Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 16

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 sixteenth volume

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

in that series. AEGL documents for selected aliphatic nitriles, benzonitrile, methacrylonitrile, allyl alcohol, hydrogen selenide, ketene, and tear gas 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 selected aliphatic nitriles (interim reports 19b and 21b), benzonitrile (interim reports 19b and 21b), methacrylonitrile (interim reports 19a, 20a, and 21a), allyl alcohol (interim reports 10, 12, 14, 18, and 21a), hydrogen selenide (interim report 16), ketene (interim reports 17 and 21a), and tear gas (interim reports 19a and 21a): Deepak Bhalla (Wayne State University), Harvey Clewell (The Hamner Institutes for Health Sciences), Jeffrey Fisher (U.S. Food and Drug Administration), Sidney Green (Howard University), David Gaylor (Gaylor and Associates, LLC), Sam Kacew (University of Ottawa), A. Wallace Hayes (Harvard School of Public Health), Rogene Henderson (Lovelace Respiratory Research Institute [retired]), James McDougal (Wright State University [retired]), Charles Reinhardt (DuPont Haskell Laboratory [retired]), Andrew Salmon (California Environmental Protection Agency), Kenneth Still (Portland State University), Joyce Tsuji (Exponent, Inc.), Bernard Wagner (New York University Medical Center [retired]), and Judith Zelikoff (New York University).

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of this volume before its release. The review of interim reports was overseen by David Gaylor (Gaylor and

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

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

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

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

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

This report is the sixteenth 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 extrapolation of data from other routes would lead to additional uncertainty in the AEGL estimate.

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

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

REVIEW OF AEGL REPORTS

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

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

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

Because of the enormous amount of data presented in AEGL reports, the NRC committee cannot verify all of the data used by NAC. The NRC committee relies on NAC and the contractors for the accuracy and completeness of the toxicity data cited in the AEGL reports. Thus far, the committee has prepared fifteen reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009, 2010a,b, 2011, 2012a,b,c, 2013a,b). This report is the sixteenth volume in that series. AEGL documents for selected aliphatic nitriles, benzonitrile, methacrylonitrile, allyl alcohol, hydrogen selenide, ketene, and tear gas 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

4

Allyl Alcohol[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

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

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

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

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

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

SUMMARY

Allyl alcohol is a colorless liquid that is a potent sensory irritant. Signs of intoxication following inhalation exposure to allyl alcohol vapor include lacrimation, pulmonary edema and congestion, and inflammation, hemorrhage, and degeneration of the liver and kidneys. Human data include studies of voluntary exposures to allyl alcohol for short durations and general descriptions of symptoms after accidental occupational exposures at unknown concentrations and durations. Animal data include a relatively recent detailed inhalation study in rats, studies in which only lethality was evaluated, studies of subchronic exposures, and single-exposure experiments in which only the RD_{50} (concentration that reduces the respiratory rate of test organisms by 50%) was measured.

Data from the study by Nielsen et al. (1984) were used as the basis of the AEGL-1 values for allyl alcohol. An RD_{10} of 0.27 ppm (30 min) in mice was used an estimate of the threshold for irritation. A total uncertainty factor of 3 was applied, as irritant effects are not expected to vary greatly between species or individuals. Time scaling was not applied because of the short duration of exposure.

The Kirkpatrick (2008) study in rats was selected as the basis for deriving AEGL-2 values. No-effect levels for disabling effects (reduced response to stimulus and gasping) from allyl alcohol were 51 ppm for 1 h, 22 ppm for 4 h, and 10 ppm for 8 h; these values were used as the points-of-departure for the 1-,

4- and 8-h AEGL-2 values, respectively. A total uncertainty factor of 30 was applied. An interspecies uncertainty factor of 3 was used because similar 1-h no-effect levels for lethality have been reported for rats (200-423 ppm) (Union Carbide and Carbon Corporation 1951; Kirkpatrick 2008), mice (200 ppm) (Union Carbide and Carbon Corporation 1951), and rabbits (200 ppm) (Union Carbide and Carbon Corporation 1951). An intraspecies factor of 10 was applied because of the uncertainty about whether effects are due to allyl alcohol, one of its metabolites, or both. Furthermore, humans have genetic polymorphisms for aldehyde dehydrogenase. Time scaling was performed for the 10- and 30-min values using the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). An empirical value for n of 0.95 was derived from rat lethality data (see Appendix A).

AEGL-3 values for allyl alcohol are based on the calculated LC_{01} (lethal concentration, 1% lethality) values in rats of 2,600 ppm for 10 min, 820 ppm for 30 min, 400 ppm for 1 h, 93 ppm for 4 h, and 45 ppm for 8 h. LC_{01} values were calculated using the ten Berge software program and rat mortality data from four studies (McCord 1932; Smyth and Carpenter 1948; Union Carbide and Carbon Corporation 1951; Kirkpatrick 2008) (see Appendix A). As noted for AEGL-2, the ten Berge program estimated a value for n of 0.95 for time scaling. A total uncertainty factor of 30 was applied for the same reasons described for the AEGL-2 values.

A level of distinct odor awareness, which is the concentration above which more than half of the exposed population is predicted to experience at least a distinct odor intensity and about 10% will experience a strong odor intensity, could not be determined due to inadequate data. Although odor thresholds of 1.4 and 2.1 ppm have been reported for allyl alcohol, concurrent odor-threshold data for the reference chemical n-butanol (odor detection threshold 0.04 ppm) were not available.

AEGL values for allyl alcohol are presented in Table 4-1.

TABLE 4-1 AEGL Values for Allyl Alcohol

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	0.09 ppm (0.22 mg/m^3)	0.09 ppm (0.22 mg/m^3)	0.09 ppm (0.22 mg/m^3)	0.09 ppm (0.22 mg/m^3)	0.09 ppm (0.22 mg/m^3)	Irritation threshold in mice (Nielsen et al. 1984)
AEGL-2 (disabling)	11 ppm (27 mg/m^3)	3.5 ppm (8.5 mg/m^3)	1.7 ppm (4.1 mg/m^3)	0.73 ppm (1.8 mg/m^3)	0.33 ppm (0.80 mg/m^3)	Gasping and reduced response to stimulus in rats (Kirkpatrick 2008)
AEGL-3 (lethal)	87 ppm (210 mg/m^3)	27 ppm (65 mg/m^3)	13 ppm (31 mg/m^3)	3.1 ppm (7.5 mg/m^3)	1.5 ppm (3.6 mg/m^3)	Estimated LC_{01} value in rats (McCord 1932; Smyth and Carpenter 1948;Union Carbide and Carbon Corporation 1951; Kirkpatrick 2008)

1. INTRODUCTION

Allyl alcohol is a colorless liquid that is a potent sensory irritant. The chemical has a pungent, mustard-like odor, with a reported odor-recognition concentration of 0.78 ppm (Dunlap et al. 1958; HSDB 2013) and odor-detection threshold of 1.4-2.1 ppm (AIHA 1989). Primarily used in the production of allyl esters for use in resins and plasticizers, allyl alcohol is also used as an intermediate in the production of pharmaceuticals and other organic chemicals, as a fungicide and herbicide, in the production of glycerol and acrolein, and as a flavoring agent (Tabershaw et al. 1977; ACGIH 2001; O'Neil et al. 2006). Allyl alcohol is not currently registered for pesticide use in the United States, but approved pesticide uses may change periodically (HSDB 2013). Allyl alcohol is produced from the isomerization of propylene oxide at a high temperature using a lithium phosphate catalyst (Lyondell 2006; HSDB 2013). Acrolein is an intermediate in manufacturing processes and, therefore, may be a contaminant of allyl alcohol (Nagato 2004). Information on the production volume and sales quantities of ally alcohol was not available from the US Environmental Protection Agency's nonconfidential Chemical Data Reporting (EPA 2013a). The 2006 Inventory Update Rule estimated nonconfidential production volumes of allyl alcohol of 100-500 million pounds (EPA 2010). EPA's Toxic Release Inventory (EPA 2013b) reported a total environmental release and off-site waste transfer value of 484,955 pounds. Allyl alcohol is transported by rail, truck, ship, and aircraft (Lyondell 2006). In the atmosphere, allyl alcohol is degraded by reaction with photochemically-produced hydroxyl radicals. On the basis of a rate constant of 3.0×10^{-11} cu cm/molecule-sec at 25 ºC, the half-life for that reaction in the atmosphere is approximately 4.32 h (EPA 2013c). The physical and chemical properties of allyl alcohol are presented in Table 4-2.

Vaporized and liquid allyl alcohol is intensely irritating to intact skin, eyes, and mucous membranes. Contact of ally alcohol with the eye can produce corneal burns. Direct skin contact can produce first- and second-degree burns and can induce epidermal necrosis. At sufficiently high concentrations, inhaled allyl alcohol can induce pulmonary edema (Shell Chemical Corporation 1957). Human data included controlled studies with human volunteers; no lethality or epidemiologic data on allyl alcohol inhalation exposure were available. Studies addressing lethal and nonlethal toxicity of allyl alcohol in laboratory animals were available.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No reports of death following inhalation exposure to allyl alcohol were found in the published literature. Toennes et al. (2002) reported a case of an individual dying within 100 min of ingesting a weed killer containing 85% (w/v)

allyl alcohol. Kononenko (1970) briefly described a case in which a man died within 90 min of ingesting allylic alcohol at approximately 150 mL; loss of consciousness was reported to occur 20 min after ingestion.

2.2. Nonlethal Toxicity

2.2.1. Acute Studies

Groups of five to seven volunteers, ranging in age from 19 to 39 years, were exposed to allyl alcohol for 5 min in an exposure room from one to three times per week over a total of 50 days (Dunlap et al. 1958). The 18,000-L exposure room had a revolving fan for mixing the vapor in the room. Vapor was generated by flash vaporization of allyl alcohol using a heat source. Five minutes of

TABLE 4-2 Chemical and Physical Properties of Allyl Alcohol

Parameter	Data	Reference
Synonyms	2-propen-1-ol; 1-propenol-3-ol; vinyl carbinol	O'Neil et al. 2006
CAS registry no.	107-18-6	ACGIH 2001
Chemical formula	C_3H_6O	O'Neil et al. 2006
Molecular weight	58.08	O'Neil et al. 2006
Physical state	Liquid	O'Neil et al. 2006
Color	Colorless	O'Neil et al. 2006
Melting point	-50°C	O'Neil et al. 2006
Boiling point	96-97°C	O'Neil et al. 2006
Freezing point	-129°C	HSDB 2013
Flash point	20.9°C	NIOSH 2011
Specific gravity (water = 1)	0.8540 at 20/4°C	NIOSH 2011; O'Neil et al. 2006
Solubility	Miscible with water, alcohol, chloroform, ether, petroleum ether	O'Neil et al. 2006
Vapor density (air = 1)	2.0	HSDB 2013
Vapor pressure	25.4 mmHg at 25°C;17 mmHg at 20°C	ACGIH 2001; HSDB 2013
Conversion factors in air	1 ppm = 2.42 mg/m^3 1 mg/m^3 = 0.413 ppm	ACGIH 2001; NIOSH 2011

vaporization and equilibration were allowed before the volunteers entered the room for the static exposure. Volunteers were exposed to allyl alcohol at 0.78, 6.25, 12.5, or 25.0 ppm; whether these concentrations were calculated or measured was not specified. Volunteers were prepared to describe their reactions by reviewing with them the different subjective sensations associated with a particular level of response, but the subject was not aware of the nature of the material. During the static exposure at 1-min intervals, they graded their ocular and nasal irritation, olfactory recognition, central-nervous-system effects, and pulmonary effects as absent, slight, moderate, severe, or extreme. A summary of the findings is presented in Table 4-3. After each exposure, the eyes of each subject were visually inspected, and physical examination of the chest was made at the end of the day's run or when the subject noted subjective symptoms. Olfactory recognition was noted as at least slight by five of six subjects at the lowest concentration of 0.78 ppm, and became at least moderate at 6.25 ppm in two of six subjects. At 12.5 ppm, nasal irritation of moderate or greater severity was experienced by four of seven volunteers, and all subjects described nasal irritation as moderate or greater at 25.0 ppm. Ocular irritation was slight in one of six and one of seven individuals at 6.25 and 12.5 ppm, respectively, and was moderate or greater at 25.0 ppm in all five exposed volunteers. The investigators described the ocular irritation at 25.0 ppm as severe, but it was not clear whether responses varied with repeated exposure. Separate from these tests with volunteers, Dunlap et al. (1958) described symptoms in workers who were exposed to "moderate" concentrations of allyl alcohol (concentrations not specified). Symptoms included lacrimation, retrobulbar pain, and blurred vision, which persisted for 24-48 h after exposure ended. No permanent damage to the cornea was reported.

Ten volunteers were exposed to allyl alcohol at 2 ppm for 1-3 min (Torkelson et al. 1959a). Groups of two or three volunteers entered a large exposure chamber once the desired concentration of allyl alcohol was achieved (methods described in Torkelson et al. 1959b). Half of the volunteers reported a distinct odor but no irritation. McCord (1932) commented that workers exposed to allyl alcohol (concentration, duration, and exposure situation not reported) had signs and symptoms of severe irritation of the mucous membranes, including edema, excessive secretions, conjunctivitis, and lacrimation, and that exposure at 5 ppm would produce some irritation. One worker was temporarily blinded by delayed corneal necrosis after exposure to the vapor, although the nature of the exposure was not described (Smyth 1956). The investigators reported that the primary toxic effect following exposure to allyl alcohol vapor is irritation manifested by pulmonary edema and disabling corneal injury.

Odor-detection threshold values for allyl alcohol reported by the American Industrial Hygiene Association (AIHA 1989) were 1.4 ppm (3.3 mg/m^3) and 2.1 ppm (5 mg/m^3). Those values are based on two studies (Katz and Talbert 1930; Dravnieks 1974) judged by AIHA to be acceptable.

TABLE 4-3 Summary of Sensory Responses to Ally Alcohol During 5-Minute Exposure

		Olfactory Recognition		Ocular Irritation		Nasal Irritation	
Concentration (ppm)	No. Subjects	Any Response[a]	≥ Moderate[b]	Any Response[a]	≥ Moderate[b]	Any Response[a]	≥ Moderate[b]
0.78	6	5	1	0	0	2	0
6.25	6	5	2	1	0	3	1
12.5	7	6	1	1	0	7	4
25.0	5	3	1	5	5[c]	5	5

Source: Adapted from Dunlap et al. 1958.
[a]Number of people showing any response.
[b]Number of people with responses greater than "slight."
[c]Response was graded as severe.

2.2.2. Epidemiologic Studies

Epidemiologic studies of human exposure to allyl alcohol were not available.

2.3. Developmental and Reproductive Toxicity

No human data on the developmental and reproductive toxicity of allyl alcohol were available.

2.4. Genotoxicity

No information on the genotoxicity of allyl alcohol in humans was available.

2.5. Carcinogenicity

No information on the potential carcinogenicity of allyl alcohol in humans was available.

2.6. Summary

There were no reported cases of human deaths following inhalation exposure to allyl alcohol, and no case reports of accidental occupational exposures. Volunteers exposed to allyl alcohol for 5 min reported nasal irritation at 12.5 ppm and severe ocular irritation at 25 ppm. Workers exposed to moderate concentrations (not specified) were reported to experience lacrimation, retrobulbar pain, and blurred vision. Odor-detection thresholds of 1.4 ppm and 2.1 ppm and an odor-recognition threshold of 0.78 ppm were reported for allyl alcohol.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Monkeys

One monkey (sex not specified) exposed to allyl alcohol at 1,000 ppm died 4 h into the exposure (McCord 1932). Prior to death, the monkey vomited, had diarrhea, and appeared to be in severe pain. Necropsy revealed subcutaneous hemorrhage of the abdomen, petechial hemorrhage and inflammation of the intestine, a distended gastrointestinal tract, and hemorrhage of the spleen and kidneys. Inflammation was found in the brain, meninges, and blood vessels, and the lungs had edema with hemorrhagic exudate.

3.1.2. Rats

Groups of five male and five female Crl:CD(SD) rats were exposed by whole body inhalation to allyl alcohol vapor at measured concentrations of 0, 51, 220, or 403 ppm (nominal concentrations were 0, 50, 200, or 400 ppm) for 1 h; at 0, 22, 52, or 102 ppm (nominal concentrations were 0, 20, 50, or 100 ppm) for 4 h; or at 0, 10, 21, or 52 ppm (nominal concentrations were 0, 10, 20, or 50 ppm) for 8 h (Kirkpatrick 2008). All animals survived to the end of the study, except for one male rat exposed at 52 ppm for 8 h that died the day after exposure. The dead rat had severe ulceration and degeneration of the olfactory epithelium, mild hemorrhage and edema in the lungs, moderate to severe erosion of the epithelium in the larynx and trachea, and severe epithelial ulceration in the larynx. Further details are provided in Section 3.2.1.

Groups of six male Long-Evans rats were exposed to allyl alcohol at 40-2,300 ppm (individual concentrations not specified) for 1, 4, or 8 h to determine LC_{50} values (lethal concentration, 50% lethality) for allyl alcohol, (Dunlap et al. 1958). No mention was made of a concurrent control group. Exposures were conducted in a 19.5-L cylindrical glass chamber, and airflow was set at 8.6-12.9 L/min. Vapor concentrations of allyl alcohol were analyzed by drawing a sample of air through distilled water, adding bromine in acetic acid in the presence of mercapturic acetate as a catalyst, reducing the excess bromine with iodide, and then titrating the iodine with thiosulfate. The analyses showed that concentrations of allyl alcohol were 15-25% less than nominal concentrations. Animals were observed for at least 10 days after exposure. The uncorrected 1-, 4-, and 8-h LC_{50} values were 1,060, 165, and 76 ppm, respectively. Dunlap et al. (1958) conducted studies of different exposure routes with several species (inhalation [rats], intragastric administration [rabbit, mouse, and rat], intraperitoneal injection [mouse and rat], and percutaneous [rabbits]), but did not describe signs of toxicity and pathologic effects separately for the different exposure routes. Therefore, it was unclear whether some signs of toxicity were specifically related to inhalation exposure or were independent of the route of exposure. General

signs of toxicity in rats were lacrimation and tremors, with coma preceding death. Gross necropsy findings in both rats and rabbits (findings not presented separately) included pulmonary edema and congestion, visceral congestion, and discolored liver. Microscopic examination of rats and rabbits showed hepatic damage, including congestion of the periportal sinusoids, periportal necrosis, central pallor, and central necrosis. The kidneys of rats were swollen and discolored. A published abstract by Dunlap and Hine (1955) indicates that toxic signs and pathologic changes are not dependent on the route of exposure to allyl alcohol. The abstract states that allyl alcohol-induced lesions, such as necrosis, hemorrhage, and discoloration of the liver, discoloration of the kidneys, and congestion and hemorrhage of the intestines, did not vary with the route of administration. However, ocular and nasal irritation and profuse lacrimation were specifically noted for test of single 1-h inhalation exposures in rats (concentrations not specified), from which the 1-h LC_{50} value of 1,060 ppm was derived (also reported in Dunlap et al. 1958).

Six Sherman rats (sex not specified) were exposed to allyl alcohol vapor at 1,000 ppm for 1 h, and were observed for 14 days (Smyth and Carpenter 1948). No details about the exposure conditions were provided, exposure concentration was not confirmed by analytic methods, and no controls were used. Four of rats died. In another study by this group (Carpenter et al. 1949), a 4-h exposure to allyl alcohol at 250 ppm killed two of six, three of six, or four of six Sherman rats; no additional information was provided.

McCord (1932) exposed rats (strain and sex not specified) to several concentrations of allyl alcohol vapor for various durations. Six rats exposed at 1,000 ppm died 3 h into an intended 7-h exposure. Necropsy results were not described, but were reported to be similar to the findings in the monkey (see Section 3.1.1) and rabbits (see Section 3.1.4). (The primary findings in the monkey and rabbits were hemorrhage in the lungs, intestinal tract, bladder, and kidneys.) Four rats exposed at 200 ppm for 7 h/day died on the first or second day of exposure, and necropsy revealed similar findings. Four of five rats exposed at 50 ppm for 7 h/day died after approximately 30 days of exposure (it was inferred from the study description that exposures were conducted 7 days/week until termination). Necropsy information was not provided. No changes were observed in any of the control animals (number and treatment of controls not described).

Union Carbide and Carbon Corporation (1951) tabulated the mortality results of inhalation toxicity studies of allyl alcohol in rats. No information about controls, method of exposure, strain or sex of rats, analytic verification of concentrations, or period of observation was provided. The mortality results of the studies are presented in Table 4-4.

In a series of three experiments, groups of 10 Long-Evans male rats were exposed to allyl alcohol at 0, 1, 2, 5, 20, 40, 60, 100, or 150 ppm for 7 h/day, 5 days/week for a total of 60 exposures (Dunlap et al. 1958). Analyses of the vapor concentrations at 40 ppm and greater were within 10% of nominal concentrations (information on the measured concentrations at the lower concentrations

was not provided). Animals were observed daily and weighed weekly. After 90 days, the survivors were killed and necropsies were performed. Liver, kidneys, and lungs from all animals were weighed and examined microscopically. The thyroid, heart, thymus, pancreas, spleen, adrenal glands, testes, bladder, and brain were removed from every other animal and examined microscopically. Exposure to allyl alcohol at 1, 2, 5, and 20 ppm failed to produce any clinical signs of toxicity or abnormal gross or microscopic effects, although the animals in the 20-ppm group experienced a significant reduction in body weight gain. Rats exposed at 150 ppm exhibited gasping, severe depression, nasal discharge, and ocular irritation. All of the rats in the 150-ppm group died; four died during the first exposure, two after the first exposure, two during the second exposure, and two by the tenth exposure. The two rats surviving until the tenth exposure were lethargic, had red-rimmed eyes, and lost a third of their original body weight. Necropsy findings included hemorrhagic livers, pale and spotted lungs, and bloated gastrointestinal tracts. Slight congestion of the liver and lungs were found during microscopic evaluation. Rats exposed to allyl alcohol at 100, 60, or 40 ppm had similar but less intense signs, lesions, and microscopic findings. Six of the 10 rats exposed at 100 ppm died by the forty-sixth exposure, and the remaining rats were accidentally killed on exposure day 56. Gasping and muzzle rubbing occurred during the first few exposures at 60 ppm but disappeared thereafter, and persistent ocular discharge was observed throughout the experiment. The 60-ppm group also had statistically increased hepatic and renal weights, and one death occurred (day not specified). All signs of irritation in animals exposed at 40 ppm resolved after the first few exposures, but pulmonary weight was statistically increased at necropsy.

A toxicity data sheet by the Shell Chemical Corporation (1957) appears to include some of the same data that was published by Dunlap et al. (1958). Rats were exposed to allyl alcohol for 8 h at 1, 5, 10, 20, 40, 60, 100, or 150 ppm for a total of 60 exposures over 90 days (Shell Chemical Corporation 1957). Information on the strain, sex, and number of rats was not specified. No adverse effects were found in animals exposed at 20 ppm or less. Decreased growth and mild to moderate pulmonary congestion were found in the 40-ppm group. Animals in the 60-ppm group developed pulmonary congestion and increased renal and pulmonary weights, and one of 10 rats died. All animals exposed at 100 ppm died after 32 exposures and rats exposed at 150 ppm died after two exposures.

TABLE 4-4 Summary of Mortality Data in Rats Exposed to Allyl Alcohol

Concentration (ppm)	Time (h)	Deaths
200	1	0/10
1,000	0.5	1/6
1,000	1	4/6
1,000	2	6/6

Source: Union Carbide and Carbon Corporation 1951.

3.1.3. Mice

Union Carbide and Carbon Corporation (1951) tabulated the mortality results of inhalation toxicity studies of allyl alcohol in mice. No information about controls, method of exposure, strain or sex of mice, analytic verification of concentration, or the period of observation was provided. The mortality results of the studies are presented in Table 4-5.

Groups of 10 mice (strain and sex not specified) exposed to allyl alcohol between 2,450 and 26,000 ppm died within 165 and 24 min, respectively (Shell Chemical Corporation 1957). All animals developed spastic paralysis of the extremities, particularly of the hindlimbs, before dying convulsively. Necropsy results included irritation and inflammation of the respiratory tract and irritation and congestion of the liver, kidneys, and spleen. All mice exposed at 22,000 ppm for 10 min died (no other details provided). No deaths resulted when mice were exposed at 12,200 ppm for 10 min, but all died when exposed for another 10 min period (period of observation and time between exposures not specified). When mice were exposed daily to allyl alcohol at 2,450 ppm for 10 min, 10% of the animals died within three exposures and 30% were dead after nine exposures. Necropsy revealed irritation and inflammation of the respiratory tract and congestion of the gastrointestinal tract. Mice repeatedly exposed to allyl alcohol at 2,450 ppm developed severe ocular and nasal irritation.

3.1.4. Rabbits

When two rabbits (strain and sex not specified) were exposed to allyl alcohol at 1,000 ppm, one died 3.5 h into the exposure and the other died 4.25 h into the exposure (McCord 1932). The rabbits had rales, and fluid dripped from their noses and mouths. Pulmonary hemorrhage, hemorrhage and inflammation of the intestinal tract, bladder, and kidneys, and gaseous distention of the gastrointestinal tract were found in both rabbits at necropsy. One rabbit also had hemorrhaging of the eyes, opaque sclerae, and inflamed genitalia. In a second experiment, three rabbits were exposed to allyl alcohol at 200 ppm for 7 h/day.

TABLE 4-5 Summary of Mortality Data in Mice Exposed to Allyl Alcohol

Concentration (ppm)	Time (h)	Deaths
200	1	0/10
500	0.5	0/10
500	1	4/10
1,000	1	6/10
1,000	2	8/10
1,000	4	10/10

Source: Union Carbide and Carbon Corporation 1951.

Labored and noisy breathing and discharge from the nose and mouth were observed within 1 h of exposure. One rabbit convulsed and died after three days of exposure, a second rabbit died after six days of exposure, and the third died after 18 days of exposure. The noisy and labored breathing and oral and nasal discharge continued with the exposures. Necropsy of the animals revealed findings similar to those described above. In a third experiment, two rabbits were exposed to allyl alcohol at 50 ppm for 7 h/day. One rabbit died after 14 exposures, and the second was killed after 28 exposures. Necropsy of the rabbits revealed findings similar to those described above. No changes were observed in control animals (number and treatment of controls not specified).

Union Carbide and Carbon Corporation (1951) reported the mortality results of inhalation toxicity studies of allyl alcohol in rabbits. No information about controls, method of exposure, strain or sex of rabbits, analytic verification of concentrations, or the period of observation was given. None of the 10 rabbit exposed at 200 ppm for 1 h died, and no deaths occurred in four rabbits exposed at 500 ppm for 2 h. All four rabbits exposed to allyl alcohol at 500 pp m for 4 h died. The report also claimed that allyl alcohol at 3,400 ppm for 2-5 min will cause necrosis of the cornea of rabbits, but no data were included.

3.1.5. Guinea Pigs

Four guinea pigs were individually exposed to allyl alcohol in a bell jar, in which allyl alcohol was present in a petri dish below the jar (Adams 1958). The exact exposure concentrations were unknown. One guinea pig started to exhibit signs of irritation within 2 min of exposure, with lacrimation and exophthalmos developing soon thereafter. When the animal was removed after 30 min, marked lacrimation and exudation of serous fluid from the nose and mouth was observed, and the exophthalmos was pronounced. The guinea pig died 50 min post-exposure from respiratory failure. A second guinea pig was exposed in the bell jar until it died; death occurred after 55 min. Clinical signs included exophthalmos, lacrimation, and oral and nasal serous fluid exudate. A third guinea pig was exposed to allyl alcohol for 20 min. It also developed exophthalmos with lacrimation and nasal discharge, and died of respiratory failure 5 h post-exposure. A fourth guinea pig was exposed for 15 min and developed the same clinical signs as the others, but recovered and was still alive 6 days post-exposure.

3.2. Nonlethal Toxicity

3.2.1. Rats

Groups of three male and three female Crl:CD(SD) rats were exposed by whole body inhalation to allyl alcohol at concentrations of 423 ppm or 638 ppm for 1 h, 114 ppm for 4 h, or 52 ppm for 8 h (Kirkpatrick 2008). Animals were examined for clinical signs 30 min into the exposure (all animals), 1 h into the

exposure (animals exposed for 4 and 8 h), 4 h into the exposure (animals exposed for 8 h), and within 1 h after exposure (all animals). Animals were observed for 6 days post-exposure and then killed without further examination. Animals were observed for mortality twice per day, body weight was recorded prior to exposure and on post-exposure day 5, and clinical examinations were performed daily. All animals survived to the end of the study, and no adverse effects on body weight were found. Clinical signs included gasping during and after exposure, labored respiration during exposure, and red and/or clear material around the mouth or nose and reddened limns after the exposure. The investigator noted that reddened limbs were considered an alcohol flush reaction caused by the presence of the aldehyde metabolite, acrolein. Thus, "alcohol flushing" observed in this study does not appear to be the result of a direct-acting irritant effect of allyl alcohol. One male rat exposed at 114 ppm for 1 h exhibited slight gait impairment at 1 h post-exposure; gait impairment was not observed in any other animals. A summary of the incidence of selected clinical observations from this study is presented in Table 4-6.

TABLE 4-6 Summary of Selected Clinical Observations in Rats Exposed to Allyl Alcohol

	1 h		4 h	8 h
Observation	423 ppm	638 ppm	114 ppm	52 ppm
Number of animals	6	6	6	6
Gasping				
Total affected	2	2	4	3
30-min into exposure	0	1	1	3
1 h into exposure	2	0	1	0
1 h post-exposure	0	1	3	0
Recovery period	0	0	0	0
Labored respiration				
Total affected	0	0	0	2
8-h into exposure	–	–	–	2
Recovery period	0	0	0	0
Reddend forelimbs				
Total affected	0	4	6	3
1 h post-exposure	0	4	6	3
Recovery period	0	0	0	0
Reddend hindlimbs				
Total affected	0	3	6	4
1 h post-exposure	0	3	6	4
Recovery period	0	0	0	0
Material around mouth/nose				
Total affected	3	5	4	2
1 h post-exposure	3	5	4	1
Recovery period	0	0	0	2

Source: Kirkpatrick 2008.

Groups of five male and five female Crl:CD(SD) rats were exposed by whole body inhalation to allyl alcohol vapor at measured concentrations of 0, 51, 220, or 403 ppm (nominal concentrations were 0, 50, 200, or 400 ppm) for 1 h; 0, 22, 52, or 102 ppm (nominal concentrations were 0, 20, 50, or 100 ppm) for 4 h; or 0, 10, 21, or 52 ppm (nominal concentrations were 0, 10, 20, or 50 ppm) for 8 h (Kirkpatrick 2008). Chamber concentrations were measured by gas chromatography at approximately 30-min intervals for the 1-h exposure, and at 60-min intervals for the 4- and 8-h exposures. Observations for clinical signs were performed 30 min into the exposure (all exposures), 1 h into the exposure (4- and 8-h exposures), and 4 h into the exposure (8-h exposure). Near the end of the exposure, response to a loud noise stimulus was tested by striking the cage. Clinical examinations, involving handling and open field arena observations, were performed immediately after the exposure, within an hour post-exposure, twice on day 1, and once daily until the end of the study. Body weight was recorded on days 0, 1, 6, and 13. When the animals were killed on day 14, blood was collected for analyses of hematology and clinical chemistry parameters; a complete gross necropsy was performed; liver, kidney and lung weights were recorded; and selected tissues (kidneys, larynx, liver, lungs, nasal tissues, trachea, and gross lesions) were processed and examined for histopathologic changes. All animals survived to the end of the study, except for one male rat exposed at 52 ppm for 8 h. The rat died the day after exposure, and death was attributed to ulceration of the respiratory and olfactory epithelium in the nasal passages, resulting in diminished breathing capacity and hypoxia. In the remaining rats, no exposure-related changes were observed in body weight, hematology or clinical chemistry parameters, or during gross necropsy or histopathologic examination of the kidneys, liver, or lungs.

Exposure to allyl alcohol at 51, 220, and 403 ppm for 1 h produced gasping in one female rat exposed at 403 ppm after 30 min of exposure (Kirkpatrick 2008). The incidences of alcohol flushing and material around the mouth exhibited a concentration-related increase at 220 and 403 ppm. A clear concentration-related response was not established in the novel stimulus/arousal response findings. Histopathologic examination of the nasal cavity revealed reversible changes. The incidence of chronic inflammation was increased at 202 and 403 ppm. Although the incidences of degeneration of the olfactory epithelium, metaplasia of olfactory epithelium, and hemorrhage did not follow a definitive concentration-related response, they were attributed to allyl alcohol because these effects were not found in control animals.

For the 4-h exposures, minimal clinical signs were observed in rats exposed to allyl alcohol at 22 ppm; only one animal exhibited material around the mouth (Kirkpatrick 2008). Exposure at 52 and 102 ppm produced a concentration-related increase in the number of animals exhibiting gasping, alcohol flushing, material around the mouth, and a reduced response to cage stimulus. An increased incidence of yellow material around the urogenital area was observed 1 h post-exposure in females of the 102-ppm group. Histopathologic examinations of the nasal cavity revealed reversible changes, including degeneration of

the olfactory and respiratory epithelium, chronic inflammation, and goblet cell hyperplasia.

For the 8-h exposures, clinical effects were minimal in rats exposed at 10 and 21 ppm; a few animals had reddened limbs and material around the mouth, one rat at each concentration had yellow material around the urogenital area, and one rat in the 21-ppm group had rales/increased respiration (Kirkpatrick 2008). Exposure to allyl alcohol at 52 ppm for 8 h produced gasping, increased respiration, and red material around the mouth, yellow material around the urogenital area (three of 10 rats), and killed one male rat. The rat that died exhibited gasping, rales, and red material around the nose 1 h post-exposure, and rales and red material around the mouth and nose approximately 7 h before death. Reddened forelimbs were present in only a few animals. Clinical signs were generally noted 1 h post-exposure, and were resolved by the end of the recovery period. A concentration-related increase in the number of animals with a reduced response to cage stimulus was found in the 21- and 52-ppm groups. Histopathologic examination of the nasal cavity of rats exposed at 10 or 21 ppm revealed reversible changes, including degeneration of the olfactory and respiratory epithelium, chronic inflammation, and goblet cell hyperplasia. Exposure at 52 ppm produced similar but generally more severe lesions. Two rats (including the one that died) developed severe irreversible changes. The rat that died had severe ulceration and degeneration of olfactory epithelium, mild hemorrhage and edema in the lungs, moderate to severe erosion of the epithelium in the larynx and trachea, and severe epithelial ulceration in the larynx. Another male rat had severe, irreversible metaplasia and severe ulceration of the olfactory epithelium, along with the degeneration and subacute inflammation seen in almost all rats in the 52-ppm group.

Summaries of clinical signs and histopathologic findings from this study are presented in Tables 4-7 and 4-8, respectively.

3.2.2. Mice

Groups of four male Ssc:CF-1 mice were exposed to allyl alcohol at 0.42, 2.00, 4.55, or 18.10 ppm for 30 min to determine the RD_{50} for sensory irritation (Nielsen et al. 1984). RD_{50} values represent the concentration of an airborne sensory irritant that produces a 50% reduction in the respiratory rate, the decreased respiratory rate being caused by stimulation of the trigeminal nerve in the nasal mucosa. The mice were placed in a body plethysmograph attached to an exposure chamber such that the animal's head protruded into the chamber. Animals in the chambers were observed for 5-15 min to establish a baseline respiratory rate before beginning exposure to allyl alcohol. An RD_{50} of 3.9 ppm (95% C.I.: 2.4-6.5 ppm) was determined on the basis of the maximum decrease in respiratory rate within the first 10 min of exposure, and another value of 4.8 ppm (95% C.I.: 2.7-10.2 ppm) was determined on the basis of the mean value

TABLE 4-7 Summary of Clinical Signs in Rats Exposed to Ally Alcohol

	Concentration (ppm)											
	1 h				4 h				8 h			
End Point	0	51	220	403	0	22	52	102	0	10	21	52
No. animals	10	10	10	10	10	10	10	10	10	10	10	10
Clinical signs (total)												
Gasping	0	0	0	1	0	0	1	6	0	0	0	7
Rales/increased respiration	0	0	0	0	0	0	0	0	0	0	1	3
Reddened forelimbs	0	1	8	9	0	0	2	7	0	1	2	3
Reddened hindlimbs	0	1	7	9	0	0	2	6	0	0	1	0
Reddened ears	0	0	0	4	0	0	0	0	0	0	0	0
Red/clear material around mouth	0	0	3	5	0	1	3	8	2	3	2	8
Clinical signs (1 h post-exposure)												
Gasping	0	0	0	0	0	0	1	5	0	0	0	6
Rales/increased respiration	0	0	0	0	0	0	0	0	0	0	1	2
Reddened forelimbs	0	1	8	9	0	0	2	7	0	1	2	3
Reddened hindlimbs	0	1	7	9	0	0	2	6	0	0	1	0
Reddened ears	0	0	0	4	0	0	0	0	0	0	0	0
Red/clear material around mouth	0	0	3	5	0	1	3	8	0	1	3	8
Response to cage stimulus												
No reaction	2	0	6	3	0	0	2	4	0	0	3	4
Slight reaction	8	10	4	7	10	10	8	4	10	10	7	6
Energetic response (jump/vocalization)	0	0	0	0	0	0	0	2	0	0	0	0

Source: Kirkpatrick 2008.

TABLE 4-8 Summary of Selected Nasal Histopathologic Findings in Rats Exposed to Ally Alcohol[a]

	Concentration (ppm)											
	1 h				4 h				8 h			
End Point	0	51	220	403	0	22	52	102	0	10	21	52[b]
No. animals	10	10	10	10	10	10	10	10	10	10	10	10
Degeneration, olfactory epithelium												
Total	0	2	1	3	0	0	2	10	0	4	6	9
Minimal	–	0	0	2	–	–	2	3	–	1	1	1
Mild	–	2	1	0	–	–	0	5	–	3	4	1
Moderate	–	0	0	1	–	–	0	2	–	0	1	4
Severe	–	0	0	0	–	–	0	0	–	0	0	1
Severe, irreversible	–	0	0	0	–	–	0	0	–	0	0	2
Inflammation, chronic and subacute												
Total	3	2	4	9	0	7	7	8	3	7	9	10
Minimal	1	2	1	2	–	2	1	0	2	1	0	1
Mild	2	0	2	6	–	4	3	6	1	6	8	6
Moderate	0	0	1	1	–	1	3	2	0	0	1	3
Hyperplasia, goblet cell												
Total	1	2	2	1	0	1	5	4	0	4	4	5
Minimal	0	1	0	0	–	0	2	1	–	1	3	0
Mild	1	1	2	1	–	1	3	1	–	3	1	3
Moderate	0	0	0	0	–	0	0	2	–	0	0	2
Degeneration, respiratory epithelium												
Total	0	0	0	0	0	0	1	2	0	0	0	2

Minimal	–	–	–	–	–	–	1	0	–	–	–	0
Mild	–	–	–	–	–	–	0	2	–	–	–	0
Moderate	–	–	–	–	–	–	0	0	–	–	–	2
Metaplasia, olfactory epithelium												
Total	0	1	0	0	0	0	0	0	0	0	0	1
Mild	–	1	–	–	–	–	–	–	–	–	–	0
Severe, irreversible	–	0	–	–	–	–	–	–	–	–	–	1

[a]Summary of number of animals with lesion taking into account all six nasal levels; grade for each lesion is the highest grade for any of the six nasal levels.
[b]Results for the rat that died are included. Other effects found in this group that are not included in the table were severe, irreversible ulceration (two males) and severe erosion (one male) of the olfactory epithelium.
Source: Kirkpatrick 2008.

during the last 10 min of exposure. The onset of decreased respiratory rate occurred rapidly, plateaued within 10 min of exposure, and quickly subsided following termination of the exposure. Threshold values for irritation can be estimated using RD_{50} values. ASTM (2012) estimated a threshold value for allyl alcohol of 0.301 ppm based on 3% of the RD_{50} value. For this report the threshold for irritation was estimated by deriving an RD_{10} value of 0.27 ppm, using digitized data from Figure 2 of the Nielsen et al. (1984) report. Although studies of intravenous administration of allyl alcohol have demonstrated that conversion of allyl alcohol to acrolein is required to produce systemic toxicity (Serafini-Cessi 1972; Patel et al. 1983), the Nielsen et al. (1984) study did not find evidence of such a conversion in that there was no delay in the appearance, development, or resolution of the irritant response. However, no empirical data on the rates or extent of metabolism of allyl alcohol by pulmonary-tract tissues were presented. To determine if allyl alcohol produced pulmonary irritation at concentrations producing sensory irritation, concurrent exposures of tracheally cannulated mice to allyl alcohol were performed. Such exposure did not cause any pulmonary irritation at the RD_{50} concentration producing sensory irritation.

James et al. (1987) reported an RD_{50} for allyl alcohol of 2.5 ppm (2.0-3.2 ppm) in male ICR mice. Because the investigators used allyl alcohol to verify their experimental system with that of already published methods, no specific information was provided about how the RD_{50} was generated. Thus, it was inferred that the method was the same as that described for the test compound, methylisocyanate vapor. Exposures were performed in glass exposure chambers, and vapor concentrations were measured by a gas analyzer. Animals were observed in the chambers for 10 min to establish a baseline respiratory rate, and were then exposed to allyl alcohol for 30 min.

Groups of 10 male Swiss OF_1 mice were exposed to allyl alcohol at 2.4 or 6.4 ppm under three regimens: for 6 h/day for 4 days, for 6 h/day for 9 days (5 consecutive days the first week, 4 consecutive days the second week), or for 6 h/day, 5 days/week for 2 weeks (Zissu 1995). The target (nominal) concentrations were based on an RD_{50} value of 1.6 ppm, and 3 times the RD_{50} value of 4.8 ppm. Groups of five mice were used as controls. Histopathologic examination revealed lesions of the upper respiratory tract epithelium (hyperplasia, inflammatory infiltrates, and desquamation of epithelial cells) and olfactory epithelium (a slight loss of isolated sensory cells) in mice from the 2.4- and 6.4-ppm groups. The lesions were most severe in the group exposed for 4 days, and became less severe in the animals exposed for longer durations. No pathologic changes were found in the trachea or lungs of exposed animals. The target RD_{50} of 1.6 ppm was chosen from a published review (Bos et al. 1992) that summarized sensory irritation data for a large number of chemicals. The original reference (Muller and Greff 1984) investigated the correlation between selected physio-chemical parameters and sensory irritation for four chemical groups.

3.2.3. Dogs, Guinea Pigs, and Rabbits

Torkelson et al. (1959a) evaluated the toxicity allyl alcohol in rats, guinea pigs, rabbits, and dogs, but did not distinguish effects by species. Therefore, the results of this study are presented collectively in this section. Groups of 12 male and 12 female rats, nine male and nine female guinea pigs, and three male and three female rabbits were exposed repeatedly to ally alcohol vapor at 7 ppm (6.6-7.1 ppm) for 7 h/day for a total of 28 exposures and at 2 ppm (0.6-3.2 ppm) for 7 h/day for a total of 127-134 exposures (Torkelson et al. 1959a; methods reported in Torkelson et al. 1959b). In studies of dogs, one male and one female beagle were exposed to allyl alcohol at 2 ppm for 6 months. All exposures were conducted for 7 h/day, 5 days/week. Two control groups were used, a group exposed to air under similar test conditions and a group that was unexposed. None of the animals exposed to allyl alcohol at 7 ppm exhibited any clinical signs of toxicity or changes in body or organ weight, but microscopic examination found mild and reversible hepatic and renal degeneration in almost all animals. Livers had dilation of the sinusoids, cloudy swelling, and focal necrosis, and kidneys showed epithelial necrosis in the convoluted tubules, proliferation of the interstitial tissue, and changes similar to those seen in glomerulonephritis. Animals exposed at 2 ppm exhibited no measurable adverse effects as judged by clinical signs, mortality, body or organ weight, or gross and microscopic examination of tissues (noses not examined).

The potential of allyl alcohol to induce ocular damage was assessed in albino rabbits (Carpenter and Smyth 1946). Application of 0.02 mL of allyl alcohol into the eye resulted in an injury score of 5 on a 10-point scale, which was considered severe injury by the investigators. In another study, the eyes of New Zealand White rabbits were treated with 100 µL of allyl alcohol (Jacobs and Martens 1989). Mean scores of 2.8, 1.23, and 2.09 for erythema, chemosis, and corneal opacity (maximum possible scores of 3, 4, and 4, respectively) were recorded after 24, 48, and 72 h (scores for each time period were pooled). The mean percentage of corneal swelling was 76%.

3.3. Developmental and Reproductive Effects

No studies of reproductive and developmental effects in animals exposed to allyl alcohol by inhalation were found.

However, several oral exposure studies have been conducted. No evidence of reproductive toxicity (measured by changes in reproductive organ weights, sperm parameters, or number of implants) or dominant lethality was observed in male Sprague Dawley rats administered allyl alcohol at 25 mg/kg for 5-7 days/week for 33 weeks and mated with unexposed females during exposure weeks 1-11 (Jenkinson and Anderson 1990). Additionally, no significant alterations in the numbers of runts, gross abnormalities, or abnormal fetuses were observed. UNEP (2005) summarized two developmental and reproductive tox-

icity studies in rats exposed to allyl alcohol by gavage; neither study found significant alterations in malformations or variations in the offspring. A decrease in pup viability index was observed in the offspring of rats administered allyl alcohol at 40 mg/kg/day before mating and through lactation day 3 (males were also exposed before mating). The second study found no effect on pup viability, but found an increased frequency of total litter losses from exposure at 35 and 50 mg/kg/day on gestation days 9-19. In both studies, maternal toxicity (including mortality) was also observed at these concentrations. The first study also found an increase in estrous-cycle length and in the number of females with irregular estrous cycles in the group exposed at 40 mg/kg/day.

3.4. Genotoxicity

Allyl alcohol was mutagenic in cultured V79 cells using 6-thioguanine resistance as the measure of mutagenicity (Smith et al. 1990). At doses of 1 and 2 μM, the number of mutants per 106 survivors were 14 ± 8 and 37 ± 12, respectively, values similar to those produced by acrolein (Smith et al. 1990). A positive test was obtained in a modified Ames assay (tester strain TA100) without metabolic activation (750 revertants/μmole), but the mutagenic activity was greatly reduced with metabolic activation (approximately150 revertants/μmole) (Lutz et al. 1982). It has been suggested that bacterial alcohol dehydrogenase converts allyl alcohol to acrolein, which may be responsible for the mutagenic activity, and that the addition of the S9 mix inactivates acrolein by binding of the metabolite by the amino and sulfhydryl groups present in the mix (Lutz et al. 1982). Allyl alcohol tested positive for mutagenesis at concentrations of 50-300 μg/plate in the *Salmonella* tester strain TA1535 in the presence of hamster S9, but not in the presence of rat S9, and was cytotoxic at a concentration of 500 μg/plate (Lijinsky and Andrews 1980). Allyl alcohol was not mutagenic in strains TA1537, TA1538, TA98, or TA100 in the presence or absence of rat or hamster S9 (Lijinsky and Andrews 1980). Bignami et al. (1977) reported that allyl alcohol failed to increase the numbers of revertants in *Salmonella typhimurium* strains TA1535, TA100, TA1538, and TA98 (details not provided), and allyl alcohol did not induce point mutations in *Aspergillus nidulans*. Similarly, NTP (2006) found that allyl alcohol was not mutagenic in *S. typhmurium* strains TA97, TA98, TA100, or TA1535 with or without S9 metabolic activation. Intraperitoneal injections of allyl alcohol at 3-50 mg/kg/day did not increase the induction of micronucleated erythrocytes in rats (NTP 2006).

3.5. Carcinogenicity

Not enough data are available to provide a quantitative assessment of the carcinogenic potential of allyl alcohol. The carcinogenic potential of allyl alcohol has not been classified by EPA (2012a) or IARC. No evidence of carcinogenicity was found in a study in which male and female F344 rats were adminis-

tered allyl alcohol at 300 mg/L in drinking water for 106 weeks, or when 20 male Syrian golden hamsters were administered allyl alcohol at 2 mg in corn oil by gavage once a week for 60 weeks (Lijinsky and Reuber 1987). The median time-to-death and incidence of tumors was comparable in treated animals and controls. Further details, such as body- and organ-weight changes, were not provided.

Although no data are available to assess the potential for allyl alcohol to cause cancer, some of its metabolites are recognized carcinogens. EPA (2012b) has classified the allyl alcohol metabolite glycidaldehyde as a probable human carcinogen (B2) on the basis of an increased incidence of malignant tumors in rats and mice following subcutaneous injection of glycidaldehyde and of skin carcinomas following dermal application to mice. For acrolein, EPA (2003, p. 57) has determined that the "existing data are inadequate for an assessment of human carcinogenic potential for either the oral or inhalation route of exposure."

3.6. Summary

A summary of acute animal lethality data is presented in Table 4-9, and summaries of acute and repeat-exposure nonlethality data in animals are presented in 4-10 and 4-11, respectively. Similar 1-h no-effect levels for lethality have been reported for rats (200-423 ppm) (Union Carbide and Carbon Corporation 1951; Kirkpatrick 2008), mice (200 ppm) (Union Carbide and Carbon Corporation 1951), and rabbits (200 ppm) (Union Carbide and Carbon Corporation 1951).

Rats survived exposure to allyl alcohol at concentrations of 423 or 638 ppm for 1 h, 114 ppm for 4 h, or 52 ppm for 8 h (Kirkpatrick 2008). Clinical signs in all exposure groups included gasping during and after exposure, and material around the mouth and nose and alcohol flushing after exposure. Two rats exposed at 52 ppm for 8 h exhibited labored respiration during exposure. In another study, rats were exposed to allyl alcohol vapor at concentrations of 51, 220, or 403 ppm for 1 h; 22, 52, or 102 ppm for 4 h; or 10, 21, or 52 ppm for 8 h (Kirkpatrick 2008). All animals survived to study termination except for one male rat exposed at 52 ppm for 8 h. Reversible histopathologic changes were observed in the nasal cavity of exposed rats, and clinical signs included material around the mouth, alcohol flushing, and gasping. Exposure at higher concentrations at each duration generally resulted in increased incidences of clinical signs and histopathologic changes in the nasal cavity. Other data on nonlethal exposures to allyl alcohol included two RD_{50} studies in mice, in which RD_{50} values of 3.9 ppm and 2.5 ppm were reported (Nielsen et al. 1984; James et al. 1987). A few studies investigating the effects of repeated inhalation exposure in animals were available. One study found histopathologic lesions in the upper-respiratory-tract epithelium and olfactory epithelium of mice after exposure at 2.4 ppm for 6 h/day for 4 days, and the lesions decreased in severity in groups

TABLE 4-9 Summary of Acute Lethality Data in Laboratory Animals Exposed to Allyl Alcohol

Species	Concentration (ppm)	Exposure Duration	Deaths	Reference
Monkey	1,000	4 h	1/1	McCord 1932
Mouse	200	1 h	0/10	Union Carbide and Carbon Corporation 1951
Mouse	500	0.5 h	0/10	Union Carbide and Carbon Corporation 1951
	500	1 h	4/10	
Mouse	1,000	1 h	6/10	Union Carbide and Carbon Corporation 1951
	1,000	2 h	8/10	
	1,000	4 h	10/10	
Mouse	22,000	10 min	10/10	Shell Chemical Corporation 1957
	12,200	2 × 10 min	10/10 (after 2nd exposure)	
Rat	1,060	1 h	LC_{50}	Dunlap and Hine 1955; Dunlap et al. 1958
	165	4 h	LC_{50}	
	76	8 h	LC_{50}	
Rat	638	1 h	0/6	Kirkpatrick 2008
	423	1 h	0/6	
	114	4 h	0/6	
	52	8 h	0/6	
Rat	51	1 h	0/10	Kirkpatrick 2008
	220	1 h	0/10	
	403	1 h	0/10	
Rat	22	4 h	0/10	Kirkpatrick 2008
	52	4 h	0/10	
	102	4 h	0/10	

Rat	10	8 h	0/10	Kirkpatrick 2008
	21	8 h	0/10	
	52	8 h	1/10	
Rat	200	1 h	0/10	Union Carbide and Carbon Corporation 1951
Rat	1,000	0.5 h	1/6	Union Carbide and Carbon Corporation 1951
	1,000	1 h	4/6	
	1,000	2 h	6/6	
Rat	1,000	1 h	4/6	Smyth and Carpenter 1948
Rat	1,000	3 h	6/6 (during exposure)	McCord 1932
	200	2 × 7 h	4/4 (by end of 2nd exposure)	
	50	7 h/d for 30 d	4/5	
Rat	60	7 h/d, 5d/wk for 60 exposures	1/10 (by 60th exposure)	Dunlap et al. 1958
	100	7 h/d, 5d/wk for 60 exposures	6/10 (by 56th exposure)	
	150	7 h/d, 5d/wk for 60 exposures	10/10 (by 10th exposure)	
Rabbit	200	1 h	0/10	Union Carbide and Carbon Corporation 1951
Rabbit	500	2 h	0/4	Union Carbide and Carbon Corporation 1951
	500	4 h	4/4	
Rabbit	1,000	3.5 h	1/1	McCord 1932
	1,000	4.25 h	1/1	

TABLE 4-10 Summary of Acute Nonlethal Inhalation Data in Laboratory Animals Exposed to Allyl Alcohol

Species	Exposure Duration	Concentration (ppm)	Effects	Reference
Mouse	10 min	3.9	RD_{50}	Nielsen et al. 1984
Mouse	10 min	2.5	RD_{50}	James et al. 1987
Rat	1 h	638	Gasping, flushing[a], material around mouth/nose.	Kirkpatrick 2008
	1 h	423	Gasping, material around mouth/nose.	
	4 h	114	Gasping, flushing[a], material around mouth/nose.	
	8 h	52	Gasping, labored respiration, flushing[a], material around mouth/nose.	
Rat	1 h	51	Some flushing[a], olfactory degeneration and inflammation.	Kirkpatrick 2008
		220	Same as above (more affected); plus reduced response to stimulus, material around mouth/nose.	
		403	Same as above (more affected); plus gasping.	
Rat	4 h	22	One rat with material around mouth/nose, nasal inflammation.	Kirkpatrick 2008
		52	Same as above (more affected); plus gasping, some flushing[a], reduced response to stimulus, olfactory/respiratory degeneration.	
		102	Same as above (more affected); plus respiratory degeneration.	
Rat	8 h	10	One rat with flushing[a], material around mouth/nose.	Kirkpatrick 2008
		21	Same as above (more affected); plus reduced response to stimulus, some increased respiration and flushing[a], olfactory degeneration and inflammation.	
		52	1/10 died, gasping, irreversible nasal histopathologic changes.	

[a]Flushing characterized by reddened limbs/ears; considered an alcohol flush reaction caused by the presence of the aldehyde metabolite, acrolein.

TABLE 4-11 Summary of Nonlethal Inhalation Data in Laboratory Animals Exposed Repeatedly to Allyl Alcohol

Species	Exposure Duration	Concentration (ppm)	Effects	Reference
Mouse	6 h/d for 4 d	2.4	Histopathologic changes in upper respiratory tract epithelium (hyperplasia, inflammatory infiltrates, desquamation) and olfactory epithelium (slight loss of isolated sensory cells).	Zissu 1995
Rat	7 h/d, 5 d/wk for 60 exposures	1	No observed adverse effects.	Dunlap et al. 1958
		2	No observed adverse effects.	
		5	No observed adverse effects.	
		20	Reduced body weight gain.	
Rat	7 h/d, 5 d/wk for 90 d	40	Irritation (gasping, ocular irritation, nasal discharge) disappeared after first few exposures, increase pulmonary weight.	Dunlap et al. 1958
Rat	7 h/d, 5 d/wk for 90 d	60	Irritation (gasping, muzzle rubbing) disappeared after first few exposures, persistent ocular discharge, increased pulmonary and renal weights, 1/10 died after 4th exposure.	
Rat, guinea pig, rabbit	7 h/d, 5 d/wk for 127-134 exposures	7	Hepatic lesions (degeneration, dilation of sinusoids, cloudy swelling, focal necrosis) and renal lesions (degeneration, epithelial necrosis in convoluted tubules, proliferation of interstial tissue).	Torkelson et al. 1959a
Rat, guinea pig, rabbit	7 h/d, 5 d/wk for 28 exposures	2	No adverse effects.	Torkelson et al. 1959a

exposed for 9 days or 2 weeks (Zissu 1995). Rats repeatedly exposed by inhalation to allyl alcohol at 1, 2, 5, or 20 ppm had no gross signs of toxicity, but repeated exposures at 40 ppm resulted in transient irritation and increased pulmonary weight (Dunlap et al. 1958). Repeated inhalation exposure to allyl alcohol at 2 ppm for 7 h/day for a total of 28 exposures resulted in no measurable adverse effects in rats, guinea pigs, rabbits, and dogs (Torkelson et al. 1959a). Rats, guinea pigs, and rabbits exposed at 7 ppm for 7 h/day for a total of 127-134 exposures exhibited only mild and reversible microscopic hepatic and renal damage.

Other acute animal toxicity animal data focused on lethality. Mice, rats, and rabbits survived exposure to allyl alcohol at 200 ppm for 1 h; mice survived exposure at 500 ppm for 0.5 h, but not 1 h; and rabbits survived a 2-h but not a 4-h exposure at 500 ppm (Union Carbide and Carbon Corporation 1951). Exposure at 1,000 ppm for as little as 0.5 h and up to 4 h killed monkeys, mice, rats, and rabbits (McCord 1932; Smyth and Carpenter 1948; Union Carbide and Carbon Corporation 1951). The only LC_{50} values available were based on tests that reported only target concentrations, and were unreliable because Dunlap et al. (1958) stated that actual concentrations ranged from 15-25% less than target concentrations. The uncorrected LC_{50} values in rats were 1,060 ppm for 1 h, 165 ppm for 4 h, and 76 ppm for 8 h. Repeated exposures of rats to allyl alcohol at 60, 100, or 150 ppm for 7 h/day, 5 days/week for 60 exposures resulted in mortality.

Only oral exposure studies on the potential developmental and reproductive toxicity of allyl alcohol were available. The studies found reproductive effects (decreased pup viability or total litter losses) at maternally toxic doses. Allyl alcohol was genotoxic in prokaryotic systems. No relevant data were available to assess the potential carcinogenicity of inhaled allyl alcohol. No evidence of carcinogenicity was observed in rats or hamsters orally administered allyl alcohol for 106 or 60 weeks, respectively.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Mechanism of Toxicity

Signs of toxicity in animals after acute and repeated inhalation exposure to allyl alcohol include lacrimation, pulmonary edema and congestion, gasping, alcohol flushing, material around the nose and mouth, and labored breathing. Histopathologic examination of rats after acute exposure to allyl alcohol revealed nasal lesions which progressed in incidence and severity with increasing duration and concentration, ultimately resulting in death due to reduced breathing capacity (Kirkpatrick 2008). These findings contrast with those found by McCord (1932) of pulmonary congestion leading to edema and compensatory emphysema, with degeneration of the cells in the convoluted tubules of the kidneys, liver, myocardium, ganglion cells of the spinal cord, and retina.

Mode-of-action information on allyl alcohol has focused on how the chemical causes periportal necrosis in the liver. It appears that this effect is more apt to occur after oral, intraperitoneal, or intravenous administration; thus, its relevance to effects after acute inhalation exposure is uncertain. Studies of the mechanism of allyl alcohol-induced liver necrosis and covalent binding to liver macromolecules found that metabolism of allyl alcohol to the reactive metabolite acrolein is required (Reid 1972; Serafini-Cessi 1972; Patel et al. 1983). This reaction is mediated by the cytosolic liver enzyme alcohol dehydrogenase (ADH) in the presence of NAD^+. The importance of ADH activity was exemplified in a study in which an ADH-negative strain of deer mice was resistant to allyl alcohol toxicity, while the ADH-positive strain of deer mice exhibited dose-dependent necrosis of periportal regions of the liver and increased plasma concentrations of lactate dehydrogenase, sorbitol dehydrogenase, and serum glutamate oxaloacetate transaminase activity 24 h after intraperitoneal injection (Belinsky et al. 1985). Another study found that old male rats were more susceptible to allyl alcohol-induced hepatotoxicity than young adult male rats because old rats had increased ADH activity (Rikans and Moore 1987). Acrolein can be detoxified to acrylic acid by further metabolism by aldehyde dehydrogenase or by conjugation with glutathione (Rikans 1987; Rikans and Moore 1987). Depletion of glutathione, followed by lipid peroxidation and hepatic necrosis, have been shown occur in both in vivo and in vitro studies of allyl alcohol (Badr et al. 1986; Belinsky et al. 1986; Jaeschke et al. 1987; Penttila et al. 1987; Miccadei et al. 1988; Penttila 1988; Pompella et al. 1988; Maellaro et al. 1990; Comporti 1991). Hormann et al. (1989) proposed that inactivation of thiol groups is critical for allyl alcohol hepatotoxicity on the basis of a study in which isolated rat hepatocytes exposed to allyl alcohol exhibited an initial rapid depletion of glutathione, followed by an increase in malondialdehyde, a decrease in protein sulfhydryl groups, and eventual loss of membrane integrity. When sulfhydryl compounds were added to the hepatocytes, however, hepatocytes were protected against cytotoxicity. Because mechanistic studies have reported that allyl alcohol-induced hepatotoxicity is also oxygen dependent, further experiments were conducted to elucidate which cell types are involved. It was determined that the presence of Kupffer cells is required to produce O_2-dependent hepatic necrosis (Przybocki et al. 1992).

Because one primary route of allyl alcohol exposure is inhalation, Patel et al. (1980) compared the metabolism of allyl alcohol in lung and liver preparations from male Holtzman rats. In the lungs, allyl alcohol was rapidly epoxidized to glycidol, and then further metabolized to glycerol, most likely by the action of epoxide hydrase. Allyl alcohol was not metabolized to the reactive metabolite acrolein because rat lungs do not contain appreciable ADH activity. Likewise, the amount of ADH activity in human lungs is only a small percentage of the ADH activity in liver; one study reported that ADH activity in the human lung was 1-8% of the ADH activity measured in liver (Moser et al. 1968). No study was available on the capability of rodent nasal and oral epithelial tissues to convert allyl alcohol to acrolein. It is currently unknown if the

parent alcohol is a direct irritant or if conversion to the acrolein metabolite is required to produce irritation. Liver preparations metabolized allyl alcohol to acrolein, acrylic acid, glycidaldehyde, and glyceraldehyde. It is unlikely that much glycidol and glycerol would be produced in the liver, as most of the hepatic allyl alcohol delivered dose would be converted to acrolein.

No quantitative information was available on systemic absorption and distribution of allyl alcohol following inhalation exposure. Although studies investigating intravenous administration of allyl alcohol demonstrated that conversion of allyl alcohol to acrolein was required to produce toxicity, the study by Nielsen et al. (1984) did not find evidence of such a conversion occurring; there was no delay in the appearance, development, or disappearance of the measured irritant response in mice. The in vitro study by Patel et al. (1980) demonstrated that the lungs will not metabolize allyl alcohol to the reactive metabolite acrolein, and it is unknown how much of the allyl alcohol will be distributed to the liver where the metabolic conversion will occur. The study investigating lung pathology in mice following repeated exposure at an RD_{50} concentration did not investigate whether any pathologic changes had occurred in other organs such as the liver and kidney (Zissu 1995). Therefore, it is unknown whether inhalation exposure at lower concentrations of allyl alcohol will produce toxicity confined to the lungs, or if some systemic toxicity will also be produced. It should again be noted that subchronic exposure of rats, guinea pigs, and rabbits to allyl alcohol at 2 ppm did not result in any measurable adverse effects (Torkelson et al. 1959a).

4.2. Structure-Activity Relationships

Groups of four male Ssc:CF-1 mice were exposed by inhalation to allyl acetate, allyl alcohol, allyl ether, or acrolein to evaluate the sensory and pulmonary irritation of propene derivatives (Nielsen et al. 1984). The four derivatives did not vary much in their ability to elicit sensory irritation as assessed by RD_{50} measurements; the RD_{50}s were 2.9, 3.9, 5.0, and 2.9 ppm, respectively. However, when the potency was expressed in terms of the thermodynamic activity, acrolein was 10 times more potent than the other three derivatives. Further experiments in which tracheally cannulated mice were exposed to the respective RD_{50} concentrations of the propene derivatives did not reveal any pulmonary irritation.

A number of studies investigating a homologous series of nonreactive alcohols demonstrated that both the odor and nasal pungency thresholds and ocular irritation thresholds in normosmics and nasal pungency thresholds in anosmics decreased with increasing chain length (Cometto-Muniz and Cain 1990, 1993, 1994, 1995). Although quantitative structure-activity relationship equations have been developed to predict nasal pungency, a condition of the equations is that the volatile organic compounds must be nonreactive (Abraham et al. 1996, 1998). Allyl compounds are reactive and are specifically excluded. If one

uses the algorithm to predict the potency of a reactive compound, the predicted minimum potency will be less than the observed potency.

NTP (2006) conducted studies comparing the toxicity of allyl alcohol, allyl acetate, and acrolein in male and female rats and mice exposed via gavage for 14 weeks, in an effort to discern the role of metabolism to acrolein in the toxicity of the other two compounds. Apart from one female rat exposed at 6 mg/kg that was killed moribund, all rats and mice survived exposure at doses up to 25 mg/kg (rats) or 50 mg/kg (mice). In contrast, all rats exposed at 10 mg/kg and all mice exposed at 20 mg/kg acrolein died. Rats exposed to allyl acetate survived at doses up to 50 mg/kg (all died at 100 mg/kg), and all but one female mouse survived exposure at up to 32 mg/kg. The forestomach was the primary organ affected by all three compounds. Exposure to allyl alcohol resulted in minimal to mild squamous epithelial hyperplasia in rats and mice at doses up to 50 mg/kg. Exposure to acrolein at doses of 10 mg/kg and higher resulted in more severe lesions of necrosis, hemorrhage, and chronic active inflammation in rats and mice. These more severe lesions were also seen at the highest doses of allyl acetate (100 mg/kg in rats or 62.5 mg/kg or higher in mice). NTP (2006) suggested that the forestomach toxicity of allyl alcohol and allyl acetate may have resulted from their metabolism to acrolein in the forestomach.

Renal toxicity was not observed in either species or with any of the three test compounds in the oral subchronic study (NTP 2006). Allyl alcohol was hepatotoxic to mice and female rats, and allyl acetate also resulted in hepatotoxicity in both species, while acrolein did not. NTP (2006) postulated that the reaction of acrolein with gut contents reduced its systemic bioavailability and, thus, its hepatotoxic potential, whereas the bioavailability of allyl alcohol and allyl acetate would not have been similarly affected due to these compounds' lower reactivity.

4.3. Susceptible Populations

Exposure at high concentrations of inhaled allyl alcohol can produce pulmonary congestion, edema, and compensatory emphysema, so it is likely that people with pulmonary conditions would be at increased risk of such effects (McCord 1932). People with pre-existing pulmonary disease might be at special risk to the pulmonary effects of allyl alcohol at lower concentrations; however, at high concentrations, people with pulmonary disease and healthy individuals will probably be affected similarly. Allyl alcohol exposure can result in hepatotoxicity, so individuals with compromised hepatic function may also be at an increased risk. More specifically, variations in the amount of ADH or glutathione will influence the extent of hepatotoxicity. This is due to the fact that allyl alcohol-induced hepatotoxicity depends on the conversion of allyl alcohol to acrolein by ADH (Serafini-Cessi 1972; Patel et al. 1983). Acrolein is then detoxified by further metabolism to acrylic acid by aldehyde dehydrogenase or by conjugation with glutathione (Rikans 1987; Rikans and Moore 1987). Hepatic

damage can also be influenced by bacterial infections, as demonstrated in a study reporting that allyl alcohol-treated rats pretreated with bacterial endotoxin experienced enhanced hepatic damage compared with rats given allyl alcohol alone (Sneed et al. 1997). Allyl alcohol exposure can also result in renal damage; thus, individuals with pre-exisiting renal conditions may be at an increased risk.

4.4. Concentration-Exposure Duration Relationship

The experimentally-derived exposure values in toxicity studies are scaled to the AEGL durations using the concentration-time relationship given by the equation $C^n \times t = k$, where C is concentration, t is time, and k is a constant. The value of the exponent n generally ranges from 0.8 to 3.5, and should be derived empirically from acute inhalation toxicity experiments, in which both the concentration and exposure duration are variables (ten Berge et al. 1986). For the AEGL-3 values, the LC_{01} values for each AEGL duration were calculated by the ten Berge software program using all available individual rat mortality data (see Appendix A); the ten Berge program estimated an n value of 0.95.

4.5. Other Relevant Information

An in vitro study conducted by Berry and Easty (1993) compared the corneal toxicity of allyl alcohol in isolated rabbit and human eyes and found a similar degree of ocular damage in both species.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Five of six human volunteers exposed to allyl alcohol for 5 min reported olfactory recognition at the lowest concentration of 0.78 ppm (Dunlap et al. 1958). Nasal irritation was reported as slight in two of six subjects exposed at 0.78 ppm and three of six subjects exposed at 6.25 ppm for 5 min. Nasal irritation of moderate or greater severity was reported in one of six subjects exposed to allyl alcohol for 5 min at 6.25 ppm, in four of seven volunteers exposed at 12.5 ppm, and in all five subjects exposed at 25 ppm. Slight ocular irritation was reported by one of six and one of seven individuals exposed for 5 min at 6.25 or 12.5 ppm, respectively. Severe ocular irritation was reported by all five volunteers exposed to allyl alcohol at 25 ppm for 5 min. Data from this study were not used to derive AEGL-1 values, because of the short exposure duration and uncertainties about the exposures, but the data are supportive of the AEGL-1 values. Humans reported severe ocular irritation at 25 ppm for 5 min, and rats exposed at 600 ppm for 1 h did not exhibit any signs of ocular irritation (Dunlap et al. 1958; Kirkpatrick 2008). Ocular irritation noted by the human volunteers was possibly the result of acrolein contamination.

5.2. Animal Data Relevant to AEGL-1

Exposure to allyl alcohol at 51 ppm for 1 h, at 22 ppm for 4 h, or at 10 ppm for 8 h produced reversible histopathologic changes in the nasal cavity of rats, including degeneration of the olfactory epithelium, chronic inflammation, and goblet cell hyperplasia (Kirkpatrick 2008). Clinical signs included material around the mouth and alcohol flushing. Exposure at higher concentrations at each duration resulted in increased incidences of histopathologic changes in the nasal cavity, gasping, and reduced reaction to cage stimulus. A study in mice identified an RD_{50} (concentration that reduces respiratory rate by 50%) of 3.9 ppm (30 min) (Nielsen et al. 1984). This test quantitatively measures irritant effects as indicated by a reflex decrease in respiration (ASTM 2012). An RD_{10} value of 0.27 ppm was calculated to estimate the threshold for irritation.

5.3. Derivation of AEGL-1 Values

Data from the Nielsen et al. (1984) study in mice were used as the basis for deriving AEGL-1 values. An RD_{10} value of 0.27 ppm (30 min) was an estimate of the threshold for irritation. A total uncertainty factor of 3 was applied, as irritant effects are not expected to vary greatly between species or individuals. Time scaling was not applied due to the short duration of exposure. The AEGL-1 values are supported by results of the Dunlap et al. (1958) study. If AEGL-1 values had been based on human data from that study, AEGL-1 values would have been 0.27 ppm (point of departure of 0.78 ppm, a total uncertainty factor of 3, and no time scaling).

AEGL-1 values for allyl alcohol are presented in Table 4-12, and the calculations are presented in Appendix B.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

Slight nasal irritation was reported by two of six human volunteers exposed to allyl alcohol for 5 min at 0.78 ppm and three of six subjects exposed at 6.25 ppm (Dunlap et al. 1958). Nasal irritation of moderate or greater severity was reported in one of six subjects exposed at 6.25 ppm, by four of seven volunteers exposed at 12.5 ppm, and in all five subjects exposed at 25 ppm. Slight ocular irritation was reported by one of six and one of seven individuals exposed for 5 min at 6.25 or 12.5 ppm, respectively. Severe ocular irritation was reported by all five volunteers exposed at 25 ppm for 5 min. These data were not used to derive AEGL-2 values, because of the short exposure duration and uncertainties about the exposures. Although humans reported severe ocular irritation at 25 ppm for 5 min, and rats exposed at 600 ppm for 1 h did not exhibit any signs of ocular irritation (Dunlap et al. 1958; Kirkpatrick 2008). Ocular irritation noted by the human volunteers was possibly the result of acrolein contamination.

TABLE 4-12 AEGL-1 Values for Allyl Alcohol

10 min	30 min	1 h	4 h	8 h
0.090 ppm (0.22 mg/m^3)	0.090 ppm (0.22 mg/m^3)	0.090 ppm (0.22 mg/m^3)	0.090 ppm (0.22 mg/m^3)	0.090 ppm (0.22 mg/m^3)

6.2. Animal Data Relevant to AEGL-2

Rats were exposed to allyl alcohol vapor at concentrations of 0, 51, 220, or 403 ppm for 1 h, 0, 22, 52, or 102 ppm for 4 h, and 0, 10, 21, or 52 ppm for 8 h (Kirkpatrick 2008). In studies of 1-h exposures, minimal effects were observed at 51 ppm. At concentrations of 220 and 430 ppm, reduced responses to stimulus, concentration-related increases in alcohol flushing, material around the mouth, and chronic inflammation in the nasal cavity were found. Olfactory epithelium degeneration and goblet cell hyperplasia were present in 1-3 rats at all concentrations, and one rat exposed at 403 ppm exhibited gasping during exposure. In rats exposed for 4 h, 22 ppm produced material around the mouth in one rat, goblet cell hyperplasia in one rat, and chronic inflammation in the nasal cavity. Exposure at 52 and 102 ppm generally resulted in concentration-related increases in alcohol flushing, material around the mouth, gasping, reduced response to cage stimulus, olfactory and respiratory epithelium degeneration, chronic inflammation in the nasal cavity, and goblet cell hyperplasia. In rat exposed for 8 h, clinical effects were minimal at 10 and 21 ppm (a few rats had alcohol flushing, material around the mouth, one rat at each concentration had yellow material around the urogenital area, and one rat in the 21-ppm group had rales/increased respiration). One rat in the 52-ppm group died. A concentration-related increase in the number of animals with a reduced response to cage stimulus was observed at 21 and 52 ppm. Histopathologic examination of the nasal cavity of rats exposed at 10 or 21 ppm revealed reversible changes, including degeneration of the olfactory and respiratory epithelium, chronic inflammation, and goblet cell hyperplasia. Exposure at 52 ppm produced similar but generally more severe lesions.

Other inhalation data were not appropriate for deriving AEGL-2 values. In a study by Dunalp et al. (1958), rats were exposed repeatedly to allyl alcohol at 20, 40, or 60 ppm for 7 h. No measurable adverse effects were found in the 20-ppm group. At 40 ppm, irritation (which resolved after the first few exposures) and increased lung weight were observed. At 60 ppm, irritation evidenced by gasping and muzzle-rubbing (which disappeared after the first few exposures), persistent ocular discharge, and one death were observed.

6.3. Derivation of AEGL-2 Values

The Kirkpatrick (2008) study in rats was selected as the basis for deriving AEGL-2 values for allyl alcohol. No-effect levels for disabling effects (reduced response to stimulus and gasping) were 51 ppm for 1 h, 22 ppm for 4 h, and 10

ppm for 8 h. These values were used as the points-of-departure for the 1-, 4- and 8-h AEGL-2 values, respectively. A total uncertainty factor of 30 was applied. An interspecies uncertainty factor of 3 was used because similar 1-h no-effect levels for lethality have been reported for rats (200-423 ppm) (Union Carbide and Carbon Corporation 1951; Kirkpatrick 2008), mice (200 ppm) (Union Carbide and Carbon Corporation 1951), and rabbits (200 ppm) (Union Carbide and Carbon Corporation 1951). An intraspecies factor of 10 was applied because of the uncertainty about whether the disabling effects are due to allyl alcohol, one of its metabolites, or both. Also, humans have genetic polymorphisms for aldehyde dehydrogenase. Time scaling was performed for the 10- and 30-min AEGL values using the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). An empirical value for n of 0.95 was derived from rat lethality data (see Appendix A).

AEGL-2 values for allyl alcohol are presented in Table 4-13, and the calculations are presented in Appendix B.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data on allyl alcohol were relevant for deriving AEGL- value3. No reports of death following accidental exposure to allyl alcohol were found.

7.2. Animal Data Relevant to AEGL-3

Groups of five rats per sex were exposed to allyl alcohol vapor at concentrations of 0, 51, 220, or 403 ppm for 1 h, at 0, 22, 52, or 102 ppm for 4 h, and at 0, 10, 21, or 52 ppm for 8 h (Kirkpatrick 2008). All animals survived to study termination except for one male rat exposed at 52 ppm for 8 h. The rat died the day after exposure, and death was attributed to ulceration of the respiratory and olfactory epithelium in the nasal passages, resulting in diminished breathing capacity and hypoxia. Another male rat had irreversible nasal histopathologic lesions. The histopathologic changes that were observed in the nasal cavities of all other exposed rats were considered reversible. In a preliminary study by Kirkpatrick (2008), groups of three rats per sex were exposed to allyl alcohol at concentrations of 423 ppm or 638 ppm for 1 h, 114 ppm for 4 h, and 52 ppm for 8 h. All animals survived to study termination. Clinical signs in all exposure groups included gasping during and after exposure, material around the mouth and nose, and alcohol flushing after the exposure. Two rats exposed at 52 ppm for 8 h exhibited labored respiration during exposure. Histopathologic examinations were not performed.

Mice, rats, and rabbits survived exposure to allyl alcohol at 200 ppm for 1 h. Mice survived exposure to allyl alcohol at 500 ppm for 30 min but not for 1 h. Rabbits survived a 2-h but not a 4-h exposure to allyl alcohol at 500 ppm (Union

Carbide and Carbon Corporation 1951). Exposure to allyl alcohol at 1,000 ppm for as little as 30 min and up to 4 h killed monkeys, mice, rats, and rabbits (McCord 1932; Smyth and Carpenter 1948; Union Carbide and Carbon Corporation 1951). Dunlap et al. (1958) reported 1-, 4-, and 8-h LC_{50} values in rats of 1,060 ppm, 165 ppm, and 76 ppm, respectively (actual exposure concentrations were 15-25% less than the target concentrations, but no corrected concentrations were provided).

7.3. Derivation of AEGL-3 Values

AEGL-3 values are based on the calculated LC_{01} values for allyl alcohol in rats of 2,600 ppm for 10 min, 820 ppm for 30 min, 400 ppm for 1 h, 93 ppm for 4 h, and 45 ppm for 8 h. LC_{01} estimates were calculated using the ten Berge software program and rat mortality data from four studies (McCord 1932; Smyth and Carpenter 1948; Union Carbide and Carbon Corporation 1951; Kirkpatrick 2008) (see Appendix A). The ten Berge program estimated an n = 0.95 for time scaling. An interspecies uncertainty factor of 3 was used because similar 1-h no-effect levels for lethality have been reported for rats (200-423 ppm) (Union Carbide and Carbon Corporation 1951; Kirkpatrick 2008), mice (200 ppm) (Union Carbide and Carbon Corporation 1951), and rabbits (200 ppm) (Union Carbide and Carbon Corporation 1951). An intraspecies factor of 10 was applied because of the uncertainty about whether lethal effects are due to allyl alcohol, one of its metabolites, or both. Furthermore, humans have genetic polymorphisms for aldehyde dehydrogenase. AEGL-3 values for allyl alcohol are presented in Table 4-14, and the calculations are presented in Appendix B.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

A summary of AEGL values for allyl alcohol is presented in Table 4-15. AEGL-1 values are based on the RD_{10} value in mice, which was an estimate of the threshold for irritation.AEGL-2 values are based on no-effect levels for disabling effects observed in rats. AEGL-3 values for allyl alcohol are based on LC_{01} estimates calculated using the ten Berge software program and rat mortality data from several studies.

TABLE 4-13 AEGL-2 Values for Allyl Alcohol

10 min	30 min	1 h	4 h	8 h
11 ppm (27 mg/m^3)	3.5 ppm (8.5 mg/m^3)	1.7 ppm (4.1 mg/m^3)	0.73 ppm (1.8 mg/m^3)	0.33 ppm (0.80 mg/m^3)

8.2. Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures to allyl alcohol are presented in Table 4-16.

8.3. Data Adequacy and Research Needs

Human data available for allyl alcohol AEGL derivations are limited. In one study from 1958, humans were exposed to allyl alcohol for only 5 min and nose and eye irritation was recorded (Dunlap et al. 1958). The study results are of limited utility due to the short exposure duration, and are questionable in the context of other study results. Humans reported severe eye irritation at 25 ppm for 5 min, while rats exposed to 600 ppm for 1 h did not exhibit any signs of eye irritation. It is possible that the eye irritation noted by the human volunteers was the result of acrolein contamination. The only other human data available are case reports of corneal damage (Smyth 1956) and occupational accounts of pulmonary edema, conjunctivitis, and lacrimation after exposures to unknown concentrations, frequencies, or durations (McCord 1932).

Major data gaps include the lack of lifetime inhalation carcinogenicity bioassays on allyl alcohol and the lack of in vivo assays for clastogenicity or confirmatory evidence of genotoxicity. The NAC recognizes the potential for ally alcohol to be a carcinogen, considering the evidence that allyl alcohol can be metabolized to acrolein. However, at this time there are not enough data to provide a quantitative assessment of the carcinogenic potential of allyl alcohol. In order to determine whether the pronounced upper respiratory tract irritation (McCord 1932; Dunlap et al. 1958) is due to the parent molecule or to its irritant/carcinogenic aldehyde metabolites (acrolein, glycidaldehyde) (Beauchamp et al. 1985), pharmocokinetic and disposition data in target tissues are necessary. Fundamental research including quantification and extrapolation of irritant response for ally alcohol and related material is lacking.

TABLE 4-14 AEGL-3 Values for Allyl Alcohol

10 min	30 min	1 h	4 h	8 h
87 ppm (210 mg/m^3)	27 ppm (65 mg/m^3)	13 ppm (31 mg/m^3)	3.1 ppm (7.5 mg/m^3)	1.5 ppm (3.6 mg/m^3)

TABLE 4-15 AEGL Values for Allyl Alcohol

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	0.09 ppm (0.22 mg/m^3)	0.09 ppm (0.22 mg/m^3)	0.09 ppm (0.22 mg/m^3)	0.09 ppm (0.22 mg/m^3)	0.09 ppm (0.22 mg/m^3)
AEGL-2 (disabling)	11 ppm (27 mg/m^3)	3.5 ppm (8.5 mg/m^3)	1.7 ppm (4.1 mg/m^3)	0.73 ppm (1.8 mg/m^3)	0.33 ppm (0.80 mg/m^3)
AEGL-3 (lethal)	87 ppm (210 mg/m^3)	27 ppm (65 mg/m^3)	13 ppm (31 mg/m^3)	3.1 ppm (7.5 mg/m^3)	1.5 ppm (3.6 mg/m^3)

TABLE 4-16 Standards and Guidelines for Allyl Alcohol

	Exposure Duration					
Guideline	10 min	15 min	30 min	1 h	4 h	8 h
AEGL-1	0.09 ppm (0.22 mg/m^3)	–	0.09 ppm (0.22 mg/m^3)	0.09 ppm (0.22 mg/m^3)	0.09 ppm (0.22 mg/m^3)	0.09 ppm (0.22 mg/m^3)
AEGL-2	11 ppm (27 mg/m^3)	–	3.5 ppm (8.5 mg/m^3)	1.7 ppm (4.1 mg/m^3)	0.73 ppm (1.8 mg/m^3)	0.33 ppm (0.80 mg/m^3)
AEGL-3	87 ppm (210 mg/m^3)	–	27 ppm (65 mg/m^3)	13 ppm (31 mg/m^3)	3.1 ppm (7.5 mg/m^3)	1.5 ppm (3.6 mg/m^3)
IDLH (NIOSH)[a]	–	–	–	20 ppm	–	–
TLV-TWA (ACGIH)[b]	–	–	–	–	–	0.5 ppm (1.21 mg/m^3) [skin]
PEL-TWA (OSHA)[c]	–	–	–	–	–	2 ppm (5 mg/m^3) [skin]
REL-TWA (NIOSH)[d]	–	–	–	–	–	2 ppm (5 mg/m^3) [skin]
REL-STEL (NIOSH)[e]	–	4 ppm (10 mg/m^3) [skin]	–	–	–	–
MAK (Germany)[f]	–	–	–	–	–	Not established; carcinogenicity category 3
MAC (The Netherlands)[g]	–	–	–	–	–	2 ppm (5 mg/m^3)

[a]IDLH (immediately dangerous to life or health, National Institute for Occupational Safety and Health [NIOSH 1994, 2011]) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms, or any irreversible health effects. The ILDH value for allyl alcohol is based on severe ocular irritation in humans exposed at 25 ppm (Dunlap et al. 1958).

[b]TLV-TWA (threshold limit value – time-weighted average, American Conference of Governmental Industrial Hygienists [ACGIH 2013]) 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. The skin designation indicates the potential for dermal absorption; skin exposure should be prevented as necessary.

[c]PEL-TWA (permissible exposure limit – time-weighted average, Occupational Safety and Health Administration `[(29 CFR 1910.1000) [2006]) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 8 h/day, 40 h/week. The skin designation indicates the potential for dermal absorption; skin exposure should be prevented as necessary.

[d]REL-TWA (recommended exposure limit – time-weighted average, National Institute for Occupational Safety and Health [NIOSH 2011]) is defined analogous to the ACGIH TLV-TWA. The skin designation indicates the potential for dermal absorption; skin exposure should be prevented as necessary.
[e]REL-STEL (recommended exposure limit – short-term exposure limit, National Institute for Occupational Safety and Health) (NIOSH 2011) is a 15-min time-weighted average exposure that should not be exceeded at any time during a workday. The skin designation indicates the potential for dermal absorption; skin exposure should be prevented as necessary.
[f]MAK (maximale argeitsplatzkonzentration [maximum workplace concentration], Deutsche Forschungsgemeinschaft [German Research Association]) (DFG 2012) is defined analogous to the ACGIH TLV-TWA. Carcinogenicity category 3B is defined as: "Substances that cause concern that they could be carcinogenic for man but cannot be assessed conclusively because of lack of data. In vitro test or animal studies have yielded evidence of carcinogenicity that is not sufficient for classification of the substance in one of the other categories. The classification of Category 3 is provisional. Further studies are required before a final decision can be made. A MAK value can be established provided no genotoxic effects have been detected."
[g]MAC (maximaal aanvaaarde concentratie [maximum accepted concentration], SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], Dutch Expert Committee for Occupational Standards, The Netherlands (MSZW 2004) is defined analogous to the ACGIH TLV-TWA.

A level of distinct odor awareness (LOA), which represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity and about 10 % of the population will experience a strong odor intensity, could not be determined due to inadequate data. Although odor thresholds for allyl alcohol have been reported (1.4 ppm and 2.1 ppm), concurrent odor threshold data for the reference chemical n-butanol (odor detection threshold 0.04 ppm) were not available.

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APPENDIX A

DERIVATION OF LC_{01} VALUES AND TIME-SCALING EXPONENT FOR ALLY ALCOHOL

Filename: allyl alcohol for Log Probit Model
Date: 13 November 2008 Time: 14:07:13

Sequence No.	Concentration (ppm)	Minutes	Exposed	Responded
1	51	60	10	0
2	220	60	10	0
3	403	60	10	0
4	22	240	10	0
5	52	240	10	0
6	102	240	10	0
7	10	480	10	0
8	21	480	10	0
9	52	480	10	1
10	200	60	10	0
11	1,000	30	6	1
12	1,000	60	6	4
13	1,000	120	6	6
14	1,000	60	6	4
15	1,000	180	6	6
16	638	60	6	0
17	423	60	6	0
18	114	240	6	0
19	52	480	6	0

Used Probit Equation Y = B0 + B1*X1 + B2*X2
X1 = conc ppm, ln-transformed
X2 = minutes, ln-transformed

Chi-square = 6.50
Degrees of freedom = 16
Probability model = 9.82E-01

Ln(Likelihood) = -7.40

B 0 = -2.7460E+01	Student t = -3.3238
B 1 = 2.9303E+00	Student t = 4.2466
B 2 = 3.0760E+00	Student t = 3.3390

Variance B 0 0 = 6.8256E+01
Covariance B 0 1= -5.6297E+00
Covariance B 0 2 = -7.5164E+00
Variance B 1 1 = 4.7615E-01
Covariance B 1 2 = 6.0522E-01
Variance B 2 2 = 8.4867E-01

Estimation ratio between regression coefficients of ln(conc) and ln(minutes)
Point estimate = 0.953
Lower limit (95% CL) = 0.758
Upper limit (95% CL) = 1.147

Estimation of Conc ppm at response of 1%
Minutes = 480
Point estimate Conc ppm = 4.482E+01 for response of 1%
Lower limit (95% CL) Conc ppm = 2.858E+01 for response of 1%
Upper limit (95% CL) Conc ppm = 6.399E+01 for response of 1%

Estimation of Conc ppm at response of 1%
Minutes = 240
Point estimate Conc ppm = 9.279E+01 for response of 1%
Lower limit (95% CL) Conc ppm = 6.111E+01 for response of 1%
Upper limit (95% CL) Conc ppm = 1.180E+02 for response of 1%

Estimation of Conc ppm at response of 1%
Minutes = 60
Point estimate Conc ppm = 3.976E+02 for response of 1%
Lower limit (95% CL Conc ppm = 2.194E+02 for response of 1%
Upper limit (95% CL) Conc ppm = 5.115E+02 for response of 1%

Estimation of Conc ppm at response of 1%
Minutes = 30
Point estimate Conc ppm = 8.232E+02 for response of 1%
Lower limit (95% CL) Conc ppm = 3.833E+02 for response of 1%
Upper limit (95% CL) Conc ppm = 1.154E+03 for response of 1%

Estimation of Conc ppm at response of 1%
Minutes = 10
Point estimate Conc ppm = 2.608E+03 for response of 1%
Lower limit (95% CL) Conc ppm = 8.960E+02 for response of 1%
Upper limit (95% CL) Conc ppm = 4.347E+03 for response of 1%

APPENDIX B

DERIVATION OF AEGL VALUES FOR ALLYL ALCOHOL

Derivation of AEGL-1 Values

Key study:	Nielsen, G.D., J.C. Bakbo, and E. Holst. 1984. Sensory irritation and pulmonary irritation by airborne allyl acetate, allyl alcohol, and allyl ether compared to acrolein. Acta Pharmacol. Toxicol. 54(4):292-298.
Toxicity end point:	RD_{10} = 27 ppm (estimated threshold for irritation)
Time scaling:	Not applied
Uncertainty factors:	3, because irritant effects are not expected to vary greatly between species or individuals
Calculation:	0.27 ppm ÷ 3 = 0.090 ppm (applied to all AEGL-1 durations)

Derivation of AEGL-2 Values

Key study:	Kirkpatrick, D.T. 2008. Acute Inhalation Toxicity Study of Allyl Alcohol in Albino Rats (with 1-, 4-, and 8-hour Exposure Durations). Study Number WIL-14068; WIL Research Laboratories, LLC., Ashland, OH.
Toxicity end point:	No effect level for disabling effects: 51 ppm for 1 h, 22 ppm for 4 h, and 10 ppm for 8 h
Time scaling:	Performed for the 10- and 30-min values. $C^n \times t = k$, where n = 0.95 (derived from rat lethality data; see Appendix B) $C^{0.95} \times t = k$ $(51 \text{ ppm})^{0.95} \times 1 \text{ h} = 42 \text{ ppm-h}$
Uncertainty Factors:	3 for interspecies differences 10 for intraspecies variability
Calculations:	
10-min AEGL-2:	$C^{0.95} \times 0.0167 \text{ h} = 42 \text{ ppm-h}$ $C^{0.95} = 251 \text{ ppm}$ C = 336 ppm 336 ÷ 30 = 11 ppm

30-min AEGL-2: $C^{0.95} \times 0.5$ h = 42 ppm-h
$C^{0.95}$ = 84 ppm
C = 106 ppm
106 ÷ 30 = 3.5 ppm

1-h AEGL-2: 51 ppm ÷ 30 = 1.7 ppm

4-h AEGL-2: 22 ppm ÷ 30 = 0.73

8-h AEGL-2: 10 ppm ÷ 30 = 0.33

Derivation of AEGL-3 Values

Key studies: Kirkpatrick, D.T. 2008. Acute Inhalation Toxicity Study of Allyl Alcohol in Albino Rats (with 1-, 4-, and 8-hour Exposure Durations). Study Number WIL-14068; WIL Research Laboratories, LLC., Ashland, OH.

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Toxicity end point: Calculated LC_{01} values: 2,600 ppm for 10 min, 820 ppm for 30 min, 400 ppm for 1 h, 93 ppm for 4 h, and 45 ppm for 8 h.

Time scaling: A point of departure for each AEGL exposure duration was calculated using ten Berge program; the program calculated an n value 0.95 (see Appendix B).

Uncertainty factors: 3 for interspecies differences
10 for intraspecies variability

Calculations:

10-min AEGL-3:	2,600 ppm ÷ 30 = 87 ppm
30-min AEGL-3:	820 ppm ÷ 30 = 27 ppm
1-h AEGL-3:	400 ppm ÷ 30 = 13 ppm
4-h AEGL-3:	93 ppm ÷ 30 = 3.1 ppm
8-h AEGL-3:	45 ppm ÷ 30 = 1.5 ppm

APPENDIX C

ACUTE EXPOSURE GUIDELINE LEVELS FOR ALLY ALCOHOL

Derivation Summary

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
0.090 ppm (0.22 mg/m^3)	0.090 ppm (0.22 mg/m^3)	0.090 ppm (0.22 mg/m^3)	0.090 ppm (0.22 mg/m^3)	0.090 ppm (0.22 mg/m^3)

Key reference: Nielsen, G.D., J.C. Bakbo, and E. Holst. 1984. Sensory irritation and pulmonary irritation by airborne allyl acetate, allyl alcohol, and allyl ether compared to acrolein. Acta Pharmacol. Toxicol. 54(4):292-298.

Test species/Strain/Sex/Number: Mice, Ssc:CF-1; 4 males per group

Exposure route/Concentrations/Durations: Inhalation (head only), 0.42, 2.00, 4.55, or 18.10 ppm for 30 min

Effects: Reduction in respiratory rate, RD_{50} = 3.9 ppm; RD_{10} = 0.27 ppm

End point/Concentration/Rationale: Estimate of irritation threshold, RD_{10} = 0.27 ppm

Uncertainty factors/Rationale:
Total uncertainty factor: 3, irritant effects are not expected to vary greatly between species or individuals.

Modifying factor: None

Animal-to-human dosimetric adjustment: None

Time scaling: None

Data adequacy: Data are adequate to derive AEGL-1 values.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
11 ppm (27 mg/m^3)	3.5 ppm (8.5 mg/m^3)	1.7 ppm (4.1 mg/m^3)	0.73 ppm (1.8 mg/m^3)	0.33 ppm (0.80 mg/m^3)

Key reference: Kirkpatrick, D.T. 2008. Acute Inhalation Toxicity Study of Allyl Alcohol in Albino Rats (with 1-, 4-, and 8-Hour Exposure Durations). Study Number WIL-14068; WIL Research Laboratories, LLC., Ashland, OH.

Test species/Strain/Sex/Number: Rats, Crl:CD(DS), 5 males and 5 females per group

Exposure route/Concentrations/Durations: Inhalation; 51, 220, or 403 ppm for 1 h, 22, 52, or 102 ppm for 4 h, and 10, 21, or 52 ppm for 8 h.

Effects:

Duration	Concentration	Effects
1h	51 ppm	Alcohol flush and nasal irritation.
	220 ppm	Same as at 51 ppm, plus decreased response to stimulus.

Duration	Concentration	Effects
	403 ppm	Same as at 220 ppm, plus gasping.
4 h	22 ppm	Clear red material around mouth.
	52 ppm	Same as at 22 ppm, plus nasal irritation, gasping, and reduce response to stimulus.
	102 ppm	Same as at 52 ppm.
8 h	10 ppm	Alcohol flush and nasal irritation.
	21 ppm	Same as at 10 ppm, plus gasping and reduced response to stimulus.
	52 ppm	Same as at 21 ppm.

End point/Concentration/Rationale: No-effect level for AEGL-2 effects; 51 ppm for 1 h, 22 ppm for 4 h, and 10 ppm for 8 h.

Uncertainty factors/Rationale:
Total uncertainty factor: 30
Interspecies: 3, similar 1-h no-effect levels for lethality reported for rats (200-423 ppm), mice (200 ppm), and rabbits (200 ppm).
Intraspecies: 10, unknown if effects of allyl alcohol are due to parent compound, metabolites, or both. Also, accounts for genetic polymorphisms for aldehyde dehydrogenase in humans.

Modifying factor: None

Animal-to-human dosimetric adjustment: None

Time scaling: Performed for the 10- and 30-min values. $C^n \times t = k$, where n = 0.95 (derived from rat lethality data; see Appendix B).

Data adequacy: Data sufficient to derive AELG-2 values.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
87 ppm (210 mg/m^3)	27 ppm (65 mg/m^3)	13 ppm (31 mg/m^3)	3.1 ppm (7.5 mg/m^3)	1.5 ppm (3.6 mg/m^3)

Key references: Kirkpatrick, D.T. 2008. Acute Inhalation Toxicity Study of Allyl Alcohol in Albino Rats (with 1-, 4-, and 8-Hour Exposure Durations). Study Number WIL-14068; WIL Research Laboratories, LLC, Ashland, OH.

McCord, C.P. 1932. The toxicity of allyl alcohol. J. Am. Med. Assoc. 98(26):2269-2270.

Smyth, H.F., and C.P. Carpenter. 1948. Further experience with the range finding test in the industrial toxicology laboratory. J. Ind. Hyg. Toxicol. 30(1):63-68.

Union Carbide and Carbon Corporation. 1951. Initial submission: Letter from DuPont Chem Regarding a Letter About Toxicity Studies with Allyl Alcohol, Union Carbide and Carbon Corporation, New York, January 29, 1951. Subbmited by DuPont, Wilmington, DE to EPA with cover letter dated October 27, 1992. EPA Document No. 88-920009857. Microfische No. OTS0571508.

Test species/Strain/Sex/Number: Rat (see table below for number of animals for each study)

(Continued)

AEGL-3 VALUES Continued

Exposure route/Concentrations/Durations: Inhalation, 10-1,000 ppm for 1-8 h

Effects:

Concentration (ppm)	Minutes	Exposed	Responded	Reference
51	60	10	0	Kirkpatrick 2008
220	60	10	0	Kirkpatrick 2008
403	60	10	0	Kirkpatrick 2008
22	240	10	0	Kirkpatrick 2008
52	240	10	0	Kirkpatrick 2008
102	240	10	0	Kirkpatrick 2008
10	480	10	0	Kirkpatrick 2008
21	480	10	0	Kirkpatrick 2008
52	480	10	1	Kirkpatrick 2008
200	60	10	0	Union Carbide and Carbon Corporation 1951
1,000	30	6	1	Union Carbide and Carbon Corporation 1951
1,000	60	6	4	Union Carbide and Carbon Corporation 1951
1,000	120	6	6	Union Carbide and Carbon Corporation 1951
1,000	60	6	4	Smyth and Carpenter 1948
1,000	180	6	6	McCord 1932
638	60	6	0	Kirkpatrick 2008
423	60	6	0	Kirkpatrick 2008
114	240	6	0	Kirkpatrick 2008
52	480	6	0	Kirkpatrick 2008

End point/Concentration/Rationale: Estimated lethality thresholds, LC_{01}s of 2,600 ppm for 10 min, 820 ppm for 30 min, 400 ppm for 1 h, 93 ppm for 4 h, and 45 ppm for 8 h. LC_{01} values calculated using log-probit model of ten Berge (see Appendix B).

Uncertainty factors/Rationale:
Total uncertainty factor: 30
Interspecies: 3, similar 1-h no-effect levels for lethality reported for rats (200-423 ppm), mice (200 ppm), and rabbits (200 ppm).
Intraspecies: 10, unknown if effects of allyl alcohol are due to parent compound, metabolites, or both. Also, accounts for genetic polymorphisms for aldehyde dehydrogenase in humans.

Modifying factor: None

Animal-to-human dosimetric adjustment: None

Time scaling: A point of departure for each AEGL exposure duration was calculated using ten Berge program; program calculated an n value 0.95 (see Appendix B).

Data adequacy: Data were adequate to derive AEGL-3 values. The most recent study with measured concentrations of allyl alcohol reported minimal mortality; therefore, mortality data from earlier studies with less than adequate analytic techniques were included.

APPENDIX D

CATEGORY PLOT FOR ALLYL ALCOHOL

A useful way to evaluate AEGL values in the context of empirical data is presented in Figure D-1. For this plot, toxic responses were placed into severity categories. The severity categories fit into definitions of the AEGL health effects of no effects, discomfort, disabling, some lethality (an experimental concentration at which some of the animals died and some did not), and lethal. The effects that place an experimental result into a particular category vary according to the spectrum of data available on a specific chemical and the effects from exposure to that chemical. The doses often span a several orders of magnitude, especially when human data are available. Therefore, the concentration in the plot is placed on a log scale. The graph in Figure D-1 plots the AEGL values for allyl alcohol and acute human and animal toxicity data for the chemical.

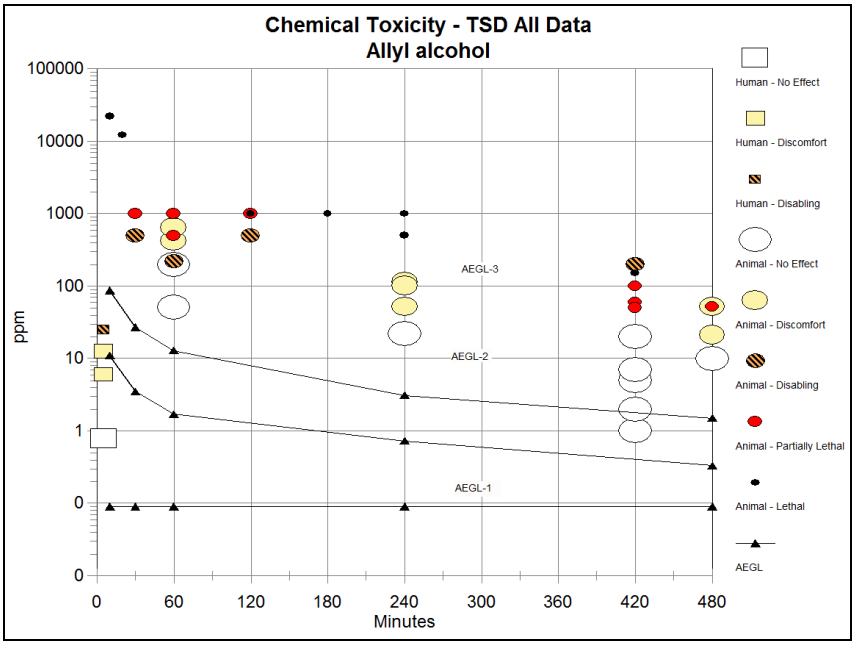

FIGURE D-1 Category plot of toxicity data and AEGL values for allyl alcohol.

TABLE D-1 Data Used in Category Plot for Allyl Alcohol

Source	Species	Sex	No. of Exposures	ppm	Minutes	Category	Comments
AEGL-1				0.090	10	AEGL	
AEGL-1				0.090	30	AEGL	
AEGL-1				0.090	60	AEGL	
AEGL-1				0.090	240	AEGL	
AEGL-1				0.090	480	AEGL	
AEGL-2				11	10	AEGL	
AEGL-2				3.5	30	AEGL	
AEGL-2				1.7	60	AEGL	
AEGL-2				0.73	240	AEGL	
AEGL-2				0.33	480	AEGL	
AEGL-3				87	10	AEGL	
AEGL-3				27	30	AEGL	
AEGL-3				13	60	AEGL	
AEGL-3				3.1	240	AEGL	
AEGL-3				1.5	480	AEGL	
Dunlap et al. 1958	Human			0.78	5	0	
Dunlap et al.1958	Human			6	5	1	
Dunlap et al. 1958	Human			12.5	5	1	
Dunlap et al. 1958	Human			25	5	2	Severe ocular irritation
Dunlap et al. 1958	Rat	Both	1	60.0	420	SL	
Dunlap et al. 1958	Rat	Both	1	100.0	420	SL	

Dunlap et al. 1958	Rat	Both	1	150.0	420	3	
Dunlap et al. 1958	Rat		1	20.0	420	0	
Dunlap et al. 1958	Rat		1	1.0	420	0	
Dunlap et al. 1958	Rat		1	2	420	0	
Dunlap et al. 1958	Rat		1	5	420	0	
Kirkpatrick 2008	Rat	Both	1	51	60	0	
Kirkpatrick 2008	Rat	Both	1	423	60	1	
Kirkpatrick 2008	Rat	Both	1	220	60	2	
Kirkpatrick 2008	Rat	Both	1	638	60	1	
Kirkpatrick 2008	Rat	Both	1	114.0	240	1	
Kirkpatrick 2008	Rat	Both	1	22	240	0	
Kirkpatrick 2008	Rat	Both	1	52.0	480	1	
Kirkpatrick 2008	Rat	Both	1	52.0	240	1	
Kirkpatrick 2008	Rat	Both	1	102.0	240	1	
Kirkpatrick 2008	Rat	Both	1	10.0	480	0	
Kirkpatrick 2008	Rat	Both	1	21.0	480	1	
Kirkpatrick 2008	Rat	Both	1	52.0	480	SL	Mortality (1/10)
McCord 1932	Monkey		1	1,000	240	3	Mortality (1/1)
McCord 1932	Rat		1	1,000	180	3	Mortality (6/6)
McCord 1932	Rat		1		420		Mortality (4/4)
McCord 1932	Rat		1	50.0	420	SL	Mortality (4/5)

(Continued)

TABLE D-1 Continued

Source	Species	Sex	No. of Exposures	ppm	Minutes	Category	Comments
McCord 1932	Rat	Both	1		420		Mortality (4/4)
Shell Chemical Corp. 1957	Mouse		1	22,000	10	3	Mortality (10/10)
Shell Chemical Corp. 1957	Mouse		1	12,200	20	3	Mortality (10/10)
Smyth and Carpenter 1948	Rat		1	1,000	60	SL	Mortality (4/6)
Torkelson et al. 1959a,b	Dog	Both	1	2.0	420	0	
Torkelson et al. 1959a,b	Guinea Pig	Both	1	7.0	420	0	
Torkelson et al. 1959a,b	Guinea Pig	Both	1	2.0	420	0	
Torkelson et al. 1959a,b	Rabbit		1	200.0	420	2	
Torkelson et al. 1959a,b	Rabbit	Both	1	7.0	420	0	
Torkelson et al. 1959a,b	Rabbit	Both	1	2.0	420	0	
Torkelson et al. 1959a,b	Rat	Both	1	7.0	420	0	
Torkelson et al. 1959a,b	Rat	Both	1	2.0	420	0	
Union Carbide and Carbon Corporation 1951	Mouse		1	200	60	0	
Union Carbide and Carbon Corporation 1951	Mouse		1	500	30	2	
Union Carbide and Carbon Corporation 1951	Mouse		1	500	60	SL	Mortality (4/10)
Union Carbide and Carbon Corporation 1951	Mouse		1	1,000	60	SL	Mortality (6/10)
Union Carbide and Carbon Corporation 1951	Mouse		1	1,000	120	SL	Mortality (8/10)

Union Carbide and Carbon Corporation 1951	Mouse		1	1,000.0	240	3	Mortality (10/10)
Union Carbide and Carbon Corporation 1951	Rabbit	Both	1	500	120	2	
Union Carbide and Carbon Corporation 1951	Rabbits		1	500.0	240	3	Mortality (4/4)
Union Carbide and Carbon Corporation 1951	Rat		1	1,000	30	SL	Mortality (1/6)
Union Carbide and Carbon Corporation 1951	Rat		1	1,000	60	SL	Mortality (4/6)
Union Carbide and Carbon Corporation 1951	Rat		1	1,000	120	3	Mortality (6/6)

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