigs. Data were collected for the end points of unconsciousness, muscular incoordination, and side position. As the side-position data are considered more reliable from cage-side observation, these data were used to derive the value of n. Because VC is not a potent irritant, the short-term time points are considered reliable and not affected by bradypnea.

The time after which side position was observed in mice and guinea pigs is presented in Tables B-1 and B-2, respectively. Regression analysis of the data is shown in Figure B-1.

**TABLE B-1** Observations of Side Position in Mice Exposed to Vinyl Chloride

| Concentration | Time (min) | Log concentration | Log time |
|---|---|---|---|
| 100,000 | 20 | 5 | 1.301 |
| 200,000 | 5 | 5.301 | 0.699 |
| 300,000 | 2 | 5.477 | 0.301 |

**TABLE B-2** Observations of Side Position in Guinea Pigs Exposed to Vinyl Chloride

| Concentration | Time (min) | Log concentration | Log time |
|---|---|---|---|
| 100,000 | 30 | 5 | 1.477 |
| 200,000 | 10 | 5.301 | 1 |
| 300,000 | 3.5 | 5.477 | 0.544 |

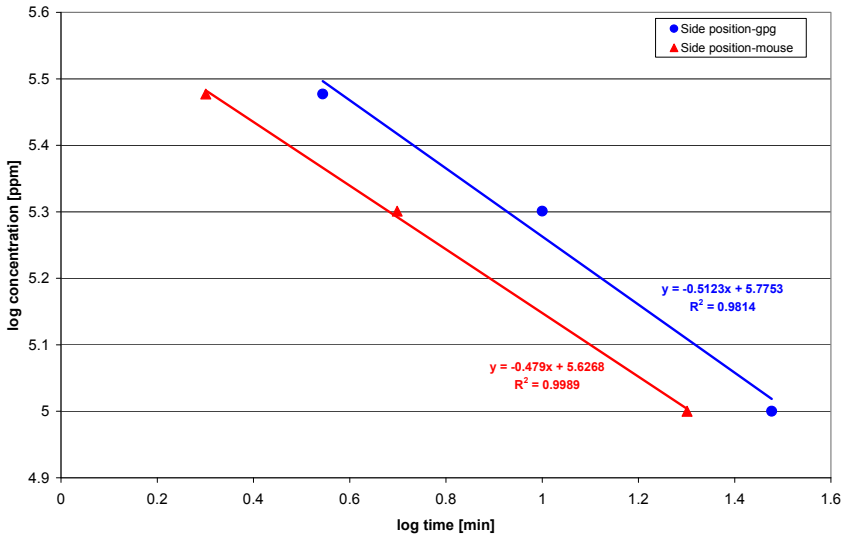


**FIGURE B-1** Regression analysis of the log-log transformed concentration-time curve for side position in mice and guinea pigs exposed to vinyl chloride. Source: Data from Mastromatteo et al. 1960.

The slope of the regression line was -0.479 and -0.5123 in mice and guinea pigs, respectively, corresponding to a value of 2.1 and 2.0 for n.

The end point of side position was used to derive n = 2, which is used for the time extrapolation for AEGL-2 (central nervous system effects) and AEGL-3 (cardiac sensitization) values for up to 2 h. Concentrations for these "less-than-steady-state" durations (10, 30, 60 and 120 min) should be calculated according to $C^2 * t$ = concentrations.

Although the end points for AEGL-2 (anesthesia) and AEGL-3 (cardiac sensitization) values occur by different mechanisms (Himmel 2008), it is appropriate to use the same n value for both calculations. Anesthesia is related to the concentration of VC in the brain, and brain concentration of VC is directly related to blood concentrations. Cardiac sensitization is related to VC concentration in the blood (Brock et al. 2003; ECETOC 2009). Therefore, both end points should follow the same $C \times t$ relationship.

## APPENDIX C

## CANCER ASSESSMENT OF VINYL CHLORIDE

The most recently published cancer risk estimate from EPA (2000a,b) appears to be the best unit risk estimate currently available for VC. The values are $8.8 \times 10^{-6}$ $(\mu g/m^3)^{-1}$ for continuous lifetime exposure, including childhood, and $4.4 \times 10^{-6}$ $(\mu g/m^3)^{-1}$ for continuous exposure as an adult. These risk values indicate that exposure during childhood results in a similar tumor incidence as exposure in adulthood. EPA used the physiologically-based pharmacokinetic model of Clewell et al. (1995, 2001) to calculate the inhalation unit risk. These values are based on model-derived estimates of the internal dose of the active metabolite in animals and the continuous external exposure in humans that would result in these same internal doses of the active metabolite.

Two calculations for cancer risk are presented below. Calculation A is based on EPA's unit risk for continuous lifetime exposure (EPA 2000a,b), transformed to a single 24-h exposure estimate by the default procedure recommended in the standard operating procedures for developing AEGLs (NRC 2001). The procedure involves linear transformation, and correction by a factor of 6 to account for the relevance of sensitive stages in development. Exposures of less than 24 h are derived using the physiologically-based pharmacokinetic model of Clewell et al. (1995, 2001). Calculation B is based on the cancer incidence observed in the 5-week animal study by Maltoni et al. (1981), assuming that 5 weeks of exposure of animals is equivalent to about 150 weeks exposure of humans, with linear transformation to a single 24-h exposure without further correction for potential sensitive stages of tumor development. Exposures of less than 24 h are derived using the model of Clewell et al. (1995, 2001).

### Calculation A

EPA's unit risk estimate for continuous lifetime exposure (inclusive of childhood) is $8.8 \times 10^{-6}$ $(\mu g/m^3)^{-1}$. This unit risk was derived using the model of Clewell et al. (1995, 2001) which relates liver tumor incidence in animals with the lifetime average daily dose of the VC metabolite in the liver believed to be responsible for the tumor response (the internal dose of the metabolite). The model uses human parameters to transform that internal dose to an external exposure concentration for humans. With a unit risk for continuous lifetime exposure of $8.8 \times 10^{-6}$ per $\mu g/m^3$, the exposure for a risk of 1 in 10,000 is 11.36 $\mu g/m^3$. To convert a 70-year exposure to a 24-h exposure, the exposure is multiplied by the number of days in 70 years:

$$11.36\ \mu g/m^3 \times 25{,}600 = 291\ mg/m^3$$

Under this strict C × t assumption, these exposures are considered equipotent.

To account for uncertainty regarding the variability in the stage of the cancer process at which VC or its metabolites may act, a multistage factor of 6 is applied (NRC 2001):

$$291 \text{ mg/m}^3 \times 1/6 = 48.5 \text{ mg/m}^3 \text{ (18.4 ppm)}$$

On the basis of this transformation, a 24-h VC exposure at this concentration would result in a $1 \times 10^{-4}$ risk. For $1 \times 10^{-5}$ and $1 \times 10^{-6}$ risks, the value at $1 \times 10^{-4}$ is reduced 10- and 100-fold, respectively. This estimate is based on the assumption of a strict C × t relationship.

**Calculation B**

As mentioned above for Calculation A, the basis of EPA's cancer risk estimate for VC is the internal dose, the lifetime average daily dose of VC metabolite in the liver. For numerous reasons, this metric may be quite different after a single exposure to VC of less than 24 h. Rather than make assumptions about the relationship of C × t, a physiologically-based pharmacokinetic model was used to estimate the internal dose to the liver under different external exposure regimes. These data are shown in the Table C-1 and Figure C-1.

The external 24-h exposure to VC corresponding to a $1 \times 10^{-4}$ risk is 48.5 mg/m$^3$. Values for less than 24-h exposure are determined by interpolation using Table C-1. The internal dose metric (mg/L liver) corresponding to a $1 \times 10^{-4}$ risk from a 24-h exposure to VC is 51.4 mg/L ([48.5 mg/m$^3$ ÷ 100 mg/m$^3$] × 106 mg/L). The external exposure necessary to achieve a VC concentration of 51.4 mg/L in the liver after an 8-h exposure is 147 mg/m$^3$ ([51.4 mg/L ÷ 35.0 mg/L] × 100 mg/m$^3$). A corresponding calculation was made for the other durations (0.5, 1, 4, and 8 h) and each risk level ($1 \times 10^{-4}$, $1 \times 10^{-5}$, and $1 \times 10^{-6}$).

If exposure is limited to a fraction of a 24-h period, the exposure corresponding to the various cancer risk levels is presented in Table C-2. Comparison of the VC concentrations corresponding to a cancer risk of $1 \times 10^{-4}$ and AEGL values are presented in Table C-3.

Calculation B is based on the cancer incidence as evident from a 5-week animal study by Maltoni et al. (1981), assuming that 5 weeks of exposure to animals is equivalent to about 150 weeks exposure to humans, with linear transformation to a single 24-h exposure without correction for potential sensitive stages of tumor development. Exposures of less than 24 h are derived using the physiologically-based pharmacokinetic model of Clewell et al. (1995, 2001).

The study was considered relevant because investigations were performed with newborn rats, which represent a sensitive subgroup for carcinogenesis, exposure was over a short period of time, and the end point (incidence of liver angiosarcoma) is relevant to humans. The data are shown in Table C-4.

**TABLE C-1** Dose in the Liver of Active Metabolite 24 Hours After Exposure to Vinyl Chloride

| | Dose in Liver, mg/L | | | | |
|---|---|---|---|---|---|
| Concentration ($mg/m^3$) | 0.5 h | 1 h | 4 h | 8 h | 24 h/70 y |
| 1 | 0.022 | 0.044 | 0.176 | 0.352 | 1.07 |
| 10 | 0.22 | 0.441 | 1.76 | 3.52 | 10.7 |
| 100 | 2.19 | 4.38 | 17.5 | 35 | 106 |
| 200 | 4.36 | 8.72 | 34.8 | 69.4 | 211 |
| 300 | 6.5 | 13 | 51.8 | 103 | 313 |
| 400 | 8.61 | 17.2 | 68.4 | 136 | 413 |
| 500 | 10.7 | 21.3 | 84.5 | 169 | 510 |
| 600 | 12.7 | 25.2 | 100 | 199 | 604 |
| 700 | 14.6 | 29.1 | 115 | 229 | 692 |
| 800 | 16.5 | 32.7 | 129 | 256 | 775 |
| 900 | 18.2 | 36.1 | 142 | 282 | 850 |
| 1,000 | 19.9 | 39.3 | 153 | 304 | 917 |
| 2,000 | 30.4 | 57.7 | 211 | 412 | 1,220 |
| 3,000 | 35.7 | 65.8 | 231 | 442 | 1,300 |
| 4,000 | 39.7 | 71.9 | 243 | 461 | 1,350 |
| 5,000 | 43.3 | 77.2 | 254 | 476 | 1,390 |
| 6,000 | 46.6 | 82.1 | 264 | 490 | 1,420 |
| 7,000 | 49.7 | 86.7 | 273 | 502 | 1,460 |
| 8,000 | 52.3 | 91.1 | 279 | 513 | 1,490 |
| 9,000 | 54.7 | 95.3 | 284 | 523 | 1,520 |
| 10,000 | 57 | 99.3 | 289 | 533 | 1,540 |

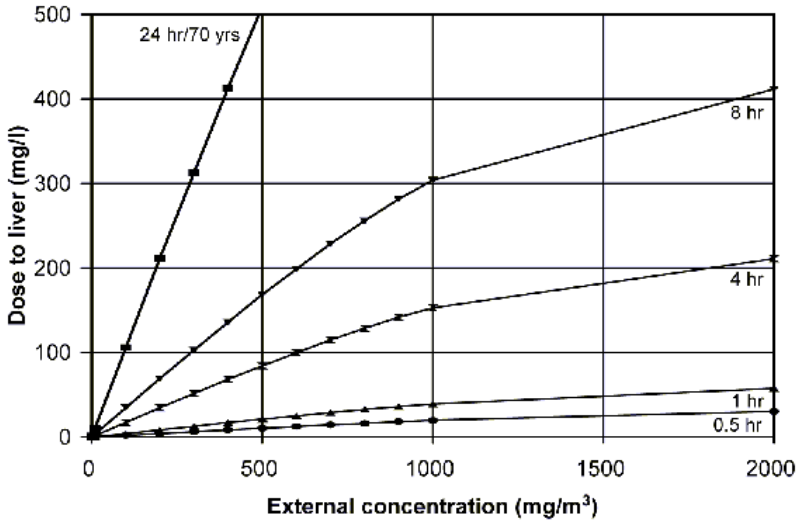


**FIGURE C-1** External concentration and dose to liver of vinyl chloride calculated by physiologically-based pharmacokinetic modeling by EPA. Source: Gary Foureman, EPA, personal commun., June 2003.

**TABLE C-2** Cancer Risks from Vinyl Chloride Based on Calculation A

| Risk Level | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|
| $1\times 10^{-4}$ | 2,990 ppm<br>7,870 mg/m$^3$ | 676 ppm<br>1,780 mg/m$^3$ | 113 ppm<br>298 mg/m$^3$ | 55.9 ppm<br>147 mg/m$^3$ |
| $1 \times 10^{-5}$ | 89.7 ppm<br>236 mg/m$^3$ | 44.5 ppm<br>117 mg/m$^3$ | 11.1 ppm<br>29.2 mg/m$^3$ | 5.55 ppm<br>14.6 mg/m$^3$ |
| $1 \times 10^{-6}$ | 8.97 ppm<br>23.3 mg/m$^3$ | 4.45 ppm<br>11.6 mg/m$^3$ | 1.11 ppm<br>2.92 mg/m$^3$ | 0.555 ppm<br>1.46 mg/m$^3$ |

**TABLE C-3** Comparison of AEGL Values for Vinyl Chloride and Cancer Risks Based on Calculation A

| | 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|---|
| $1 \times 10^{-4}$ risk | — | 2,990 ppm<br>7,870 mg/m$^3$ | 676 ppm<br>1,780 mg/m$^3$ | 113 ppm<br>298 mg/m$^3$ | 55.9 ppm<br>147 mg/m$^3$ |
| AEGL-1 | 450 ppm<br>1,200 mg/m$^3$ | 310 ppm<br>800 mg/m$^3$ | 250 ppm<br>650 mg/m$^3$ | 140 ppm<br>360 mg/m$^3$ | 70 ppm<br>180 mg/m$^3$ |
| AEGL-2 | 2,800 ppm<br>7,300 mg/m$^3$ | 1,600 ppm<br>4,100 mg/m$^3$ | 1,200 ppm<br>3,100 mg/m$^3$ | 820 ppm<br>2,100 mg/m$^3$ | 820 ppm<br>2,100 mg/m$^3$ |
| AEGL-3 | 12,000 ppm<br>31,000 mg/m$^3$ | 6,800 ppm<br>18,000 mg/m$^3$ | 4,800 ppm<br>12,000 mg/m$^3$ | 3,400 ppm<br>8,800 mg/m$^3$ | 3,400 ppm<br>8,800 mg/m$^3$ |

**TABLE C-4** Incidence of Tumors in Studies by Maltoni et al. (1981)

| Concentration (ppm) | Angiosarcoma | Hepatoma |
|---|---|---|
| Experiment BT 14: 4 h/d, 5 d/wk for 5 wk starting at day 1 | | |
| 6,000 | 20/42 (48%), all[a]<br>17/42 (40.5%), LAS[b] | 20/42 (47.6%) |
| 10,000 | 18/44 (41%), all<br>15/44 (34.1%), LAS | 20/44 (45.4%) |
| Experiment BT 1: 4 h/d, 5 d/wk for 52 wk starting at age 13 wk | | |
| 6,000 | 22/42 (52%), all<br>13/42 (31%), LAS | 1/27 (3.7%) |
| 10,000 | 13/46 (28%), all<br>7/46 (15%), LAS | 1/24 (4.2%) |

[a]All angiosarcomas, including angioma.
[b]Liver angiosarcoma only.
Source: EPA 2000a.

Derivation of an inhalation unit risk for exposure to young animals was based on a VC concentration of 6,000 ppm, at which there was an incidence of liver angiosarcomas of 40.5%. A concentration of 6,000 ppm corresponds to a human equivalent concentration of 51 ppm (132 $mg/m^3$), according to the physiologically-based pharmacokinetic model of Clewell et al. (1995). Corresponding data are shown in Table C-4 (note: exposure to rats exposure was intermittent (4 h/day, 5 days/week) compared with human equivalent concentration for continuous exposure [24 h/day]). Saturation in rats leads to only minor increases of metabolite concentrations, when exposure to VC exceeds 250 ppm (intermittent exposure). The derivation of the inhalation unit risk is based on the assumption that the tumor response is a linear function of the concentration of the active metabolite in the liver (human equivalent concentrations presented in Table C-5).

The dose associated with a risk of $1 \times 10^{-4}$ is 33.0 $\mu g/m^3$

$$132\ mg/m^3 = 40.5\%$$
$$\geq 3.3\ mg/m^3 = 1\%$$
$$\geq 33\ \mu g/m^3 = 0.01\% = 1{:}10{,}000$$

To convert from a 5-week exposure to a 24-h exposure, consideration was given to the ratio between the lifespan of rats and humans. Newborn rats grow about 30 times faster than newborn humans (NRC 1993), which is similar to the ratio of a 75-year lifetime in humans to a 2.5-year lifetime in rats (30:1).

5 week × 7 days/week × 30 = 1,050 days
33.0 μg/m$^3$ × 1,050 days = 34.7 mg/m$^3$ (14 ppm)

An additional factor to adjust for uncertainties with assessing potential cancer risks under short-term exposures is not applied, as exposure was short-term in the underlying study. Therefore, on the basis of the potential carcinogenicity of VC during early life, a 24-h exposure corresponding to a 1 ×10$^{-4}$ risk would be 34.7 mg/m$^3$ (13.2 ppm). For risks of 1 × 10$^{-5}$ and 1 × 10$^{-6}$, the concentration associated with a risk of 1 × 10$^{-4}$ is reduced by 10- and 100-fold, respectively.

If the exposure is limited to a fraction of a 24-h period, the exposure corresponding to the various risk levels are presented in Table C-6. These values were calculated using the physiologically-based pharmacokinetic model for VC described above for Calculation A. Comparison of the VC concentrations corresponding to a cancer risk of 1 × 10$^{-4}$ and AEGL values are presented in Table C-7.

**TABLE C-5** Human Equivalent Concentrations of Vinyl Chloride from Animal Studies

| Administered Concentration (ppm)[a] | Metabolite in liver (mg/L)[b] | Human Equivalent Concentration (ppm)[c] |
|---|---|---|
| 0 | 0 | 0 |
| 1 | 0.59 | 0.2 |
| 5 | 2.96 | 1 |
| 10 | 5.9 | 2 |
| 25 | 14.61 | 4.6 |
| 50 | 31.27 | 10.1 |
| 100 | 55.95 | 19 |
| 150 | 76.67 | 26 |
| 200 | 90 | 31 |
| 250 | 103.45 | 35 |
| 500 | 116.94 | 40 |
| 2,500 | 134.37 | 48 |
| 6,000 | 143.72 | 51 |

[a]Animals exposed 4 h/day, 5 days/week for 52 weeks.
[b]Dose metric (lifetime average delivered dose in female rats) calculated from physiologically-based pharmacokinetic modeling of the administered animal concentration.
[c]Continuous concentration of VC over a lifetime required to produce an equivalent concentration (mg/L) of metabolite in the liver.
Source: EPA 2000a,b.

A similar result is obtained if the tumor data from Froment et al. (1994) are used. Froment et al. exposed newborn animals to only one concentration of VC (500 ppm). Hence, fewer extrapolations were needed compared with the Maltoni et al. (1981) data (data and calculation not shown). For both calculations, there is uncertainty about the influence of exposure to VC via mother's milk. Because of metabolic saturation at high-level inhalation exposure, this influence might have been limited. However, no estimate of the quantitative consequences of this multipathway exposure can be given.

There is great uncertainty in these calculations. Appendix D summarizes a number of epidemiologic studies of occupational exposure to VC. There is no evidence from these studies that short-term exposure to VC results in an increased prevalence of tumors. For example, Ward et al. (2000) and Mundt et al. (1999) report that workplace exposures of <4 years or <6 years show no increase in the prevalence of liver or liver and biliary tract cancer. In addition, Ward et al. (2000) showed that cumulative exposures to VC of <734 ppm/year were not associated with a statistically significant increase in liver cancer. When the exposure was <287 ppm/year, there were no angiosarcomas reported in workers. A concentration of 40 ppm for 8 h (estimated from Calculation B to be associated with a cancer risk of $1 \times 10^{-4}$) is equivalent to a cumulative exposure of 0.16 ppm/year. Thus, human experience with VC is inconsistent with the cancer risk values calculated from the laboratory animal data.

**TABLE C-6** Cancer Risks from Vinyl Chloride Based on Calculation B

| Cancer Risk | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|
| $1 \times 10^{-4}$ | 1,180 ppm<br>3,110 mg/m$^3$ | 350 ppm<br>922 mg/m$^3$ | 80.9 ppm<br>213 mg/m$^3$ | 40.3 ppm<br>106 mg/m$^3$ |
| $1 \times 10^{-5}$ | 64.6 ppm<br>170 mg/m$^3$ | 32.1 ppm<br>84.4 mg/m$^3$ | 7.98 ppm<br>21.0 mg/m$^3$ | 3.99 ppm<br>10.5 mg/m$^3$ |
| $1 \times 10^{-6}$ | 6.38 ppm<br>16.8 mg/m$^3$ | 3.19 ppm<br>8.40 mg/m$^3$ | 0.798 ppm<br>2.10 mg/m$^3$ | 0.399 ppm<br>1.05 mg/m$^3$ |

**TABLE C-7** Comparison of AEGL Values for Vinyl Chloride and Cancer Risks Based on Calculation B

| | 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|---|
| $1 \times 10^{-4}$ risk | — | 1,180 ppm<br>3,110 mg/m$^3$ | 350 ppm<br>922 mg/m$^3$ | 80.9 ppm<br>213 mg/m$^3$ | 40.3 ppm<br>106 mg/m$^3$ |
| AEGL-1 | 450 ppm<br>1,200 mg/m$^3$ | 310 ppm<br>800 mg/m$^3$ | 250 ppm<br>650 mg/m$^3$ | 140 ppm<br>360 mg/m$^3$ | 70 ppm<br>180 mg/m$^3$ |
| AEGL-2 | 2,800 ppm<br>7,300 mg/m$^3$ | 1,600 ppm<br>4,100 mg/m$^3$ | 1,200 ppm<br>3,100 mg/m$^3$ | 820 ppm<br>2,100 mg/m$^3$ | 820 ppm<br>2,100 mg/m$^3$ |
| AEGL-3 | 12,000 ppm<br>31,000 mg/m$^3$ | 6,800 ppm<br>18,000 mg/m$^3$ | 4,800 ppm<br>12,000 mg/m$^3$ | 3,400 ppm<br>8,800 mg/m$^3$ | 3,400 ppm<br>8,800 mg/m$^3$ |

# APPENDIX D

## OCCUPATIONAL EPIDEMIOLOGIC STUDIES OF VINYL CHLORIDE

Two large studies of workers employed in industries using VC monomer and polyvinyl chloride before 1974 were evaluated. Both studies were retrospective cohort mortality studies. The first study was conducted in Europe and included study populations in Italy, Norway, Sweden, and the United Kingdom. The second study included plants in the United States and Canada. Each study was updated multiple times and has been the subject of numerous publications. Only the results from the most recent updates are discussed here. The focus is to review the liver cancer incidence in workers exposed to VC for relatively short-term periods or where the cumulative dose (ppm/year) was known to have been low. Both studies have more deaths from angiosarcomas of the liver than expected among workers with high or long-term exposure to VC (Mundt et al. 1999; Ward et al. 2000). A third study from Weber et al. (1981) conducted in Germany had results that conflict with the two other studies.

### European Study

The European study included approximately 12,700 men with at least 1 year of employment in the VC or polyvinyl chloride industry from 1955 to 1974 (Ward et al. 2000). Three of the 19 plants had incomplete records, so the starting date for data from those three plants ranged from 1961 to 1974. The vital status follow-up was complete through 1997. Age- and calendar-period specific mortality rates for males from Italy, Norway, Sweden, and the United Kingdom were used to calculate the standardized mortality ratios (SMRs) and 95% confidence intervals (CIs). Typical exposure scenarios were estimated by industrial hygienists on the basis of job exposure matrices. These matrices were based primarily on job title and were reviewed by two other industrial hygienists with several years of experience in the VC industry. Information provided in the job exposure matrix was used to develop a ranked exposure index. Quantitative estimates of exposure were obtained for 82% of the cohort.

The total number of person-years at risk for the cohort was 324,701. The work force was classified by duration of employment: <3, 3-6, 7-11, 12-18, and >19 ppm-years. The SMR for liver cancer for workers with <3 years experience was 62 (95% CI: 2-345), below the expected value (see Table D-1). For workers exposed to VC for a longer duration, the incidence of liver cancer was higher than expected. In general, the incidence of liver cancer increased with years of employment in the industry.

**TABLE D-1** Liver Cancer Incidence for All European Countries by Duration of Employment

| Duration of Employment (years) | Number of Individuals[a] | Number of Person (years) | Incidence (observed/ expected) | SMR (95% CI)[b] |
|---|---|---|---|---|
| <3 | 10,961 | 91,970 | 1/1.61 | 62 (2-345) |
| 3-6 | 8,999 | 79,747 | 3/1.44 | 208 (43-609) |
| 7-11 | 6,919 | 65,789 | 7/1.35 | 517 (208-1,060) |
| 12-18 | 4,610 | 55,149 | 5/1.42 | 352 (114-821) |
| 1>9 | 2,006 | 32,050 | 13/1.46 | 893 (475-1,530) |
| Total | 12,700 | 324,706 | 29/7.29 | 398 (267-572) |

[a]The number of individuals cited for various employment intervals is greater than 12,700 because individuals can meet more than one criteria as defined by the author.
[b]Observed/expected × 100.
Abbreviations: CI, confidence interval; SMR, standardized mortality ratio.
Source: Adapted from Ward et al. 2000.

In addition, Ward et al. (2000) examined cumulative exposures in the cohort (see Table D-2). The work force was subdivided into 0-734, 735-2,379, 2,380-5,188, 5,189-7,531 and >7,532 ppm/years. The SMR was 107 (95% CI: 54-192) based on 11 observed liver cancers and 10.26 expected. Assuming workers are employed in the industry for up to 30 years, to be included in this first category, the highest average concentration the worker would have been exposed to was ~25 ppm. Workers with shorter work histories may have been exposed at much higher concentrations. Under this scenario there was no increase in the incidence of liver cancer. As previously noted, the incidence of liver cancer increased with cumulative exposure; the SMR was 1,140 (95% CI: 571-2,050) for workers with a cumulative exposure of >7,532 ppm/years. However, of the 11 liver cancers observed in the 0-734 ppm/year cumulative exposure group, four were angiosarcomas. These angiosarcomas occurred in individuals with 287-734 ppm/years cumulative exposure (Ward et al. 2001). There were no angiosarcomas reported in workers with less than 287 ppm/years of cumulative exposure.

### North American Study

The North American study consisted of approximately 10,100 men employed for at least 1 year in the VC or polyvinyl chloride industry from 1942-1974 (Mundt et al. 1999). This group was followed through December 31, 1995. Thus, most workers were followed for at least 21 years. Because the industries were located in 16 states and one province of Canada, mortality rates for 16

states were used to calculate SMRs. For the Canadian province, mortality-rate data from Michigan was used because it is the state closest to the Canadian plant. As of December 31, 1995, 30% of the study group was deceased. Although the authors of previous studies have attempted to categorize individuals by exposures, no consistent criteria have been used and thus no attempt was made to estimate exposure levels in this study.

The age at first exposure, duration of exposure, and year of first exposure appeared to be related to cancer of the liver and biliary tract. Of these, duration of exposure had the greatest significance and appeared to be independent of age at first exposure and year of first exposure (see Table D-3). Mundt et al. (2000) categorized the cohort into groups working 1-4, 5-9, 10-19, or >20 years in the VC industry. Nearly half of the cohort worked for <5 years in the industry, with fewer workers in each of the subsequent groups. These data show that working in the VC industry for 1-4 years resulted in a slightly lower liver cancer rate than expected. Working in this industry for longer periods of time resulted in higher death rates than expected for liver and biliary tract cancer. Mundt et al. also examined the incidence of angiosarcomas in relation to duration of exposure. Three individuals working in the VC industry for 1-4 years had angiosarcomas of the liver. No further information on exposure or job classification was provided.

**TABLE D-2** Liver Cancer Incidence for All European Countries by Cumulative Exposure

| Cumulative Exposure (ppm-years) | Number of Individuals[a] | Number of Person (years) | Incidence (observed/ expected) | SMR (95% CI)[b] |
|---|---|---|---|---|
| Unknown | 2,243 | 52,300 | 2/3.19 | 63 (8-227) |
| 0-734 | 9,552 | 188,204 | 11/10.26 | 107 (54-192) |
| 735-2,379 | 2,772 | 43,174 | 9/3.32 | 271 (124-515) |
| 2,380-5,188 | 1,463 | 26,480 | 10/2.62 | 382 (183-703) |
| 5,189-7,531 | 515 | 9,274 | 10/1.77 | 566 (271-1,040) |
| >7,532 | 215 | 5,274 | 11/0.96 | 1,140 (571-2,050 |
| Total | 12,700 | 324,706 | 53/22.11 | 240 (1,800-3,140) |

[a]The number of individuals cited for various employment intervals is greater than 12,700 because individuals can meet more than one criteria as defined by the author.b
[b]Observed/expected × 100.
Abbreviations: CI, confidence interval; SMR, standardized mortality ratio.
Source: Adapted from Ward et al. 2000.

**TABLE D-3** Liver and Biliary-Tract Cancer Incidence in the United States by Duration of Employment

| Duration of Employment (years) | Number of Individuals | Number of Person (years) | Incidence (observed/ expected) | SMR (95% CI)[a] |
|---|---|---|---|---|
| 1-4 | 4,774 | 136,200 | 7/8.43 | 83 (33-171) |
| 5-9 | 2,383 | 71,806 | 10/4.65 | 215 (103-396) |
| 10-19 | 1,992 | 69,015 | 39/5.74 | 679 (483-929) |
| >20 | 960 | 39,524 | 24/3.49 | 688 (440-1,023) |
| Total | 10,109 | | | |

[a]Observed/expected × 100.
Abbreviations: CI, confidence interval; SMR, standardized mortality ratio.
Source: Adapted from Mundt et al. 1999.

Both studies have shown that people working in the VC industry for <3 years or exposed to low concentration of VC have liver-cancer rates very close to expected values. A low incidence of angiosarcomas of the liver was reported by both Ward et al. (2000) and Mundt et al. (2000), but the Ward study suggested this was related to higher cumulative exposure.

### Weber et al. (1981)

Three German cohorts were investigated in a study by Weber et al. (1981): Group 1 (1,021 VC and polyvinyl-chloride production workers; 73,734 person years), Group 2 (4,910 reference persons; 76,029 person years), and Group 3 (4,007 polyvinyl-chloride processing workers; 52,896 person years). Reference mortality rates from West Germany were used for comparison. Twelve cases of malignant tumors of the liver were found in production workers (SMR = 1,523), four cases in the reference group (SMR = 401), and three cases in processing workers (SMR = 434). No confidence intervals were provided, and the VC concentrations were unknown. Subclassification according to duration of employment demonstrates increased mortality after little more than 1 year of exposure (see Table D-4). Results from this study and the ones cited above were included in a meta-analysis by Boffetta et al. (2003), which illustrated the conflicting information about the minimum exposure duration and increased tumor risk in workers (see Figure 1 in Boffetta et al. 2003).

**TABLE D-4** Standardized Mortality Ratios for Malignant Tumors of the Liver by Duration of Exposure

| Employment Duration (months) | Cases | SMR | Confidence Interval |
|---|---|---|---|
| <12 | 0 | — | — |
| 13-60 | 2 | 874 | Beyond 95$^{th}$ confidence interval |
| 61-120 | 3 | 1,525 | Beyond 99$^{th}$ confidence interval |
| >121 | 7 | 2,528 | Beyond 99$^{th}$ confidence interval |
| Total | 12 | | |

Source: Adapted from Weber et al. 1981.

# APPENDIX E

## ACUTE EXPOSURE GUIDELINE LEVELS FOR VINYL CHLORIDE

### Derivation Summary for Vinyl Chloride

**AEGL-1 VALUES**

| 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|
| 450 ppm | 310 ppm | 250 ppm | 140 ppm | 70 ppm |

Reference: Baretta, E.D., R.D. Stewart, and J.E. Mutchler. 1969. Monitoring exposures to vinyl chloride vapor: Breath analysis and continuous air sampling. Am. Ind. Hyg. Assoc. J. 30(6):537-544.

Test species/Strain/Sex/Number: Human volunteers, male, 4-7 individuals.

Exposure route/Concentrations/Durations: Inhalation, 459-491 ppm, 3.5 h

Effects: Mild headache and dryness of eyes and nose in 2/7 subjects.

End point/Concentration/Rationale: End points relevant for the derivation of AEGL-1 values for VC are headache, odor recognition or detection, and irritation. Mild headache was reported in two subjects after acute exposure; mild headache can be regarded as no-effect level for notable discomfort. No appropriate studies of odor recognition or detection were available for VC. Irritation in humans and animals is reported only at very high concentrations that are lethal or cause unconsciousness. The mechanism by which headaches develop is not understood.

Uncertainty factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1 was applied because the study involved humans.
Intraspecies: 3 is used to account for toxicodynamic differences among individuals. The effects are probably from VC in the blood and not a metabolite. Only small interindividual differences in pharmacokinetics of VC are expected, as the concentration of VC required to elicit the effect is greater than that required for saturation of the metabolic pathways.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: The duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of $n = 3$ for shorter exposure periods and $n = 1$ for longer exposure periods, because there were no suitable experimental data for deriving the value of n. Extrapolation from a 3.5-h exposure to a 10-min exposure is justified because humans exposed to VC at 4,000 ppm for 5 min did not experience headaches (Lester et al. 1963).

Data adequacy: The study of Baretta et al. (1969) qualified for the derivation of AEGL-1 values and the end point is supported by several findings from occupational studies (Lilis et al. 1975; Suciu et al. 1975; EPA 1987). Confirmation of the observed effects in other studies with controlled exposure would be helpful, but may not be performed for ethical reasons.

**AEGL-2 VALUES**

| 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|
| 2,800 ppm | 1,600 ppm | 1,200 ppm | 820 ppm | 820 ppm |

References: Lester, D., L.A. Greenberg, and W.R. Adams. 1963. Effects of single and repeated exposures of humans and rats to vinyl chloride. Am. Ind. Hyg. Assoc. J. 24(3):265-275.
Clark, D.G., and D.J. Tinston. 1973. Correlation of the cardiac sensitizing potential of halogenated hydrocarbons with their physicochemical properties. Br. J. Pharmacol. 49(2):355-357.
Mastromatteo, E., A.M. Fisher, H. Christie, and H. Danziger. 1960. Acute inhalation toxicity of vinyl chloride to laboratory animals. Am. Ind. Hyg. Assoc. J. 21:394-398.

Test species/Strain/Sex/Number: Human, male and female, 3 per sex

Exposure route/Concentrations/Durations: Inhalation, single exposure, VC at 0, 4,000, 8,000, 12,000, 16,000, or 20,000 ppm for 5 min.

Effects: After a 5-min exposure at 16,000 ppm, five of six persons had dizziness, lightheadedness, nausea, and visual and auditory dulling. At concentrations of 12,000 ppm, one of six persons reported "swimming head, reeling," and another was unsure of an effect and felt somewhat dizzy. A single person reported slight effects ("slightly heady") of questionable meaning at 8,000 ppm (this person also felt slightly heady at sham exposure and reported no response at 12,000 ppm). No effects were observed at 4,000 ppm. A concentration of 12,000 ppm was regarded as a no-effect level for impaired ability to escape.

End point/Concentration/Rationale: Severe dizziness may influence ability to escape, so is relevant as an end point for AEGL-2. No such effects were seen with VC at 12,000 ppm. AEGL-2 values are supported by the estimated no-effect level for cardiac sensitization of 17,000 ppm in dogs after epinephrine challenge (calculated by dividing the $EC_{50}$ from the study by Clark and Tinston [1973] of 50,000 by 3).

Uncertainty factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1 was applied because the study involved humans
Intraspecies: 3 is used to account for toxicodynamic differences among individuals. The effects are probably from VC in the blood and not a metabolite. Only small interindividual differences in pharmacokinetics of VC are expected, as the concentration of VC required to elicit the effect is greater than that required for saturation of the metabolic pathways.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: By analogy to other anesthetics, the effects are assumed to be solely concentration dependent. Thus, after reaching steady state after about 2 h, no increase in effect by duration is expected at 4 and 8 h. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using a factor of n = 2 based on data from

*(Continued)*

**AEGL-2 VALUES** Continued

| 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|
| 2,800 ppm | 1,600 ppm | 1,200 ppm | 820 ppm | 820 ppm |

*(continued)*

Mastromatteo et al. (1960). Mastromatteo et al. observed various time-dependent prenarcotic effects in mice and guinea pigs after less than steady-state exposure conditions. Time extrapolation was performed from 5 min to 10 min, 30 min, 60 min, and 2 h.

Data adequacy: The overall quality of the key study (Lester et al. 1963) is medium. A dose-response relationship was observed that supported the quantitative estimates. Subjective reporting of effects leads to limited precision.

**AEGL-3 VALUES**

| 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|
| 12,000 ppm | 6,800 ppm | 4,800 ppm | 3,400 ppm | 3,400 ppm |

References: Clark, D.G., and D.J. Tinston. 1973. Correlation of the cardiac sensitizing potential of halogenated hydrocarbons with their physicochemical properties. Br. J. Pharmacol. 49(2):355-357.
Clark, D.G., and D.J. Tinston. 1982. Acute inhalation toxicity of some halogenated and non-halogenated hydrocarbons. Hum. Toxicol. 1(3):239-247.
Aviado, D.M., and M.A. Belej. 1974. Toxicity of aerosol propellants in the respiratory and circulatory systems. I. Cardiac arrhythmia in the mouse. Toxicology 2(1):31-42.
Belej, M.A., D.G. Smith, and D.M. Aviado. 1974. Toxicity of aerosol propellants in the respiratory and circulatory systems. IV. Cardiotoxicity in the monkey. Toxicology 2(4):381-395.
Prodan, L., I. Suciu, V. Pislaru, E. Ilea, and L. Pascu. 1975. Experimental acute toxicity of vinyl chloride (monochloroethene). Ann. NY Acad. Sci. 246:154-158.
Mastromatteo, E., A.M. Fisher, H. Christie, and H. Danziger. 1960. Acute inhalation toxicity of vinyl chloride to laboratory animals. Am. Ind. Hyg. Assoc. J. 21:394-398.

Test species/Strain/Sex/Number: Dog, beagle, sex not reported, 4-7 dogs/dose (Clark and Tinston 1973)

Exposure route/Concentrations/Durations: Inhalation, several doses, 5 min (Clark and Tinston 1973)

Effects: Short-term exposure (5 min) of dogs to VC induced cardiac sensitization towards epinephrine ($EC_{50}$: 50,000 and 71,000 ppm in two independent experiments; Clark and Tinston 1973, 1982). The lower $EC_{50}$ of 50,000 ppm was taken as the no-effect level for life-threatening effects. These effects also were seen in mice at higher concentrations (Aviado and Belej 1974). In monkeys, only myocardial depression after inhalation of VC at 2.5-10% was observed. It was unclear whether an additional challenge with epinephrine was applied (Belej et al. 1974). Severe cardiac sensitization is a life-threatening effect, but at 50,000 ppm no animals died.

*(Continued)*

**AEGL-3 VALUES** Continued

| 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|
| 12,000 ppm | 6,800 ppm | 4,800 ppm | 3,400 ppm | 3,400 ppm |

End point/Concentration/Rationale: Considering possible sensitive subpopulations and increased excitement in case of emergency reaction, epinephrine-induced cardiac reactions might occur and could be enhanced by exposure to high concentrations of VC. The respective effects are well known for certain unsubstituted and halogenated hydrocarbons. The test method using beagle dogs is well established. Cardiac sensitization data are supported by lethality data at slightly higher concentrations (Prodan et al. 1975).

Uncertainty factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1 was used because the cardiac sensitization model with the dog is considered an appropriate model for humans and is highly sensitive as the response is optimized by the exogenous administration of epinephrine (Brock et al. 2003; ECETOC 2009). This protocol is designed conservatively with built in safety factors and thus no additional safety factor is needed (ECETOC 2009).
Intraspecies: 3 was used to account for toxicodynamic differences among individuals. Only small interindividual differences in pharmacokinetics of VC are expected, as the concentration of VC required to elicit the effect is greater than that required for saturation of the metabolic pathways.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Insufficient data

Time scaling: By analogy with other halocarbons (e.g., Halon 1211, HFC 134a) that induce cardiac sensitization, the effects are assumed to be solely concentration dependent. Thus, after reaching steady state after about 2 h, no increase of effect by duration is expected at 4 and 8 h. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using a factor of n = 2 based on data from Mastromatteo et al. (1960). Mastromatteo et al. observed various time-dependent prenarcotic effects (muscular incoordination, side position, and unconsciousness, effects which occur immediately before lethality) in mice and guinea pigs after less than steady-state exposure conditions. Time extrapolation was performed from 5 min to 10 min, 30 min, 60 min, and 2 h.

Data adequacy: Because of discrepancies between the two studies by Clark and Tinston (1973, 1982), the data quality is judged to be medium. Adequate data from human experience is lacking.