Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 14

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 fourteenth volume in that series. AEGL documents for BZ (2-quinuclidinyl benzilate), ethyl

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

phosphorodichloridate, hexane, methanesulfonyl chloride, nitric acid, propargyl alcohol, and vinyl acetate monomer 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 interim reports of the committee that led to this report were reviewed in draft form by individuals selected for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of the committee interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for BZ (interim reports 19a, 20a, and 21a), ethyl phosphorodichloridate (interim reports 20a and 21a), hexane (interim reports 17 and 21a), methanesulfonyl chloride (interim reports 20a and 21a), nitric acid (interim reports 15, 18, and 21a), propargyl alcohol (interim reports 16 and 19a), and vinyl acetate monomer (interim reports 18 and 21a): Harvey Clewell (The Hamner Institutes for Health Sciences), Jeffrey Fisher (U.S. Food and Drug Administration), Sam Kacew (University of Ottawa), A. Wallace Hayes (Harvard School of Public Health), Rogene Henderson (Lovelace Respiratory Research Institute [retired]), James McDougal (Wright State University [retired], Charles Reinhardt (DuPont Haskell Laboratory [retired]), Andrew Salmon (California Environmental Protection Agency), Kenneth Still, Occupational Toxicology Associates, 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 reports 15-21 was overseen by Robert Goyer (University of Western Ontario [retired]). Appointed by the NRC, he was responsible for making certain that an independent examination of the interim reports was

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

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

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

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 14

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

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

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

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

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

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

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

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

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

[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.

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 extrap-

olation of data from other routes would lead to additional uncertainty in the AEGL estimate.

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

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

REVIEW OF AEGL REPORTS

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

The AEGL draft reports 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 recommenda-

tions 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 thirteen reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009, 2010a,b, 2011, 2012a,b,c). This report is the fourteenth volume in that series. AEGL documents for BZ (2-quinuclidinyl benzilate), ethyl phosphorodichloridate, hexane, methanesulfonyl chloride, nitric acid, propargyl alcohol, and vinyl acetate monomer 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

7

Vinyl Acetate[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 Claudia Troxel (Oak Ridge National Laboratory), Heather Carlson-Lynch (SRC, Inc.), Chemical Manager Richard Thomas (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 concentrations for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Vinyl acetate is a colorless, flammable liquid with low solubility in water (Rhum 1970; O'Neil et al. 2006). It is manufactured by reacting ethylene with sodium acetate (Bisesi 2001). U.S. production of vinyl acetate in 1993 was reported to be 2.83 billion pounds (Reisch 1994). Vinyl acetate is mainly used as a monomer in the production of poly(vinyl acetate) and vinyl acetate copolymers, which in turn are used to produce water-based paints, adhesives, and other coatings and bindings (Rhum 1970). Poly(vinyl acetate) is also a precursor for the synthesis of poly(vinyl alcohol) and poly(vinyl acetate) resins, or is copolymerized with vinyl chloride or ethylene to form polymers or with acrylonitrile to form acrylic fibers.

The odor of vinyl acetate has been described as immediately pleasant, but then quickly sharp and irritating (Rhum 1970). The odor detection threshold is 0.12 ppm, and the recognition threshold is 0.4 ppm (Hellman and Small 1974; AIHA 1989; EPA 1992).

AEGL-1 values are based on a human study that reported throat irritation from inhalation of vinyl acetate. Irritation was minimal or slight after 2 min at 4-20 ppm, slight and persistent after 4 h at 20 ppm, and persistent after 2 h at 34 ppm (Smyth and Carpenter 1973). A no-effect level for notable discomfort of 20 ppm was selected as the point of departure. An intraspecies uncertainty factor of 3 was applied because throat irritation is caused by a local effect of the chemical and the response is not expected to vary greatly among individuals. Because irritation is considered a threshold effect and should not vary over time, the same AEGL-1 value of 6.7 ppm was used for all exposure durations.

AEGL-2 values are based on a no-observed-effect level (200 ppm for 6 h) for serious, long-lasting histopathologic nasal lesions in rats (Bogdanffy et al. 1997). A total uncertainty factor of 10 was applied: 3 for interspecies differences and 3 for intraspecies variability. A factor of 3 for interspecies differences was applied because nasal toxicity appears to depend on the metabolism of vinyl acetate to the metabolites acetic acid and acetaldehyde via carboxylesterase and aldehyde dehydrogenase. Metabolism studies found little difference in carboxylesterase-mediated metabolism of vinyl acetate in the nasal cavity of mice, rats, and humans, particularly in the olfactory epithelium (Bogdanffy and Taylor 1993; Bogdanffy et al. 1998). Esterase distribution in the nasal respiratory tissue of humans is believed to be similar to that of rats (Andersen et al. 2002). An intraspecies uncertainty factor of 10 would normally be applied because of the variability in the olfactory nasal tissue of humans with respect to surface area, composition of epithelial tissue layers (respiratory-type tissue can be interspersed with more characteristic olfactory tissue), and age-related changes (Andersen et al. 2002). However, a total uncertainty factor of 30 would result in an 8-h AEGL-2 value (5 ppm) lower than the AEGL-1 value of 6.7 ppm. Reducing an uncertainty factor is appropriate when the weight of evidence indicates that a higher uncertainty factor would result in AEGL values at odds with human data (NRC 2001). Therefore, the intraspecies uncertainty factor was reduced to 3.

Time scaling was performed by using the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data on vinyl acetate were insufficient for determining an empirical value of n; therefore, default values of n = 1 for extrapolating from shorter to longer durations and n = 3 for extrapolating from longer to shorter durations were used. The 10-min AEGL-2 value was set equal to the 30-min value because of the uncertainties associated with extrapolating a 6-h exposure to a 10-min AEGL value (NRC 2001).

AEGL-3 values for vinyl acetate were based on the highest nonlethal concentration (1,000 ppm) after a single 6-h exposure (Bogdanffy et al. 1997) or after repeated 6-h exposures of rats and mice (Owen 1979a,b; 1980a,b). A total uncertainty factor of 10 was applied: 3 for interspecies differences and 3 for intraspecies variability. An interspecies uncertainty factor of 3 was applied because nasal toxicity is expected to be similar between species (see rationale in discussion of AEGL-2 values above). An intraspecies uncertainty factor of 3 instead of 10 was applied because the higher value would have resulted an 8-h AEGL-3 value (25 ppm) that is lower than concentrations that, did not result in serious health effects in a human volunteer study. In that study, no life-threatening effects were observed in humans exposed to vinyl acetate at 34 ppm for 2 h or at 72 ppm for 30 min (Smyth and Carpenter 1973). Reduction of an uncertainty factor is appropriate when the weight of evidence indicates that a higher uncertainty factor would result in AEGL values at odds with human data (NRC 2001). Therefore, the intraspecies factor was reduced to 3. Time scaling was performed in the same manner as for AEGL-2 values. The 10-min AEGL-3

value was set equal to the 30-min value because of the uncertainties associated with extrapolating a 6-h exposure to a 10-min AEGL value (NRC 2001).

A level of distinct odor awareness (LOA) of 0.25 ppm was derived on the basis of the odor detection threshold for vinyl acetate reported by Hellman and Small (1974) (see Appendix C for the derivation). The LOA is the concentration above which more than half of the exposed population are predicted to perceive at least a distinct odor intensity; about 10% of the population will perceive a strong odor intensity. The LOA should help chemical emergency responders with assessing the public awareness of exposure to vinyl acetate by its odor.

A carcinogenicity assessment for vinyl acetate was not appropriate for an acute exposure scenario because the proposed mechanism of carcinogenicity suggests a nonlinear mode of action requiring continuous exposure to vinyl acetate. Therefore, a one-time exposure even to high concentrations of vinyl acetate would not be expected to result in tumor development. AEGL values for vinyl acetate are presented in Table 7-1.

1. INTRODUCTION

Vinyl acetate is a colorless, flammable liquid with low solubility in water (Rhum 1970; O'Neil et al. 2006). Its odor has been described as being immediately pleasant, but then quickly sharp and irritating (Rhum 1970). The odor detection threshold is reported to be 0.12 ppm, and the recognition threshold is 0.4 ppm (Hellman and Small 1974; AIHA 1989; EPA 1992). Other reported odor thresholds were rejected by EPA (1992) and AIHA (1989) because they were the minimum perceptible value or the result of a passive exposure.

Vinyl acetate is manufactured by reacting ethylene with sodium acetate (Bisesi 2001). U.S. production of vinyl acetate in 1993 was reported to be 2.83 billion pounds (Reisch 1994). Vinyl acetate is primarily used as a monomer in the production of poly(vinyl acetate) and vinyl acetate copolymers, which in turn are used to produce water-based paints, adhesives, and other coating and binding applications (Rhum 1970). Poly(vinyl acetate) is also a precursor for the synthesis of poly(vinyl alcohol) and poly(vinyl acetate) resins, or is copolymerized with vinyl chloride or ethylene to form polymers or with acrylonitrile for acrylic fibers.

The chemical and physical properties of vinyl acetate are presented in Table 7-2.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data on lethality in humans after acute exposure to vinyl acetate were found.

TABLE 7-1 AEGL Values for Vinyl Acetate

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	No effect level for notable discomfort in humans (Smyth and Carpenter 1973)
AEGL-2 (disabling)	46 ppm (160 mg/m^3)	46 ppm (160 mg/m^3)	36 ppm (130 mg/m^3)	23 ppm (81 mg/m^3)	15 ppm (53 mg/m^3)	No effect level for serious, long-lasting histopathologic nasal lesions in rats (Bogdanffy et al. 1997)
AEGL-3 (lethal)	230 ppm (810 mg/m^3)	230 ppm (810 mg/m^3)	180 ppm (630 mg/m^3)	110 ppm (390 mg/m^3)	75 ppm (260 mg/m^3)	Highest nonlethal concentration (1,000 ppm) in rats or mice (Owen 1979a,b; 1980a,b; Bogdanffy et al. 1997)

TABLE 7-2 Chemical and Physical Properties of Vinyl Acetate

Parameter	Value	Reference
Synonyms	Acetic acid ethenyl ester; acetic acid vinyl ester; 1-acetoxyethylene; ethynyl acetate; vinyl ethanoate	O'Neil et al. 2006; NIOSH 2011
CAS registry no.	108-05-4	O'Neil et al. 2006
Chemical formula	$C_4H_6O_2$	O'Neil et al. 2006
Molecular weight	86.09	O'Neil et al. 2006
Physical state	Liquid	O'Neil et al. 2006
Melting point	-100°C, -93°C	O'Neil et al. 2006
Boiling point	72.7°C	O'Neil et al. 2006
Liquid density (water = 1)	0.9317	ACGIH 2001
Vapor density (air =1)	3.0	Bisesi 2001
Solubility in water	1 g/50 mL at 20°C	O'Neil et al. 2006
Vapor pressure	115 mmHg at 25°C	ACGIH 2001
Conversion factors	1 ppm = 3.52 mg/m^3 1 mg/m^3 = 0.284 ppm	NIOSH 2011

2.2. Nonlethal Toxicity

Groups of three to nine volunteers were exposed to various concentrations of vinyl acetate for durations ranging from 2 min to 4 h (Smyth and Carpenter 1973). Vinyl acetate vapor was generated by feeding metered air through a spirally corrugated surface of a minimally heated Pyrex tube. Calculated concentration was corrected using a curve based on a gas chromatographic analysis of calculated concentrations ranging from 0.6 to 16,000 ppm. The concentrations were unknown to the volunteers, the concentrations were presented in random order, and symptoms were reported privately. No information was provided on the exposure chamber, whether the volunteers were previously exposed or naive, or how much time elapsed between exposures. The results of this study are presented in Table 7-3.

TABLE 7-3 Human Sensory Response to Controlled Exposures to Vinyl Acetate[a]

Concentration (ppm)[a]	No. of Subjects	Exposure Duration (min)	Response
0.6	9	2	None
1.3	9	2	9 immediate odor; 5 no odor at 2 min
4	9	2	9 immediate odor; 3 no odor at 2 min; 1 minimal ocular, nasal, and throat irritation
8	9	2	9 immediate odor; 1 no odor at 2 min; 2 minimal ocular, nasal, and throat irritation
20	9	2	9 immediate odor; 1 minimal ocular, nasal, and throat irritation
20	3	240	3 complete olfactory fatigue in 3-116 min (average 63 min) 1 persistent slight throat irritation
34	3	120	1 complete, 2 partial olfactory fatigue; 1 transient, 1 persistent throat irritation
72	4	30	4 strong odor, partial olfactory fatigue; 4 slight throat irritation 20-60 min after exposure; ocular irritation until 60 min after exposure; subjects expressed unwillingness to work at this concentration for 8 h

Source: Smyth and Carpenter 1973.
[a]Corrected using calibration curve.

The medical division of Union Carbide Company undertook a study to evaluate three end points: the average environmental concentrations of vinyl acetate to which chemical workers are exposed; potential chronic health effects that might have resulted from exposure to vinyl acetate; and subjective descriptions of effects from short-term exposure to vinyl acetate (Deese and Joyner 1969). To determine average environmental concentrations of vinyl acetate, air samples were measured during normal operating conditions in three different production units. Forty samples (and two blanks) were taken from the three units during two sampling periods approximately one month apart. The total sampling time was more than 18 h. Samples were taken from three to six designated sites in each of the three production units. Sampling sites were determined by the amount of time the operator spent in each area, the investigator's observation of probable exposure based on personal subjective responses, and the operator's description of duties and exposures. Short-term and long-term air samples were taken. For short-term samples (10 min), a minimum of 15 L of air was collected by scrubbing air through a fritted glass midget impinger bubbler and a standard midget impinger in series. Long-term samples (2 h) of 180 L were collected using standard Greenburg-Smith impingers. Calibrated rotometers metered the collection at a rate of 1.5 L/min, and a vacuum was maintained using appropriate equipment. Vinyl aceate was measured by gas chromatography. Concentrations ranged from 0 to 59.3 ppm; 83% of the samples were less than 10 ppm. The 8-h time-weighted averages (TWAs) for the three production facilities were 8.2, 5.2, and 7.7 ppm. Some operations, such as maintenance, resulted in brief exposures at higher concentrations. For example, concentrations measured in the breathing zone of workers as they opened the hopper door to unplug material flow were 123.3, 125.6, and 326.5 ppm. Exposures lasted for 3 min and occurred twice a day. The concentrations of vinyl acetate documented in this study were believed also represent exposures over the previous 5 years, because operating conditions, process methods, and physical equipment had not changed over that time period.

To evaluate the potential health effects resulting from long-term exposure to vinyl acetate, company medical records were evaluated and compared with a control group (Deese and Joyner 1969). Twenty-one of 26 vinyl acetate operators participated in the study. Sixteen operators had worked with vinyl acetate for more than 15 years, and six for 20 years or more. Each participant was matched by taking the next operator listed alphabetically in the medical division files who had an age within 5 years of the operator's and who had never worked in the vinyl acetate complex. The control group comprised individuals exposed to many chemicals commonly used in the petrochemical industry, but their exposures were not categorized for this study. Medical records of the participants were evaluated for the following: all sickness-related absences between January 1 and December 31 (classified according to etiology and duration); all initial visits to the medical division over the same interval; and all reported exposures to vinyl acetate. No exposure-related differences in blood

chemistry results, pulmonary pathology, work days lost, or total number of initial visits for occupational injury or illness were found. Vinyl acetate workers had a higher number of total days lost due to respiratory illness and gastrointestinal conditions. Closer examination of the records revealed that these differences were primarily because of two individuals; one operator had a recurrent upper-respiratory-tract infection and one had cholecystitis. Vinyl acetate operators completed a questionnaire at the same time as their screening examination. When asked if vinyl acetate bothers them under normal working conditions, 13 (61%) responded no, two complained of odor, two reported nasal and throat irritation, three reported dermal irritation, and one replied that it "does bother". When asked if vinyl acetate irritated their eyes, nose, or throat, 15 (71%) responded no, two responded "some", three reported ocular irritation, and one described irritation that is noticeable but worse at certain times. When asked for other comments, one individual reported he liked the odor and another reported that breathing the fumes hurt his chest (Deese and Joyner 1969).

In the third and final part of the study, individuals were asked to provide subjective descriptions about odor, ocular irritation, and upper respiratory irritation during 10-min air sampling of vinyl acetate. The individuals included one of the investigators, a laboratory analyst assisting in sampling, and one chemical operator from each of the production units. Vinyl acetate concentrations ranged from 0.4 to 21.6 ppm (exact concentrations reported at the three plant units were 0.4, 0.8, 2.7, 4.2, 4.2, 5.7, 6.8, 7.6, 7.6, 9.5, 9.9, or 21.6 ppm). Odor was generally described as slight at 0.4 to 9.9 ppm, although no odor was detected by a few subjects. At 21.6 ppm, odor was described as marked by all three individuals. Ocular irritation was not reported at concentrations of 9.9 ppm or lower, with the exception of slight ocular irritation reported by the investigator at 5.7 and 6.8 ppm. At 21.6 ppm, all three individuals agreed that the ocular irritation would be "intolerable over an extended period of time". Upper respiratory irritation (cough and hoarseness) was present at 21.6 ppm in all three subjects. Hoarseness was noted by the investigator at 4.2 and 5.7 ppm.

Data from the study of Deese and Joyner (1969) conflict with those reported by Smyth and Carpenter (1973). Three subjects in the first study reported upper respiratory irritation when exposed for 10 min at 21.6 ppm whereas three volunteers in the second study tolerated vinyl acetate at 20 ppm for 4 h with only one subject reporting olfactory fatigue and slight but persistent throat irritation. Examination of the sampling data from Deese and Joyner (1969) indicates that 21.6 ppm was measured in the production area associated with the highest concentration of vinyl acetate (49.3 ppm in a 10-min sample) measured in any part of the facility. Thus, the subjects might have been briefly exposed to a much higher concentration of vinyl acetate during the sampling period. Furthermore, Deese and Joyner (1969) noted that the odor threshold of vinyl acetate was difficult to measure in the facility because of the "intermittent and unpredictable presence of odors of other assorted chemicals in the subject's environment"; similarly, the ocular irritation reported at 21.6 ppm might have been confounded by concurrent exposure to other irritant compounds.

Air emissions around Monsanto production facilities were evaluated to assess the potential for human health effects (Monsanto Company 1989). Emission of vinyl acetate was identified as a concern at the Decatur production plant because of its carcinogenicity. Ambient air sampling at four locations in the Texas City, Texas, area revealed concentrations ranging from 0.07 to 0.57 ppm (0.25-2.0 mg/m^3). To conduct a safety assessment, the maximum annual-average concentration of vinyl acetate was estimated using a dispersion model developed by the U.S. Environmental Protection Agency. The modeled annual-average concentration for community exposure was estimated to be 1.8×10^{-3} ppb (5.52×10^{-3} µg/m^3), with the highest exposure being 8.3×10^{-2} ppb (0.25 µg/m^3).

Several studies investigating the potential health effects of workers chronically exposed to vinyl acetate were published in the Russian literature. Agaronyan and Amatuni (1980) examined the prevalence of neurotoxicity and cardiovascular effects in workers exposed at a "polyvinylacetate" plant compared with workers in a mechanical department of a different factory. Poly-vinylacetate workers were divided into three groups on the basis of neurotoxici-ty: those that had no signs of central nervous system toxicity, those that had the beginning phase of neurotoxicity (as defined by neuroasthenia), and those with asthenovegetative syndrome with pronounced autonomic-dystonia and involvement of the hypothalamic regions. Incidence of cardiovascular effects increased with increasing neurotoxicity and included: piercing pain in the area of the heart, palpitations, muffled heart sounds, systolic murmur, hypertension, and electrocardiogram findings of tachycardia, bradycardia, decreased P wave, widened QRS complex, prolonged Q-T, and decreased T wave. Amatuni and Agaronyan (1979, 1980) also investigated the same workers for potential pulmonary effects after chronic exposure to vinyl acetate. They reported a progressive and significant increase in the frequency of impaired pulmonary function in proportion to length employment (from 16.6 ± 8.7% at less than a year to 48.4 ± 5.1% ($p < 0.001$) at 15 years and longer). Pulmonary effects included decreases in vital capacity, forced expired volume in one second (FEV_1), maximal voluntary ventilation (MVV), and expiratory and inspiratory capacity (C_{exp}; C_{insp}), and clinical manifestations of chronic bronchitis. In another study, Agaronyan and Amatuni (1982) evaluated the pulmonary ventilation function of workers at the beginning of the study and after 5 years of employment. They found statistically significant decreases in ventilation parameters primarily indicative of obstructive and mixed impairment of pulmonary ventilation function. Limitations of the Russian studies include occupational exposures to multiple chemicals and of documented concentrations of vinyl acetate.

2.3. Developmental and Reproductive Toxicity

No studies of potential developmental or reproductive effects in humans after inhalation exposure to vinyl acetate were found.

2.4. Genotoxicity

In vitro incubation of vinyl acetate with human lymphocytes or leukocytes has resulted in chromosome aberrations, increased sister chromatid exchanges (SCEs), and DNA cross-linking. Human whole-blood lymphocyte cultures incubated for 48 h with vinyl acetate at 0.125, 0.25, 0.5, 1, or 2 mM exhibited a peak in the frequency of micronucleated lymphocytes at 0.5 and 1 mM (3.2 ± 1% and 3.1 ± 0.7%, respectively, vs. 0.9 ± 0.1% for controls) (Mäki-Paakkanen and Norppa 1987). A concentration of 2 mM was considered a toxic, resulting in a decreased frequency of micronucleated lymphocytes due to inhibition of mitosis. Whole blood cultures and isolated lymphocytes incubated with vinyl acetate for 48 h at 0.25, 0.5, 1, or 2 mM showed a concentration-dependent increase in chromatid-type aberrations and a slight increase in chromosome-type breaks, but no effects at 0.125 mM (Jantunen et al. 1986). Concentration-related increases in SCEs and chromosome aberrations (in first division cells) were found in human whole-blood lymphocyte cultures and purified lymphocyte cultures incubated with vinyl acetate at 0.1-1 mM for 48 h (Mäki-Paakkanen et al. 1984; Norppa et al. 1985). The most common chromosome aberration was the chromatid-type break; at 1 mM, 84% of the cells were aberrant and 38% had a chromatid-type exchange. Purified lymphocyte cultures exhibited a more pronounced effect on both SCEs and the number of aberrant cells (Norppa et al. 1985). Cultured human lymphocytes exposed to vinyl acetate at 0.1-2.4 mM exhibited a linear increase in SCEs with increasing exposure duration up to 24 h (He and Lambert 1985). A two-fold higher SCE frequency was observed in cells exposed in the late G_1 phase compared with cells exposed during the early G_1 phase. Cells treated during the first G_1 phase had a statistically significant increase in SCEs in three subsequent cell cycles. Human leukocytes incubated with vinyl acetate at 10 or 20 mM for 4 h at 37°C did not have evidence of direct DNA strand breaks, but had concentration-dependent DNA cross-linking (Lambert et al. 1985).

2.5. Carcinogenicity

A series of epidemiologic studies were conducted to investigate the potential link between employment at a Texas petrochemical plant and an increased incidence of mortality from brain cancer, specifically gliomas (Alexander et al. 1980; Austin and Schnatter 1983a,b; Leffingwell et al. 1983; Waxweiler et al. 1983). Although vinyl acetate was one of the chemicals with a greater apparent risk (Leffingwell et al. 1983), no statistically significant associations were found between exposure to specific chemicals and mortality from brain cancer (Austin and Schnatter 1983a; Leffingwell et al. 1983). Confounding factors include, but are not limited to, concurrent exposure to other chemicals, exposure to unknown concentrations of the chemicals of concern, and the use of in-plant controls (might have obscured a significant finding).

2.6. Summary

Human data on acute exposure to vinyl acetate are limited. Odor detection and recognition threshold values for vinyl acetate are 0.12 and 0.4 ppm, respectively (Hellman and Small 1974; AIHA 1989; EPA 1992). A controlled-exposure study by Smyth and Carpenter (1973) reported that a 2-min exposure to vinyl acetate at 4, 8, or 20 ppm resulted in minimal ocular, nasal, and throat irritation in one of two volunteers. One of three individuals complained of persistent throat irritation when the concentration was increased to 34 ppm for 2 h, and all four test subjects exposed at 72 ppm for 30 min reported ocular irritation and slight throat irritation for up to 60 min post-exposure. The study by Deese and Joyner (1969) did not have controlled exposure to vinyl acetate, but was simply a survey of subjective symptoms reported by three individuals during air sampling of the work environment. All three subjects reported that ocular irritation was intolerable at 21.6 ppm, and slight cough and hoarseness were noted in two individuals. Slight ocular irritation at 5.7 or 6.8 ppm was also reported by one individual.

In vitro genotoxicty studies with human lymphocytes or leukocytes have reported that vinyl acetate increased the number of chromosome aberrations, sister chromatid exchanges, and DNA-crosslinking. Epidemiologic studies have not identified any clear relationship between vinyl acetate and brain cancer.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Groups of six male and six female rats were exposed to vinyl acetate for 4 h at nominal concentrations of 2,000, 4,000, or 8,000 ppm (Smyth and Carpenter 1973). The nominal concentrations were corrected using a curve based on a gas chromatographic analysis of calculated concentrations ranging from 0.6 to 16,000 ppm; the corrected concentrations were 1,640, 3,280, and 6,560 ppm. No information was provided regarding a control group, the strain or age of the rats, or the exposure chamber. Vinyl acetate vapor was generated by feeding liquid vinyl acetate at a constant rate through a spirally corrugated surface of a minimally heated Pyrex tube, through which metered air was passed. Although not specifically stated, an observation period of 14 days was inferred from the results of the group of studies reported by Smyth and Carpenter (1973). Clinical signs, body weight changes, and mortality data are presented in Table 7-4. Gross necropsy of the animals that died revealed pulmonary congestion and hemorrhage, froth in the trachea, and opaque corneas. The LC_{50} (lethal concentration, 50% lethality) was calculated to be 3,680 (2,660-5,100) ppm using the moving average table of Weil (1952).

TABLE 7-4 Results of 4-Hour Inhalation Study of Rats Exposed to Vinyl Acetate

Concentration (ppm)	Mortality	Time of Death (no. animals)	Average Weight Change (g)	Clinical Signs
1,640	0/12	–	+60	Extremities congested at 1 h.
3,280	4/12	During exposure (3), day 9 (1)	+27	Gasping at 50 min; clonic convulsions at 150 min; death at 3 h.
6,560	12/12	During exposure (12)	–	Gasping at 10 min; prostrate at 25 min; clonic convulsions at 50 min; death at 90 min.

Source: Smyth and Carpenter 1973.

The following acute lethality studies in rats lacked adequate reporting of study details, so exposure concentrations were assumed to be nominal. Gage (1970) exposed four male and four female Alderley Park specific pathogen-free rats to air saturated with vinyl acetate for 5 min (Gage 1970). Exposure produced rapid anesthesia and death. Six Sherman rats (sex not specified) were exposed to vinyl acetate vapor at 4,000 ppm for 4 h (no details about exposure conditions were provided) and observed for 14 days for mortality (Smyth and Carpenter 1948). Three of the six rats died. Exposure concentration was not confirmed by analytical methods, and no controls were used. Rumiantsev et al. (1981) reported a 4-h LC_{50} value of 3,238 ppm in rats. Animals were observed for 30 days. No specifics were provided about the deaths other than they occurred during exposure or in the days following exposure.

3.1.2. Mice

Groups of six mice were exposed to vinyl acetate for 4 h at nominal concentrations of 500, 1,000, 2,000, 4,000, or 8,000 ppm (calculated concentrations of 410, 820, 1,640, 3,280, and 6,560 ppm as corrected using a curve based on a gas chromatographic analysis of concentrations ranging from 0.6 to 16,000 ppm) (Smyth and Carpenter 1973). No information was provided about the sex, strain, or age of the mice, the exposure chamber, or a control group. Vinyl acetate vapor was generated by feeding liquid vinyl acetate at a constant rate through a spirally corrugated surface of a minimally heated Pyrex tube, through which metered air was passed. Although not specifically stated, an observation period of 14 days was inferred from the results of the group of studies reported by Smyth and Carpenter (1973). Clinical signs, body weight changes, and mortality data are presented in Table 7-5. Gross necropsy of the animals that died revealed pulmonary congestion and excess pleural fluid. The LC_{50} was calculated to be 1,460 (925 2,305) ppm using the moving average table of Weil (1952).

TABLE 7-5 Results of 4-Hour Inhalation Study of Mice Exposed to Vinyl Acetate

Concentration (ppm)	Mortality	Time of Death	Average Weight Change (g)	Clinical Signs
410	0/6	–	+4	None
820	1/6	Day 8	+3	Labored breathing at 2 min.
1,640	4/6	During exposure	-2.5	Gasping at 5 min; clonic convulsions and death at 15 min; labored breathing in survivors.
3,280	5/6	During exposure	+1	Gasping at 5 min; clonic convulsions and death at 30 min; opaque eyes and poor coordination in one survivor.
6,560	6/6	During exposure	–	Gasping at 5 min; deaths at 15, 15, 15, 20, 20, and 65 min.

Source: Smyth and Carpenter 1973.

Rumiantsev et al. (1981) reported a 2-h LC_{50} of 3,010 ppm in mice. Animals were observed for 30 days. No specifics were provided about the deaths other than they occurred during exposure or in the days following exposure.

3.1.3. Guinea Pigs

Groups of six male guinea pigs were exposed to vinyl acetate for 4 h at nominal concentrations of 2,000, 4,000, 8,000, or 16,000 ppm (calculated concentrations of 1,640, 3,280, 6,560, and 13,120 ppm as corrected using a curve based on a gas chromatographic analysis of concentrations ranging from 0.6 to 16,000 ppm) (Smyth and Carpenter 1973). No information was provided about the age of the guinea pigs, the exposure chamber, or a control group. Vinyl acetate vapor was generated by feeding liquid vinyl acetate at a constant rate through a spirally corrugated surface of a minimally heated Pyrex tube, through which metered air was passed. Although not specifically stated, an observation period of 14 days was inferred from the group of studies reported by Smyth and Carpenter (1973). Clinical signs, body weight changes, and mortality data are presented in Table 7-6. Gross necropsy of the animals that died revealed congestion, emphysema, and scattered hemorrhages in the lungs. The LC_{50} was calculated to be 5,210 (3,500-7,740) ppm using the moving average table of Weil (1952).

TABLE 7-6 Results of 4-Hour Inhalation Exposure Study of Vinyl Acetate in Guinea Pigs

Concentration (ppm)	Mortality	Time of Death (no. animals)	Average Weight Change (g)	Clinical Signs
1,640	0/6	–	+57	Lacrimation at 30 min; eyes and noses wet at end of exposure.
3,280	1/6	During exposure (1)	+33	Labored breathing and poor coordination at 55 min; lacrimation at 90 min; death at 2 h; survivors normal.
6,560	4/6	During exposure (3); day 3 (1)	-4	Gasping at 10 min; clonic convulsions at 18 min; deaths at 55, 60, and 105 min; survivors weak.
13,120	6/6	During exposure (6)	–	Gasping and nose rubbing at 2 min; lacrimation at 10 min; prostrate at 22 min; deaths at 30, 35, 45, 75, 85, and 107 min.

Source: Smyth and Carpenter 1973.

3.1.4. Rabbits

Groups of four male rabbits were exposed to vinyl acetate for 4 h at nominal concentrations of 2,000, 4,000, or 8,000 ppm (calculated concentrations of 1,640, 3,280, or 6,560 ppm as corrected using a curve based on a gas chromatographic analysis of concentrations ranging from 0.6 to 16,000 ppm) (Smyth and Carpenter 1973). No information was provided about the strain or age of the rabbits, the exposure chamber, or a control group. Vinyl acetate vapor was generated by feeding liquid vinyl acetate at a constant rate through a spirally corrugated surface of a minimally heated Pyrex tube, through which metered air was passed. The results of the study are presented in Table 7-7. Gross necropsy of the animals that died revealed bloody nostrils, froth in the trachea, excess pleural fluid, and pulmonary hemorrhage. The LC_{50} was calculated to be 2,760 (1,800-4,200) ppm using the moving average table of Weil (1952).

3.2. Nonlethal Toxicity

3.2.1. Dogs

One male beagle dog per group was exposed to vinyl acetate for 4 h at nominal concentrations of 62.5, 125, 250, 1,000, 2,000, or 4,000 ppm (calculat-

ed concentrations of 51.25, 102.5, 205, 820, 1,640, or 3,280 ppm as corrected by using a curve based on a gas chromatographic analysis of concentrations ranging from 0.6 to 16,000 ppm) (Smyth and Carpenter 1973). Vinyl acetate vapor was generated by feeding metered air through a spirally corrugated surface of a minimally heated Pyrex tube. No controls were used, and no details were provided about the exposure chamber. All animals survived. Results of the study are presented in Table 7-8; no further details were provided.

3.2.2. Rats

Gage (1970) conducted a series of experiments in which Alderley Park specific pathogen-free rats were exposed to vinyl acetate at 100, 250, 630, or 2,000 ppm for 6 h/day for a total of 15 exposures. Animals were exposed in a glass desiccator with wire mesh separating the animals. The purity of the chemical was not determined. Appropriate nominal concentrations were produced by injecting vinyl acetate at a known rate into a metered flow of air using a controlled fluid-feed atomizer, but analytic concentrations in the chamber were not determined during the exposures. No clinical signs or abnormal necropsy findings were observed at 100 ppm. Low body weight gain was noted in females exposed at 250 or 630 ppm, but gross necropsy and blood and urine analyses were normal. Exposure to vinyl acetate at 2,000 ppm produced clinical signs of ocular and nasal irritation, respiratory difficulty, poor condition, and low body weight gain, and histopathologic examination of the lungs revealed excess macrophages. No further details were provided.

TABLE 7-7 Results of 4-Hour Inhalation Study of Vinyl Acetate in Rabbits

Concentration (ppm)	Mortality	Time of Death	Average Weight Change (g)	Clinical Signs
1,640	0/4	–	+225	None
3,280	3/4	Day 4, 7, 13	-300	Red noses at 30 min; cloudy eyes at 90 min; normal at end of exposure.
6,560	4/4	During exposure, days 2 and 4	-206	Labored breathing and poor coordination at 15 min; convulsions at 17 min; red noses and lacrimation at 55 min; cloudy eyes at 70 min; deaths at 60 and 100 min; bloody nose at 2 h.

Source: Smyth and Carpenter 1973.

TABLE 7-8 Results of 4-Hour Inhalation Exposure in Dogs

Concentration (ppm)	Clinical Signs
51.25	None
102.5	None
205	Blinking at 1 min; red sclera red at 1 h.
820	Lacrimation at 2 min; red sclera at 4 h.
1,640	Blinking and sneezing immediately; lacrimation at 5 min; inflamed eyelids at 30 min; nasal froth at 4 h.
3,280	Rubbing of eyes and nose immediately; tremors at 2.5 h; froth from nostrils at 3.5 h; red eyes.

Source: Smyth and Carpenter 1973.

To investigate the effect of vinyl acetate on nasal epithelial cell proliferation, groups of five male Sprague-Dawley rats were exposed by whole body inhalation at target concentrations of 0, 50, 200, 600, or 1,000 ppm (actual exposure concentrations 0, 50.8, 199.6, 598.5, and 1,007.3 ppm) for 6 h once or for 6 h/day for a total of 5 or 20 consecutive exposures (Bogdanffy et al. 1997). Rats were exposed in a 150-L stainless steel and glass dynamic inhalation chamber with an air flow of approximately 35 L/min. Chamber atmospheres were analyzed directly using gas chromatography. Rats were weighed three times per week and were observed for clinical signs. Animals received intraperitoneal injection of 5-bromo-2'-deoxyuridine (BrdU) 16 h after the last exposure, and were killed 2 h later. The respiratory tract of the rats was examined for gross changes, and the nasal cavities were removed and prepared for histopathologic examination. Five cross sections of the nose were examined, and sections of the duodenum were used as a positive control for the BrdU procedure. No clinical signs or gross necropsy abnormalities were reported. Body weight gain in the 1,000-ppm group was decreased, with the maximum decrease occurring on exposure day 5 (86% of controls). Histopathologic examination revealed concentration-related olfactory epithelial changes in the 600- and 1,000-ppm groups, but the incidence and severity of the lesions were low. Some rats developed degeneration, necrosis, and exfoliation after one exposure; the most affected regions were the dorsal one-third of the nasal septum and dorsolateral wall, Masera's organ, and the medial-most extent of the ethmoid turbinates (see Table 7-9 for incidence data). In a personal communication with one of the study authors, Frame (S.R. Frame, DuPont, Haskell Laboratory, Newark, DE, personal commun., December 1, 2004) concluded that the changes observed at 600 and 1,000 ppm were likely to be completely reversible both morphologically and functionally, on the basis of the focal and limited nature of the olfactory lesions and the known regenerative capacity of olfactory tissue. After 5 or 20 exposures, post-necrotic repair and adaptation were found; changes included regenerative hyperplasia of the olfactory epithelium and attenuation

and disorganization of the olfactory mucosa and occasional areas of squamous metaplasia (Bogdanffy et al. 1997). Additionally, olfactory nerve bundles in the olfactory lumina exhibited degeneration and atrophy. Cell labeling of rats after one 6-h exposure revealed a concentration-related increase in cell proliferation in the respiratory and olfactory epithelium, generally confined to the basal cells of the epithelial cell layer. Increase in the labeling index was statistically significant in the 600- and 1,000-ppm groups. No statistically significant increases in the labeling indexes were found in olfactory or respiratory epithelium of rats exposed five times. However, cell proliferation of the olfactory epithelium (primarily the basal cells) was statistically significantly increased in the 600- and 1,000-ppm groups after 20 exposures. Such an increase was not evident in the respiratory epithelium. The investigators concluded that the cell proliferation response could be a two-phase reaction, the first involving chemical insult of the tissue followed by early regenerative repair (exposure days 1-5) and the second involving cellular and biochemical adaptation.

TABLE 7-9 Histopathologic Observations in Nasal Epithelium of Rats Exposed to Vinyl Acetate for 6 Hours

Section of the Nose	Observation	Concentration (ppm)[a] 0	600	1,000
Level II	Degeneration/necrosis; respiratory epithelium			
	Minimal	–	–	1
	Degeneration/necrosis; olfactory epithelium			
	Minimal	–	2	1
	Mild	–	1	2
	Moderate	–	1	2
Level III	Degeneration/necrosis; respiratory epithelium			
	Minimal	–	–	1
	Degeneration/necrosis; olfactory epithelium			
	Minimal	–	2	–
	Mild	–	3	4
	Moderate	–	–	1
Level IV	Degeneration/necrosis; olfactory epithelium			
	Minimal	–	4	1
	Mild	–	1	3
	Moderate	–	–	–
Level V	Degeneration/necrosis; olfactory epithelium			
	Minimal	–	2	3

[a]Nasal cavities of rats exposed to vinyl acetate at 50 or 200 ppm were histologically normal.

Source: Bogdanffy et al. 1997. Reprinted with permission; copyright 1997, *Inhalation Toxicology*.

3.2.3. Mice

The RD_{50} (concentration that reduces respiratory rate by 50%) for vinyl acetate was 380 ppm in mice tested according to the ASTM E981 protocol (Dudek et al. 1996).

3.3. Developmental and Reproductive Toxicity

Vinyl acetate was administered to 24 confirmed-mated Sprague-Dawley rats by whole-body inhalation at concentrations of 0, 50, 200, or 1,000 ppm for 6 h/day on days 6 through 15 of gestation (Hurtt et al. 1995). Observations for clinical signs of maternal toxicity were made daily and body weight was recorded on gestation days (GDs) 0, 2, 4, 6, 10, 15, and 20; however, food and water consumption were not measured. On GD 20, dams were sacrificed, subjected to gross necropsy, and all fetuses were examined externally and viscerally (half by dissection and evisceration and the remaining half by Wilson's technique). The total numbers of fetuses examined (number of litters) were 322 (24), 320 (22), 345 (24), and 327 (22) for the 0-, 50-, 200-, and 1,000-ppm groups, respectively. Approximately half of the fetuses were examined for skeletal malformations and variations. Maternal toxicity was evident in the 1,000-ppm group; dams had significantly ($p < 0.05$) decreased mean absolute body weight on GDs 10, 15, and 20 (91, 88, and 89% of controls, respectively) and decreased body weight gain over GDs 6-10 (-10.3 g vs. 17.5 g for controls), GDs 10-15 (64% of controls), and GDs 6-15 (24% of controls). Weight gain in this group was comparable with controls over GDs 15-20 (96% of controls). Because food consumption was not measured, it is unknown whether the decreased body weight was an effect of decreased food consumption. Delays in fetal growth were present in the 1,000-ppm group and included significantly ($p < 0.05$) decreased mean fetal weight (72% of controls), decreased crown-to-rump length (88% of controls), and delays in ossification. Evidence of delayed ossification (number of fetuses [litter] in the 1,000-ppm group vs. controls) included incompletely ossified occipital bone (41 [12] vs. 1 [1]); unossified No. 2 sternebra (28 [10] vs. 0 [0]); unossified No. 5 sternebra (118 [22] vs. 17 [11]); unossified No. 6 sternebra (126 [22] vs. 16 [7]); and bipartite vertebra (52 [18] vs. 24 [13]). The delays in fetal growth correlate with maternal toxicity in the high-concentration group. The investigators concluded that vinyl acetate is not uniquely toxic to the fetus.

3.4. Genotoxicity and Cytotoxicity

Vinyl acetate was not mutagenic to *Salmonella typhimurium* strains TA 1535, 1537, 1538, 98, or 100 with or without metabolic activation at a maximum, nontoxic concentration of 1,000 µg/plate (Lijinsky and Andrews 1980); to *S. typhimurium* strains TA 97, 98, or 100 at 100-500 µg/mL (Brams et

al. 1987); or to *S. typhimurium* strain TA 102 (vinyl acetate concentrations not specified) (Jung et al. 1992; Müller et al. 1993). Vinyl acetate was not mutagenic in *Escherichia coli* strain PQ37 using the SOS chromotest (Brams et al. 1987).

A statistically significant and concentration-related increase in sister chromatid exchanges was found in both Chinese hamster ovary cells incubated with vinyl acetate at 0.125-1 mM without metabolic activation and after a 4-h pulse treatment with vinyl acetate at 0.3-5 mM with or without metabolic activation (Mäki-Paakkanen et al. 1984; Norppa et al. 1985). Male C57B1/6 mice exhibited a statistically significant increase in micronucleated polychromatic erythrocytes in the bone marrow 30 h after intraperitoneal injection of vinyl acetate at 1,000 or 2,000 mg/kg (1.33 ± 0.29% and 1.57 ± 0.19%, respectively, vs. 0.6 ± 0.10% for olive oil-treated controls), but no increase was seen after injection with 250 or 500 mg/kg (Mäki-Paakkanen and Norppa 1987). Injections of vinyl acetate at 1,000 and 2,000 mg/kg were fatal to 6/14 and 8/14 mice, respectively.

Hepatic DNA adducts were not formed in male or female F344 rats administered ^{14}C-labeled vinyl acetate by oral gavage (1 mCi of radioactivity; rats killed 4 h after administration) or by inhalation (1,200 to 1,800 ppm in static exposure chamber for 4 h) (Simon et al. 1985b). Accumulation of DNA-protein crosslinks followed S-phase kinetics when pUC13 plasmid DNA, calf histones, and rat liver microsomes were incubated with vinyl acetate at 1-100 mM for 3 h at 37°C (Kuykendall and Bogdanffy 1992a,b). DNA-protein crosslink formation was inhibited by the addition of a carboxylesterase inhibitor (bis-[p-nitrophenyl]phosphate, or BNPP) and by the removal of the rat liver microsomes.

To evaluate cytotoxicity in nasal tissues, explants of the maxilloturbinate (lined with pure populations of respiratory epithelia) and endoturbinate-1 (lined with pure populations of olfactory epithelia) from rat nasal cavities were incubated with vinyl acetate at 0, 20, 25, 50, 100, or 200 mM, followed by assaying for acid phosphatase release (Kuykendall et al. 1993a). Vinyl acetate was cytotoxic at 100 and 200 mM after incubation for 20 min and at 50 mM after incubation for at least 1 h, but 25 mM was not cytotoxic after incubation for up to 2 h. Therefore, vinyl acetate at 50 mM for 1 h was chosen to study the effects of a carboxylesterase inhibitor (BNPP) or aldehyde scavenger (semicarbazide) on vinyl acetate - mediated cytotoxicity. To assess the effects of BNPP on vinyl acetate induced cytotoxicity, acetaldehyde production was measured in the nasal tissues first. Acetaldehyde production increased steadily for up to 60 min in respiratory turbinates and up to 40 min in olfactory turbinates, reaching a plateau when acetaldehyde concentrations reached approximately 16 mM. Therefore, BNPP pre-treatment was assessed using a 20-min incubation period with vinyl acetate at 50 mM. Treatment with BNPP for 3 days before tissue collection reduced the cytotoxic effect of vinyl acetate, resulting in only a two-fold increase in acid phosphatase production compared with a three- to four-fold increase without BNPP. BNPP also inhibited the metabolism of vinyl acetate; acetaldehyde release

into the media was reduced by 59% or 37% in respiratory and olfactory turbinates, respectively. When turbinates were incubated with semicarbazide, no effect on cytotoxicity was noted. Further evaluations demonstrated that the vinyl-acetate-induced cytotoxicity was the result of acetic acid production, not acetaldehyde production.

Kuykendall et al. (1993a,b) also assessed the formation of DNA-protein crosslinks in rat nasal epithelial tissues by vinyl acetate and acetaldehyde. Isolated epithelial cells from both olfactory and respiratory turbinates incubated with vinyl aceatate at 0-75 mM generally exhibited a concentration-related increase in DNA-protein crosslink formation. Olfactory and respiratory cells had comparable DNA-protein crosslink formation, as assessed by the absolute difference in DNA accumulation in the protein-bound phases. Epithelial cells were then pre-incubated with increasing concentrations of BNPP for 30 min before the addition of vinyl acetate at 25 mM to assess whether carboxylesterase-dependent metabolism of vinyl acetate to acetaldehyde is necessary for DNA-protein crosslink formation. DNA-protein crosslink formation in respiratory and olfactory cells was 3.9- and 2.9-fold higher, respectively, in cells exposed to vinyl acetate alone compared with untreated cells. When cells were pretreated with BNPP at 1 mM, crosslink formation in respiratory and olfactory cells was reduced by 76% and 78%, respectively. Reduction in crosslink formation was dependent on BNPP concentration.

3.5. Repeated Exposure Data

A 4-week range finding study and a 3-month subchronic study in rats and mice were performed by the same laboratory and are described below. Although repeated-exposure studies are not relevant for derivation of acute exposure values, they do support the premise that exposure to "lower" concentrations of vinyl acetate is compensated for by nasal scrubbing, whereas exposure to concentrations exceeding the scrubbing capacity of the nasal cavity result in lower-respiratory-tract effects.

Groups of five male and five female Sprague-Dawley rats or CD 1 mice were exposed to vinyl acetate at 0, 50, 150, 500, or 1,000 ppm for 6 h/day, 5 days/week for 4 weeks (Owen 1979a,b). The 50-ppm exposure was increased to 1,500 ppm on day 10 (rats) or day 8 (mouse) because marked clinical effects were not observed in the 1,000-ppm groups. Animals were exposed in a stainless steel and glass dynamic inhalation exposure chamber, and chamber concentrations were measured every 15 min by gas chromatography. Mean measured concentrations for the rat and mouse were 51.3, 150.5, 497.6, 1,000.2, and 1,488.5 (rats) or 1,488.7 (mouse) ppm. All animals survived treatment. Although similar effects were found in rats and mice, mice were more sensitive. A concentration-related increase in incidence and severity of respiratory distress and hunched posture was reported in rats exposed to vinyl acetate at 500 ppm or greater and in mice exposed at 150 ppm or greater, but incidence data were not

provided. A concentration-related decrease in overall body weight gain was also noted. Body weight gain in the 150-, 500-, 1,000-, and 50/1,500-ppm groups was 104, 102, 81, and 79% of controls, respectively, for male rats and 95, 92, 80, and 78% of controls, respectively for female rats. In mice, weights were 67, 44, 33, and 33% of controls for male mice, respectively, and 80, 80, 40, and 0% of controls, respectively, for female mice. No gross necropsy findings were reported, and no hematopoietic abnormalities were found in the analysis of bone marrow samples. Spleen weight relative to body weight was decreased at concentrations of 1,000 or 50/1,500 ppm in male rats (85 and 82% of controls, respectively), male mice (80 and 74% of controls, respectively), and female mice (74 and 72% of controls, respectively). The biologic relevance of this finding is unknown. A histopathology report of a 28-day study that appears to be from this study was included a 3-month study by Owen (1980a). Findings in the nasal turbinates, trachea, and bronchi of mice exposed at 50/1,500 ppm were similar to those reported in the 3-month study described below.

In a subchronic study, groups of 10 male and 10 female CD rats or CD-1 mice were exposed to vinyl aceatate at 0, 50, 200, or 1,000 ppm for 6 h/day, 5 days/week for 13 weeks (Owen 1980a,b). Animals were exposed in a stainless steel and glass dynamic inhalation exposure chamber, and chamber concentrations measured every 15 min by gas chromatography. Mean measured concentrations were 0.5, 51, 200, and 999 ppm. A number of effects were noted in rats exposed at 1,000 ppm, including: intermittent respiratory distress, hunched posture, and ruffled fur (incidence data were not provided); decreased overall body weight gain (62% and 56% of controls for males and females, respectively; $p < 0.01$); smaller volume and more concentrated urine compared with controls; and increased lung weight relative to body weight (126% and 130% of controls for males and females, respectively; $p < 0.01$) (Owen 1980b). No effects were noted during ophthalmoscopic examination, hematology or blood chemistry analysis, or gross or microscopic examination (nasal turbinate was included in the microscopic examination).

Mice appeared to be more sensitive to vinyl acetate (Owen 1980a). Intermittent respiratory distress, hunched posture, and ruffled fur were noted in the 200-ppm group over the first 9 days of exposure. The 1,000-ppm group exhibited respiratory distress throughout the exposure and hunched posture and ruffled fur intermittently (incidence data were not provided). Other effects were limited to the 1,000-ppm group. Nine animals in that group died as a consequence of routine blood sampling. It was postulated that vinyl acetate made mice more susceptible to the anesthesia used during the sampling period. Males and females had decreased overall body weight gain (40% and 50% of controls, respectively; $p < 0.01$) and increased lung weight relative to body weight (148% and 155% of controls, respectively; $p < 0.01$). Microscopic examination revealed exposure-related lesions in the upper and lower respiratory tissues of mice exposed at 1,000 ppm. Upper respiratory tract lesions were confined to the nasal cavity and included focal to diffuse rhinitis with associated exudation and transudation into the nasal passages and occasional mucosal

metaplasia. Inflammation was chronic in nature and associated with hyperplasia of epithelial goblet cells. Findings in the laryngeal sections were difficult to assess because of variation in the section (mucosal epithelium undergoes changes from an oral to respiratory epithelium in this section). Non-inflammatory changes were noted in the trachea as well as several areas of suspected metaplasia or hyperplasia. Metaplasia was characterized by a loss of ciliated epithelium and reduction in epithelial size from a columnar to a cuboidal cell. Changes in the pulmonary parenchyma were confined to the bronchial system and manifested as multifocal bronchitis to bronchiolitis, multifocal bronchiectasis, bronchial epithelial metaplasia and hyperplasia, and occasional bronchiolar or bronchial exudation. The investigator commented that these lesions were consistent with changes often observed in mice experimentally or naturally infected with respiratory pathogens. However, the absence of similar changes in control mice precludes an interpretation of infectious pathogenesis. Exposure to vinyl acetate might be synergistic with the induction of microbial pathogens.

3.6. Chronic Toxicity and Carcinogenicity

In a chronic toxicity and oncogenicity study, groups of male and female Crl:CD(SD)BR (Sprague-Dawley) rats and Crl:CD-1(ICR)BR mice were exposed to vinyl acetate at concentrations of 0, 50, 200, or 600 ppm for 6 h/day, 5 days/week for 104 weeks via whole body inhalation (Bogdanffy et al. 1994). Chamber concentrations were measured every 15 min using a gas chromatograph. The main group consisted of groups of 60 mice or rats of each sex that were exposed for 104 weeks; clinical laboratory evaluations were conducted on 10 animals from each group during week 104. In addition, three satellite groups of 10 male and 10 female rats or mice had the following evaluations: clinical laboratory evaluations at week 51 and necropsy at weeks 52-53; clinical laboratory evaluations at week 81 and necropsy at weeks 82-83; and exposure to vinyl acetate for 70 weeks followed by a 15-week recovery period. Clinical signs of rough coat and hunched posture were noted at all concentrations and are believed to be an effect of inhalation exposure.

In rats, exposure to vinyl acetate at 600 ppm resulted in statistically decreased body weight gain and decreased absolute body weight (approximately 10% less than controls at 104 week) (Bogdanffy et al. 1994). Following the recovery period, male rats in the 600-ppm group exhibited a statistically significant increase in body weight gain compared with controls. No effects on body weight gain were observed at 50 or 200 ppm. Clinical pathology evaluation revealed a statistically significant decrease in blood glucose in 600-ppm females at weeks 51, 81, and 104, and a statistically significant decrease in urine volume in all 600-ppm rats at weeks 51 (males only), 81, and 104. Corresponding increases in specific gravity and decreased pH were observed but the differences were not always statistically significant. The investigators attributed effects on blood

glucose and urinary parameters to decreased food and water consumption; however, food and water consumption were not measured. Gross necropsy revealed increases in relative lung weight in the 200- and 600-ppm groups at week 53, the 600-ppm group at week 83, and all treated groups at week 104. Following the 15-week recovery period, no statistically significant differences in terminal body weight or organ weights were observed in any groups of exposed females, whereas body weight gain in male rats remained slightly depressed. Histopathologic examination revealed non-neoplastic changes in the lungs and nose. Findings in the lungs of male and female rats exposed at 600 ppm included bronchial exfoliation, intraluminal fibrous projections, macrophage accumulation, and peribronchiolar/perivascular lymphoid aggregates. Nasal lesions were found in rats exposed at 200 and 600 ppm, and included olfactory epithelial atrophy, squamous metaplasia, regeneration, inflammatory cell infiltrate, and leukocytic exudate; epithelial nest-like folds; basal cell hyperplasia; turbinate leukocyte exudate; and submucosal inflammatory cell infiltrate. Neoplastic changes were confined primarily to the nasal cavity of rats exposed at 600 ppm. Findings in the control, 50-, 200-, and 600-ppm groups included squamous cell carcinoma (males: 0/59, 0/60, 0/59, and 2/59, respectively; females: 0/60, 0/60, 0/60, and 4/59, respectively), carcinoma in situ (males: 0/59, 0/60, 0/59, and 1/59, respectively), and benign lesion of inverted papilloma (males: 0/59, 0/60, 0/59, and 4/59, respectively). Additionally, one female rat exposed at 600 ppm had a squamous cell carcinoma in the larynx.

In mice, body weight gain was statistically decreased in the 200- and 600-ppm groups throughout the study, and in the 50-ppm group through week 52 (Bogdanffy et al. 1994). Absolute body weight in the 600-ppm group at week 104 was approximately 15% less than controls. Following the 15-week recovery period, 600-ppm male mice and all exposed female mice exhibited a statistically significant increase in body weight gain compared with controls. No significant differences were noted in hematology or clinical chemistry parameters. Gross necropsy revealed increases in absolute and relative lung weights in 600-ppm males at weeks 53, 83, and 104, in 600-ppm females at weeks 83 and 104, and 200-ppm males only at week 83. No statistically significant differences in final body weights or organ weights were found after a 15-week recovery period. Histopathologic examination revealed non-neoplastic changes in the lungs, nose, and trachea. Findings in the lungs were present primarily in mice exposed at 600 ppm, and included accumulation of alveolar and brown pigmented macrophages, intra-alveolar eosinophilic material, intraluminal fibroepithelial projections, bronchial gland dilation, bronchial/bronchiolar epithelial flattening and exfoliation, and bronchial/bronchiolar epithelial disorganization. Non-neoplastic nasal lesions were found in the 200- and 600-ppm groups, and included olfactory epithelial atrophy (mainly dorsal meatus or widespread), inflammatory exudate, mucosal inflammatory infiltrate, submucosal gland hyperplasia, squamous metaplasia at the naso/maxilloturbinate region, and replacement of olfactory epithelium by respiratory epithelium. Epithelial hyperplasia of the trachea and bronchi was also evident in 600-ppm group. Neoplastic changes

were confined to a moderately invasive squamous cell carcinoma in a major bronchus of the lung of a 600-ppm male and a single adenocarcinoma in a control male.

The International Agency for Research on Cancer (IARC 1995) has concluded there is inadequate evidence in humans and limited evidence in experimental animals of the carcinogenicity of vinyl acetate . Therefore, IARC states that vinyl acetate is possibly carcinogenic to humans (Group 2B). The weight of the evidence was: (1) vinyl acetate is rapidly transformed into acetaldehyde; (2) sufficient evidence of carcinogenicity of acetaldehyde in experimental animals (both vinyl acetate and acetaldehyde induce nasal cancer in rats after administration by inhalation); and (3) vinyl acetate and acetaldehyde are genotoxic in human cells in vitro and in animals in vivo.

3.7. Summary

Acute toxicity studies of vinyl acetate included a series of studies in dogs, rats, mice, guinea pigs, ands rabbits performed by Smyth and Carpenter (1973); a study in rats by Gage (1970); an RD_{50} value reported in mice (Dudek et al. 1996); and a study investigating the histopathologic lesions in the rat nasal cavity (Bogdanffy et al. 1997). Tables 7-10and 7-11 summarize the lethal and nonlethal effects of vinyl acetate .

The Smyth and Carpenter study provided the best general toxicity data. Nonlethal concentrations produced signs of congested extremities in rats and lacrimation in guinea pigs, but no signs were noted in mice or rabbits. Dogs exhibited lacrimation, nasal froth, and tremors. Lethal concentrations produced signs of irritation (gasping and lacrimation) and central nervous system effects (poor coordination, prostration, and clonic convulsions). Gross necropsy of animals that died indicated that mortality was due to pulmonary irritation (pulmonary congestion, hemorrhages, and excess pleural fluid). Limitations of the Smyth and Carpenter studies include incomplete reporting of study details (no details about exposure chamber, strain and age of animals not specified) and a lack of a control group. Chamber concentrations were not measured, but the nominal concentrations were corrected against a calibration curve.

The Gage (1970) study is of limited utility because the purity of the chemical is unknown, the exposure concentrations were nominal, and clinical signs were reported as a general statement, so it is not known when the clinical signs first occurred. The Dudek et al. (1996) data was published in an abstract, with the RD_{50} being the only toxicity end point investigated.

The Bogdanffy et al. (1997) study primarily focused on histopathologic lesions of the rat nasal epithelium. A single, 6-h exposure to vinyl acetate at 600 or 1,000 ppm resulted in increased cell proliferation in the respiratory and olfactory epithelium, with 200 ppm being a no-observed-adverse-effect level for all histologic effects.

A developmental toxicity study of vinyl acetate in rats reported maternal toxicity at 1,000 ppm, as evidenced by decreased maternal body weight and

body weight gain, and developmental toxicity in the form of delayed fetal growth (Hurtt et al. 1995). Results of genotoxicity testing indicate that vinyl acetate is clastogenic (proposed to result from the metabolite acetaldehdye) and cytotoxic (proposed to be caused by the metabolite acetic acid). A carcinogenicity bioassay reported that rats exposed to vinyl acetate at 600 ppm developed nasal papillomas, squamous cell carcinomas, and carcinoma in situ, but that mice did not develop nasal tumors.

TABLE 7-10 Summary of 4-Hour Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	No. Deaths	Gross Necropsy Findings of Animals That Died
General Mortality Data			
Rat	1,640	0/12	–
	3,280	4/12 (3 died during exposure)	Pulmonary congestion and hemorrhage, froth in trachea, and opaque corneas.
	6,560	12/12 (90 min)	
Mouse	410	0/10	–
	820	1/6 (8 d post-exposure)	Pulmonary congestion, excess pleural fluid.
	1,640	4/6 (during exposure)	
	3,280	5/6 (during exposure)	
	6,560	6/6 (during exposure)	
Guinea pig	1,640	0/6	–
	3,280	1/6 (during exposure)	Pulmonary congestion and emphysema, scattered hemorrhages in the lungs.
	6,560	4/6 (3 during exposure)	
	13,120	6/6 (during exposure)	
Rabbit	1,640	0/4	–
	3,280	3/4	Bloody nostrils, froth in trachea, excess pleural fluid, pulmonary hemorrhages.
	6,560	4/4 (2 during exposure)	
Calculated 4-Hour LC_{50} Data			
Rat	3,680	LC_{50}	–
Mouse	1,460	LC_{50}	–
Guinea pig	5,210	LC_{50}	–
Rabbit	2,760	LC_{50}	–

Source: Smyth and Carpenter 1973.

TABLE 7-11 Summary of Nonlethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Duration	Effect	Reference
Dog	51.25	4	None	Smyth and Carpenter 1973
Dog	102.5	4	None	Smyth and Carpenter 1973
Dog	205	4	Blinking at 1 min, red sclera at 1 h.	Smyth and Carpenter 1973
Dog	820	4	Lacrimation at 2 min, red sclera at 4 h.	Smyth and Carpenter 1973
Dog	1,640	4	Blinking and sneezing at start of exposure; lacrimation at 5 min; inflamed eyelids at 30 min; nasal froth at 4 h.	Smyth and Carpenter 1973
Dog	3,280	4	Rubbing of eyes and nose at start of exposure; tremors at 2.5 h; froth from nostrils at 3.5 h; red eyes.	Smyth and Carpenter 1973
Rat	1,640	4	Extremities congested at 1 h; no effect level for death (0/12).	Smyth and Carpenter 1973
Rat	600	6	Degeneration and necrosis in olfactory epithelium; increase in cell proliferation in nasal respiratory and olfactory epithelium.	Bogdanffy et al. 1997
Rat	1,000	6	Degeneration and necrosis in olfactory and respiratory epithelium; increase in cell proliferation in nasal respiratory and olfactory epithelium.	Bogdanffy et al. 1997
Mouse	410	4	No clinical signs; no effect l evel for death (0/6).	Smyth and Carpenter 1973
Mouse	380	–	RD_{50}	Dudek et al. 1996
Guinea pigs	1,640	4	Lacrimation at 30 min; wet eyes and nose at end of exposure. No effect level for death (0/6).	Smyth and Carpenter 1973
Rabbits	1,640	4	No clinical signs; no effect level for death (0/4).	Smyth and Carpenter 1973

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Groups of male and female Sprague-Dawley rats were exposed for 6 h to ^{14}C-vinyl acetate vapor at 750 ppm by nose-only inhalation to assess excretion,

metabolism, and tissue distribution (Strong et al. 1980). The mean proportion of radioactivity recovered over a 96-h post-exposure period was 4.8% in urine, 3.6% in feces, 74.6% in expired air, and 16.4% in the carcass. The amount recovered in the expired air was almost exclusively $^{14}CO_2$. No radiolabeled carbonates or bicarbonates were recovered in the urine or feces. Tissue distribution measurements of rats killed immediately after exposure revealed that the highest mean concentration of radioactivity (reported as µg equivalents of ^{14}C-vinyl acetate/g) was found in the Harderian gland (2,045 µg equivalents/g), followed by the ileum (393 µg equivalents/g) and submaxillary salivary gland (341 µg equivalents/g). Radioactivity levels in the gastrointestinal tract contents, liver, kidneys, lung, brain, stomach, colon, and ovaries ranged from 150-300 µg equivalents/g. The pattern of distribution was essentially the same but at lower concentrations at 1-, 6-, or 72-h post-exposure, with the highest concentrations at 72 h found in the Harderian gland (193 µg equivalents/g), adrenal gland (112 µg equivalents/g), and ovaries (99 µg equivalents/g). No difference in the pattern of distribution was found between sexes (except for the gonads), or following oral administration. A separate study investigating the metabolic fate of ^{14}C-vinyl acetate at 1,000 ppm administered for 6 h by nose-only inhalation to Sprague-Dawley rats resulted in similar results (Cresswell et al. 1979).

The study by Bogdanffy et al. (1997) provided information on the deposition of inhaled vinyl acetate in the rat nasal cavity. Histopathology results demonstrated a strong anterior to posterior gradient, with the response moving anterior to posterior with increasing concentrations. These findings are indicative of a material in which deposition is metabolically dependent. As vinyl acetate concentration increases, fractional deposition decreases due, in part, to saturation of the metabolism-dependent component of deposition.

The primary metabolic pathway of vinyl acetate is hydrolysis by carboxylesterases to acetic acid and vinyl alcohol, which rearranges to form acetaldehyde (see Figure 7-1 and Table 7-12) (Simon et al. 1985a; Fedtke and Wiegand 1990; Kuykendall et al. 1993a; Bogdanffy and Taylor 1993). Acetaldehyde can be further metabolized to acetate, which can be incorporated into the carbon pool via formation of acetyl coenzyme A and can ultimately result in the formation of CO_2 (Strong et al. 1980). Acetaldehyde can also be oxidized to acetic acid by aldehyde dehydrogenase, a NADH-dependent reaction (Andersen et al. 2002). Monooxygenases do not play a significant role in the metabolism of vinyl acetate, and epoxide formation is not expected to be significant (Simon et al. 1985a; Bogdanffy et al. 1999a). A gas-uptake kinetic study in rats revealed a linear, concentration-dependent decay of vinyl acetate up to a concentration of 650 ppm, indicating the possibility of metabolic saturation (Simon et al. 1985a). At concentrations below saturation, the maximal clearance in rats was 30,000 mg/h/kg, similar to the maximal ventilation rate of 32,000 mg/h/kg. Therefore, the metabolic rate of vinyl acetate is determined by the ventilation rate when metabolic saturation has not been reached.

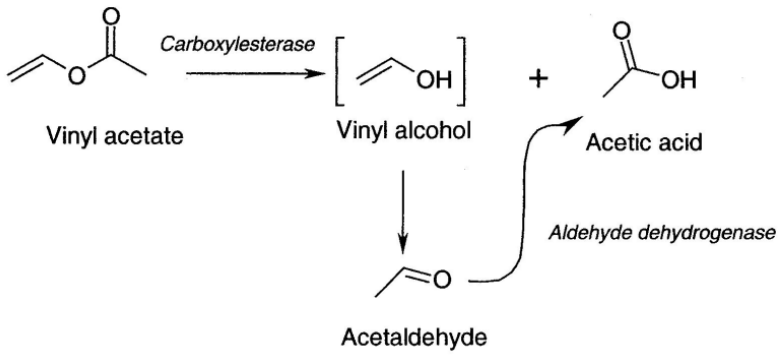

FIGURE 7-1 Pathways of vinyl acetate metabolism. Vinyl alcohol is an unstable intermediate that has not been isolated. Source: Bogdanffy et al. 2001. Permission needed to reprint- appears as Figure 2 in paper. Reprinted with permission; copyright 2001, *Inhalation Toxicology*.

TABLE 7-12 Degradation of Vinyl Acetate and Production of Acetaldehyde with Time

	Vinyl Acetate		Concentration (μmol/mL)		
Source (Incubate)	Concentration (ppm)	Time (sec)	Vinyl Acetate	Acetaldehyde	Reference
Human plasma	29	0	0.307	0.025	Strong et al. 1980
		550	0.024	0.292	
	129	0	1.380	0.000	
		720	0.031	1.177	
Human whole blood	129	0	1.380	0.000	Strong et al. 1980
		0	0.074	1.187	
Rat plasma	25	0	0.280	No data	Cresswell et al. 1979
		270	0.011	0.263	
	100	0	1.11	0.052	
		270	0.079	1.05	
Rat whole blood	100	0	1.10	0.014	Cresswell et al. 1979
		565	ND	1.06	
Homogenized rat liver	100	0	0.924	0.064	Cresswell et al. 1979
		260	0.041	0.969	
Homogenized mouse liver		0	0.570	0.050	Cresswell et al. 1979
		320	0.020	0.533	

Information on the kinetics of vinyl acetate hydrolysis is available for whole blood, plasma, erythrocytes, liver microsomes, and nasal tissue. The half-life of vinyl acetate in whole blood and liver homogenates was comparable in rats (60-125 and 50-167 seconds, respectively) and mice (114 and 66 seconds, respectively), with the most active compartment being plasma (57-72 and 36 seconds for rats and mice, respectively) (Creswell et al. 1979; Fedtke and Wiegand 1990). Hydrolysis of vinyl acetate in humans was generally slower than in rats and mice, with a half-life in human whole blood of 210-246 seconds and in human plasma of 150 or 3,720 seconds. However, the half-life of vinyl acetate in erythrocytes was similar in humans (330 seconds) and rats (336 seconds) (Fedtke and Wiegand 1990). Kinetic parameters of enzyme-mediated hydrolysis by rat liver and lung microsomes, rat and human plasma, and purified carboxylesterase are presented in Table 7-13.

Because the nasal cavity was the target organ of toxicity after chronic exposure to vinyl acetate, metabolism of vinyl acetate by nasal tissue was examined. Through the use of a carboxylesterase inhibitor (BNPP) and mono-oxygenase inhibitors (such as diallyl sulfide), metabolism of vinyl acetate by the nose was shown to be carboxylesterase dependent (Plowchalk et al. 1997; Bogdanffy et al. 1999a). Histochemical staining of the rat nasal cavity revealed that a high-affinity carboxylesterase was bound to the luminal plasma membrane (Bogdanffy et al. 1999a). To examine the kinetics of nasal carboxylesterase-mediated metabolism of vinyl acetate, homogenized samples of nasal respiratory and olfactory mucosa from male and female rats and mice were incubated with vinyl acetate (Bogdanffy and Taylor 1993). Few difference in kinetics between male or female rats or mice were observed; however, the olfactory mucosa had higher activity than the respiratory mucosa (see Table 7-13), a result also seen after histochemical staining of the nasal passages of Fischer 344 rats and $B6C3F_1$ mice (Bogdanffy et al. 1987). An in vitro gas technique using whole-tissue samples and physiologically-based pharmacokinetic modeling were used to investigate differences in vinyl acetate metabolism in rat and human nasal tissues (Bogdanffy et al. 1998). Rat respiratory carboxylesterase and aldehyde dehydrogenase activities were approximately three and two times higher than those of humans, respectively, whereas rat olfactory enzyme activities were equivalent to humans (see Table 7-14). K_m values did not differ between species.

As observed in the whole-body gas uptake study (Simon et al. 1985a), substrate inhibition of rat nasal carboxylesterase in vitro was found at high concentrations of vinyl acetate (Bogdanffy and Taylor 1993). This is also evident from studies that demonstrated that in vivo deposition of vinyl acetate in the upper respiratory tract of the rat is concentration dependent (Plowchalk et al. 1997). At low concentrations, removal of vinyl acetate from the airstream is highly efficient; more than 93% was extracted by the rat nose at concentrations of 76 ppm or less. At vinyl acetate concentrations of 76-550 ppm, extraction progressively decreased to about 40% and remained at that level until a vinyl acetate concentration of approximately 2,000 ppm. Acetaldehyde in expired air

increased to an apparent maximum of 227 ppm, which corresponded to a vinyl acetate concentration of 1,000 ppm.

TABLE 7-13 Kinetics of Vinyl Acetate from Various Sources

Source of Enzyme	pH	K_m (mM)	V_{max} (μmol/min/mg protein)	Reference
Rat liver microsomes	8.0	0.73	23	Simon et al. 1985a
Rat lung microsomes	8.0	6.1	6.2	Simon et al. 1985a
Rat plasma	8.0	4.0	0.56	Simon et al. 1985a
Human plasma	8.0	7.1	0.69	Simon et al. 1985a
Respiratory nasal mucosa (mice and rats)	7.4	0.3-0.43	22-46	Bogdanffy and Taylor 1993
Olfactory nasal mucosa (rats and mice)	7.4	0.20-0.52	89-165	Bogdanffy and Taylor 1993
Purified carboxyl esterase	8.0	0.65	238	Simon et al. 1985a

TABLE 7-14 Kinetic Constants for Individual Tissue Specimens Derived from a Mini Vapor Uptake Technique

			V_{max}	
Enzyme	Tissue	K_m (mg/mL)	Activity/Specimen (mg/h)	Activity/Epithelial Cell Volume (mg/h/mm^3)
Rat tissues				
Carboxylesterase	Maxilloturbinate[a]	0.04	2.10	1.89
	3EV[a]	0.05	1.68	1.82
Aldehyde dehydrogenase	Maxilloturbinate	0.80	0.05	0.15
	3EV	0.80	0.10	0.07
Human tissues				
Carboxylesterase	Middle turbinate[a]	0.05	1.50	0.57
	Dorsal meatus[a]	0.05	0.90	1.94
Aldehyde dehydrogenase	Middle turbinate	1.10	0.30	0.08
	Dorsal meatus	1.10	0.05	0.08

[a]Maxilloturbinate (rat) and middle turbinate (human) are lined with respiratory epithelium. 3EV (ventral scroll of the third ethnoturbinate) (rat) and dorsal meatus (human) are lined with olfactory epithelium.
Source: Bogdanffy et al. 1998. Reprinted with permission; copyright 1998, *Toxicological Sciences*.

4.2. Mechanism of Toxicity

Several papers have been written about the mode of action of vinyl acetate (Bogdanffy et al. 1999b, 2001; Andersen et al. 2002; Bogdanffy 2002; Bolt 2003; Bogdanffy and Valentine 2003; Hengstler et al. 2003). Metabolism studies have demonstrated that vinyl acetate is metabolized to acetic acid and vinyl alcohol, which rearranges to form acetaldehyde (Simon et al. 1985a; Bogdanffy and Taylor 1993). Acetaldehyde can be further metabolized to acetic acid. Genotoxicity and cytotoxicity tests demonstrated that clastogenicity and cytotoxicity required the presence of carboxylesterases (Kuykendall and Bogdanffy 1992a,b; Kuykendall et al. 1993a). Production of of acetic acid was shown to be responsible for the observed cytotoxicity, and acetaldehyde was responsible for the DNA-protein crosslinking observed in test systems (Kuykendall et al. 1993a). The proposed mechanism of cytotoxicity is lowering of inter- and intra-cellular pH by the production of acetic acid (Kuykendall et al. 1993a; Plowchalk et al. 1997; Bogdanffy et al. 2001). An in vitro study measuring the pH of individual rat respiratory and olfactory nasal epithelial cells before and during exposure to vinyl acetate confirmed a concentration-related decrease in pH with increasing vinyl acetate concentration, with a maximum decrease in pH of 0.3 pH units (Lantz et al. 2003). The cytotoxic response leads to cellular degeneration followed by cellular proliferation (Kuykendall et al. 1993a; Plowchalk et al. 1997; Bogdanffy et al. 2001). Clastogenic effects include chromosomal aberrations, sister chromatid exchange, and DNA crosslinking in human lymphocytes (Mäki-Paakkanen et al. 1984; He and Lambert 1985; Lambert et al. 1985; Norppa et al. 1985; Jantunen et al. 1986; Mäki-Paakkanen and Norppa 1987); Chinese hamster ovary cells (Mäki-Paakkanen et al. 1984; Norppa et al. 1985); rat liver microsomes (Kuykendall and Bogdanffy 1992a,b); and rat nasal epithelial tissues (Kuyendall et al. 1993a,b). Clastogenic effects appear to be due to the production of acetaldehyde, a weak DNA protein crosslinking agent (Kuykendall et al. 1993a) in combination with a lowering of pH (Morita 1995). Acetaldehyde-induced DNA protein crosslinks are more stable at a pH lower than the physiologic pH (Kuyendall and Bogdanffy 1992a). Therefore, the following continuum of response has been proposed for vinyl acetate (Bogdanffy et al. 2001):

Vinyl acetate metabolism
↓
Reduction of pH
↓
Cytotoxic response - olfactory degeneration
↓
Cellular proliferation
↓
Tumorigenic response

Metabolic saturation of vinyl acetate occurs. Simon et al. (1985a) reported that metabolic saturation is reached around 650 ppm in rats. In the rat nose, removal of vinyl acetate from the airstream is highly efficient at low concentrations (more than 93% was extracted at concentrations of 76 ppm or less), but becomes less efficient with increasing concentrations (extraction progressively decreased to about 40% at 76-550 ppm and remained at that level up to a concentration of about 2,000 ppm) (Plowchalk et al. 1997). Therefore, olfactory degeneration would be the primary end point until metabolic saturation in the nasal cavity is reached. Once metabolic saturation has occurred, vinyl acetate would be able to move further down into the respiratory tract. This is evidenced by the strong anterior to posterior gradient seen in the rat nasal cavity during histopathologic examination after acute exposure to inhaled vinyl acetate (Bogdanffy et al. 1997), by the histopathologic changes noted in the lungs of rats and mice exposed at 600 ppm in a 2-year bioassay (Bogdanffy et al. 1994), and by the pulmonary changes found in rats, mice, guinea pigs, and rabbits exposed to acute, lethal concentrations (Smyth and Carpenter 1973).

4.3. Structure-Activity Relationships

Structure-activity relationships were not used for deriving AEGL values for vinyl acetate .

4.4. Other Relevant Information

4.4.1. Species Variability

Four-hour LC_{50} data varied by a factor of 3.6; the most sensitive species was the mouse, followed by the rabbits, rat, and guinea pig (Smyth and Carpenter 1973). Regardless of species, the cause of death was attributed to pulmonary distress.

Olfactory degeneration is the proposed primary end point of inhaled vinyl acetate until metabolic saturation in the nasal cavity is reached (Bogdanffy et al. 1997). Therefore, much research is available regarding the metabolism of vinyl acetate by the nasal cavity. In general, little difference was observed between male and female mice and rats and humans in the carboxylesterase-mediated metabolism of vinyl acetate, particularly by the olfactory epithelium (Bogdanffy and Taylor 1993; Bogdanffy et al. 1998). Esterase distribution in the nasal respiratory tissue of humans is believed to be similar to that of rats (Andersen et al. 2002). However, considerable variability in olfactory nasal tissue occurs in humans with regard to surface area, composition of epithelial tissue layers (respiratory-type tissue can be interspersed with more characteristic olfactory tissue), and age-related changes (Andersen et al. 2002). Children appear to have histologic organization similar to rodents, in that the olfactory epithelium is well-developed and delineated. Aging humans develop a very heterogenous

mucosa with respiratory-like epithelial cells populating the olfactory region. Glandular structures become sparse and non-esterase-containing tissues fill the submucosa. However, esterase histochemistry of adult olfactory mucosa revealed that sustentacular cells and Bowman's glands do contain significant quantities of carboxylesterase.

4.4.2. Susceptible Populations

Data regarding populations susceptible to vinyl acetate were not available. Although older populations may not be as susceptible to olfactory degeneration as younger ones, they may have increased susceptibility of the respiratory epithelium or even greater pulmonary susceptibility because of decreased removal of vinyl acetate in the nose.

4.4.3. Concentration-Exposure Duration Relationship

The relationship between concentration and duration of exposure as related to lethality was examined by ten Berge et al. (1986) for approximately 20 irritant or systemically-acting vapors and gases. Individual animal data sets were analyzed by probit analysis, with exposure duration and exposure concentration as independent variables. An exponential equation $C^n \times t = k$, where the value of n ranged from 0.8 to 3.5 for different chemicals, was found to be an accurate quantitative descriptor for the chemicals evaluated. Approximately 90% of the values of n range between n = 1 and n = 3. Consequently, these values were selected as the reasonable lower and upper bounds of n. A value of n = 1 is used when extrapolating from shorter to longer durations because the extrapolated values represent the most conservative approach in the absence of other data. Conversely, a value of n = 3 is used when extrapolating from longer to shorter durations because the extrapolated values are more conservative in the absence of other data.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

In a controlled-exposure study, a 2-min exposure of nine subjects to vinyl acetate at 4, 8, or 20 ppm resulted in minimal ocular, nasal, and throat irritation in one or two people (Smyth and Carpenter 1973). For longer durations, one of three individuals reported persistent slight irritation of the throat after being exposed for 4 h at 20 ppm and two of three individuals complained of throat irritation (transient in one and persistent in the other) after being exposed for 2 h at 34 ppm. Exposure at 72 ppm for 30 min resulted in ocular irritation and slight throat irritation for up to 60 min after exposure ended in all four test subjects;

irritation was so severe that subjects expressed unwillingness to work at that concentration for 8 h.

In an occupational health report, Deese and Joyner (1969) reported that ocular irritation from exposure to vinyl acetate at 21.6 ppm would be "intolerable over an extended period"; a slight cough and hoarseness were also reported by three subjects exposed at this concentration. In addition, slight ocular irritation in one of three individuals was reported at 5.7 or 6.8 ppm, and hoarseness in one of three was reported at 4.2 and 5.7 ppm. These findings conflict with those of the human volunteer study by Smyth and Carpenter (1973), in which 20 ppm was tolerated by three subjects for 4 h and findings were limited to olfactory fatigue and slight throat irritation in one individual. The Deese and Joyner (1969) study is of limited use for deriving AEGL values because it was not a controlled-exposure study. As noted earlier, the subjects might have been briefly exposed at a concentration higher than 21.6 ppm. Furthermore, coexposure to other chemicals used in the production facility might have exacerbated or contributed to the ocular irritation. Therefore, this study was not used for deriving AEGL-1 values.

5.2. Animal Data Relevant to AEGL-1

Irritation was noted in a dog exposed to vinyl acetate at 205 ppm for 4 h (blinking was observed after 1 min and the sclera were red after 1 h) (Smyth and Carpenter 1973). In the Bogdanffy et al. (1997) study, no histopathologic effects was found in the olfactory or respiratory epithelium of rats exposed to vinyl acetate at 0, 50, or 200 ppm for 6 h/day, 5 days/week for 1, 5, or 20 days. Thus, 200 ppm is a no-observed-effect level for these end points.

5.3. Derivation of AEGL-1 Values

AEGL-1 values are based on the no-effect level for notable discomfort found in a study of human volunteers (Smyth and Carpenter 1973). This study was selected over the occupational health report (Deese and Joyner 1969) or the rat study (Bogdanffy et al. 1997) because it was a controlled-exposure study in humans. Slight throat irritation was reported by one of three individuals exposed to vinyl acetate at 20 ppm for 4 h; therefore, effects at 20 ppm are considered to be mild and below a notable discomfort threshold. An intraspecies uncertainty factor of 3 was applied because the irritation is caused by a local effect of the chemical and the response is not expected to vary greatly among individuals. Because irritation is considered a threshold effect and should not vary over time, AEGL-1 values were not scaled across time; instead, the same threshold value was adopted for all the exposure durations. The importance of concentration over exposure duration in the irritant response to vinyl acetate is supported by other findings in the Smyth and Carpenter (1973) study. Similar slight irritation was reported in one individual exposed to vinyl acetate at 20 ppm after 2 min

and 4 h. More subjects reported irritation of greater severity when exposed at higher concentrations for shorter durations (e.g., 34 ppm for 2 h or 72 ppm for 30 min). However, the data are limited because of the small number of subjects and varying exposure concentrations. AEGL-1 values for vinyl acetate are presented in Table 7-15.

The AEGL-1 value of 6.7 ppm is similar to the range of concentrations that caused hoarseness and slight ocular irritation in one of three people exposed at 4.2 and 5.7 ppm in a vinyl acetate production facility (Deese and Joyner 1969); however, the data are potentially confounded by variable exposure conditions and concurrent exposure to other chemicals.

A level of distinct odor awareness (LOA) of 0.25 ppm was derived on the basis of the odor detection threshold for vinyl acetate reported by Hellman and Small (1974) (see Appendix C for the derivation). The LOA is the concentration above which more than half of the exposed population is predicted to perceive at least a distinct odor intensity; about 10% of the population will perceive a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of exposure to vinyl acetate from its odor.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

A study by Smyth and Carpenter (1973) reported that controlled exposure to vinyl acetate at 34 ppm for 2 h resulted in persistent throat irritation in one of three individuals, and exposure at 72 ppm for 30 min resulted in ocular irritation and slight throat irritation for up to 60 min after exposure ended in all four subjects. Irritation at 72 ppm was so severe that subjects expressed an unwillingness to work at this concentration for 8 h.

6.2. Animal Data Relevant to AEGL-2

No histopathologic changes or cell proliferation were found in the olfactory or respiratory epithelium of rats exposed to vinyl acteate for 6 h at 0, 50, or 200 ppm. However, concentration-related olfactory epithelium changes (degeneration, necrosis, and exfoliation) and a concentration-related increase in cell proliferation in both the respiratory and olfactory epithelium were found in rats exposed at 600 and 1,000 ppm (Bogdanffy et al. 1997). Whether the lesions were reversible could not be determined because a recovery phase was not included in the study. However, the effects should be completely reversible from both a morphologic and functional standpoint, based on the focal and limited nature of the olfactory lesions, as well as the known regenerative capacity of the olfactory tissue (S.R. Frame, DuPont, Haskell Laboratory, Newark, DE, personal commun., December 1, 2004).

TABLE 7-15 AEGL-1 Values for Vinyl Acetate

10 min	30 min	1 h	4 h	8 h
6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)

6.3. Derivation of AEGL-2 Values

Although human data are preferred over animal data to derive AEGL values, the human study by Smyth and Carpenter was not used because its findings of notable discomfort are not relevant AEGL-2 effects. Therefore, the rat data reported by Bogdanffy et al. (1997) are the basis for the AEGL-2 values. In that study, rats exposed for 6 h to vinyl acetate at 600 and 1,000 ppm had histopathologic changes in the olfactory epithelium; no lesions were observed at 200 or 50 ppm. At 600 ppm, minimal or mild olfactory degeneration and necrosis was observed in 5/5 male rats and moderately severe lesion(s) were found in one nasal segment of 1/5 rats. At 1,000 ppm, 1/5 rats exhibited minimal degeneration and necrosis of the respiratory epithelium, and 2/5 rats had moderately severe lesions of the olfactory epithelium (Bogdanffy et al. 1997). The olfactory lesions are predicted to be reversible (S.R. Frame, DuPont, Haskell Laboratory, Newark, DE, personal commun., December 1, 2004). However, because the study did not include a recovery group, there are no data with which to empirically demonstrate that the effects were reversed. It is plausible that the effects at 600 and 1,000 ppm could be relevant AEGL-2 effects of "other serious, long-lasting adverse health effects" (NRC 2001). In a review of the toxicologic pathology of the nasal epithelium, Harkema et al. (2006) noted that olfactory epithelium damaged by exposure to toxic irritants may recover to near normal morphology, but that recovery may take weeks or months. In addition, some modification of the mucosa may occur during recovery, leading to olfactory epithelium cells that resemble respiratory epithelium. Because the reversibility of the lesions is uncertain, 200 ppm was selected as the point of departure for deriving AEGL-2 values. This concentration is considered a no-effect level for serious, long-lasting histopathologic nasal lesions in rats exposed for 6 h.

A total uncertainty factor of 10 was applied;: 3 for interspecies differences and 3 for intraspecies variability. An interspecies uncertainty factor of 3 was applied because the mechanism of nasal toxicity appears to depend on the metabolism of vinyl acetate to the metabolites acetic acid and acetaldehyde via carboxylesterase and aldehyde dehydrogenase. Studies of the metabolism of vinyl acetate by the nasal cavity reported little difference among male and female mice and rats and humans in the carboxylesterase-mediated metabolism of vinyl acetate, particularly by olfactory epithelium (Bogdanffy and Taylor 1993; Bogdanffy et al. 1998). Esterase distribution in the nasal respiratory tissue of humans is believed to be similar to that of rats (Andersen et al. 2002). An

intraspecies uncertainty factor of 10 would normally be applied because considerable variability in olfactory nasal tissue occurs in humans with regard to surface area, composition of epithelial tissue layers (respiratory-type tissue can be interspersed with more characteristic olfactory tissue), and age-related changes (Andersen et al. 2002). However, a total uncertainty factor of 30 would result in an 8-h AEGL-2 value (5 ppm) lower than the AEGL-1 value of 6.7 ppm. Reduction of an uncertainty factor is appropriate when the weight of evidence indicates that a higher uncertainty factor would result in AEGL values at odds with human data (NRC 2001). Therefore, the intraspecies uncertainty factor was reduced to 3.

The experimentally derived exposure values were scaled to AEGL time frames using the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 0.8 to 3.5 (ten Berge et al. 1986). The value of n was not empirically derived because of insufficient data on vinyl acetate; therefore, default values of n = 1 for extrapolating from shorter to longer durations and n = 3 for extrapolating from longer to shorter durations were used. The 10-min AEGL-2 value was set equal to the 30-min AEGL-2 of 46 ppm because of the uncertainty in extrapolating a 6-h exposure to a 10-min value (NRC 2001).

AEGL-2 values for vinyl acetate are presented in Table 7-16.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human data relevant to AEGL-3 values were available.

7.2. Summary of Animal Data Relevant to AEGL-3

Mortality data on vinyl acetate were available for rats, mice, guinea pigs, and rabbits (Smyth and Carpenter 1973). Chamber concentrations were not measured, but nominal concentrations were corrected against a calibration curve. Lethal concentrations produced signs of irritation (gasping and lacrimation) and central nervous system effects (poor coordination, prostration, and clonic convulsions), and death was attributed to pulmonary irritation (pulmonary congestion, hemorrhages, and excess pleural fluid).

Nonlethal concentrations of vinyl acetate produced signs of congested extremities in rats, lacrimation in guinea pigs, and no signs in mice or rabbits (Smyth and Carpenter 1973). Dogs exhibited lacrimation, nasal froth, and tremors when exposed for 4 h at 3,280 ppm, and irritation but no central nervous system effects at 1,640 ppm (Smyth and Carpenter 1973). Exposure to vinyl acetate at 1,000 ppm for 6 h/day, 5 days/week for 4 weeks was not lethal to male and female rats or mice (Owen 1979a,b; 1980a,b).

TABLE 7-16 AEGL-2 Values for Vinyl Acetate

10 min	30 min	1 h	4 h	8 h
46 ppm (160 mg/m^3)	46 ppm (160 mg/m^3)	36 ppm (130 mg/m^3)	23 ppm (81 mg/m^3)	15 ppm (53 mg/m^3)

As discussed in the context of AEGL-2 values, no histopathologic effects or cell proliferation were noted in the olfactory or respiratory epithelium of rats exposed to vinyl acetate for 6 h at 0, 50, or 200 ppm, but concentration-related olfactory epithelium changes (degeneration, necrosis, and exfoliation) and a concentration-related increase in cell proliferation in both the respiratory and olfactory epithelium were present in animals exposed at 600 and 1,000 ppm (Bogdanffy et al. 1997).

A carcinogenicity assessment was not appropriate for an acute exposure scenario because the proposed mechanism of carcinogenicity suggests a nonlinear mode of action requiring continued exposure to vinyl acetate. Therefore, a one-time exposure at even high concentrations of vinyl acetate would not be expected to result in tumor development.

7.3. Derivation of AEGL-3 Values

The 4-h mortality data for vinyl acetate in five species reported by Smyth and Carpenter (1973) were not suitable for modeling. In studies with rats, mice, and guinea pigs, deaths occurred during exposure at all but the lowest concentration of vinyl acetate. In rabbits, deaths occurred at only the highest concentration. The time of death for each of the rats and mice were not specified, so the data could not be modeled. Times of death for guinea pigs and rabbits were reported, but efforts to model the data were unsuccessful. Only one dog per exposure was tested by Smyth and Carpenter (1973), so those data were also unsuitable for modeling.

In the absence of modeling results to determine a lethality threshold for vinyl acetate, the highest nonlethal concentrations found in different species were considered. Vinyl acetate at 1,640 ppm was nonlethal in rats, guinea pigs, and rabbits exposed for 4 h. In mice, no death occurred in six mice exposed at 410 ppm, and one of six mice died after exposure at 820 ppm (Smyth and Carpenter 1973). In other studies, 1,000 ppm was nonlethal to rats exposed for 6 h (Bogdanffy et al. 1997) or to rats and mice exposed for 6 h/day, 5 days/week for 4 or 13 weeks (Owen 1979a,b; 1980a,b).

Data from the Smyth and Carpenter (1973) study of mice exposed once to vinyl acetate appear to conflict with the results of repeated exposure studies. Smyth and Carpenter (1973) observed one death among six mice exposed for 4 h at 820 ppm; the exposure concentration was calculated as 1,000 ppm and then corrected to 820 ppm on the basis of gas chromatography measurements of calculated concentrations. In contrast, 10 mice (5/sex) survived exposure to vi-

nyl acetate at 1,000 ppm (measured by gas chromatography at 15-min intervals) for 6 h/day, 5/days/week for 4 weeks, and a separate group of 10 mice survived 1,500 ppm for 20 days (initial concentration of 50 ppm was increased to 1,500 ppm on day 8 of the study and continued to the end of the study at 28 days) (Owen 1979a). In a subchronic study, a group of 20 mice (10/sex) survived exposure to vinyl acetate at 1,000 ppm for 6 h/day, 5 days/week for at least 4 weeks (9/20 mice died as a result of routine blood sampling during week 5, 6, or 12) (Owen 1980a). Finally, 104/120 mice survived exposure to vinyl acetate at 600 ppm for 6 h/day, 5 days/week for 104 weeks (Bogdanffy et al. 1994). Among the acute and subchronic studies, the Owen (1979a, 1980a) studies are considered more reliable than those of Smyth and Carpenter (1973) because group sizes were larger, sex and strain of the animals were reported, exposure concentrations were measured by gas chromatography at 15-min intervals, and the study design and findings were reported in more detail.

A point of departure of 1,000 ppm for 6 h was used to derive AEGL-3 values. That concentration was nonlethal in rats exposed for a single 6-h duration (Bogdanffy et al. 1997), as well as in both rats and mice exposed repeatedly for 6 h/day, 5 days/week for 4 weeks (Owen 1979a,b, 1980a,b). A total uncertainty factor of 10 was applied: 3 for interspecies differences and 3 for intraspecies variability. An interspecies uncertainty factor of 3 is applied because the mechanism of nasal toxicity appears to depend on the metabolism of vinyl acetate to the metabolites acetic acid and acetaldehyde via carboxylesterase and aldehyde dehydrogenase. Studies investigating the metabolism of vinyl acetate by the nasal cavity reported little difference among male and female mice, rats, and humans in the carboxylesterase-mediated metabolism of vinyl acetate, particularly by olfactory epithelium (Bogdanffy and Taylor 1993; Bogdanffy et al. 1998). Esterase distribution in the nasal respiratory tissue of humans is believed to be similar to that of rats (Andersen et al. 2002). An intraspecies uncertainty factor of 3 was applied instead of 10. Application of a higher total uncertainty factor of 30 would result in an 8-h AEGL-3 value (25 ppm) lower than concentrations that did not result in serious health effects in a human volunteer study, albeit at shorter exposure durations. No life-threatening effects were found in human volunteers exposed to vinyl acetate at 34 ppm for 2 h or at 72 ppm for 30 min (Smyth and Carpenter 1973). Reduction of an uncertainty factor is appropriate when the weight of evidence indicates that a higher uncertainty factor would result in AEGL values at odds with human data (NRC 2001). Therefore, an intraspecies uncertainty factor of 3 was used.

Time scaling was performed in the same manner described for AEGL-2 values (see Section 6.3). Similarly, the 10-min AEGL-3 value was set equal to the 30-min AEGL-3 of 230 ppm because of the uncertainty in extrapolating a 6-h exposure to a 10-min value (NRC 2001).

AEGL-3 values for vinyl acetate are presented in Table 7-17.

8. SUMMARY OF AEGL VALUES

8.1. AEGL Values and Toxicity End Points

The Smyth and Carpenter (1973) study was used to derive AEGL-1 values for vinyl acetate on the basis of irritation in humans, but there were inadequate data from other human studies of AEGL-1 effects to verify consistency. AEGL-2 values are based on a no-effect level for serious, long-lasting nasal histopathologic lesions in rats. AEGL-3 values are based on the highest nonlethal concentration in rats and mice exposed for 6 h per day for up to 28 days (Owen 1979a,b, 1980a,b; Bogdanffy et al. 1997). AEGL values for vinyl acetate are presented in Table 7-18.

8.2. Comparison with Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures to vinyl acetate are presented in Table 7-19. The emergency response planning guideline 1 (ERPG-1) for vinyl acetate of 5 ppm is similar to the AEGL-1 value of 6.7 ppm. The ERPG-2 of 75 ppm is based on evidence that healthy humans can tolerate irritant effects at 72 ppm for 30 min (Smyth and Carpenter 1973) and that no effects were observed in subchronic studies in animals at concentrations up to 200 ppm (Owen 1980a,b; Bogdanffy et al. 1997). The difference between the ERPG-2 and AEGL-2 values appears to be due to the use of an uncertainty factor for intraspecies differences in deriving the AEGL-2 value, which was not used in determining the ERPG-2 value.

TABLE 7-17 AEGL-3 Values for Vinyl Acetate

10 min	30 min	1 h	4 h	8 h
230 ppm (810 mg/m^3)	230 ppm (810 mg/m^3)	180 ppm (630 mg/m^3)	110 ppm (390 mg/m^3)	75 ppm (260 mg/m^3)

TABLE 7-18 AEGL Values for Vinyl Acetate

	Exposure Duration				
Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)
AEGL-2 (disabling)	46 ppm (160 mg/m^3)	46 ppm (160 mg/m^3)	36 ppm (130 mg/m^3)	23 ppm (81 mg/m^3)	15 ppm (53 mg/m^3)
AEGL-3 (lethal)	230 ppm (810 mg/m^3)	230 ppm (810 mg/m^3)	180 ppm (630 mg/m^3)	110 ppm (390 mg/m^3)	75 ppm (260 mg/m^3)

TABLE 7-19 Standards and Guidelines for Vinyl Acetate

	Exposure Duration					
Guideline	10 min	15 min	30 min	1 h	4 h	8 h
AEGL-1	6.7 ppm		6.7 ppm	6.7 ppm	6.7 ppm	6.7 ppm
AEGL-2	46 ppm		46 ppm	36 ppm	23 ppm	15 ppm
AEGL-3	230 ppm		230 ppm	180 ppm	110 ppm	75 ppm
ERPG-1 (AIHA)[a]				5 ppm		
ERPG-2 (AIHA)				75 ppm		
ERPG-3 (AIHA)				500 ppm		
TLV-TWA (ACGIH®)[b]						10 ppm (A3)
REL-C (NIOSH)[c]		4 ppm				
TLV-STEL (ACGIH®)[d]		15 ppm				
MAC (The Netherlands)[e]						5 ppm

[a]ERPG (emergency response planning guidelines, American Industrial Hygiene Association [AIHA 2004]).
ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.
ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action.
ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects.
[b]TLV-TWA (threshold limit value - time weighted average, American Conference of Governmental Industrial Hygienists [ACGIH 2012]) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. Notation of 3A designates that vinyl acetate is a confirmed animal carcinogen with unknown relevance to humans.
[c]REL-C (recommended exposure limits - ceiling, National Institute for Occupational Safety and Health [NIOSH 2011]) is a ceiling value that must not be exceeded during any part of the workday.
[d]TLV-STEL (threshold limit value - short-term exposure limit, American Conference of Governmental Industrial Hygienists [ACGIH 2012]) is a 15-min time-weighted average exposure that should not be exceeded at any time during a workday, even if the 8-h time-weighted average is within the TLV-TWA. The TLV-STEL is the concentration to which it is believed that workers can be exposed continuously for a short period of time without suffering from: (1) irritation, (2) chronic or irreversible tissue damage, (3) dose-rate-dependent toxic effects, or (4) narcosis of sufficient degree to increase the likelihood of accidental injury, impaired self-rescue, or materially reduced work efficiency.
[e]MAC (maximaal aanvaaarde concentratie [maximal accepted concentration], Dutch Expert Committee for Occupational Standards, , The Netherlands [MSZE 2004]) is defined analogous to the ACGIH TLV-TWA.

AIHA (2004) selected an ERPG-3 of 500 ppm for vinyl acetate on the basis of a study reporting the death of one of six mice exposed at 1,000 ppm (810 ppm after adjustment based on gas chromotograpic calibration) (Smyth and Carpenter 1973) and chronic studies in which rats and mice survived exposure to vinyl acetate at 600 ppm (Bogdanffy et al. 1994). AIHA (2004) reported that mice were the most sensitive species, and that all species exhibited signs consistent with respiratory tract irritation. The organization concluded that "It is believed that nearly all individuals could be exposed to 500 ppm vinyl acetate for up to 1 h without experiencing or developing life-threatening health effects". Thus, the primary difference between the ERPG-3 and AEGL-3 derivations appears to be that the AEGL-3 values incorporate uncertainty factors for interspecies differences and intraspecies variability.

Occupational standards for repeated 8-h exposures to vinyl acetate are 5 ppm (MSZW 2004) and 10 ppm (ACGIH 2012), and 15-min occupational exposure limits are 4 ppm (NIOSH 2011) and 15 ppm (ACGIH 2012). These standards are in the same range as the AEGL-1 of 6.7 ppm for protection against notable irritation.

8.3. Data Adequacy and Research Needs

Although data were considered adequate for derivation of all three AEGL levels, the overall database on vinyl acetate was limited. The volunteer study with controlled exposure to vinyl acetate (Smyth and Carpenter 1973) had inadequate documentation of the study design and findings, and exposure concentrations were calculated rather than measured. In the occupational health study, exposures were variable and subjects were likely exposed to other airborne contaminants concurrently (Deese and Joyner 1969). The animal database for nonlethal effects of vinyl acetate is more robust, and includes single-day, 4-week, 13-week, and chronic exposure studies (Owen 1979a,b, 1980a,b; Bogdanffy et al. 1994, 1997). However, lethality data were only available from the studies by Smyth and Carpenter (1973), which lacked analytic confirmation of exposure concentrations and had results that appear to conflict with those from repeated exposure studies. Thus, well-conducted animal lethality studies would enhance the toxicologic database, as would more rigorous occupational health studies or controlled-exposure experiments in humans.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR VINYL ACETATE

Derivation of AEGL-1 Values

Key study:	Smyth, H.F., and C.P. Carpenter. 1973. Initial Submission: Vinyl Acetate: Single Animal Inhalation and Human Sensory Response with Cover Letter Dated 08/27/92. Special Report 36-52. Carnegie-Mellon Institute, Pittsburgh, PA. Submitted to EPA by Union Carbide Corporation, Danbury. CT. EPA Document. No. 88-920010328. Microfiche No. OTS 0571724.
Toxicity end point:	Human exposure to vinyl acetate at 20 ppm for 4 h resulted in one of three individuals complaining of persistent, slight throat irritation, and exposure at 34 ppm for 2 h resulted in one of three individuals complaining of persistent throat irritation (no longer slight). Therefore, 20 ppm represents a no-effect level for notable discomfort.
Time scaling:	None; because irritation is considered a threshold effect and should not vary over time, the AEGL-1 value is not scaled across time. The threshold is used at the point of departure for all AEGL-1 durations.
Uncertainty factors:	3 for intraspecies variability
Calculations:	
10- and 30-min, 1-, 4-, and 8-h AEGL-1	20 ppm ÷ 3 = 6.7 ppm

Derivation of AEGL-2 Values

Key study:	Bogdanffy, M.S., N.L. Gladnick, T. Kegelman, and S.R. Frame. 1997. Four week inhalation cell proliferation study of the effects of vinyl acetate on rat nasal epithelium. Inhal. Toxicol. 9(1):331-350.

Toxicity end points:	No-observed-effect level of 200 ppm for 6 h for serious, long-lasting histopathologic nasal lesions in rats.
Time scaling	$C^n \times t = k$ (defaults of n = 1 for extrapolating from shorter to longer durations and n = 3 for extrapolating from longer to shorter durations) $(200 \text{ ppm})^1 \times 6 \text{ h} = 1{,}200 \text{ ppm-h}$ $(200 \text{ ppm})^3 \times 6 \text{ h} = 4.8 \times 10^7 \text{ ppm-h}$
Uncertainty factors:	3 for interspecies differences; the mechanism of nasal toxicity appears to depend on the metabolism of vinyl acetate to the metabolites acetic acid and acetaldehyde via carboxylesterase and aldehyde dehydrogenase. Studies investigating the metabolism of vinyl acetate by the nasal cavity found little difference among mice, rats, and humans in the carboxylesterase-mediated metabolism of vinyl acetate, particularly by olfactory epithelium (Bogdanffy and Taylor 1993; Bogdanffy et al. 1998). Esterase distribution in the nasal respiratory tissue of humans is believed to be similar to that of rats (Andersen et al. 2002). 3 for intraspecies variability; the usual factor of 10 would result in an 8-h AEGL-2 value of 5 ppm, a concentration lower than the AEGL-1 value of 6.7 ppm. Reduction of an uncertainty factor is appropriate when the weight of evidence indicates that a higher uncertainty factor would result in AEGL values at odds with human data (NRC 2001).
Modifying factor:	Not applicable
Calculations:	
10-min AEGL-2:	Set equal to the 30-min AEGL-2 value of 46 ppm, because of uncertainty in extrapolating a 6-h exposure to 10-min value (NRC 2001).
30-min AEGL-2:	$C^3 \times 0.5 \text{ h} = 4.8 \times 10^7 \text{ ppm-h}$ $C^3 = 9.6 \times 10^7 \text{ ppm}$ $C = 460 \text{ ppm} \div 10 = 46 \text{ ppm}$

1-h AEGL-2: $C^3 \times 1\ h = 4.8 \times 10^7$ ppm-h
$C^3 = 4.8 \times 10^7$ ppm
C = 360 ppm ÷ 10 = 36 ppm

4-h AEGL-2: $C^3 \times 4\ h = 4.8 \times 10^7$ ppm-h
$C^3 = 1.2 \times 10^7$ ppm
C = 230 ppm ÷ 10 = 23 ppm

8-h AEGL-2: $C^1 \times 8\ h = 1{,}200$ ppm-h
$C^1 = 150$ ppm
C = 150 ppm ÷ 10 = 15 ppm

Derivation of AEGL-3 Values

Key studies:

Bogdanffy, M.S., N.L. Gladnick, T. Kegelman, and S.R. Frame. 1997. Four week inhalation cell proliferation study of the effects of vinyl acetate on rat nasal epithelium. Inhal. Toxicol. 9(1):331-350.

Owen, P.E. 1979a. Vinyl Acetate: 4 Week Inhalation Dose Range Study in the Mouse. Report No. 1884-51/3. Prepared for Society of the Plastics Industry Inc., New York, by Hazleton Laboratories Europe, Ltd., Harrogate, England, August 1979. EPA Document No. FYI-OTS-0184-0278SU. Microfiche No. OTS0278.

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Owen, P.E. 1980b. Vinyl Acetate: 3 Month Inhalation Toxicity Study in the Rat. Report No. 2286-51/5. Prepared for The Society of the Plastics Industry Inc., New York, by Hazleton Laboratories Europe, Ltd., Harrogate, England, May 1980. EPA Document No. FYI-OTS-0184-0278SU. Microfiche No. OTS0278.

Toxicity end points:	1,000 ppm for 6 h was nonlethal in rats and mice.
Time scaling:	$C^n \times t = k$ (defaults of n = 1 for extrapolating from shorter to longer durations and n = 3 for extrapolating from longer to shorter durations) $(1{,}000 \text{ ppm})^1 \times 6 \text{ h} = 6{,}000 \text{ ppm-h}$ $(1{,}000 \text{ ppm})^3 \times 6 \text{ h} = 6.0 \times 10^9 \text{ ppm-h}$
Uncertainty factors:	3 for interspecies differences; the mechanism of nasal toxicity appears to depend on the metabolism of vinyl acetate to the metabolites acetic acid and acetaldehyde via carboxylesterase and aldehyde dehydrogenase. Studies investigating the metabolism of vinyl acetate by the nasal cavity found little difference among mice, rats, and humans in the carboxylesterase-mediated metabolism of vinyl acetate, particularly by olfactory epithelium (Bogdanffy and Taylor 1993; Bogdanffy et al. 1998). Esterase distribution in the nasal respiratory tissue of humans is believed to be similar to that of rats (Andersen et al. 2002). 3 for intraspecies variability; the usual factor of 10 would result in an 8-h AEGL-3 value of 25 ppm, a concentration lower than concentrations that did not result in serious health effects in a human volunteer study. Reduction of an uncertainty factor is appropriate when the weight of the evidence indicates that a higher uncertainty factor would result in AEGL values at odds with human data (NRC 2001).
Modifying factor:	Not applicable
Calculations:	
10-min AEGL-3:	Set equal to the 30-min AEGL-3 value of 230 ppm, because of uncertainty in extrapolating a 6-h exposure to 10-min value (NRC 2001).
30-min AEGL-3:	$C^3 \times 0.5 \text{ h} = 6.0 \times 10^9 \text{ ppm-h}$ $C^3 = 1.2 \times 10^{10} \text{ ppm}$ $C = 2{,}289 \text{ ppm} \div 10 = 230 \text{ ppm}$
1-h AEGL-3:	$C^3 \times 1 \text{ h} = 6.0 \times 10^9 \text{ ppm-h}$ $C^3 = 6.0 \times 10^9 \text{ ppm}$ $C = 1{,}817 \text{ ppm} \div 10 = 180 \text{ ppm}$

4-h AEGL-3: $C^3 \times 4\ h = 6.0 \times 10^9$ ppm-h
$C^3 = 1.5 \times 10^8$ ppm
C = 1,144 ppm ÷ 10 = 110 ppm

8-h AEGL-3: $C^1 \times 8\ h = 6{,}000$ ppm-h
$C^1 = 750$ ppm
C = 750 ppm ÷ 10 = 75 ppm

APPENDIX B

CALCULATION OF LEVEL OF DISTINCT ODOR AWARENESS FOR VINYL ACETATE

The level of distinct odor awareness (LOA) represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, and about 10% of the population will experience strong odor intensity. The LOA should help chemical emergency responders assess the public awareness of the exposure to vinyl acetate on the basis of odor perception. The LOA for vinyl acetate was derived according to the guidance of van Doorn et al. (2002).

For derivation of an odor detection threshold (OT_{50}), a study by Hellman and Small (1974) was used. The study also determined an odor threshold for the reference chemical n-butanol (odor detection threshold 0.04 ppm):

- Odor detection threshold for vinyl acetate : 0.12 ppm
- Odor detection threshold for n-butanol: 0.3 ppm
- Corrected OT_{50} for vinyl acetate : (0.12 ppm × 0.04) ÷ 0.3 = 0.016 ppm

The concentration (C) leading to an odor intensity (I) of distinct odor detection (I = 3) is derived using the Fechner function:

$$I = k_w \times \log (C \div OT_{50}) + 0.5$$

For the Fechner coefficient, the default of $k_w = 2.33$ will be used due to the lack of chemical-specific data:

$$3 = 2.33 \times \log (C \div 0.016) + 0.5$$

which can be rearranged to:

$$\log (C \div 0.016) = (3 - 0.5) \div 2.33 = 1.07$$

and results in:

$$C = 10^{1.07} \times 0.016 = 11.8 \times 0.016 = 0.1888 \text{ ppm}$$

The resulting concentration is multiplied by an empirical field correction factor. The factor takes into account that everyday life factors, such as sex, age, sleep, smoking, upper airway infections, allergies, and distractions, increase the odor detection threshold by a factor of 4. In addition, it takes into account that odor perception is very fast (about 5 seconds), which leads to the perception of concentration peaks. On the basis of current knowledge, a factor of 1/3 is

applied to adjust for peak exposure. Adjustment for distraction and peak exposure lead to a correction factor of 1.33 (4 ÷ 3).

$$\text{LOA} = \text{C} \times 1.33 = 0.189 \text{ ppm} \times 1.33 = 0.25 \text{ ppm}$$

The LOA for vinyl acetate is 0.25 ppm.

APPENDIX C

CATEGORY PLOT FOR VINYL ACETATE

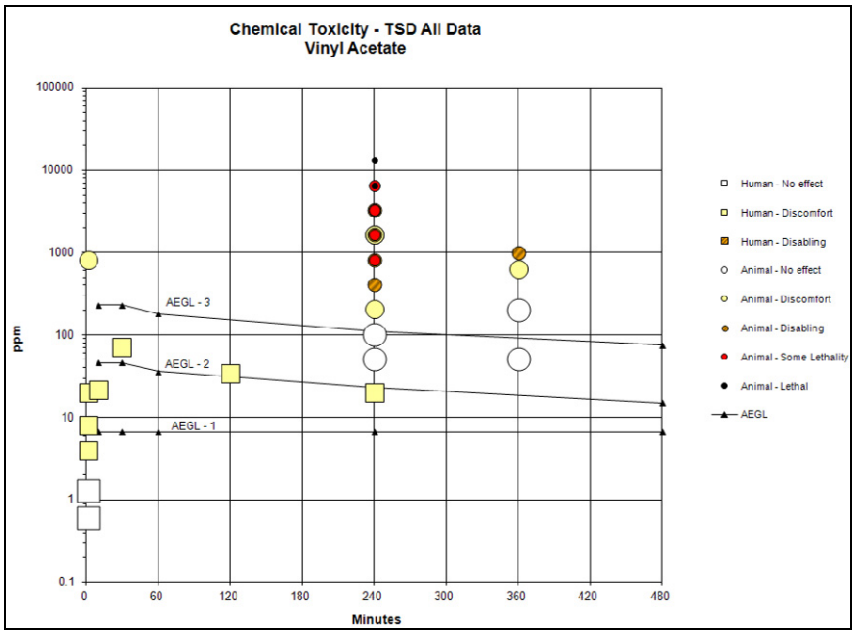

FIGURE C-1 Categoray plot of animal and human toxicity data on vinyl acetate compared with AEGL values.

TABLE C-1 Data Used in Category Plot for Vinyl Acetate

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
NAC/AEGL-1				6.7	10	AEGL	
NAC/AEGL-1				6.7	30	AEGL	
NAC/AEGL-1				6.7	60	AEGL	
NAC/AEGL-1				6.7	240	AEGL	
NAC/AEGL-1				6.7	480	AEGL	
NAC/AEGL-2				46	10	AEGL	
NAC/AEGL-2				46	30	AEGL	
NAC/AEGL-2				36	60	AEGL	
NAC/AEGL-2				23	240	AEGL	
NAC/AEGL-2				15	480	AEGL	
NAC/AEGL-3				230	10	AEGL	
NAC/AEGL-3				230	30	AEGL	
NAC/AEGL-3				180	60	AEGL	
NAC/AEGL-3				110	240	AEGL	
NAC/AEGL-3				75	480	AEGL	
Smyth and Carpenter 1973	Human		1	0.6	2	0	No effects
	Human		1	1.3	2	0	Odor detection
	Human		1	4	2	1	Odor detection; minimal ocular, nasal, throat irritation
	Human		1	8	2	1	Odor detection; minimal ocular, nasal, throat irritation
	Human		1	20	2	1	Odor detection; minimal ocular, nasal, throat irritation

(Continued)

TABLE C-1 Continued

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
	Human		1	20	240	1	Olfactory fatigue; throat irritation
	Human		1	34	120	1	Olfactory fatigue; throat irritation
	Human		1	72	30	1	Olfactory fatigue; throat irritation
Deese and Joyner 1969	Human		1	21.6	10	1	Odor detection, upper respiratory irritation
Smyth and Carpenter 1973	Rat	Both	1	1,640	240	2	Congestion
	Rat	Both	1	3,280	240	SL	Mortality (4/12); gasping, convulsions
	Rat		1	6,560	240	3	Mortality (12/12)
Smyth and Carpenter 1973	Mouse		1	410	240	2	
	Mouse		1	820	240	SL	Mortality (1/6), labored breathing
	Mouse		1	1,640	240	SL	Mortality (4/6), gasping, convulsions
	Mouse		1	3,280	240	SL	Mortality (5/6), gasping, convulsions, ocular effects
	Mouse		1	6,560	240	3	Mortality (6/6)
Smyth and Carpenter 1973	Guinea pig	Male	1	1,640	240	1	Lacrimation
	Guinea pig	Male	1	3,280	240	SL	Mortality (1/6), labored breathing, lacrimation
	Guinea pig	Male	1	6,560	240	SL	Mortality (4/6), gasping, convulsions
	Guinea pig	Male	1	13,120	240	3	Mortality (4/6), gasping, nose rubbing, lacrimation
	Rabbit	Male	1	3,280	240	SL	Mortality (3/4), red nose, cloudy eyes
	Rabbit	Male	1	6,560	240	3	Mortality (4/4); labored breathing, convulsions, cloudy eyes, bloody nose

	Dog	Male	1	51.25	240	0	No effects
	Dog	Male	1	102.5	240	0	No effects
	Dog	Male	1	205	240	1	Blinking, red sclera
	Dog	Male	1	820	240	2	Lacrimation, red sclera
	Dog	Male	1	1,640	240	1	Blinking, sneezing, lacrimation, inflamed eyelids, nasal froth
	Dog	Male	1	3,280	240	2	Ocular and nasal irritation, tremors, froth from nostrils
	Dog		1	820	2	1	Lacrimation
Gage 1970	Rat		1	630	360	1	Low body weight
Bogdanffy et al. 1997	Rat		1	50.8	360	0	No effects
	Rat		1	199.6	360	0	No effects
	Rat		1	1,007.3	360	2	Histopathologic changes (nasal epithelium)

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

APPENDIX D

ACUTE EXPOSURE GUIDELINE LEVELS FOR VINYL ACETATE

Derivation Summary

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)

Key reference: Smyth, H.F., and C.P. Carpenter. 1973. Initial Submission: Vinyl Acetate: Single Animal Inhalation and Human Sensory Response with Cover Letter Dated 08/27/92. Special Report 36-52. Carnegie-Mellon Institute, Pittsburgh, PA. Submitted to EPA by Union Carbide Corporation, Danbury, CT. EPA Document. No. 88-920010328. Microfiche No. OTS 0571724.

Test species/Strain/Number: Human volunteers, 3-9 subjects (3 volunteers at concentration selected as point of departure)

Exposure route/Concentrations/Durations: 0.6, 1.3, 4, 8, or 20 ppm for 2 min; 20 ppm for 4 h; 34 ppm for 2 h; 72 ppm for 30 min

Effects:

Concentration (ppm)	No. of subjects	Duration (min)	Response
0.6	9	2	None
1.3	9	2	9 immediate odor; 5 no odor at 2 min
4	9	2	9 immediate odor, 3 no odor at 2 min; 1 minimal ocular, nasal, and throat irritation
8	9	2	9 immediate odor; 1 no odor at 2 min; 2 minimal ocular, nasal, and throat irritation
20	9	2	9 immediate odor;1 minimal ocular, nasal, and throat irritation
20	3	240	3 complete olfactory fatigue in 3-116 min; 1 persistent slight throat irritation
34	3	120	1 complete, 2 partial olfactory fatigue; 1 transient, 1 persistent throat irritation
72	4	30	4 strong odor, partial olfactory fatigue; 4 slight throat irritation 20-60 min after exposure; ocular irritation up to 60 min after exposure; subjects expressed unwillingness to work at this concentration for 8 h.

End point/Concentration/Rationale: Exposure to vinyl acetate at 4-20 ppm for 2 min and 20 ppm for 240 min produced slight throat irritation; exposure at 34 ppm for 2 h resulted in one of three individuals complaining of persistent throat irritation; and exposure at 72 ppm for 30 min resulted in irritation severe enough that the exposed subjects expressed unwillingness to work at that concentration for 8 h (Smyth and Carpenter 1973). Therefore, 20 ppm for 4 h represents a no-effect level for notable discomfort.

Uncertainty factors/Rationale:
Total uncertainty factor: 3
Intraspecies: 3, because irritation is caused by a local effect of the chemical and the response is not expected to vary greatly among individuals.

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: Because irritation is considered a threshold effect and should not vary over time, AEGL-1 values are not scaled across time. The threshold value was applied to all AEGL durations.

Data adequacy: The key study lacked measured exposure concentrations, but provided adequate basis for AEGL-1 values and is supported to some extent by occupational health data.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
46 ppm (160 mg/m^3)	46 ppm (160 mg/m^3)	36 ppm (130 mg/m^3)	23 ppm (81 mg/m^3)	15 ppm (53 mg/m^3)

Key reference: Bogdanffy, M.S., N.L. Gladnick, T. Kegelman, and S.R. Frame. 1997. Four-week inhalation cell proliferation study of the effects of vinyl acetate on rat nasal epithelium. Inhal. Toxicol. 9(1):331-350.

Test species/Strain/Number: Rat, Sprague-Dawley, 5 males/group

Exposure route/Concentrations/Durations: Inhalation, 0, 50, 200, 600, or 1,000 ppm for 6 h

Effects:
0, 50, 200 ppm: No effects
600 ppm: Degenerative lesions and increased cell proliferation in olfactory epithelium
1,000 ppm: Increased incidence and severity of lesions in olfactory epithelium; some minimal lesions in respiratory epithelium; increased cell proliferation in olfactory epithelium.

End point/Concentration/Rationale: 200 ppm for 6 h is a no-observed-effect level for serious, long-lasting histopathologic nasal lesions

Uncertainty factors/Rationale:
Total uncertainty factor: 10:

(Continued)

AEGL-2 VALUES Continued

Interspecies: 3, because the mechanism of nasal toxicity appears to depend on the metabolism of vinyl acetate to the metabolites acetic acid and acetaldehyde via carboxylesterase and aldehyde dehydrogenase. Studies investigating the metabolism of vinyl acetate by the nasal cavity found little difference among mice, rats and humans in the carboxylesterase-mediated metabolism of vinyl acetate, particularly by olfactory epithelium (Bogdanffy and Taylor 1993; Bogdanffy et al. 1998). Esterase distribution in the nasal respiratory tissue of humans is believed to be similar to that of rats (Andersen et al. 2002).
Intraspecies: 3, because the usual factor of 10 would result in an 8-h AEGL-2 value of 5 ppm, a concentration lower than the AEGL-1 value of 6.7 ppm. Reduction of an uncertainty factor is appropriate when the weight of evidence indicates that a higher uncertainty factor would result in AEGL values at odds with human data (NRC 2001).

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: The experimentally derived exposure values were scaled to AEGL durations using the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 0.8 to 3.5 (ten Berge et al. 1986). The value of n was not empirically derived because of insufficient data on vinyl acetate; therefore, the default values of n = 1 for extrapolating from shorter to longer durations and n = 3 for extrapolating from longer to shorter durations were used. The 10-min AEGL-2 value was set equal to the 30-min value of 46 ppm because of the uncertainty associated with extrapolating a 6-h exposure duration to a 10-min AEGL value (NRC 2001).

Data adequacy: The database for nonlethal effects of vinyl acetate includes single exposure (Bogdanffy et al. 1997), 4-week (Owen 1979a,b), 13-week (Owen 1980a,b), and chronic (Bogdanffy et al. 1994) studies of mice and rats exposed via inhalation, and provides a robust basis for AEGL-2 values.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
230 ppm (810 mg/m^3)	230 ppm (810 mg/m^3)	180 ppm (630 mg/m^3)	110 ppm (390 mg/m^3)	75 ppm (260 mg/m^3)

Key references: Bogdanffy, M.S., N.L. Gladnick, T. Kegelman, and S.R. Frame. 1997. Four-week inhalation cell proliferation study of the effects of vinyl acetate on rat nasal epithelium. Inhal. Toxicol. 9(1):331-350.
Owen, P.E. 1979a. Vinyl Acetate: 4 Week Inhalation Dose Range Study in the Mouse. Report No. 1884-51/3. Prepared for Society of the Plastics Industry Inc., New York, by Hazleton Laboratories Europe, Ltd., Harrogate, England, August 1979. EPA Document No. FYI-OTS-0184-0278SU. Microfiche No. OTS0278.
Owen, P.E. 1979b. Vinyl Acetate: 4 Week Inhalation Dose Range Study in the Rat.

Report No. 1835-51/3. Prepared for Society of the Plastics Industry Inc., New York, by Hazleton Laboratories Europe, Ltd., Harrogate, England, August 1979. EPA Document No. FYI-OTS-0184-0278SU. Microfiche No. OTS0278.
Owen, P.E. 1980a. Vinyl Acetate: 3 Month Inhalation Toxicity Study in the Mouse. Report No. 2303-51/5. Prepared for The Society of the Plastics Industry Inc., New York, by Hazleton Laboratories Europe, Ltd., Harrogate, England, May 1980. EPA Document No. FYI-OTS-0184-0278SU. Microfiche No. OTS0278.
Owen, P.E. 1980b. Vinyl Acetate: 3 Month Inhalation Toxicity Study in the Rat. Report No. 2286-51/5. Prepared for The Society of the Plastics Industry Inc., New York, by Hazleton Laboratories Europe, Ltd., Harrogate, England, May 1980. EPA Document No. FYI-OTS-0184-0278SU. Microfiche No. OTS0278.

Test species/Strain/Number: Rat (Sprague-Dawley and CD) and mouse (CD-1), 5-20 males and females

Exposure route/Concentrations/Durations: 0, 50, 150, 200, 500, 600, or 1,000 ppm for 6 h/day for 1-28 days

Effects: No lethality at 1,000 ppm

End point/Concentration/Rationale: 1,000 ppm for 6 h is considered a threshold for lethality

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, because the mechanism of nasal toxicity appears to depend on the metabolism of vinyl acetate to the metabolites acetic acid and acetaldehyde via carboxylesterase and aldehyde dehydrogenase. Studies investigating the metabolism of vinyl acetate by the nasal cavity found little difference among mice, rats and humans in the carboxylesterase-mediated metabolism of vinyl acetate, particularly by olfactory epithelium (Bogdanffy and Taylor 1993; Bogdanffy et al. 1998). Esterase distribution in the nasal respiratory tissue of humans is believed to be similar to that of rats (Andersen et al. 2002).
Intraspecies: 3, because the usual factor of 10 would result in an 8-h AEGL-3 value of 25 ppm, a concentration lower than experimental concentrations that did not result in serious health effects in a human volunteer study. Reduction of an uncertainty factor is appropriate when the weight of the evidence indicates that a higher uncertainty factor would result in AEGL values at odds with human data (NRC 2001).

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: The experimentally derived exposure values were scaled to AEGL durations using the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 0.8 to 3.5 (ten Berge et al. 1986). The value of n was not empirically derived because of insufficient data on vinyl acetate; therefore, the default values of n = 1 for extrapolating from shorter to longer durations and n = 3 for extrapolating from longer to shorter durations were used.

(Continued)

AEGL-3 VALUES Continued

The 10-min AEGL-3 was set equal to the 30-min value of 230 ppm because of the uncertainty associated with extrapolating a 6-h exposure duration to a 10-min value (NRC 2001).

Data adequacy: The animal database for nonlethal effects of vinyl acetate is robust, and includes single day, 4-week, 13-week, and chronic exposure studies (Owen 1979a,b, 1980a,b; Bogdanffy et al. 1994, 1997). These studies provide a strong basis for identifying a nonlethal point of departure. Lethality data are only available from the poorly documented studies by Smyth and Carpenter (1973), which lacked analytic confirmation of exposure concentrations and provided data that conflict with the results of repeated exposure studies.