Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 17

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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Preface

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

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

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

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

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

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

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

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

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

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

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

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

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

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

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

For most chemicals, actual human toxicity data are not available or critical information on exposure is lacking, so toxicity data from studies conducted in laboratory animals are extrapolated to estimate the potential toxicity in humans. Such extrapolation requires experienced scientific judgment. The toxicity data for animal species most representative of humans in terms of pharmacodynamic and pharmacokinetic properties are used for determining AEGLs. If data are not available on the species that best represents humans, data from the most sensitive animal species are used. Uncertainty factors are commonly used when animal data are used to estimate risk levels for humans. The magnitude of uncertainty factors depends on the quality of the animal data used to determine the noobserved-adverse-effect level (NOAEL) and the mode of action of the substance in question. When available, pharmacokinetic data on tissue doses are considered for interspecies extrapolation.

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

REVIEW OF AEGL REPORTS

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

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

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

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

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

REFERENCES

NRC (National Research Council). 1968. Atmospheric Contaminants in Spacecraft. Washington, DC: National Academy of Sciences.

NRC (National Research Council). 1972. Atmospheric Contaminants in Manned Spacecraft. Washington, DC: National Academy of Sciences.

NRC (National Research Council). 1984a. Emergency and Continuous Exposure Limits for Selected Airborne Contaminants, Vol. 1. Washington, DC: National Academy Press.

NRC (National Research Council). 1984b. Emergency and Continuous Exposure Limits for Selected Airborne Contaminants, Vol. 2. Washington, DC: National Academy Press.

NRC (National Research Council). 1984c. Emergency and Continuous Exposure Limits for Selected Airborne Contaminants, Vol. 3. Washington, DC: National Academy Press.

NRC (National Research Council). 1984d. Toxicity Testing: Strategies to Determine Needs and Priorities. Washington, DC: National Academy Press.

NRC (National Research Council). 1985a. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 4. Washington, DC: National Academy Press.

NRC (National Research Council). 1985b. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 5. Washington, DC: National Academy Press.

NRC (National Research Council). 1986a. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 6. Washington, DC: National Academy Press.

NRC (National Research Council). 1986b. Criteria and Methods for Preparing Emergency Exposure Guidance Level (EEGL), Short-Term Public Emergency Guidance Level (SPEGL), and Continuous Exposure Guidance level (CEGL) Documents. Washington, DC: National Academy Press.

NRC (National Research Council). 1987. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 7. Washington, DC: National Academy Press.

NRC (National Research Council). 1988. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 8. Washington, DC: National Academy Press.

NRC (National Research Council). 1992. Guidelines for Developing Spacecraft Maximum Allowable Concentrations for Space Station Contaminants. Washington, DC: National Academy Press.

NRC (National Research Council). 1993. Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. Washington, DC: National Academy Press.

NRC (National Research Council). 1994. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 1. Washington, DC: National Academy Press.

NRC (National Research Council). 1996a. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 2. Washington, DC: National Academy Press.

NRC (National Research Council). 1996b. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 3. Washington, DC: National Academy Press.

NRC (National Research Council). 2000a. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 4. Washington, DC: National Academy Press.

NRC (National Research Council). 2000b. Methods for Developing Spacecraft Water Exposure Guidelines. Washington, DC: National Academy Press.

NRC (National Research Council). 2001a. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. Washington, DC: National Academy Press.

NRC (National Research Council). 2001b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 1. Washington, DC: National Academy Press.

NRC (National Research Council). 2002a. Review of Submarine Escape Action Levels for Selected Chemicals. Washington, DC: The National Academies Press.

NRC (National Research Council). 2002b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol 2. Washington, DC: The National Academies Press.

NRC (National Research Council). 2003. Acute Exposure Guideline Levels for Selected Airborne Chemical, Vol. 3. Washington, DC: The National Academies Press.

NRC (National Research Council). 2004. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 4. Washington, DC: The National Academies Press.

NRC (National Research Council). 2007a. Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants, Vol. 1. Washington, DC: The National Academies Press.

NRC (National Research Council). 2007b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 5. Washington, DC: The National Academies Press.

NRC (National Research Council). 2008a. Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants, Vol. 2. Washington, DC: The National Academies Press.

NRC (National Research Council). 2008b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 6. Washington, DC: The National Academies Press.

NRC (National Research Council). 2009. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 7. Washington, DC: The National Academies Press.

NRC (National Research Council). 2010a. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 8. Washington, DC: The National Academies Press.

NRC (National Research Council). 2010b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 9. Washington, DC: The National Academies Press.

NRC (National Research Council). 2011. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 10. Washington, DC: The National Academies Press.

NRC (National Research Council). 2012a. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 11. Washington, DC: The National Academies Press.

NRC (National Research Council). 2012b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 12. Washington, DC: The National Academies Press.

NRC (National Research Council). 2012c. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 13. Washington, DC: The National Academies Press.

NRC (National Research Council). 2013a. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 14. Washington, DC: The National Academies Press.

NRC (National Research Council). 2013b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 15. Washington, DC: The National Academies Press.

NRC (National Research Council). 2014. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 16. Washington, DC: The National Academies Press.

Appendixes

4

Epichlorohydrin[4]

Acute Exposure Guideline Levels

PREFACE

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

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

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

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

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

Epichlorohydrin is a colorless liquid at room temperature; its vapor is explosive when mixed with air. It has a sweet, pungent or chloroform-like odor. Epichlorohydrin has many uses, but it is used primarily in the manufacture of epoxy resins.

Most humans would not detect the odor of epichlorohydrin at concentrations below 10 ppm. The odor recognition level for epichlorohydrin is about 25 ppm; however, odor detection levels reported in the literature range from 0.0825 ppm. The level of distinct odor awareness for epichlorohydrin is 46 ppm. No reports of human deaths from exposure to epichlorohydrin were found. Epichlorohydrin is irritating to mucous membranes, causing burning of the eyes, nose, and pharynx in humans. A few breaths or a 30-min exposure at high (unknown) concentrations have caused irritation to eyes, throat, and respiratory tract and gastrointestinal disturbances that may be delayed in onset. Irreversible respiratory and hepatic damage, but no renal damage, have been observed in humans. Humans exposed to epichlorohydrin at 20 ppm for 1 h experienced burning of the eyes and nose; 40 ppm for less than 2 h caused throat irritation, 68 ppm for 2 min was irritating to the pharynx, and 100 ppm was reported to be intolerable and potentially associated with pulmonary edema and renal damage. Exposure to epichlorohydrin at 136

ppm for 2 min was irritating to the eyes and pharynx and caused a cooling sensation in the eyes and mouth.

Inhalation exposure of laboratory animals (rats, mice, and hamsters) to epichlorohydrin causes effects similar to those reported for humans. In acute lethality studies, death was caused by effects on the respiratory center of the central nervous system and severe respiratory irritation manifested as pulmonary hemorrhage and edema. Death usually occurred a few hours or a few days after exposure. Before death, the animals showed signs of cyanosis, muscle relaxation of the extremities, gasping, labored breathing, depressed or increased respiration, lethargy, fine tremors, and clonic convulsions. In addition, animals showed degenerative lesions of the nasal epithelium and kidneys and damage to the lower respiratory tract. Evidence of nasal irritation and renal lesions also were seen after acute inhalation exposure to epichlorohydrin at nonlethal concentrations.

AEGL-1 values were derived from the no-effect level (17 ppm) for irritation in four subjects exposed to epichlorohydrin vapor for 2 min (Kobernick et al. 1983). The total uncertainty factor was 10; a factor of 10 was applied to account for intraspecies variability. Although mild irritation experienced by humans would most likely be confined to the nasal passages and eyes, a factor of 10 was used to provide sufficient protection for asthmatic individuals. Adjusting the point-of-departure by 10 yields an AEGL value of 1.7 ppm. That concentrations was used for all of the AEGL durations because the irritant effects of epichlorohydrin are not expected to become more severe with time at that concentration. The AEGL-1 value is below the level of odor recognition (25 ppm) and the level of odor awareness (46 ppm). Therefore, odor is not a factor for early warning of exposure to epichlorohydrin.

The available human and animal studies reporting nonlethal effects were not suitable for deriving AEGL-2 values. Therefore, AEGL-2 values were derived by reducing the AEGL-3 values by a factor of 3; that approach is used when a steep concentration-response curve is observed. The AEGL-2 value of 53 ppm for a 30-min exposure was also used for the 10-min exposure, because concentrations of 100 ppm or higher may cause pulmonary edema and renal damage.

The 10-min, 30-min, and 1-h AEGL-3 values were based on the 1-h rat LC_{01} (lethal concentration, 1% lethality) of 721 ppm (Dietz et al. 1985). A total uncertainty factor of 10 was applied. A factor of 3 was selected for interspecies differences on the basis of LC_{50} values for rats, mice, guinea pigs, and rabbits, which showed little variability among species. A factor of 3 was applied for intraspecies variability, on the basis of mechanistic information and information on occupational exposures. Epichlorohydrin is an epoxide and direct alkylating agent. These effects are likely involved in the observed irritation and systemic toxicity, and are not expected to vary considerably in the population. In addition, use of higher total uncertainty factor 30 would result in an 8-h AEGL-3 value of 6.6 ppm. That concentration is inconsistent with occupational data; exposures to epichlorohydrin at 15-54 ppm were apparently not life-threatening (Pet'ko et al.

1966 [as cited in NIOSH 1976]; de Jong et al. 1988). Time scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986), where n = 0.87. The value of the exponent n was derived from rat LC_{50} (lethal concentration, 50% lethality) values for 1-, 4-, 6-, and 8-h exposures.

The 4- and 8-h AEGL-3 values were based on the 6-h rat LC_{01} of 274 ppm (Laskin et al. 1980). The same uncertainty factors and time-scaling method were the same as those used to derive the 10-min, 30-min, and 1-h AEGL-3 values.

Two inhalation studies in rats found squamous cell carcinomas of the nasal cavity after exposure to epichlorohydrin vapor. The studies showed that short-term exposure at high concentrations were more effective in inducing neoplasms than lifetime exposure at low concentrations. AEGL values calculated from the cancer unit risk for epichlorohydrin are 14,000, 4,500, 2,300, 560, and 280 ppm for 10-min, 30-min, 1-h, and 4-h, to 8-h exposures, respectively. Those values are for risks of 1 in 10,000 (10^{-4}), the level of risk most relevant for emergency exposure and response purposes. The concentrations greatly exceed values for AEGL-2 and AEGL-3. The AEGL values for epichlorohydrin are presented in Table 4-1.

1. INTRODUCTION

Epichlorohydrin is a colorless liquid at room temperature that is flammable (Berdasco and Waechter 2012). It is very reactive with metals such as zinc and aluminum, anhydrous metal halides, strong acids and bases, and alcoholcontaining materials; it attacks steel in the presence of moisture (WHO 1984). Epichlorohydrin has a sweet, pungent or chloroform-like odor (Berdasco and Waechter 2012). Additional chemical and physical properties of epichlorohydrin are presented in Table 4-2.

Epichlorohydrin is manufactured at three sites in Louisiana and Texas. Epichlorohydrin is also manufactured in Thailand (ABC-Thailand, Ltd. 2013), France (Solvay 2011), and China (Alibaba 2013; ZSITC 2013). Epichlorohydrin is primarily used in the manufacture of epoxy and phenoxy resins (ACGIH 2001). It is also used in the synthesis of glycerol, and in the production of surface active agents, pharmaceuticals, insecticides, agricultural chemicals, textile chemicals, coatings, adhesives, ion-exchange resins, solvents, plasticizers, glycidyl esters, ethynyl-ethylenic alcohols, and fatty-acid derivatives. It is used as a solvent in the rubber and paper industries (Santodonato et al. 1980).

Epichlorohydrin is a bifunctional alkylating epoxide (Laskin et al. 1980). It causes severe irritation and sensitization when the liquid comes in contact with the skin (Berdasco and Waechter 2012); contact dermatitis has been reported after occupational exposure to epichlorohydrin (HSE 1991). Severe ocular irritation, skin irritation, and delayed contact skin sensitization have been found in animals after topical application of undiluted or diluted epichlorohydrin (Berdasco and

Waechter 2012). Epichlorohydrin is moderately toxic by the oral route with LD_{50} (lethal dose, 50% lethality) values of 90-238 mg/kg in rats, guinea pigs, and mice (Berdasco and Waechter 2012).

The database that can be used to derive AEGL values for epichlorohydrin consists of acute and repeat-exposure inhalation studies in multiple species and a carcinogenicity study in rats.

TABLE 4-1 AEGL Values for Epichlorohydrin

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	No-effect level for irritation (Kobernick et al. 1983).
AEGL-2 (disabling)	53 ppm (200 mg/m^3)	53 ppm (200 mg/m^3)	24 ppm (91 mg/m^3)	14 ppm (53 mg/m^3)	6.7 ppm (25 mg/m^3)	Three-fold reduction of AEGL-3 values, except for 10 min.
AEGL-3 (lethal)	570 ppm (2,200 mg/m^3)	160 ppm (600 mg/m^3)	72 ppm (270 mg/m^3)	44 ppm (170 mg/m^3)	20 ppm (76 mg/m^3)	Lethality threshold (Dietz et al. 1985; Laskin et al. 1980)

TABLE 4-2 Physical and Chemical Data on Epichlorohydrin

Parameter	Value	Reference
Synonyms	2-(Chloromethyl) oxirane; 1-chloro-2,3epoxypropane; 3-chloro-1,2-epoxypropane; α-epichlorohydrin	HSDB 2009
CAS registry no.	106-89-8	HSDB 2009
Chemical formula	C_3H_5ClO	HSDB 2009
Molecular weight	92.53	HSDB 2009
Physical state	Colorless liquid	HSDB 2009
Melting point	-25.6°C	HSDB 2009
Boiling point	117.9°C	HSDB 2009
Density (vapor)	3.29	HSDB 2009
Solubility	65.9 g/L of water at 25°C; miscible with ether, alcohol, chloroform, trichloroethylene, carbon tetrachloride	HSDB 2009
Vapor pressure	16.4 mm Hg at 25°C	HSDB 2009

Flammability limits	3.8% volume to 21% volume in air	HSDB 2009
Concentration in saturated air	1.7% at 25°C	HSDB 2009
Flash point (open cup)	40.6°C	Sienel et al. 2000
Log K_{ow}	0.45	HSDB 2009
Henry's Law constant	3.0×10^{-5} atm-m^3/mol at 25°C	HSDB 2009
Conversion factors	1ppm = 3.78 mg/m^3 1 mg/m^3 = 0.265 ppm	NIOSH 2011

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data were available on the lethality of inhaled epichlorohydrin in humans.

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold

AIHA (1989) reported the range of odor threshold values for epichlorohydrin of 0.08-12 ppm, and Ruth (1986) reported a range of 50-80 mg/m^3 (13-21 ppm). Kobernick et al. (1983) reported that four subjects detected an at 17 ppm, and two identified the odor as epichlorohydrin. Amoore and Hautala (1983) reported an odor detection level of 0.93 ppm for humans. Berdasco and Waechter (2012) reported a mean odor threshold of 10 ppm and an odor recognition level of 25 ppm. The odor threshold during and after a 5-min exposure of unconditioned personnel to epichlorohydrin was 10-12 ppm for 50% of the subjects and 25 ppm for 100% of the subjects (Shell Oil Co. 1977). Shell Oil Co. (1977) also reported that epichlorohydrin is not detected by its odor at 5 ppm, the permissible exposure limit established by the Occupational Safety and Health Administration (29 CFR 1910.100 [2012]). The level of odor awareness determined by the method of Ruijten et al. (2009) for epichlorohydrin is 46 ppm.

2.2.2. Experimental Studies, Case Reports, and Anecdotal Data

Anecdotal information on effects of epichlorohydrin in humans has been reported in various sources. In a toxicology book, a chapter stated that humans exposed to epichlorohydrin vapor at 20 ppm for 1 h experienced burning of the eyes and nasal mucosa, that exposure at 40 ppm caused ocular and throat irritation that lasted about 48 h, and that 100 ppm was intolerable to man, with potential for

pulmonary edema and renal lesions (Lefaux 1968). The statements were attributed to an individual (C.U. Dernehl) without a specific reference. Lefaux (1968) also indicated that chronic low-level exposure caused fatigue, gastrointestinal pain, conjunctivitis, and profuse nasal discharge, citing another individual (I. Sax). The anecdotal information was repeated in later references, including that of Wexler (1971). In another book chapter, Deichmann and Gerarde (1969) reported that humans exposed to epichlorohydrin at 40 ppm for less than 2 h experienced throat irritation; no data or citation was provided to support the statement. Enterline et al. (1990) reported that during the early years (assumed to be 1948-1955) of epichlorohydrin use and production, concentrations of the chemical at a Shell chemical facility were "sufficiently high to be a source of irritation (10-20 ppm)"; the publication did not specify whether exposure concentrations were measured in that range or assumed to be in that range on the basis of worker reports of irritation. In another book chapter on epoxy compounds, Berdasco and Waechter (2012) reported that marked nasal and ocular irritation occurred only at epichlorohydrin concentrations exceeding 100 ppm; no background or reference for this statement was provided. In a toxicity and safety bulletin on epichlorohydrin (prepared in 1977 and submitted to the U.S. Environmental Protection Agency [EPA] under TSCA Section 8ECP in 1992), Shell Oil Co. (1977) reported that overexposure to epichlorohydrin vapor is manifested first by complaints of ocular, nasal, and throat irritation and possibly sneezing and bleeding of the nose in more serious cases. On the basis of industrial experience, Shell Oil Co. (1977) noted that no cases of serious pulmonary injury or systemic toxicity had been observed during the manufacture or handling of epichlorohydrin, and ocular conditions resulting from exposure to the vapor or contact with liquid epichlorohydrin were not serious and caused no loss of vision. No information on exposure conditions or concentrations was provided. In a summary of warning properties, the bulletin stated that "one report indicated eye and nose irritation only at levels exceeding 100 ppm while another stated that 40 ppm at the site of a spill caused immediate eye, nose, and throat irritation"; references were not provided for these statements.

Two case reports of accidental human exposure (Schultz 1964; NIOSH 1976) were identified in the available literature; neither included measurement or estimation of exposure concentrations. Schultz (1964) reported a case of irreversible hepatic and respiratory damage caused by accidental exposure of a worker to epichlorohydrin. A 39-year-old man took several deep breaths of a substance stored in a container under pressure that was later identified as epichlorohydrin. Initial symptoms included slight burning of the eyes and throat that increased in sensation along with a gradual swelling of the face, malaise, vomiting, and severe headache several hours later. He experienced shortness of breath and a feeling of suffocation the following night (probably more than 24 h after the accident). Clinical examination about 2 days after the accident showed inflammation of mucous membranes in the upper respiratory tract and a painfully enlarged liver, slight jaundice, increased serum bilirubin, and positive urine

urobilinogen. Five and 8 months after the accident, clinical findings included bronchial changes in the right lung, elevated blood pressure, and evidence of abnormal liver function. Two years after the accident, the patient complained of nonspecific epigastric pain; a clinical examination showed pronounced fatty liver, abnormal liver function, and chronic asthmatic bronchitis. The fatty liver and chronic asthma-like bronchitis were attributed to exposure to epichlorohydrin because there were no preexisting conditions related to these findings. There was no evidence of renal damage.

NIOSH (1976) reported on a case of a 53-year-old worker exposed to a high but unknown concentration of epichlorohydrin for 30 min (written communication by Thoburn, May 1976, no additional citation information). Several hours after exposure he experienced burning of the nose and throat, cough, chest congestion, runny nose, eye tenderness, and headache followed by nausea. The man was hospitalized briefly, and the symptoms diminished within 3-4 days; however, he reported more frequent upper-respiratory-tract infections followed by a productive cough. Clinical tests showed that the residual volume was increased by 40% (suggesting air trapping in the lungs) and arterial pO_2 of 77 mm Hg instead of 96 mm Hg. The report did not state how long after exposure these symptoms persisted.

NIOSH (1976) also reviewed a Russian study (Pet'ko et al. 1966, as cited in NIOSH 1976) of worker health in a facility producing epichlorohydrin. Workers were generally exposed at concentrations of 3.1-5.5 ppm, but concentrations during a mechanical failure reached about 55 ppm. NIOSH indicated that the study did not report the sampling method, and no further information on the sampling or analyses that resulted in these concentrations was provided by NIOSH (1976). Apart from two cases of dermatitis, Pet'ko et al. (1966, as cited in NIOSH 1976) concluded that medical examination of 49 men and 33 women in the epichlorohydrin-production areas showed no changes attributable to occupational exposure.

In the single controlled-exposure study, four human subjects were exposed to epichlorohydrin at concentrations of 17, 68, or 136 ppm for 2 min in a 6.5-ft^3 chamber (Kobernick et al. 1983). Three subjects exposed at 68 ppm reported no irritating effect, and one reported irritation to the pharynx. Two subjects exposed at 136 ppm reported a cooling sensation in the eyes and mouth and two reported irritation to the eyes or pharynx.

2.2.3. Epidemiologic Studies

Epidemiologic studies of epichlorohydrin have involved the analysis of mortality or morbidity data from two cohorts from the Shell Oil Company in its Texas and Louisiana facilities, both of which produced epichlorohydrin (Enterline et al. 1990; Tsai et al. 1990, 1996). Dow Chemical workers engaged in

epichlorohydrin production also have been the subject of mortality studies (Olsen et al. 1994).

Tsai et al. (1990) conducted a study on the prevalence of morbidity among workers engaged in the manufacture of epichlorohydrin from January 1, 1981, to December 31, 1988. Morbidity included all illnesses resulting in work absence of more than 5 days. The only illness showing a significantly elevated standardized morbidity ratio involved skin and subcutaneous tissue, particularly in workers classified as having light to moderate exposure to epichlorohydrin. Light- and moderate-exposure categories (defined as the 95% upper confidence limit of the geometric mean of personal air samples) were >0.1 ppm but ≤0.5 ppm, and >0.5 ppm but ≤1.0, respectively. The investigators noted that skin conditions were more often associated with causes unrelated to epichlorohydrin exposure, such as physical trauma and poison ivy.

Although a concern existed for a possible association between exposure to epichlorohydrin and heart disease among workers engaged in the manufacture or use of epichlorohydrin, a statistically significant increase in the standard mortality ratio (SMR) was not observed. However, Enterline et al. (1990) reported an increase in the SMR for heart disease among workers classified as having heavy exposure compared with workers in the low-exposure category. There was no significant increase compared with the reference population (local white males). Epichlorohydrin concentrations for the exposure categories were not reported, but concentrations during the early production years were high enough to cause irritation. In a subsequent study of the same cohort followed for an additional 10 years, Tsai et al. (1996) found a nonsignificant increase in the SMRs for heart disease among workers with moderate to heavy exposure to epichlorohydrin compared with those having no to light exposure.

Other epidemiologic studies have been conducted on workers with potential exposure to epichlorohydrin, but none demonstrated an association between epichlorohydrin and mortality experience due to any cause (Barbone et al. 1992, 1994; Olsen et al. 1994). Barbone et al. (1992, 1994) did not report exposure concentrations. Olsen et al. (1994) estimated that the 8-h time-weighted average (TWA) concentration of epichlorohydrin was below 1 ppm at an epoxy resin plant, and was 1-5 ppm at a glycerine department between 1957-1969; concentrations after 1970 were estimated to be less than 1 ppm. The publication did not report how the TWA estimates were derived, but did indicate that industrial hygiene records were reviewed.

2.3. Developmental and Reproductive Toxicity

Milby et al. (1981) investigated the association between fertility, as measured by sperm count and hormone concentrations, and potential exposure to epichlorohydrin at the two Shell chemical plants that produced epichlorohydrin. The control group consisted of workers from the same plant who had no known

exposure to epichlorohydrin or any chemical known to be toxic to the testes. The investigators found no association between potential exposure to epichlorohydrin and sperm count or levels of testosterone, luteinizing hormone, or follicle stimulating hormone. Exposures in one of the plants (sampling for epichlorohydrin was conducted at only one) were categorized into four groups. Three of the four categories were exposures less than 1.0 ppm, and the fourth was 1.0 ppm or greater; no information on maximum exposure concentration was provided.

Venable et al. (1980) compared the fertility status, as measured by several sperm parameters (including sperm count/cc and percent normal forms) and hormone concentrations, in 64 men employed in the three-carbon production units at Dow Chemical (Texas Division) with 63 men who had not worked with chlorinated hydrocarbons for at least 5 years prior to the study. None of the parameters showed statistically significant differences that could be attributed to work environment or exposure to epichlorohydrin. The 8-h TWA exposures to epichlorohydrin were estimated to be less than 1 ppm in all groups; no further exposure information was provided.

2.4. Carcinogenicity

EPA's Integrated Risk Information System assessment of carcinogenicity for epichlorohydrin, which was revised in 1994, considered the human data to be inadequate for evaluating the carcinogenicity of epichlorohydrin and classified epichlorohydrin as a B2 carcinogen (probable human carcinogen) on the basis of sufficient evidence of carcinogenicity in animals (EPA 1994).

More recent epidemiologic studies than those evaluated by the EPA have been conducted on cohorts with potential exposure to epichlorohydrin during its manufacture or use. Barbone et al. (1994) reported an association between occupational exposure to epichlorohydrin, particularly acute exposure, and central nervous system neoplasms (in decedents and living). However, only four cases had potential exposure to epichlorohydrin and three of the four were also potentially exposed to anthraquinone dye intermediates or azo dyes. Other epidemiologic studies produced no convincing evidence of an association between potential occupational exposure to epichlorohydrin and cancer at any site including lung cancer (Enterline et al. 1990; Tsai et al. 1990, 1996; Barbone et al. 1992; Olsen et al. 1994).

IARC (1999) reviewed and evaluated the epidemiologic and supporting data on epichlorohydrin and concluded that human data were inadequate for evaluating carcinogenicity of the chemical. It classified epichlorohydrin as 2A, *probably carcinogenic in humans*, on the basis of adequate evidence of carcinogenicity in animals.

2.5. Genotoxicity

Kučerová et al. (1977) analyzed the peripheral lymphocytes of 35 workers occupationally exposed to epichlorohydrin for 1 or 2 years (exposure range was 0.13-1.32 ppm [0.5-5.0 mg/m^3]) and compared the frequency of chromosomal aberrations with the preemployment frequency. They observed that the overall percentage of chromosomal aberrations (chromatid and chromosome beaks and exchanges; gaps excluded) were statistically significantly increased after 1 year (1.91/100 cells) and 2 years of employment (2.96/100 cells) compared with the preemployment frequency (1.42/100 cells). The frequency of chromosome breaks in lymphocytes was 2.17/100 cells or 3.26/100 cells after employment for 1 or 2 years, respectively, compared with the preemployment frequency of 1.60/100 cells. The overall percentage of cells with aberrations was 1.91% or 2.69% after employment for 1 or 2 years, respectively, compared with 1.37% before employment.

Sram et al. (1980) conducted a follow-up analysis of peripheral lymphocytes in 28 workers (23 were previously analyzed by Kučerová et al. [1977]) occupationally exposed to epichlorohydrin for an additional 2 years (total exposure duration of 4 years). Matching subjects from the working and general population were analyzed as control groups. Sram et al. (1980) found 3.12% aberrant cells (breaks and exchanges; gaps excluded) in exposed workers compared with 2.06% for the matching controls and 1.33% for the general population. All comparison groups were significantly different from each other including the two controls. The percentage of aberrant cells in the subgroup of 23 workers studied by Kučerová et al. (1977) was 3.02%. Sram et al. (1980) reported that the concentration of epichlorohydrin in the work environment was about 0.26 ppm (1 mg/m^3). Sram et al. (1983) conducted a follow-up study on the workers after an additional 4 years of exposure (total of 8 years); this group consisted of 33 workers and included the 28 previously analyzed by Sram and coworkers. The concentration of epichlorohydrin decreased from 0.26 ppm to 0.10 ppm. The percentage of aberrant cells in exposed workers decreased to 2.00%; the percentage in the matching controls was 1.68%. Chromatid and chromosome breaks were observed, but not exchanges.

Picciano (1979) compared the frequency of chromosome aberrations in peripheral lymphocytes from 93 workers occupationally exposed to epichlorohydrin with the frequency in 75 preemployment individuals (control). The frequencies of chromatid and chromosome breaks, marker chromosomes (rings, dicentrics, and translocations), severely damaged cells, and abnormal cells were increased in exposed workers. The greatest increases were in frequencies of cells with more than 12 chromatid breaks, cells with more than four chromosome breaks, the percent of individuals with more than 12 abnormal cells, and the percent of individuals with severely damaged cells. The investigators did not report the intensity or duration of exposure to epichlorohydrin.

de Jong et al. (1988) reported increased chromosome aberrations in the lymphocytes of workers involved in the manufacture of epichlorohydrin, ethylene oxide (ETO), and propylene oxide at one plant and epichlorohydrin and allyl chloride at another. They found increases in the percentage of aberrant cells (includes gaps) of 1.46% and 0.93% for the two worker groups, respectively, compared with 0.11% for a control population. The increase in the frequency of aberrations in exposed workers relative to the control population could not be attributed to epichlorohydrin alone.

Shell Oil Co. (1994) reported significant increases in the frequencies of sister chromatid exchanges, cells with high frequencies of sister chromatid exchanges, and chromosome aberrations and aberrant cells in workers exposed to epichlorohydrin. Worker exposures were measured to be 0.11-0.23 ppm for 11.15 h each day and higher concentrations of 0.19-2.57 ppm during three episodes of 15 min each per day (it is presumed that the authors intended to report 11.25, not 11.15 h, for a total duration of 12 h per day).

Giri (1997) reviewed data on chromosome aberrations in human cultured cells and noted that epichlorohydrin showed positive evidence of clastogenicity in different types of in vitro test systems.

2.6. Occupational Exposure

Concentrations of epichlorohydrin in the work environment of production facilities have ranged from TWA concentration of 0.01 ppm to 15 ppm (0.04 to 57 mg/m^3), as reported by WHO (1984). Citing a Dow Chemical Company monitoring report, NIOSH (1976) reported epichlorohydrin concentrations of 0.10-15.0 ppm for an epoxy-producing unit monitored in 1974, and concentrations of 0.01-4.69 ppm for a glycerin-producing unit monitored in 1975. de Jong et al. (1988) reported epichlorohydrin concentrations at two plants in a Shell petrochemical complex in the Netherlands. At one plant, the mean 4-8 h TWA concentration in 1977 was 6.6 ppm (25 mg/m^3), with a range of <0.03-54 ppm (<0.1-205 mg/m^3); in 1978, the mean was 1.3 ppm (5 mg/m^3), with a range of <0.03-3.17 ppm (<0.1-12 mg/m^3). In the second plant, the mean 4-8 h TWA concentration in 1977 was 1.6 ppm (6 mg/m^3), with a range of <0.03-2.9 ppm (<0.1-11 mg/m^3); in 1978, mean was 0.3 ppm (1 mg/m^3), with a range of <0.030.8 ppm (<0.1-3 mg/m^3) (de Jong et al. 1988). According to the National Occupational Exposure Survey (NOES), over 95,000 workers were potentially exposed to epichlorohydrin between 1981 and 1983 (NIOSH 2003). According to the International Information System on Occupational Exposure to Carcinogens (Carex), almost 48,000 workers in 15 European Union nations were exposed to epichlorohydrin between 1990 and 1993 (Kauppinen et al. 1998).

2.7. Summary

No lethality data in humans after acute exposure to epichlorohydrin were available, and data on acute nonlethal effects after acute exposure were limited. The odor detection levels reported in the literature ranged from 0.08 ppm to 25 ppm (Amoore and Hautala, 1983; Kobernick et al. 1983; AIHA 1989; Shell Oil Co. 1977; Berdasco and Waechter 2012).

Anecdotal reports suggest that epichlorohydrin may cause ocular and throat irritation at 10-20 ppm, prolonged ocular and throat irritation at 40 ppm, and pulmonary edema and renal lesions at concentrations greater than 100 ppm (Lefaux 1968; Deichmann and Gerarde 1969; Wexler 1971; Enterline et al. 1990). A more definitive study showed that epichlorohydrin at 68 ppm was irritating to the pharynx in one of four subjects after 2 min, and 138 ppm caused a cooling sensation in the eyes and mouth and irritation to the eyes and pharynx after 2 min (Kobernick et al. 1983). Exposure to epichlorohydrin may also cause sneezing and nosebleed (Shell Oil Co. 1977).

Two case reports of accidental exposure to epichlorohydrin provided evidence that exposure at high concentrations for only seconds (few breaths) or for 30 min caused irritation to the eyes, throat, and respiratory tract, gastrointestinal disturbances, and irreversible liver damage in one case and irreversible damage to the respiratory tract in both cases (Schultz 1964; NIOSH 1976).

Genetic toxicity studies showed that workers exposed to epichlorohydrin at average concentrations of 0.26 ppm had higher frequencies of aberrant cells and chromosome aberrations in peripheral lymphocytes when compared with unexposed workers or the general population (Sram et al. 1980). However, the unexposed workers also had a higher frequency of chromosome aberrations than the general population (Sram et al. 1980). Occupational exposure to epichlorohydrin had no reproductive effects in human males as determined by sperm count and hormone concentrations (Venable et al. 1980; Milby et al. 1981).

Occupational exposure to epichlorohydrin also has not been associated with any other long-term clinical effects. Workers exposed chronically at low concentration of epichlorohydrin for various durations showed no excess in cause-specific morbidity or mortality due to nonneoplastic or neoplastic diseases (Enterline et al. 1990; Tsai et al. 1990, 1996; Barbone et al. 1992, 1994; Olsen et al. 1994). The epidemiologic data are inadequate for evaluating the carcinogenicity of epichlorohydrin in humans (EPA 1994; IARC 1999).

Taken as a whole, the data on human exposures to epichlorohydrin suggest that chronic exposure at concentrations greater than 10 ppm may be associated with irritation, but that concentrations up to 54 ppm over 4-8 h are unlikely to trigger life-threatening effects (Pet'ko et al. 1966, as cited in NIOSH 1976).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

The literature on the acute and short-term inhalation toxicity of epichlorohydrin is extensive, consisting of lethality data from studies of rats, mice, guinea pigs, rabbits, dogs, hamsters, and cats. In some studies, animals were exposed to epichlorohydrin vapor, whereas in others they were exposed to an aerosol. Exposure conditions were either dynamic or static. Concentrations of epichlorohydrin in the chamber atmospheres were determined analytically in some studies or were calculated on the basis of the flow rate and quantity of test substance delivered to the chamber in others. Single and repeat-exposure studies were considered in the evaluation.

3.1.1. Rats

Berdasco and Waechter (2012) reported 1-h LC_{50} values for epichlorohydrin in male and female rats of 2,165 and 3,617 ppm, respectively (geometric mean = 2,798 ppm). They also reported a 4-h LC_{50} of 500 ppm and 8-h LC_{50} 250 ppm for rats.

In an acute inhalation study by Kobernick et al. (1983), groups of six young male Carworth Farm-Wistar rats were exposed for 5, 10, or 15 min to "essentially saturated" vapor of epichlorohydrin in a dynamic 9-L glass chamber and were observed for 14 days after exposure. The authors calculated the vapor concentration of epichlorohydrin from material loss and flow rate to be 23,400 ppm; analysis of the chamber concentrations was not undertaken. No rats exposed for only 5 min died within the specified time; five of six rats exposed for 10 min died within 2 days, and all six exposed for 15 min died within 12 h. Gasping was observed during exposure in all groups, and poor condition (indicative of narcosis) was observed in animals exposed for 10 or 15 min. Gross examination showed hemorrhage in the lungs, the severity of which increased with duration of exposure.

Dietz et al. (1985) exposed groups of six male and six female Fischer 344 rats to epichlorohydrin vapor at concentrations of 552, 1,008, 1,970, or 3,995 ppm for 1 h; additional groups of six male rats were exposed at 2,865 or 3,275 ppm for 1 h. The animals were exposed in 2.6-m^3 stainless-steel and glass Rochester-type inhalation chambers operated under dynamic conditions. Chamber concentrations were determined by gas chromatography seven times during each 1-h exposure. The animals were maintained for a 14-day observation period. Body weights were recorded at 2- to 3-day intervals. Necropsies were performed on all animals with special attention given to the eyes and nasal cavities. The mortality response is summarized in Table 4-3. No deaths occurred during exposure, but one female each died on days 2 and 3 after exposure at 1,970 ppm and all females exposed at 3,995 ppm died within 1 day of exposure. All males exposed at 3,995 ppm died 1-

4 days after exposure. The LC_{50} values were 3,617 ppm for males, 2,165 ppm for females, and 2,369 ppm for the combined sexes. Clinical signs were observed in all exposure groups. During exposure at 552 and 1,008 ppm, the animals huddled in their cages and completely shut their eyes; no other signs were observed. At 1,970 ppm or higher, clinical signs included ocular and nasal irritation, respiratory difficulty, and secretion of a reddish, porphyrin-like material on the facial area. At 3,275 and 3,995 ppm, hyperactivity was observed during exposure followed by lethargy after exposure, and rats exposed at 3,995 ppm became cyanotic before the end of exposure.

TABLE 4-3 Mortality in Fisher 344 Rats Exposed to Epichlorohydrin Vapor by Inhalation

Concentration		Mortality		
ppm	mg/L	Male	Female	Male + Female
552	2.088	0/6	0/6	0/12
1,008	3.814	0/6	0/6	0/12
1,970	7.453	0/6	2/6	2/12
2,865	10.839	0/6	–	0/6
3,275	12.390	0/6	–	0/6
3,995	15.114	6/6	6/6	12/12

1-h LC_{50} = 3,617 ppm (male); 2,165 ppm (female); 2,369 ppm (combined sexes)

Source: Adapted from Dietz et al. 1985.

Grigorowa et al. (1974) exposed groups of 20 male albino rats to epichlorohydrin vapor at calculated concentrations of 0.190, 0.390, 0.855, 0.915, or 1.680 mg/L (50, 103, 226, 242, or 444 ppm, respectively) for 4 h in a dynamic exposure chamber. After exposure, one-half the rats were subjected to a temperature of 35°C and relative air humidity of 35-50% for 45 min and all animals were observed for an additional 72 h. The LC_{50}s for rats exposed to epichlorohydrin without and with heat treatment were 2.40 mg/L (635 ppm) and 2.20 mg/L (582 ppm), respectively. Marked hepatic damage, which was enhanced by heat, was observed in exposed animals. Microscopic lesions were observed in the kidneys (proximal tubules), adrenal glands (medulla), and thyroid gland (follicular epithelium); heat exacerbated the toxicity in the adrenal and thyroid glands. Hemorrhage, hyperemia, and edema were observed in the lungs, but subsequent heat treatment had no effect. The investigators did not report the concentrations at which the effects were observed. Data for other measures of toxicity were not presented in a manner meaningful for derivation of acute toxicity values.

In a study conducted by Kimmerle (1967), groups of 10 rats were exposed in a 400-L test chamber to epichlorohydrin evaporated from a petri dish and distributed around the chamber room with a fan. Complete evaporation of the material produced achieved concentrations (calculated) of 132, 331, 661, or 2,646 ppm (0.50, 1.25, 2.50, or 10.00 mg/L, respectively). Each group was exposed for 4 h and observed for 14 days. Five of 10 rats exposed at 661 ppm died within 2-4 days and all 10 rats exposed at 2,646 ppm died within 1-2 days. Symptoms of toxicity (not otherwise described) were observed in all rats at the two highest concentrations, moderate irritation to mucous membranes was observed at 661 ppm, and strong irritation occurred at 2,646 ppm. The 4-h LC_{50} for epichlorohydrin vapor was 741 ppm.

Kobernick et al. (1983) reported a study in which groups of six young or mature (not otherwise specified) Carworth Farm-Wistar rats were exposed to epichlorohydrin vapor at 290 or 580 ppm (calculated concentrations) for 4 h in a dynamic 9-L glass chamber and observed for 14 days. No young or mature rats died after exposure at 290 ppm. No signs of irritation were observed at 290 ppm; the mature females lost weight during the observation period, and slight pulmonary congestion and hemorrhage were observed in all animals. All rats except four mature females died within the first 24 h after exposure at 580 ppm, and the remaining rats died within 3-12 days. Gasping was observed in females exposed at 580 ppm. The LC_{50} was 411 ppm.

In another experiment by Kobernick et al. (1983), six different animal species including rats were exposed to epichlorohydrin vapor for 4 h and observed for 14 days. Male Carworth Farm-Wistar stock rats were exposed at 580 ppm (30 rats) or 1,160 ppm (six rats) in a 193-L hardboard chamber operated under dynamic conditions. Vapor concentrations were calculated from the amount of material used, the flow rate, and the ratio of analytic to nominal concentrations (1.16) determined from a repeat-exposure study. Fifteen of 30 rats died after exposure at 580 ppm and all six rats died after exposure at 1,160 ppm.
The LC_{50} was 580 ppm. Irritation of mucous membranes was observed in all animals, and increased respiration, lethargy, and labored breathing were observed in all animals that died. Gross examination showed hemorrhagic lungs in the animals that died and in a few survivors. The investigators described only a few specific effects for each species. The difference in the mortality response of rats exposed in the 9-L glass chamber and the 193-L hardboard chamber was attributed to the generation of heat by the rats and the smaller surface:volume ratio that prevented adequate heat loss in the smaller chamber.

Slott et al. (1990) observed no overt signs of toxicity in 48 male F344 rats during or after exposure to epichlorohydrin vapor at 100 ppm for 4 h. This was a reproduction study that showed a transient effect on sperm motility (see Section 3.3).

Groups of 20 Sprague-Dawley rats (8-week old males) were exposed to epichlorohydrin vapor in 128-L or 1.3-m^3 dynamic chambers at concentrations of

283, 303, 339, 369, 421, or 445 ppm for 6 h, and were observed for 14 days (Laskin et al. 1980). Chamber atmospheres were sampled every 30 min and analyzed by a spectrophotometric procedure. Acute respiratory irritation with hemorrhage and severe edema of the lungs along with elevated lung:body weight ratios occurred at concentrations of 339 ppm and higher. Mortality in each exposure group was 0/20, 1/20, 1/20, 15/20, 16/20, and 17/20, respectively; the LC_{50} reported was approximately 360 ppm.

Weil et al. (1963) reported that four of six rats (unspecified strain and sex) died after exposure to epichlorohydrin at 250 ppm for 8 h. No additional details were provided.

Groups of 20 male Wistar rats were exposed under dynamic conditions to atomized (aerosolized) epichlorohydrin in a mixture of lutrol (ethylene glycol) and alcohol (1:1) at epichlorohydrin concentrations of 296, 638, 1,038, or 1,440 mg/m^3 4 h, and were observed for 2 weeks (Kimmerle 1967). The concentrations of epichlorohydrin in the chamber atmospheres were determined spectrophotometrically on air samples reacted with hydroxylamine. The number of deaths and time-to-death were concentration related. One rat exposed at 638 mg/m^3 died on day 7, nine exposed at 1,038 mg/m^3 died on days 1 and 6, and all 20 exposed at 1,440 mg/m^3 died on days 1 and 4. Symptoms of toxicity were observed in all rats exposed to concentrations of 638 mg/m^3 or higher. The LC_{50} reported was 960 mg/m^3.

Groups of 10 or 20 rats inhaled epichlorohydrin aerosols for 1 h in a 2-m^3 chamber, and were observed for 14 days (Kimmerle 1967). Chamber concentrations were maintained by spraying epichlorohydrin dissolved in a mixture of lutrol (ethylene glycol) and alcohol (1:1) into the chamber every 30 min. Concentrations were analyzed by spectrophotometry of air samples collected through three consecutive U tubes cooled to -60°C. The average analytic concentrations were 70, 204, 324, 500, and 3,350 mg/m^3. The method for analyzing chamber atmospheres was not reported. The chamber also contained three rabbits, five guinea pigs, and 20 mice during each exposure. Eleven of 20 rats exposed at 3,350 mg/m^3 died 3-8 days after exposure. Symptoms of toxicity were observed at 324 and 3,350 mg/m^3, but not at 500 mg/m^3. The LC_{50} was 3,073 mg/m^3.

In the next series of studies, rats were repeatedly exposed to epichlorohydrin aerosols or vapor for different durations. Groups of 10 rats were exposed by inhalation to epichlorohydrin evaporated from a petri dish at concentrations of 66 and 661 ppm (250 or 2,500 mg/m^3, respectively), 4 h/day for 5 days (Kimmerle 1967). No rats died and no symptoms of toxicity were observed at 66 ppm, but nine of 10 rats died and symptoms of toxicity were observed in all rats exposed at 661 ppm. No signs of irritation of mucous membranes were reported.

Groups of young sexually mature male and female Carworth Farm-Wistar rats (23-32 per group) were exposed to calculated concentrations of epichlorohydrin vapor in 550-L hardboard chambers operated under negative

pressure (Kobernick et al. 1983). Each group was exposed for 7 h/day, 5 days/week to epichlorohydrin at 0, 68, or 136 ppm for 45 exposures; 0, 17, or 43 ppm for 91 exposures; or 0, 5, or 8 ppm for 90 exposures. The incidences, severity, and types of effects increased as the exposure concentration increased from 5 ppm to 136 ppm. Repeated exposure to epichlorohydrin resulted in death only at 136 ppm (10 rats) and 68 ppm (5 rats). Reduced weight gain, renal toxicity, and urinary coproporphyrins were observed at 68 and 136 ppm. No definitive signs of renal toxicity occurred at less than 43 ppm; however, weight gain was depressed and coproporphyrins were found in the urine at 43 ppm.

In the another repeat-exposure study submitted by Kimmerle (1967), groups of 20 Wistar rats inhaled atomized epichlorohydrin in a mixture of lutrol (ethylene glycol) and alcohol (1:1) at epichlorohydrin concentrations of 32, 63, or 340 mg/m^3 for 4 h/day for 5 days, and were observed for 2 weeks. No animals died at 32 mg/m^3; two rats died at 63 mg/m^3, and four rats died at 340 mg/m^3. Symptoms of toxicity were observed in all rats exposed at 63 and 340 mg/m^3.

3.1.2. Mice

In 1941, Freuder and Leake reported the effects of inhaled epichlorohydrin on groups of 20-30 white mice exposed to epichlorohydrin vapors in a dynamic glass chamber at calculated concentrations of 8,300 or 16,600 ppm (0.35 or 0.70 mmol/L) for 30 min or at 2,370 ppm (0.10 mmol/L) for 60 min. All concentrations caused immediate signs of irritation to the nose and eyes, but the intensity was greater at 16,600 ppm. No additional signs were observed in mice exposed at 2,370 ppm for 1 h. Bristling of the hairs was observed almost immediately at 8,300 and 16,600 ppm and delirium (term not defined) was observed after 3 min at 16,600 ppm and after 14 min at 8,300 ppm. All animals exposed at 2,370 ppm for 60 min survived, but all mice exposed at 8,300 and 16,600 ppm for 30 min died within the first 24 h after exposure. Nno subsequent deaths occurred; however, the duration of the observation period was not reported. Before death, mice exhibited signs of cyanosis followed by muscular relaxation of the extremities, stiffening of the tail, fine tremors, depressed respiration, clonic convulsion, and finally respiratory arrest.

Grigorowa et al. (1974) exposed groups of 20 male albino mice to epichlorohydrin vapor at calculated concentrations of 50, 103, 226, 242, and 444 ppm (190, 390, 855, 915, or 1,680 mg/m^3, respectively) for 2 h in a dynamic exposure chamber as described for rats (see Section 3.1.1). The LC_{50}s for mice exposed to epichlorohydrin without and with subsequent heat treatment were 794 ppm and 1,058 ppm, respectively. Marked hepatic damage (enhanced by heat) and renal damage (not affected by heat) was observed in exposed animals. Hemorrhages, hyperemia, and edema were observed in the lungs; subsequent heat

treatment had no effect on severity of the pulmonary lesions. The investigators did not report the concentrations at which the effects were observed.

In a study reported by Kobernick et al. (1983), groups of 6 or 11 male mice (strain and age not specified) were exposed to epichlorohydrin vapor at calculated concentrations of 290, 580, or 1,160 ppm for 4 h in 193-L hardboard chambers operated under dynamic conditions. The concentrations were verified in a repeat-exposure study and adjusted by the ratio of 1.16 for analytic:nominal concentrations. The mortality response was 0/11, 0/6, and 6/6 at 290, 580, and 1,160 ppm, respectively, resulting in an LC_{50} of 820 ppm. Irritation of mucous membranes, increased respiration, lethargy, and labored breathing were observed in all animals that died, whereas only irritation of mucous membranes was observed in animals that survived.

In a study reported by Kimmerle (1967), groups of 20 male CF_1 mice were exposed for 4 h to epichlorohydrin vapor at 132, 331, 661, or 2,646 ppm. The vapor was generated by evaporation of epichlorohydrin from a petri dish as described for rats (see Section 3.1.1). No deaths, symptoms of toxicity (not otherwise described), or irritation of mucous membranes were observed at 132 and 331 ppm, but one death occurred at 661 ppm and 100% died after exposure at 2,646 ppm. Toxicity was observed in all mice exposed at 661 and 2,646 ppm, moderate irritation was observed at 661 ppm, and strong irritation occurred at 2,646 ppm. The LC_{50} was 1,153 ppm for the 4-h exposure.

All mice exposed by inhalation to epichlorohydrin at 687 ppm (10-min RC_{50}, see Section 3.2.3) for 6 h either died or were moribund within 72 h (Buckley et al. 1984). Groups of 16-24 (exact number per group not reported) male Swiss-Webster mice were exposed to epichlorohydrin vapor for 6 h. The chamber atmosphere was analyzed at least once per hour by infrared spectrophotometry. The mice were necropsied immediately or 72 h after exposure, and the heads and respiratory tracts were examined microscopically. At necropsy, a serous exudate was observed in the nose, and the abdomen was distended by gas probably caused by attempts to mouth breathe. Microscopic examination of the nasal tissue showed moderate exfoliation, erosion, ulceration, and necrosis along with minimal inflammation of the respiratory epithelium of the nose. Moderate ulceration and necrosis were observed in the olfactory epithelium. Mice exposed to epichlorohydrin vapor at 687 ppm also showed epithelial exfoliation, hyperplasia, and squamous metaplasia of the trachea and slight exfoliation of the bronchial epithelium with diffuse neutrophil infiltration.

Groups of 20 male CF_1 mice were exposed to epichlorohydrin aerosols for 1 h in a 2-m^3 chamber containing multiple species as described for rats in Section 3.1.1 (Kimmerle 1967). Chamber concentrations were maintained by spraying epichlorohydrin dissolved in a mixture of lutrol (ethylene glycol) and alcohol (1:1) into the chamber every 30 min. The average analytic concentrations were 70, 204, 324, 500, and 3,350 mg/m^3. One mouse exposed at 324 mg/m^3 and one exposed at 3,350 mg/m^3 died 7 days and 1 day, respectively, after exposure. Symptoms of

toxicity were observed in 19 mice exposed at 324 mg/m^3 and all 20 mice exposed at 3,350 mg/m^3, but in none exposed at 500 mg/m^3.

Lawrence et al. (1972, 1974) calculated the LT_{50} (time to 50% lethality) for male ICR mice (number and age not reported) exposed to epichlorohydrin vapor in an 8.75-L glass chamber operated under dynamic conditions. Chamber concentrations of epichlorohydrin were calculated from the amount of material lost and the air flow. The LT_{50} was 9.13 min at a concentration of 71,890 mg/m^3. The study author presented little detail regarding experimental procedures.

Groups of 20 male CF_1 mice were exposed repeatedly to epichlorohydrin at 66 and 661 ppm (Kimmerle 1967). Epichlorohydrin was evaporated from a petri dish placed in a 400-L chamber as described for rats (see Section 3.1.1). The mice were exposed for 4 h/day for 5 days. No mice died after exposure at 66 ppm but 18 died after exposure at 661 ppm. Symptoms of toxicity were observed in all mice exposed at 661 ppm, but signs of irritation to mucous membranes were not observed in this group.

3.1.3. Guinea Pigs

Groups of four or six male guinea pigs (unspecified strain and age) inhaled epichlorohydrin vapor in a 193-L dynamic chamber at calculated concentrations of 290, 580, or 1,160 ppm for 4 h and were observed for 14 days (Kobernick et al. 1983). No deaths occurred at 290 ppm; two of six guinea pigs exposed at 580 ppm died and all four guinea pigs exposed at 1,160 ppm died. Irritation of mucous membranes, increased respiration, lethargy, and labored breathing were observed in all animals that died, whereas only irritation of mucous membranes was observed in surviving animals. The LC_{50} was 651 ppm for the 4-h exposure.

Kimmerle (1967) reported on a study in which groups of five male Purlbright guinea pigs were exposed for 4 h to epichlorohydrin vapor at 132, 331, 661, or 2,646 ppm. Epichlorohydrin was evaporated from a petri dish as described for rats (see Section 3.1.1). All guinea pigs died after exposure at 2,646 ppm and four in each group died after exposure at 331 and 661 ppm. Moderate and strong irritation of mucous membranes was observed at 661 and 2,646 ppm, respectively, and symptoms of toxicity were observed at concentrations of 331 ppm and higher.

Groups of five male Purlbright guinea pigs were exposed to epichlorohydrin aerosols at concentrations of 70, 204, 324, 500, and 3,350 mg/m^3 for 1 h and at 171 and 498 mg/m^3 for 4 h in a 2-m^3 chamber containing multiple species as described for rats (see Section 3.1.1) (Kimmerle 1967). Two guinea pigs died after exposure at 3,350 mg/m^3 for 1 h and three died after exposure at 498 mg/m^3 for 4 h. Symptoms of toxicity were observed in all guinea pigs exposed at 324 and 3,350 mg/m^3 for 1 h and at 498 mg/m^3 for 4 h, but no symptoms of toxicity were observed in the group exposed at 498 mg/m^3 for 1 h.

In a repeat-exposure study by Kimmerle (1967), groups of five male Purlbright guinea pigs were exposed by inhalation to epichlorohydrin vapor at concentrations of 66 and 661 ppm (250 or 2,500 mg/m^3) in a 400-L chamber as described for the single exposure studies. The guinea pigs were exposed for 4 h/day for 5 days. No deaths occurred at 66 ppm, but four deaths occurred at 661 ppm. Symptoms of toxicity or irritation to mucous membranes were observed in all five guinea pigs exposed at 661 ppm, but not those exposed at 66 ppm.

3.1.4. Rabbits

Groups of three male rabbits (unspecified strain and age) were exposed by inhalation to epichlorohydrin vapor at 290, 580, or 1,160 ppm for 4 h, as described for rats in Section 3.1.1 (Kobernick et al. 1983). Three rabbits exposed at 1,160 ppm and two exposed at 580 ppm died during the 14-day observation period. Irritation of mucous membranes, increased respiration, lethargy, and labored breathing were observed in all animals that died, whereas only irritation of the mucous membranes was observed in surviving animals. The LC_{50} was 516 ppm for the 4-h exposure.

One rabbit each was exposed repeatedly to epichlorohydrin vapor at concentrations of 66 or 661 ppm (250 or 2,500 mg/m^3). The vapor was generated by evaporation of epichlorohydrin from a petri dish in a 400-L chamber (Kimmerle 1967). The rabbits were exposed for 4 h/day for 5 days. The rabbit exposed at 66 ppm survived and showed no symptoms of toxicity or irritation of the mucous membranes. The rabbit exposed at 661 ppm showed symptoms of toxicity and died 2 days after exposure.

Groups of 10 male New Zealand white rabbits were exposed to epichlorohydrin vapor at 0, 5, 25, or 50 ppm for 6 h/day, 5 days/week for 10 weeks (John et al. 1983b). The exposure was during the premating period for a reproduction study. Three rabbits died or were killed moribund during the 10-week exposure period, two at 50 ppm and one at 25 ppm. Suppurative rhinitis and diffuse pneumonia or pleuritis were observed during necropsy of the 50-ppm group and pulmonary abscesses were observed in the 25-ppm group. Surviving animals showed similar gross lesions, as well as microscopic evidence of inflammation and erosion of the nasal epithelium characterized by focal erosion and metaplasia at 50 ppm.

3.1.5. Dogs

In an acute inhalation study, one dog (male or female) per group inhaled epichlorohydrin vapor at concentrations of 72, 290, 580, or 1,160 ppm for 4 h, and were observed for 14 days (Kobernick et al. 1983). Two dogs (one male and one female) were exposed similarly at 145 ppm. Exposure conditions were as

described for rats in Section 3.1.1. The investigators noted that the dogs exposed at 145, 290, 580, or 1,160 ppm regurgitated a small dose of an herbicide (no explanation provided). The dogs exposed at 580 and 1,160 ppm developed a slightly hemorrhagic dura mater and died. Irritation of mucous membranes, increased respiration, lethargy, and labored breathing were observed in animals that died (580 and 1,160 ppm) and mucous membrane irritation was observed in surviving animals (290 ppm and higher). Gross examination showed hemorrhagic lungs in animals that died.

3.1.6. Cat

One cat each was exposed repeatedly to epichlorohydrin vapor at concentrations of 66 and 661 ppm for 4 h/day for 5 days, and were observed for an unspecified period after the last exposure (Kimmerle 1967). The chamber atmospheres were generated by evaporation of the test substance in a 400-L chamber using a fan. The cat exposed at 66 ppm survived treatment and showed no symptoms of toxicity or irritation of mucous membranes, whereas the cat exposed at 661 ppm showed symptoms of toxicity and died the third day after exposure.

3.1.7. Summary of Lethality Data

Lethality data are summarized in Tables 4-4 and 4-5.

3.2. Nonlethal Toxicity

3.2.1. Monkeys

One monkey (unspecified species) was exposed to epichlorohydrin at a concentration of 290 ppm for 4 h (Kobernick et al. 1983). The exposure conditions were the same as described for rats in Section 3.1.1. This animal survived the 14-day observation period; some mucous membrane irritation was observed. Gross examination revealed a blood clot in the midsagittal section of the brain. The monkey was suspected of having tuberculosis unrelated to treatment.

Two rhesus macaque monkeys exposed repeatedly to epichlorohydrin at 21 ppm for 7 h/day, 5 days/week for 90 exposures, had damage in the lungs and kidneys (Kobernick et al. 1983). The animals were exposed in a 550-L hardboard dynamic chamber. The chamber concentrations were determined by taking occasional air samples, analyzing the samples using a spectrophotometric procedure, and averaging all concentrations measured during exposure. Serum enzyme and hematologic parameters were not affected by exposure to

epichlorohydrin. Microscopic findings in the lungs included bronchial irritation, mucous hypersecretion, subacute bronchitis, focal proliferation of alveolar septa, and hemosiderin deposits in the lungs. Microscopic findings in the kidneys included focal cloudy swelling of proximal convoluted tubules. A control group was not described.

TABLE 4-4 Summary of Acute Lethality Data in Laboratory Animals Exposed to Epichlorohydrin Vapor

Species/Strain/Sex	Exposure Duration	LC_{50} (Exposure Range)	Comments	Reference
Rats/F344/males and females	1 h	3,617 ppm (males) 2,165 ppm (females) (552-3,995 ppm)	No deaths in males at ≤3,275 ppm or in females at ≤1,008 ppm.	
Rats/Sprague-Dawley/males	6 h	360 ppm (283-445 ppm)	LC_{Lo} = 303 ppm (1/20); respiratory irritation and severe lung edema at ≥339 ppm.	
Rats/Carworth Farm-Wistar/males and females	4 h	441 ppm (290-580 ppm)	Pulmonary irritation, but no deaths at 290 ppm; deaths at 580 ppm.	
Rats/Carworth Farm-Wistar/males	4 h	580 ppm (580-1,160 ppm)	Deaths at both concentrations; irritation of mucous membranes (all animals) and lethargy, labored breathing, and hemorrhagic lungs in animals that died.	
Rats/albino/males	4 h	635 ppm (50-444 ppm)	Toxicity in the liver, kidney, lungs, adrenal glands, thyroid gland (concentration not reported)	
Rats/Wistar/males	4 h	741 ppm (132-2,646 ppm)	Irritation at 661 and 2,646 ppm, other symptoms of toxicity not described.	
Rats/Carworth Farm-Wistar/males	5, 10, or 15 min	NA (23,400 ppm)	No deaths after 5 min; 5/6 after 10 min and 6/6 after 15 min; gasping in all groups; hemorrhagic lungs after 10 and 15 min.	
Mouse/Swiss-Webster/males	6 h	(RC_{50} = 687 ppm)	All animals dead or moribund within 72 h; moderate degeneration of nasal epithelium (respiratory and olfactory).	
Mouse/?/males	4 h	820 ppm (290-1,160 ppm)	Deaths only at 1,160 ppm; mucous membrane irritation at all concentrations, lethargy and labored breathing at 1,160 ppm.	
Mouse/CF_1/male	4 h	1,153 ppm (132-2,646 ppm)	LC_{lo} = 661 ppm (1/20); moderate mucous membrane irritation, and symptoms of toxicity at ≥661 ppm.	

Mouse/albino/males	2 h	794 ppm (50-444 ppm)	Toxicity in the liver, kidneys, and lungs (concentration not reported).	Dietz et al. 1985
				Laskin et al. 1980
				Kobernick et al. 1983
				Kobernick et al. 1983
				Grigorowa et al. 1974 Kimmerle 1967
				Kobernick et al. 1983
				Buckley et al. 1984
				Kobernick et al. 1983 Kimmerle 1967
				Grigorowa et al. 1974

(Continued)

TABLE 4-4 Continued

Species/Strain/Sex	Exposure Duration	LC_{50} (Exposure Range)	Comments	Reference
Mouse/albino/?	1 h	(2,370 ppm)	Signs of irritation, no deaths (observation period not reported).	Freuder and Leake 1941
Mouse/albino/?	30 min	(8,300, 16,000 ppm)	8,300 ppm: 100% mortality (20/20) in 24 h.	Freuder and Leake 1941
Guinea pigs/?/males	4 h	651 ppm (290-1,160 ppm)	LC_{lo} = 580 ppm (2/6); mucous membrane irritation at all concentrations; labored breathing and lethargy in non-survivors.	Kobernick et al. 1983
Guinea pigs/ Purlbright/males	4 h	275 ppm (132-2,646 ppm)	Deaths and symptoms of toxicity at ≥331 ppm; moderate to strong irritation at ≥661 ppm.	Kimmerle 1967
Dogs/males and females	4 h	(72-1,160 ppm)	Death at 580 and 1,160 ppm.	Kobernick et al. 1983
Rabbit/?/males	4 h	516 ppm (290-1,160 ppm)	Deaths at 580 (2/3) and 1,160 ppm (3/3); mucous membrane irritation at all concentrations; labored breathing and lethargy in non-survivors.	Kobernick et al. 1983

TABLE 4-5 Summary of Acute Lethality Data in Laboratory Animals Exposed to Epichlorohydrin Atmospheres Generated from Aerosols

Species/Strain/Sex	Exposure Duration	LC_{50} (Exposure Range)	Comments
Rats/Wistar/males	1 h	3,073 mg/m^3 (70-3,350 mg/m^3)[a]	No deaths at ≤500 mg/m^3; signs of toxicity at ≥324 and 3,350 mg/m^3.
Rats/Wistar/males	1 h	ND (825 or 1,375 mg/m^3)[a]	No deaths; signs of toxicity at 1,375 mg/m^3.
Rats/Wistar/males	4 h	960 mg/m^3 (296-1,440 mg/m^3)[a]	No deaths at 296 mg/m^3; signs of toxicity at ≥638 mg/m^3.
Rats/Wistar/males	4 h	ND (171 or 498 mg/m^3)[b]	No deaths or signs of toxicity.
Mouse/CF_1/males	1 h	ND (70-,350 mg/m^3)[a]	1 death (1/20) at 324 and 3,350 mg/m^3; signs of toxicity at ≥324 and 3,350 mg/m^3.
Guinea pig/males	1 h	ND (70-3,350 mg/m^3)[a]	2 deaths (2/6) at 3,350 mg/m^3; signs of toxicity at 324 and 3,350 mg/m^3.
Guinea pig/males	4 h	ND (171 or 498 mg/m^3)[a]	4 deaths (4/6) at 498 mg/m^3; signs of toxicity at 498 mg/m^3.

[a] Exposures generated by aerosolizing epichlorohydrin dissolved in a mixture of ethylene glycol and water (1:1, v:v). Concentrations analyzed by spectrophotometry of air samples collected through three consecutive U tubes cooled to -60°C.

[b] Exposures generated by aerosolizing epichlorohydrin without a solvent. Concentrations analyzed as described above.

Abbreviations: LD50, lethal concentration, 50% lethality; ND, not determined.

Source: Data from Kimmerle 1967.

3.2.2. Rats

Gardner et al. (1985) determined the concentration of inhaled epichlorohydrin that caused a 50% decrease in the respiratory rate (RD_{50}) of rats exposed to epichlorohydrin vapor; the study also was reported by Haskell Laboratory (1980). The RD_{50} model is based on stimulation of the trigeminal nerve upon contact with an airborne irritant followed by inhibition of respiration (Kane et al. 1979). Groups of four 8-week old male Crl-CD® rats were exposed head-only to epichlorohydrin vapor for 15 min, and time respiratory rates were determined using a plethysmograph. Exposure concentrations were 101.6, 363.2, 394.1, 642.7, 662.9, 913.7, and 1,963 ppm. Chamber atmospheres were sampled

every 2-3 min and analyzed by gas chromatography. The maximum decrease in the respiratory rate occurred after the 15-min exposure; partial recovery was noted during the first 5 min postexposure. A clear nasal discharge was produced in rats
Acute Exposure Guideline Levels

exposed at the highest concentration (1,963 ppm), and a slight weight loss occurred in all groups during the first 24 h postexposure. The authors did not report the duration of the postexposure observation period. The calculated RD_{50} for rats was 1,342 ppm. The maximum decrease in the respiratory rate at each concentration is presented in Table 4-6. A clear dose-response was not observed.

Robinson et al. (1995) found no histopathologic evidence of hepatic or renal damage in rats exposed to epichlorohydrin vapor at a concentration of 100 ppm for 4 h. Groups of male Fischer 344 rats were exposed to epichlorohydrin vapor in 422-L dynamic flow through inhalation chambers. The rats were either young adults (about 65 or 73 days old; six per group) or adults (96 days old; 11 per group). At least 14 grab samples per 4-h exposure period were taken from a single point near the geometric center of the chamber and analyzed for epichlorohydrin by infrared spectrophotometry. Controls were sham exposed. The study focused on various parameters of hepatic and renal damage on days 1, 2, and 3 postexposure. There was no evidence of hepatic damage in young rats as determined by organ weight, serum chemistry, or histopathologic examination. The only statistically significant change potentially relevant to renal toxicity was a 5% increase in relative kidney weight in exposed young adult rats on day 1 after exposure, which was not observed on days 2 or 3 after exposure, or at any time in adult rats. Furthermore, serum creatinine levels were unaffected by epichlorohydrin exposure in young or adult rats and blood urea nitrogen (BUN) levels decreased (15%) in adult rats on the day of exposure, but not at any other time (an increase in BUN would be indicative of possible renal toxicity). Collectively, the observations provide no consistent evidence of renal toxicity in young or adult rats. Robinson et al. (1995) did not conduct clinical observations of the rats during or after exposure.

Groups of 60 male white rats were exposed to epichlorohydrin vapors at concentrations of 1.9, 5.3, or 93 ppm (7, 20, or 350 mg/m^3) for 4 h, and they were evaluated on day 0 or 1 after exposure (Shumskaya et al. 1971). Exposure conditions (chamber size and mode of operation) and duration of the observation period were not reported by the investigators. The results showed increased hepatic and renal weights and decreased lung and spleen weights. Evaluation of urine showed increased production, decreased specific gravity, increased output of chlorides, and elevated excretion of protein at all concentrations. Bromosulfophthalein (BSP) removal from the blood was decreased at all three concentrations on the day of exposure. BSP was used to assess liver function, particularly biliary function, at the time this study was conducted.

TABLE 4-6 Reduction in Respiratory Rate of Rats Exposed to Epichlorohydrin

	Concentration (ppm)						
	101	363.2	394.1	642.7	662.9	913.7	1,963
Decease in respiratory rate, %	6 ± 15	33 ± 9	32 ± 7	52 ± 7	36 ± 19	54 ± 8	52 ± 21

In a 14-day inhalation toxicity study, groups or five male and five female Fischer rats were exposed to epichlorohydrin vapor at concentrations of 0, 10, 25, 50, 100, or 200 ppm for 6 h/day, 5 days/week, in an 8-m^3 stainless-steel and glass inhalation chamber operated under dynamic conditions (Industrial BioTest Laboratories 1977a). The analytic concentrations were 0, 9.7, 23.0, 48.8, 97.3, and 209.8 ppm. Clinical signs observed after the first exposure are summarized in Table 4-7. No clinical signs attributed to epichlorohydrin exposure were observed at 10 and 25 ppm. Clinical signs at 50 ppm and higher involved primarily the eyes and respiratory tract. The number of different clinical signs increased as the exposure concentration increased from 50 ppm to 200 ppm. One male and three females died after repeated exposure at 200 ppm for 4-11 days. Gross findings at the end of the study included areas of consolidation in the lungs of two males, pale kidneys in three males and two females, extreme intestinal bloating in one male, and red oral and nasal discharge in one female at 200 ppm.

Groups of 20 male Wistar rats exposed to aerosolized epichlorohydrin (in a 1:1 mixture of alcohol and lutrol) at concentrations of 825 or 1,375 mg/m^3 for 1 h exhibited no symptoms of toxicity at 825 mg/^{3}, but symptoms of toxicity were observed in all rats exposed at 1,375 mg/m^3 (Kimmerle 1967). Symptoms of toxicity were not observed in groups of 10 male Wistar rats exposed to aerosolized epichlorohydrin (without alcohol and lutrol) at concentrations of 171 or 498 mg/m^3 for 4 h.

Ito et al. (1995) conducted a study to determine the biochemical and histopathologic effects of inhaled epichlorohydrin on the kidneys of Wistar rats (10 weeks old rats; sex and number per group not specified). Rats were exposed to epichlorohydrin vapor at 150 ppm for 1 h or 5 ppm for 2 h/day, 6 days/week for a total of 20 exposures. Chamber concentrations were monitored by gas chromatography (no other details provided). The effects in the experimental groups were compared with those of a control group. Body weight in the rat exposed repeatedly at 5 ppm was reduced throughout the exposure period. Pathologic lesions were observed in the kidney after single and repeat exposures. Exposure at 150 ppm caused severe damage to the proximal tubular epithelium of the kidneys. Severe microscopic changes also were observed in epithelial cells (apoptosis) in distal tubules in the kidneys of rats exposed at 150 ppm. Similar but less severe damage occurred after repeat exposures at 5 ppm.

Quast et al. (1979b) conducted a 12-day inhalation study using Fischer 344 and Sprague-Dawley rats (five males and five females per group) exposed to epichlorohydrin vapor at a concentration of 100 ppm for 7 h/day, 5 days/week for a total of nine exposures. The animals were exposed under dynamic conditions in

a 4.3-m^3 Rochester-type chamber. Exposure concentrations were determined 3-7 times per day by gas chromatography. Control groups were not placed in a chamber. No signs of significant ocular or nasal irritation were observed during exposure; the animals, however, tended to huddle together and sleep. Transient moist nasal discharge, discoloration around the nasal orifice, *Acute Exposure Guideline Levels*

TABLE 4-7 Clinical Signs, Mortality, and Time of Onset in Fischer 344 Rats Exposed by Inhalation to Epichlorohydrin for 6 Hours/Day, 5 Days/Week for 14 Days

	Concentration (ppm)			
Clinical Signs	10 and 25	50	100	200
Squinting	–	+ (82 min)	+ (28 min)	+ (66 min)
Hypoactivity	–	+ (82 min)	+ (78 min)	+ (66 min)
Head shaking	–	–	+ (178 min)	–
Drooping eyelids	–	–	+ (223 min)	+ (126 min)
Irritated eyes	–	–	–	+ (136 min)
Gasping, intermittent	–	–	–	+ (171 min)
Red nasal discharge	–	–	–	+ (266 min)
Lacrimation	–	–	–	+ (336 min)
Mortality (earliest)	–	–	–	4/10 (4-11 d)

+ clinical signs observed; – no clinical signs observed Source:
Data from Industrial Bio-Test Laboratories 1977a.

sneezing, and rubbing of the nose were observed after each exposure and disappeared before the next exposure. Decreased body size (due to less filled abdominal region), food consumption, and fecal production observed after repeated exposures recovered somewhat over the weekend in the absence of exposures, but reappeared when another round of exposures was initiated. Effects at study termination attributed to epichlorohydrin included gross and histopathologic evidence of damage to nasal turbinates (degeneration, inflammation, hyperplasia, and squamous metaplasia), kidneys (increased weight and slight degeneration), and epididymis (slight change in contents). The kidneys were more affected in males than in females, and Sprague-Dawley rats were more affected than Fischer rats.

Groups of four male and four female albino Wistar rats were exposed under dynamic conditions to atomized epichlorohydrin (in propanol) diluted with air to

achieve concentrations of 9, 17, 27, or 56 ppm (Gage 1959). Exposures were for 6 h/day, 5 days/week for 18 or 19 exposures or at 120 ppm repeatedly for 11 exposures. Labored breathing was observed 3 h after initiating the first exposure at 120 ppm. Profuse nasal discharge was observed at 120 ppm, lethargy and weight loss at 56 and 120 ppm, respiratory distress and nasal discharge at 56 ppm, poor general condition at 27-120 ppm, and signs of mild nasal irritation at 27 ppm. Gross and histopathologic evidence of leucocytosis and toxicity were observed in the lung, kidneys, and liver of rats exposed at 120 ppm and evidence of toxicity was found in the lungs at 27 ppm but not at 56 ppm. No rats died after only one exposure, but one rat died after 11 exposures at 120 ppm.

Groups of 30 male and 30 female Sprague-Dawley rats were exposed to epichlorohydrin at 0, 5, 25, or 50 ppm for 6 h/day, 5 days/week for 10 weeks (John et al. 1983b). Weight gain was decreased slightly in male and female rats exposed at 50 ppm. A slight potentiation of spontaneous renal damage and degenerative changes (inflammation, hyperplasia, and metaplasia) in the respiratory epithelium of the nasal cavity were observed at 25 and 50 ppm. The damage was minimal to moderate at 25 ppm and moderate to severe at 50 ppm. All nasal and renal damage was reversed during the 10-week postexposure period. The study was a reproduction study that showed marked transient decreases in fertility in male rats exposed at 25 and 50 ppm.

Groups of 20 male and 20 female Sprague-Dawley and Fischer 344 rats were exposed to epichlorohydrin at 0, 5, 25, or 50 ppm for 6 h/day, 5 days/week for 3 months (Quast et al. 1979a). No effects were observed that could be attributed to a single exposure to epichlorohydrin. The most notable microscopic changes observed at the end of the study were inflammatory, degenerative, and reactive changes in the nasal turbinates of male and female rats of both strains exposed at 25 and 50 ppm. Other microscopic changes were observed in the liver and kidneys of males and females of both strains at 50 ppm and in the adrenal gland of males at 50 ppm.

3.2.3. Mice

Kane et al. (1979) determined the RD_{50} in groups of four specific pathogen free Swiss-Webster mice exposed to aerosolized epichlorohydrin head-only for 10 min at different concentrations. The respiratory rate was measured using a plethysmograph. Epichlorohydrin concentrations were determined spectrophotometrically after oxidation of epichlorohydrin with periodic acid. The RD_{50} was 687 ppm (95% confidence limits: 633-748 ppm). The concentrations were reported as ppm, although the exposure atmospheres were generated by aerosolizing epichlorohydrin. Presumably, the animals were actually exposed to vapor produced from the epichlorohydrin aerosol; however, that could not be confirmed from the report.

TABLE 4-8 Clinical Signs, Mortality, and Time of Onset in B6C3F$_1$ Mice Exposed by Inhalation to Epichlorohydrin for up to 6 Hours/Day, 5 Days/Week for 14 Days

	Concentration (ppm)			
Clinical Signs	10 and 25	50	100	200
Squinting	–	+ (66 min)	+ (78 min)	+ (66 min)
Hypoactivity	–	+ (217 min)	+ (178 min)	+ (126 min)
Drooping eyelids	–	–	+ (223 min)	+ (126 min)
Ruffed fur	–	–	–	+ (306 min)
Gasping	–	–	–	+ (381 min)
Mortality (earliest)	–	–	–	7/10 (6-12 d)

+ clinical signs observed; – no clinical signs observed.

Source: Data from Industrial Bio-Test Laboratories 1977b.

In a 14-day inhalation toxicity study, groups or five male and five female $B6C3F_1$ mice were exposed to epichlorohydrin vapor at concentrations of 0, 10, 25, 50, 100, or 200 ppm for 6 h/day, 5 days/week. The animals were exposed in an 8-m^3 stainless-steel and glass inhalation chamber operated under dynamic conditions (Industrial Bio-Test Laboratories 1977b). The procedure for analysis of chamber atmospheres was not reported. The analytic concentrations were 0, 9.7, 23.0, 48.8, 97.3, and 209.8 ppm. Clinical signs observed after the first exposure are summarized in Table 4-8. No clinical signs attributed to epichlorohydrin were observed in the 10- and 25-ppm groups. The number of different clinical signs increased as the exposure concentration increased from 50 ppm to 200 ppm. A total of seven deaths occurred (all five females and two males) in the 200-ppm group after day 6. Gross findings were observed only at 200 ppm, and consisted of consolidation in the lungs of one male and two female mice.

Quast et al. (1979b) conducted a 12-day inhalation study using $B6C3F_1$ mice (five males) exposed to epichlorohydrin vapor at a concentration of 100 ppm for 7 h/day, 5 days/week for a total of nine exposures. The animals were exposed under dynamic conditions in a 4.3-m^3 Rochester-type chamber. Exposure concentrations were determined by gas chromatography 3-7 times each day. Five males serving as the control group were not placed in a chamber. No signs of significant ocular or nasal irritation were observed during exposure; the animals, however, tended to huddle together and sleep. Transient moist nasal discharge, sneezing, and rubbing of the nose were observed after exposure; the signs disappeared before the next exposure. Decreases in body size, food consumption, and fecal production observed during the weekday exposures showed recovery over the weekend (no exposures), but the same effects became readily apparent upon initiation of another round of exposures. Effects at study termination attributed directly to epichlorohydrin included gross and histopathologic damage to nasal turbinates (degeneration, inflammation, hyperplasia, and squamous metaplasia) but not to the kidneys or epididymis as observed in rats.

Groups of 20 male and 20 female $B6C3F_1$ mice were exposed to epichlorohydrin at 0, 5, 25, or 50 ppm for 6 h/day, 5 days/week for 3 months (Quast et al. 1979a). No effects were observed that could be attributed to a single exposure to epichlorohydrin. The male and female mice, like the rats, had inflammatory, degenerative, and reactive changes in the nasal turbinates at 25 and 50 ppm. Other microscopic changes occurred only in the liver of males and females at 50 ppm.

In a continuous inhalation study, Formin (1966) exposed groups of 15 mice to epichlorohydrin at 0, 0.05, 0.53, or 5.3 ppm (0, 0.2, 2, or 20 mg/m^3) for 98 days. No details were provided regarding the exposure system or analysis of chamber atmospheres. Mice exposed at 0.05 ppm showed no adverse effects. On the first day of exposure, mice exposed at 5.3 ppm were noticeably excited, restless, and fairly active, and then became sluggish and somnolent before showing a gradual improvement. Body weight was 14-19% lower than that of controls by the end of

exposure. Additional effects observed after repeated exposure to epichlorohydrin included increased latent reaction period of the motor defense response to electrical stimulation (central nervous system effect) at 5.3 ppm, transient increase in the number of leukocytes with altered fluorescence at 0.53 and 5.3 ppm, decreased nucleic acids in blood at 0.53 and 5.3 ppm, and increased excretion of coproporphyrin in the urine at 5.3 ppm. Mice exposed at 5.3 ppm also had emphysema, bronchopneumonia, small edematous areas, and loosening and swelling of the adventitia of blood vessels in the lungs; foci of interstitial hemorrhages and venous congestion of the heart; cloudy swelling of the convoluted tubular epithelium of the kidney; and severe neuronal lesions in the medulla oblongata, cornu ammonis (hippocampus), and cerebellum of the central nervous system. No morphologic effects were seen in mice exposed at 0.05 and 0.53 ppm.

3.2.4. Hamsters

In a 14-day inhalation toxicity study, groups or five male and five female Syrian hamsters were exposed to epichlorohydrin vapor at concentrations of 0, 25, 50, 100, 200, or 400 ppm for 6 h/day, 5 days/week, in a 8-m^3 stainless-steel and glass inhalation chamber operated under dynamic conditions (Industrial Bio-Test Laboratories 1977c). The procedure for analysis of chamber atmospheres was not reported. The analytic concentrations were 0, 23.0, 48.8, 97.3, 209.8, and 364.3 ppm. Clinical signs observed after the first exposure are summarized in Table 4-9. The number of different clinical signs observed in each group increased as the exposure concentration increased from 50 ppm to 400 ppm. Salivation was observed before exposure was initiated. A total of four males and all five females exposed at 200 ppm died between day 4 and termination of the study; all males and females exposed at 400 ppm died between day 3 and 6 of the study. Gross findings included areas of lung consolidation in four male hamsters and one female hamster, intestinal bloating in three females, and pale kidneys in one female.

3.2.5. Rabbits

Groups of three male and female rabbits were exposed under static conditions to atomized epichlorohydrin sprayed every 30 min into a 2-m^3 chamber for a single exposure of 1 or 4 h; the animals were observed for 14 days (Kimmerle 1967). Average exposure concentrations determined analytically were 70, 204, 324, 500, and 3,350 mg/m^3 for 1 h or 171 and 498 mg/m^3 for 4 h. Other species were housed in the same chamber. Symptoms of toxicity were observed only at 3,350 mg/m^3.

Gage (1959) exposed two New Zealand white rabbits to epichlorohydrin at 35 ppm or at 16 ppm reduced to 9 ppm after the second day. The animals were exposed daily for 6 h/day, 5 days/week for a total of 20 exposures. Signs of nasal irritation were observed at 35 and 16 ppm, but not at 9 ppm. Gross and histopathologic examinations showed no signs of toxicity.

TABLE 4-9 Clinical Signs, Mortality, and Time of Onset in Syrian Hamsters Exposed by Inhalation to Epichlorohydrin for up to 6 Hours/Day, 5 Days/Week for 14 Days

	Concentration (ppm)				
Clinical Signs	25	50	100	200	400
Squinting	–	+ (82 min)	+ (78 min)	+ 66 (min)	+ (40 min)
Hypoactivity	–	+ (262 min)	+ (178 min)	+ (126 min)	+ (100 min)
Drooping eyelids	–	–	+ (223 min)	+ (126 min)	+ (100 min)
Salivation	–	–	+ (268 min)	+ (126 min)	+ (-20 min)
Excitation, intermittent	–	–	–	+ (216 min)	+ (-30 min)
Gasping, intermittent	–	–	–	+ (381 min)	–
Gasping, not intermittent	–	–	–	+ (426 min)	+ (145 min)
Mouth pouches full or full of saliva	–	–	–	+ (306 min)	+ (240 min)
Very heavy labored breathing	–	–	–	–	+ (240 min)
Mortality (earliest)	–	–	–	9/10 (7-14 d)	2/10 (3-6 d)

+ clinical signs observed; – no clinical signs observed Source:
Data from Industrial Bio-Test Laboratories 1977c.

3.2.6. Dogs

Two dogs were exposed to epichlorohydrin vapor at a concentration of 21 ppm for 7 h/day, 5 days/week for 90 exposures (Kobernick et al 1983). The animals were exposed in 550-L hardboard chambers operated under dynamic conditions. The chamber atmosphere was sampled occasionally and analyzed using a spectrophotometric procedure. One dog lost a small amount of weight. Microscopic examination showed hemosiderin deposits and diffuse congestion of alveolar capillaries in both dogs, bronchial hypersecretion of mucus in one dog, focal interstitial nephritis in both dogs, diffuse cloudy swelling of the proximal

convoluted tubules in one, and centrilobular cloudy swelling in the liver of one dog.

3.3. Developmental and Reproductive Toxicity

In developmental toxicity range finding studies, groups of five or six presumed pregnant rats and groups of five presumed pregnant rabbits were exposed to epichlorohydrin vapor under dynamic conditions at concentrations of 0, 25, 50, or 100 ppm for 7 h/day (Pilny et al. 1979). The rats were exposed on gestation days 6-15 and then killed on day 16, and the rabbits were exposed on gestation days 6-18 and then killed on day 19. At 50 and 100 ppm, female rats gained less weight and had decreased intraabdominal adipose tissue, decreased thymus size, and an increased incidence of pale liver. At 100 ppm, three of six rats had 100% resorptions, one had normal fetuses, and two had no evidence of being pregnant (no implantation sites). Three rabbits exposed at 100 ppm and one exposed at 50 ppm died at an unknown time. Decreased body weight gain, respiratory tract irritation, pneumonia, and suppurative rhinitis were observed in all rabbits at 50 and 100 ppm. Severe pneumonia was confirmed at necropsy at 50 and 100 ppm and focal pneumonia in one rabbit at 25 ppm.

No maternal or developmental effects attributed to epichlorohydrin were observed in groups of 43-46 pregnant Sprague-Dawley rats exposed to epichlorohydrin vapor at concentrations of 0, 2.5, or 25 ppm for 7 h/day on gestation days 6-15 (John et al. 1983a). The animals were exposed in a 14.3-m^3 dynamic stainless-steel and glass chamber. Chamber atmospheres were sampled two to seven times per day and analyzed by gas chromatography. Analytic concentrations of epichlorohydrin were 2.5 and 24.6 ppm. Fetuses were harvested by Cesarean section on gestation day 21. Groups of 20-25 New Zealand white rabbits exposed on gestation days 6-18 under the same conditions as the rats and evaluated on gestation day 29 also had no maternal or developmental effects attributed to epichlorohydrin (John et al. 1983a).

John et al. (1983b) examined the effects of inhaled epichlorohydrin on fertility in groups of 30 male and 30 female Sprague-Dawley rats exposed to epichlorohydrin at 0, 5, 25, or 50 ppm for 6 h/day, 5 days/week for 10 weeks (about one spermatogenic cycle), followed by a 10-week postexposure period. A sialodacryadenitis infection (sialoacryadenitis virus is a coronavirus affecting the lacrimal and salivary glands, as well as upper and lower respiratory tracts, of rats) affected both control and exposed groups during weeks 1 and 2. Fertility was assessed during exposure (weeks 2, 4, 7, and 10) and postexposure (weeks 2, 5, and 10) in male rats mated with unexposed females. Fertility in the males of the 25- and 50-ppm groups was significantly reduced during exposure weeks 2-10, as assessed by the number of implantations per unexposed female~~s~~ mated with the exposed males, but was reduced only in the 50-ppm group, as assessed by the percentage of the exposed males impregnating unexposed females.

Epichlorohydrin had no effect on the weight or histology of male reproductive organs. Fertility in exposed females was assessed by the ability of the females to produce viable litters after mating with unexposed males. Exposure to epichlorohydrin had no adverse effect on the estrous cycle, pregnancy rate, parturition, litter size, or pup viability. Renal damage and degenerative lesions in the nasal cavity were observed at 25 and 50 ppm (see Section 3.2.2).

Fertility and testicular function were evaluated in groups of 10 male New Zealand white rabbits exposed to epichlorohydrin at 0, 5, 25, or 50 ppm, as described for rats (John et al. 1983b). Semen evaluated prior to exposure, at weekly intervals from week 2 to termination of exposure, and biweekly during the postexposure period showed no effects on sperm motility, viability, concentration, or morphology. No adverse effects were observed on fertility assessed in unexposed does mated with the exposed males. Light microscopic examination of spermatozoa revealed no abnormalities. Death, pulmonary lesions, and nasal lesions occurred at 25 and 50 ppm (see Section 3.1.4).

Slott et al. (1990) evaluated the effect of inhaled epichlorohydrin on sperm motility and testicular function in male Fischer-344 rats. Groups of 48 rats (90 days old) were exposed to epichlorohydrin at 0 or 100 ppm for 4 h, and sperm motility and other parameters were evaluated immediately after exposure and on days 1, 2, 6, and 14 postexposure. The exposed rats showed no overt signs of toxicity. No adverse effects were observed on testicular or epididymal weight, caudal epididymal sperm counts, or testicular spermatid counts in rats exposed to epichlorohydrin. Evaluation of sperm motility showed transient decreases (14% to -20% of control values) in progressive (straight line) and path (smoothed curvilinear) velocities of caudal epididymal sperm on day 1 postexposure only. The authors stated that the transient nature of the decrease and the small magnitude of the effect suggested that epichlorohydrin vapor at 100 ppm did not have a significant adverse effect on reproductive parameters.

3.4. Carcinogenicity

Only two inhalation carcinogenicity studies were found. Laskin et al. (1980) reported on studies in rats exposed to epichlorohydrin vapor for a total of 30 exposures or for their entire lifetime. In the first study, two groups of male Sprague-Dawley rats were exposed to epichlorohydrin vapor at 100 ppm for 6 h/day, 5 days/week for 30 exposures, and observed until death. One group had 40 rats and the other had 100 rats. In the second study, groups of 100 male Sprague-Dawley rats were exposed to epichlorohydrin vapor at 10 or 30 ppm for 6 h/day, 5 days/week until death. A total of 150 male rats served as controls; 100 were sham-exposed and 50 were untreated. It was unclear whether each study had separate control groups. Among the 140 animals exposed at 100 ppm for 30 days, 15 developed squamous cell carcinomas in the nasal cavity, two developed a nasal

papilloma, and one developed a bronchial papilloma. The first tumor to appear was a carcinoma on day 330. After a lifetime exposure to epichlorohydrin at 30 ppm, one animal had a squamous cell carcinoma of the nasal cavity (at 752 days) and one had a nasal papilloma (at 402 days). No nasal neoplasms developed in animals exposed at 10 ppm. Nonneoplastic respiratory lesions in the 100-ppm group consisted of severe inflammation, suppuration, destruction of the mucous membrane, and mucosal metaplasia of the nasal cavity; severe inflammation in the larynx and trachea; and pulmonary edema, congestion, and pneumonia. Tubular degenerative changes in the kidney were also observed at 100 ppm. Rats exposed at 10 or 30 ppm over a lifetime developed pulmonary congestion, bronchiectasis, pneumonia, a very low incidence of mucosal metaplasia of the nasal cavity, and tubular degenerative changes in the kidney. These studies showed that: (1) epichlorohydrin is carcinogenic in rats; (2) the neoplastic response to inhaled epichlorohydrin occurs only at the site of contact; and (3) short-term intense exposure to epichlorohydrin is much more effective in inducing a neoplastic response than low-level long-term exposures (a dose-rate effect was observed [3,000 ppm-days [100 ppm × 30 days] vs. 8,700 ppm-days [30 ppm for lifetime] and 2,500 ppm-days [10 ppm for lifetime]).

Carcinogenicity studies have been conducted in rats exposed orally and topically to epichlorohydrin. Oral exposure to epichlorohydrin resulted in a dose-related increase in forestomach neoplasms (primarily squamous cell carcinomas) after gavage administration, and in papillomas after administration in drinking water. Skin tumors have been induced in mice receiving a single application of epichlorohydrin followed by repeated applications of phorbol myristate acetate (initiation/promotion protocol) (HSE 1991).

A quantitative assessment of single-exposure estimates for epichlorohydrin is presented in Appendix B.

3.5. Genotoxicity

In a review of the genetic toxicology of epichlorohydrin, Giri (1997) concluded that epichlorohydrin is a direct-acting mutagen in *Salmonella typhimurium, Escherichia coli, Saccharomyces cerevisiae, Schizosaccharomyces pombe*, and *Klebisella pneumoniae*. It is more effective as a mutagen in the absence of an exogenous metabolizing system. There is a reduction in mutagenic activity in the presence of an activation system. In vitro cytogenetic assays showed consistent positive clastogenic effects (chromosome aberrations) and sister chromatid exchanges in test systems using cultured animal cells.

In a study of mice and rats exposed to epichlorohydrin at concentrations of 1.3, 6.6, and 33 ppm (5, 25, or 125 mg/m^3) for 120 h, Sram et al. (1981) showed increased frequencies of chromosome aberrations in mouse bone marrow and spermatogonia and increased abnormal sperm in mice (unspecified strain) exposed by inhalation to concentrations of epichlorohydrin as low as 1.3 ppm. The

abstract did not state whether the animals were exposed continuously or intermittently for 120 h The frequency of sister chromatid exchanges was not increased in bone marrow cells of mice, and the frequencies of chromosome aberrations in bone marrow cells and peripheral lymphocytes were not increased or were only slightly increased in rats after inhalation exposure to epichlorohydrin.

Another inhalation study showed a significant increase in the frequency of chromosome aberrations in spleen lymphocytes in CD-1 Swiss mice exposed to mixtures containing benzene, chloroprene, xylene, and epichlorohydrin at concentrations of 0, 0.1, 1.0, or 10 ppm (epichlorohydrin concentration was one-half that of the other components) for 3 or 6 weeks (Au et al. 1988). Exposure conditions are assumed to have been continuous. The effect could not be attributed to epichlorohydrin. Mixed results have been observed in oral and parenteral studies (Giri 1997).

3.6. Summary

Inhalation exposure to epichlorohydrin causes varying degrees of irritation of the mucous membranes of contact organs and effects on the central nervous system, kidneys, and liver. Acute lethality data are summarized in Table 4-3. LC_{50} values varied considerably depending on the exposure condition (dynamic or static chambers) and the physical state (aerosol or vapor) of the epichlorohydrin (see discussion in Section 4.5). Acute LC_{50} values for epichlorohydrin vapor in rats were 2,165-3,617 ppm for a 1-h exposure, 471-635 ppm for a 4-h exposure, and 360 ppm for a 6-h exposure. LC_{50} values in other species were 794 ppm for a 2-h exposure and 820-1,153 ppm for a 4-h exposure in mice, 275651 ppm for a 4-h exposure in guinea pigs; and 516 ppm for a 4-h exposure in rabbits. Deaths were due to effects on the respiratory center of the central nervous system and severe respiratory irritation manifested as pulmonary hemorrhage and edema. Before death occurred, the animals showed signs of cyanosis, muscle relaxation of the extremities, gasping, labored breathing, depressed or increased respiration, lethargy, fine tremors, and clonic convulsions. In addition, the animals had degenerative lesions of the nasal epithelium and kidneys and damage to the lower respiratory tract.

Inhalation exposure to nonlethal concentrations of epichlorohydrin resulted in systemic but mainly portal-of-entry effects. Data are summarized in Table 4-10. The RD_{50} is 1,342 ppm for a 15-min exposure of rats and 687 ppm (aerosol) for a 10-min exposure of mice. Clinical signs indicative of nasal irritation and sometimes ocular irritation have been observed in rats, mice, guinea pigs, hamsters, and rabbits exposed at nonlethal concentrations of epichlorohydrin. The nasal epithelium shows signs of degeneration similar to that described for lethal concentrations. Severe renal damage in rats exposed to epichlorohydrin vapor at 150 ppm for 1 h has been observed by light and electron microscopy (Ito et al. 1995) and functional changes in the kidney were noted after exposure at 93 ppm

for 4 h (Shumskaya et al. 1971); however, no microscopic evidence of renal damage was found after exposure at 100 ppm for 4 h (Robinson et al. 1995). Renal damage was seen in rats, but not mice, exposed repeatedly to epichlorohydrin. Sprague-Dawley rats appeared to be more sensitive than Fischer 344 rats, and males were more severely affected than females (Quast et al. 1979a,b). Damage to the nasal epithelium was seen in both strains of rats and in mice, but the effect may be less severe in mice.

No developmental effects were observed in rats or rabbits exposed to epichlorohydrin at concentrations up to 25 ppm for 7 h/day during organogenesis (John et al. 1983a). A transient decrease in fertility was observed in male rats but not females exposed repeatedly to epichlorohydrin vapor at 25 or 50 ppm for 6 h/day for 2-10 weeks. Studies in rabbits exposed at concentrations up to 50 ppm for 6 h/day for up to 10 weeks showed no effects on sperm parameters (John et al. 1983b). However, decreases in sperm motility were observed in rats exposed at 100 ppm for 4 h (Slott et al. 1990).

Genetic toxicity studies showed that epichlorohydrin is mutagenic in bacteria and yeast without metabolic activation. In vivo studies in mice showed chromosome aberrations after exposure at concentrations as low as 1.3 ppm for 120 h (Sram et al. 1981). Carcinogenicity studies showed that 30 exposures (6-h exposures for 5 days/week) to epichlorohydrin vapor at 100 ppm followed by

TABLE 4-10 Nonlethal Effects in Animals Exposed to Epichlorohydrin by Inhalation

Species/Strain/Sex	Exposure Protocol	Effects	Reference
Single Exposures			
Rat/Crl-CD®/males	101-1,963 ppm × 15 min	6-54% decrease in respiration; RD_{50} = 1,342 ppm (50% decrease in respiratory rate).	Gardner et al. 1985
Rat/Wistar	150 ppm × 1 h	Severe renal damage.	Ito et al. 1995
Rat/F344	100 ppm × 4 h	Slight increase in renal weight in young rats; slight decrease in BUN in adult rats; no microscopic evidence of hepatic or renal damage.	Robinson et al. 1995
Rats	1.9, 5.3, or 93 ppm × 4 h	Increased hepatic and renal weight; decreased pulmonary and spleen weight; increased urinary protein and chlorides; decreased specific gravity and BSP removal from blood.	Shumskaya et al. 1971
Rat/F344/males and females	10 or 25 ppm × 6 h	No effect.	Industrial Bio-Test Laboratories 1977
	50 or 100 ppm × 28-223 min	Squinting, hypoactivity, head shaking, drooping eyelids.	
	200 ppm × 136-336 min	Same as at 100 ppm; plus irritated eyes, gasping, red nasal discharge, lacrimation.	
Mice/Swiss Webster	687 ppm × 10 min	RD_{50} (50% decrease in respiratory rate)	Kane et al. 1979
Mouse/B6C3F_1/males and females	10 or 25 ppm × 6 h	No effect.	Industrial Bio-Test Laboratories 1977b
	50, 100, or 200 ppm × 66-381 min	Squinting, hypoactivity, drooping eyelids, ruffed fur, gasping.	
Mouse	5.3 ppm × 24 h	Transient excitation, restlessness, sluggishness, somnolence.	Formin 1966
Hamster/Syrian/males and females	25 ppm × 6 h	No effects.	Industrial Bio-Test Laboratories 1977c
	50 or 100 ppm × 78-262 min	Salivation, hypoactivity, squinting, drooping eyelids.	
	200 ppm × 66-381 min	Same as at 100 ppm; plus excitation, gasping, full mouth pouch.	
	400 ppm × 20-240 min	Same as at 200 ppm; plus labored breathing.	

(Continued)

TABLE 4-10 Continued

Species/Strain/Sex	Exposure Protocol	Effects	Reference
Repeated Exposures			
Rat/Wistar	150 ppm × 1 h or 5 ppm × 2 h/day for 6 days/week for 20 exposures	Less severe renal damage than single 1-h exposure at 150 ppm.	Ito et al. 1995
Rats/Sprague-Dawley, F344/males and females	100 ppm × 7 h/day for 5 days/week for 9 exposures	Signs of nasal irritation after each exposure (discharge, sneezing, rubbing); nasal epithelial and renal degeneration after repeated exposures.	Quast et al. 1979b
Mouse/B6C3F_1/males	100 ppm ×7 h/day for 5 days/week for 9 exposures	Signs of nasal irritation after each exposure (discharge, sneezing, rubbing); nasal epithelial degeneration after repeated exposures.	Quast et al. 1979b

lifetime observation was very effective in inducing squamous cell carcinomas in the nasal cavity of rats, whereas lifetime exposure at 30 ppm (6 h/day, 5 days/week) was almost ineffective (Laskin et al. 1980). The study demonstrated that short-term exposure at high concentrations of epichlorohydrin are more effective than long-term exposure at low concentrations for nasal tumor induction; therefore, dose fractionation may not be effective for epichlorohydrin exposure.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism, Disposition, and Kinetics

In a pharmacokinetic study, groups of three or four male Fischer 344 rats were exposed (head-only) to epichlorohydrin-1,3-^{14}C vapor at 1 or 100 ppm of for 6 h. About 72% of the dose was excreted in the first 24 h and about 83% was excreted within 72 h regardless of the concentration (Smith et al. 1979). About 46% and 54% of the radioactivity was recovered from urine, 34% and 27% in expired air, and 3% from feces after exposure at 1 and 100 ppm, respectively. Excretion of epichlorohydrin was biphasic; the half-life for the slower fraction was about 24 h. The half-life for elimination from plasma was 26 h, which was comparable to that for excretion. The uptake rates at 1 and 100 ppm were 15.48 and 1,394 µg/h and the total systemic doses were 0.37 and 33 mg/kg. The volume of distribution was 385 and 350 mL/kg, and was equivalent to 38.5 and 35% of the body weight. The investigators concluded that epichlorohydrin is not extensively sequestered in a deep compartment. Six metabolites were identified by chromatography of urine; the major metabolites recovered after exposure at 1 and 100 ppm were similar in type and proportion. The parent compound was not identified as a constituent of urine, indicating complete metabolic conversion of epichlorohydrin. Tissue distribution of radioactivity immediately after exposure showed that nasal turbinates (target organ) contained the largest fraction of epichlorohydrin when calculated on the basis of grams of tissue, followed by the lacrimal glands, large intestines, kidneys, liver, adrenal glands, erythrocytes, pancreas, and lungs. Except for the lacrimal glands, radioactivity decreased in all tissues over the first 24 h.

Stott and McKenna (1984) studied the absorption of epichlorohydrin in the isolated upper and isolated lower respiratory tract and the intact animal (male Fischer 344 rats). The animals were anesthetized and exposed to epichlorohydrin at 100 ppm by nose-only inhalation or via a one-way cephalad (upper respiratory tract) or endotracheal tube (lower respiratory tract, bypassing the nose) for about 2 h. Absorption reached a plateau in about 10-20 min and remained constant for the remaining exposure period. Absorption was 61% of available compound by the upper respiratory tract at a flow rate approximating the intact

breathing rate, 73% by the lower respiratory tract, and 51% by the intact respiratory tract. The authors explained some of the discrepancies in the percentages of absorption in the isolated upper and lower respiratory tract compared with the intact animal. Air flow through the isolated upper respiratory was unidirectional, which circumvented the loss of absorbed chemical due to significant back pressure during exhalation; the lower relative humidity may have altered blood flow and consequently chemical absorption by the isolated organ; and stimulation of the trigeminal nerve may have altered uptake by the lower respiratory tract. The authors further noted that absorption by the intact animal may have been underestimated because of unavoidable rebreathing of exhaled air, the effective deadspace in the upper respiratory tract causing less effective uptake, and fluctuating airflow during normal breathing patterns in the intact animals. Doubling the flow rate decreased the absorption fraction in the upper respiratory tract by about 17%. When absorption was calculated based on surface area, the dose received by the upper respiratory tract was estimated to be 5,000-6,000 times greater than that of the lower respiratory tract.

4.2. Mechanism of Toxicity

The mechanism by which epichlorohydrin causes toxicity is not known. Epichlorohydrin is a direct alkylating agent, which may account for some of its irritant properties.

Itoh et al. (1994) examined biochemical and histologic parameters in Wistar rats. Rats given a single inhalation exposure to epichlorohydrin at 20 ppm for 90 min or were exposed repeatedly to at 5 ppm for 6 h/day for a total of 30 exposures. Findings from the treatment groups were compared the results from those of a control group. The single exposure at 20 ppm caused an increase in urinary *N*-acetyl glucosaminidase activity, but had no effect on serum chemistry values. The erythrocyte count also was increased after a single exposure at 20 ppm. Glutathione (GSH) concentrations, along with glutathione peroxidase (GSH-Px) and glutathione-S-transferase activities, were decreased in the kidney.

Ito et al. (1995) reported that renal damage after exposure at a single to epichlorohydrin at 150 ppm for 1 h was accompanied by a pronounced reduction in GSH and a moderate reduction in GSH-Px. GSH showed greater than a threefold increase (attributed to induction of tolerance to epichlorohydrin) and GSHPx only a slight decrease after repeated exposure. The liver does not appear to be a primary target for epichlorohydrin in rodents, but there was a pronounced reduction in GSH in the liver after a single low-level exposure and no effect after repeated low-level exposures. GSH depletion is probably related to the extent of damage in the kidney. The authors stated that GSH caused cellular dysfunction because of the reduced capacity to process activated oxygen. The extent of damage was greater in the kidneys than in the liver, because of higher intracellular concentrations of epichlorohydrin in the kidney.

4.3. Structure-Activity Relationships

Structurally, epichlorohydrin can be related to either ETO or propylene oxide (either as chloromethyl ethylene oxide or as chlorinated propylene oxide) All three compounds are direct alkylating agents; however, the toxicity of epichlorohydrin is more like that of propylene oxide than ETO. Both epichlorohydrin and propylene oxide caused lesions in the upper respiratory tract after a single exposure and nasal tumors after repeated exposures. Unlike ETO, neither epichlorohydrin nor propylene oxide has been found to be a developmental toxicant. Both compounds produce similar clinical signs. The 4-h LC_{50} values for epichlorohydrin and propylene oxide are 441-635 ppm and 4,000 ppm, respectively, in the rat, and 820-1,153 and 1,740 ppm, respectively, in the mouse. Values for propylene oxide were obtained from Berdasco and Waechter (2012). The data suggest that the rat is 5-10 times more sensitive to epichlorohydrin than propylene oxide, and the mouse is less than two times more sensitive to epichlorohydrin. Although the clinical signs were similar, the test concentrations eliciting clinical signs were much lower for epichlorohydrin than for propylene oxide. Therefore, epichlorohydrin is qualitatively similar but quantitatively different from propylene oxide.

4.4. Other Relevant Information

4.4.1. Species Variability

The range of LC_{50} values for inhalation exposure to epichlorohydrin vapor showed that the mouse is the least sensitive species, but that the values for the rat, guinea pig, and rabbit are within the same range. For nonlethal effects, the Industrial Bio-Test Laboratories (1977a,b,c) studies showed no difference in the lowest concentration eliciting clinical signs (50 ppm) and the type of sign observed (squinting, hypoactivity, and/or salivation) and very little difference in the time of onset. Humans exposed to epichlorohydrin experience effects similar to those observed in experimental animals: ocular and upper respiratory tract irritation. In a controlled exposure study (Kobernick et al. 1983), three of four human subjects experienced no irritation after exposure at 68 ppm for 2 min and two of four reported irritation of the eyes and pharynx after exposure at 136 ppm for 2 min. The data suggest that humans are slightly more sensitive than animals.

4.4.2. Susceptible Subpopulations

No data were available to identify populations more susceptible to epichlorohydrin. One report on exposure to ETO noted that an asthmatic worker

detectable by its odor. Epichlorohydrin and ETO have similar structures. Direct alkylation may be involved in the irritant effects on the eyes and upper respiratory tract; this mechanism is not expected to vary considerably with individuals in the population. Systemic effects of epichlorohydrin may be modulated by metabolism (deactivation), which involves glutathione conjugation. Genetic polymorphism of the glutathione-S-transferase enzymes (Finell 1996) may result in some variations in human sensitivity within the population due to the slow versus rapid deactivation of epichlorohydrin.

4.4.3. Concentration-Exposure Duration Relationship

The concentration-time relationship for many irritant and systemicallyacting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). LC_{50} data from studies of the rat can be used to determine the relationship between concentration of epichlorohydrin and exposure duration. LC_{50} values for the rat are: 2,798 ppm (geometric mean of 3,617 ppm for males and 2,165 ppm for females) for a 1-h exposure, 580 and 635 ppm for 4-h exposures, 360 ppm for a 6-h exposure, and 250 ppm for an 8-h exposure. A linear log-log relationship was observed over the 1- to 8-h exposure durations. The calculated value of n was 0.87. The data are presented in Figure 4-1 (the LC_{50} on the plot for the 4-h diratopm is the midpoint [608 ppm] between the reported values of 580 and 635 ppm).

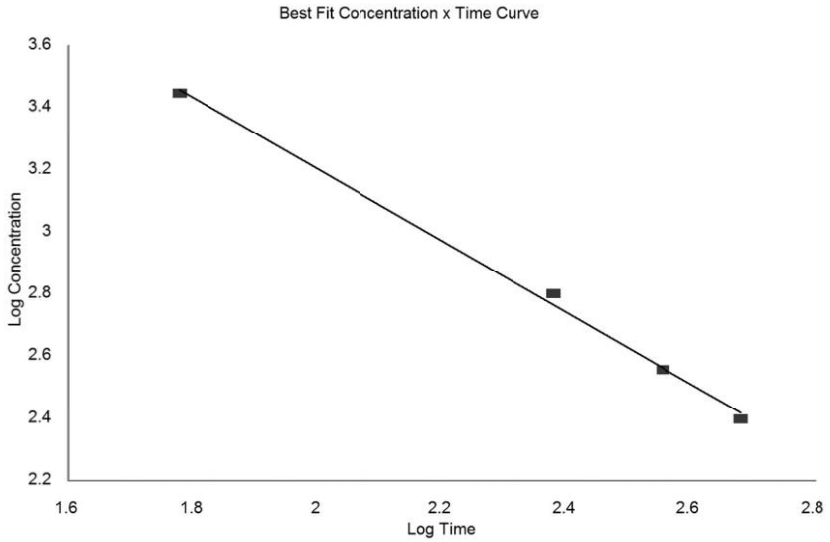

FIGURE 4-1 Concentration-time curve of LC_{50} values for epichlorohydrin in the rat.

4.5. Vapor and Aerosol Exposures

AEGL values were derived for epichlorohydrin on the basis of studies in which animals were exposed only to vapor for several reasons. First, epichlorohydrin will produce vapor when liquid epichlorohydrin or aerosolized epichlorohydrin is exposed to air (vapor pressure = 13 mm Hg at 20°C). Thus, in studies that exposed animals to epichlorohydrin aerosols, animals would have inhaled epichlorohydrin both as an aerosol and as a vapor. Second, studies using aerosols generally did not indicate whether exposure concentrations were measured and were reported as total epichlorohydrin (the sum of aerosol and vapor); thus, the nature of the actual exposure in these studies is not known. Third, aerosol studies frequently used a solvent or other stabilizing agent for which control exposures are not reported; the role of these coexposures in the observed toxicity cannot be evaluated. Finally, there are adequate data available from studies in which animals were exposed to epichlorohydrin vapor, so the aerosol data are not needed to fill any data gaps. In summary, given the uncertainties in the aerosol studies and the availability of adequate studies of epichlorohydrin administered as a vapor, aerosol studies were not used in the derivation of AEGL values.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Epichlorohydrin has a sweet, pungent or chloroform-like odor. Odor perception of epichlorohydrin by human subjects occurs in the range of 0.08-25 ppm (Amoore and Hautala 1983; Kobernick et al. 1983; AIHA 1989; Shell Oil Co. 1977; Berdasco and Waechter 2012). Kobernick et al. (1983) reported that two of four subjects exposed at 17 ppm for 2 min noted the odor of epichlorohydrin but experienced no irritation, one of four subjects exposed at 68 ppm for 2 min experienced pharyngeal irritation, and two of four subjects exposed at 135 ppm for 2 min experienced ocular and pharyngeal irritation. The odor of epichlorohydrin was detected but irritation was not reported by subjects exposed at 25 ppm for 5 min (Shell Oil Co. 1977). Lefaux (1968) and Wexler (1971) reported that humans exposed at 20 ppm for an extended period experienced burning of the eyes and nasal mucosa and that those exposed at 40 ppm for 1 h experienced throat irritation; however, no direct evidence for this conclusion was provided.

5.2. Animal Data Relevant to AEGL-1

Several datasets are relevant for deriving AEGL-1 values from animal studies. Studies of animals exposed under static conditions are considered inferior to studies in which exposures were under dynamic conditions, and were not used as basis for AEGL values. As discussed in Section 4.5, AEGL values were

derived for epichlorohydrin vapor on the basis of studies in which animals were exposed to vapor, and aerosol studies were not used. Exposure to epichlorohydrin at 101 ppm for 15 min caused a 6% decrease in the respiratory rate in rats (Gardner et al. 1985). The only evidence of possible hepatic or renal toxicity in male rats exposed to epichlorohydrin vapor at 100 ppm for 4 h was a transient 5% increase in renal weight 1 day after exposure and a transient 15% decrease in blood urea nitrogen (BUN) on the day of exposure, which were not consistently observed in young adult and adult rats (Robinson et al. 1995); neither parameter is considered sufficient evidence of toxicity. The investigators did not indicate whether they observed the animals for clinical signs. In the studies by Industrial Bio-Test Laboratories (1977a,b,c), rats, mice, and hamsters showed clinical signs, such as squinting, hypoactivity, and salivation, after a single exposure to epichlorohydrin at 50 ppm for 66-217 min. Squinting of the eyes was considered separately from ocular irritation, which occurred in rats exposed at 200 ppm for 136 min. In addition, drooping eyelids or head shaking was observed in rats, mice, and hamsters exposed at 100 ppm for at least 178 min. In a repeat inhalation study, Quast et al. (1979b) reported no clinical signs in two strains of rats and one strain of mice during exposure to epichlorohydrin vapor at 100 ppm for 7 h, but after exposure the animals showed signs of nasal irritation that disappeared before the next exposure. John et al. (1983b) reported no clinical signs of toxicity after the first exposure of rats to epichlorohydrin vapor at 5-50 ppm for 6 h.

5.3. Derivation of AEGL-1 Values

Because irritation is the most sensitive effect experienced by humans exposed to epichlorohydrin at low concentrations, that end point was used to derive AEGL-1 values. The point-of-departure was a no-effect level for irritation of 17 ppm for a 2 min exposure (Kobernick et al. 1983). The total uncertainty factor of 10 was applied, which represented uncertainties associated with intraspecies variability. Mild irritation experienced by humans (e.g., at 17 ppm) would most likely be confined to the nasal passage and eyes. Variability in pharmacokinetics would not be expected to contribute to variability in doseresponse relationships for chemicals acting at the portal of entry. However, to provide sufficient protection for asthmatic individuals, a factor of 10 was used. Applying the total uncertainty factor of 10 to the point-of-departure yields an AEGL value of 1.7 ppm. That value was applied to all the AEGL exposure durations because epichlorohydrin is an irritant and the irritation is not expected to become more severe with increasing exposure duration at that concentration. The AEGL-1 values for epichlorohydrin are presented in Table 4-11. The AEGL-1 values are below the level of odor recognition (25 ppm) and the level of odor awareness (46 ppm). Therefore, odor is not a factor for early warning of exposure to epichlorohydrin.

TABLE 4-11 AEGL-1 Values for Epichlorohydrin

10 min	30 min	1 h	4 h	8 h
1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

There are few human data relevant to AEGL-2 derivation. Irreversible hepatic and respiratory-tract damage occurred in a worker who took a few breaths of epichlorohydrin at a very high (unknown) concentration (Shultz 1964). Anecdotal information (Lefaux 1968; Deichmann and Gerarde 1969; Wexler 1971; Enterline et al. 1990; Berdasco and Waechter 2012) has suggested that exposure to epichlorohydrin at 20 ppm for 1 h caused burning to the eyes and nose, 40 ppm caused throat irritation lasting for about 48 h, and 100 ppm could not be tolerated and may be associated with pulmonary edema and renal damage. No data were provided to support these conclusions. A report by Kobernick et al. (1983) stated that one of four subjects experienced irritation of the pharynx after a 2-min exposure to epichlorohydrin vapor at 68 ppm, and two subjects experienced eye or pharyngeal irritation after a 2-min exposure at 136 ppm. Epidemiologic studies did not provide evidence of a causal association between exposure to epichlorohydrin and morbidity, including skin diseases (Tsai et al. 1990).

6.2. Animal Data Relevant to AEGL-2

A relatively large animal database was available for evaluating nonlethal toxicity of epichlorohydrin (see Table 4-9). However, the available data were not suitable for defining a point-of-departure for AEGL-2 derivation, as discussed below.

The study using the monkey is not adequate because the animals had tuberculosis, only one animal was exposed, and no other primate data were available (Kobernick et al. 1983). Two RD_{50} studies were available in rodents. One study showed that the respiration rate in rats was decreased by 33-36% during a 150-min inhalation exposures to epichlorohydrin vapor at 363, 394, and 663 ppm and by about 50% at 643, 914, and 1,963 ppm; the RD_{50} was 1,332 ppm (Gardner et al. 1985). In an aerosol study, the RD_{50} for male Swiss-Webster mice was 687 ppm for a 10-min exposure (Kane et al. 1979). The mouse RD_{50} has been used for AEGL-2 derivation (see NRC 2004) on the basis of its correlation with a human

irritation threshold (Schaper 1993). However, the mouse RD_{50} data for epichlorohydrin are not suitable for AEGL-2 derivation because the data are from an aerosol study. In addition, there are no data supporting an association between rat RD_{50} values and human irritation.

Ito et al. (1995) observed severe renal toxicity in rats exposed to epichlorohydrin vapor at 150 ppm for 1 h. This effect exceeds the threshold for an AEGL-2 effect, and no other exposure concentrations were tested; therefore, a no-effect level could not be determined. Robinson et al. (1995) reported no histopathologic evidence of hepatic or renal damage in F344 rats exposed to epichlorohydrin at 100 ppm for 4 h; the result appears to conflict with information reported by Ito et al. (1995).

In a series of studies using rats, mice, and hamsters exposed repeatedly to epichlorohydrin at concentrations ranging from 10 to 400 ppm for 6 h/day for 14 days, the investigators provided detailed information on clinical signs after each exposure (Industrial Bio-Test Laboratories 1977a,b,c). Clinical signs related to AEGL-2 derivation included gasping, irritated eyes, excitation, and labored breathing. Signs were not seen at 100 ppm in any species, but were observed at 200 ppm in rats and mice and 200 and 400 ppm in hamsters. The concentration of 100 ppm may be a no-observed-effect level for clinical effects that may impair escape; however, mortality was seen in all three species at 200 ppm, and evaluation of the kidneys was limited to gross examination at study termination (findings included lung consolidation and/or intestinal bloating and pale kidneys at 200 ppm and higher in all species). In a repeated inhalation study using two strains of rats (Fischer 344 and Sprague-Dawley) and $B6C3F_1$ mice (Quast et al. 1979b), the animals huddled together and slept during exposure to epichlorohydrin at 100 ppm for 7 h/day. Transient signs of nasal irritation were the only clinical findings seen after each individual exposure. Exposure to epichlorohydrin for 5 days/week for 9 days resulted in histopathologic evidence of damage to nasal turbinates, kidneys, and epididymis; the findings are considered to be above the threshold for AEGL-2 effects.

On the first day of a continuous-exposure study, mice showed excitation and restlessness followed by sluggishness and somnolence and gradual recovery at 5.3 ppm (Formin 1966). The study provided no information on exposure conditions or analytic measurements and was not considered for use in deriving AEGL-2 values. The study in rabbits exposed to epichlorohydrin at 19-886 ppm for 1 h or at 45 and 132 ppm for 4 h was conducted using a static chamber (Kimmerle 1967) and atomized epichlorohydrin, and is not considered reliable for purposes of AEGL derivation.

Several developmental and reproductive toxicity studies were available; inhalation exposure to epichlorohydrin at concentrations of 2.5 or 25 ppm did not induce developmental effects in rats or rabbits exposed during organogenesis (John et al. 1983a). Transient infertility was induced in male rats exposed to epichlorohydrin at concentrations of 25 or 50 ppm for 6 h/day, 5 days/week for 2-

10 weeks (one spermatogenic cycle), but no effects were observed on fertility when exposed females were mated with unexposed males (John et al. 1983b). No reproductive effects were observed in male rabbits exposed under conditions similar to those used for the rats (John et al. 1983b). Slott et al. (1990) reported altered sperm motility in male rabbits exposed to epichlorohydrin at 100 ppm for 4 h; the effect is not considered to be irreversible nor of sufficient severity to reflect an AEGL-2 effect.

Finally, as discussed in Section 4.5, AEGL values were derived for epichlorohydrin vapor based on studies in which animals were exposed to vapor. Aerosol studies (e.g., Gage 1959; Kane et al. 1979; Kimmerle 1967) were not used to derive AEGL values.

6.3. Derivation of AEGL-2 Values

The human and animal data showed that exposure to epichlorohydrin is associated with various degrees of ocular and respiratory-tract irritation. Adequate data were not available for deriving AEGL-2 values from studies with humans or animals, as discussed above in Sections 6.1 and 6.2. Therefore, AEGL-2 values were estimated by reducing the AEGL-3 values by a factor of 3. That approach is used in cases of a steep-concentration-response curve (NRC 2001); the steep concentration-response curve is seen in a 1-h study of rats in which no deaths occurred among six rats exposed to epichlorohydrin at 3,275 ppm epichlorohydrin, and all 12 rats exposed at 3,995 ppm died (Dietz et al. 1985).

Reducing the 10-min AEGL-3 value by a factor of 3 yields a10-min AEGL-2 value of 188 ppm. Anecdotal information provided by Lefaux (1968) suggested that concentrations greater than 100 ppm for short intervals might result in pulmonary edema and renal damage. Although the information is anecdotal, support for the effects comes from a study of rats exposed to epichlorohydrin at 150 ppm for 1 h that exhibited evidence of severe renal damage (Ito et al. 1995). Therefore, t

The 30-min AEGL-2 value of 53 ppm was applied to the 10-min exposure to be protective of the lungs and kidneys. AEGL-2 values are presented in Table 4-12.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data are available on the lethal effects of single inhalation exposures to epichlorohydrin.

7.2. Animal Data Relevant to AEGL-3

A large number of lethality studies are available for deriving AEGL-3 values. Studies of animals exposed under static conditions are considered inferior to studies in which exposures were under dynamic conditions, and were not used as basis for AEGL values. As discussed in Section 4.5, AEGLs were derived for epichlorohydrin vapor on the basis of studies in which animals were exposed to vapor, and aerosol studies were not used.

TABLE 4-12 AEGL-2 Values for Epichlorohydrin

10 min	30 min	1 h	4 h	8 h
53 ppm (200 mg/m^3)	53 ppm (200 mg/m^3)	24 ppm 91 (mg/m^3)	14 ppm (53 mg/m^3)	6.7 ppm (25 mg/m^3)

Animals exposed at lethal concentrations of epichlorohydrin vapor showed signs of cyanosis, muscle relaxation, lethargy, tremors, increased or decreased respiration, labored breathing, clonic convulsions, and respiratory arrest. Microscopic examination of the respiratory tract showed exfoliation, erosion, ulceration, and necrosis of the nasal epithelium and hemorrhage, congestion, edema, or pneumonia in the lower respiratory tract. Systemic effects may include severe renal or hepatic damage. Six studies provided data that could be used to derive AEGL-3 values; they include rat studies by Dietz et al. (1985), Kobernick et al. (1983), and Laskin et al. (1980) and mouse, guinea pig, and rabbit studies by Kobernick et al. (1983). The studies were conducted using dynamic chambers, whereas in the other lethality studies, the animals were exposed to vapor in static chambers or they were exposed to aerosolized epichlorohydrin as discussed in Section 3.1.

7.3. Derivation of AEGL-3 Values

The LC_{50} values, and the corresponding estimates for the threshold for lethality (LC_{01} values), derived by probit analysis of the mortality data from five studies are presented in Table 4-13. The best datasets are obtained from the rat studies by Laskin et al. (1980) and Dietz et al. (1985). Although all the studies were conducted in dynamic chambers, Laskin et al. (1980) and Dietz et al. (1985) measured chamber concentrations analytically, whereas Kobernick et al. (1983) calculated the nominal chamber concentrations. Therefore, AEGL-3 values are calculated from the Laskin et al. (1980) and Dietz et al. (1985) data.

The 10-min, 30-min, and 1-h AEGL-3 values are based on the 1-h rat LC_{01} of 721 ppm (Dietz et al. 1985). A total uncertainty factor of 10 was applied. A factor of 3 was used to account for interspecies differences. The 4-h LC_{50} values for rats, mice, guinea pigs, and rabbits ranged from 573 to 820 ppm; thus, showing

very little variability among the species. Although limited, the data suggest humans are more sensitive than animals to inhaled epichlorohydrin but are within a factor of about 2.5. Epichlorohydrin at 50 ppm for 66-262 min caused squinting, hypoactivity, and salivation in animals, whereas 20 ppm for 1 h caused burning of eyes and nose in humans. In addition, epichlorohydrin is an epoxide and direct alkylating agent, similar in structure to ETO; a factor of 3 was also used for ETO (NRC 2010). A factor of 3 was applied for intraspecies variability. Epichlorohydrin is an epoxide and direct alkylating agent. The irritation and systemic toxicity caused by epichlorohydrin are likely to involve its alkylating activity. Therefore, the concentrations causing severe pulmonary irritation are not expected to vary considerably in the population. The systemic toxicity may be modulated by the detoxification enzymes, most likely epoxide hydrolase and glutathione-S-transferase activity. The structural similarity of epichlorohydrin to ETO suggests that metabolism involving the glutathione-Stransferase enzyme system, which is genetically polymorphic in human, may be similar. This similarity in structure provides additional support for an intraspecies factor of 3. A factor of 3 is also supported by human data. Use of higher total uncertainty factor of 30 would result in an 8-h AEGL-3 value of 6.6 ppm; however, occupational exposures as high as 15-54 ppm have occurred (Pet'ko et al. 1966 [as cited in NIOSH 1976]; de Jong et al. 1988) and were apparently not life-threatening. Time scaling was performed using he equation $C^n \times t = k$ (ten Berge et al. 1986), where n = 0.87. An empirical value for the exponent n was derived from rat LC_{50} values for 1-, 4-, 6-, and 8-h exposures.

The 4- and 8-h AEGL-3 values were based on the 6-h rat LC_{01} of 274 ppm (Laskin et al. 1980). The uncertainty factors and time-scaling method were the same as those used to derive the AEGL-3 values for the 10-min, 30-min, and 1-h durations. The 8-h AEGL-3 of 20 ppm is supported by a chronic exposure study in rats, in which exposure to epichlorohydrin at 30 ppm for 6 h/day for a lifetime did not result in any mortality. AEGL-3 values for epichlorohydrin are presented in Table 4-14.

TABLE 4-13 LC_{50} Values and Lethality Thresholds (LC_{01}) for Animals Exposed to Epichlorohydrin Vapor

Species/Sex	Exposure Duration (min)	LC_{50}[a] (ppm)	LC_{01}[a] (ppm)	Reference
Rat/male	360	373	274 ± 13.1[b]	Laskin et al. 1980
Rat/male	240	580	182 ± 125	Kobernick et al. 1983
Rat/male, female combined	60	2,369	721 ± 225	Dietz et al. 1985
Mouse/male	240	820	468 ± 116	Kobernick et al. 1983

Guinea pig/male	240	666	170 ± 115	Kobernick et al. 1983
Rabbit/male	240	573	100 ±112	Kobernick et al. 1983

[a] Values derived by probit analysis (Number Cruncher Statistical Syste sis, Version 5.5). [b] ±Standard error. ı: Survival Analy-

TABLE 4-14 AEGL-3 Values for Epichlorohydrin

10 min	30 min	1 h	4 h	8 h
570 ppm (2,200 mg/m^3)	160 ppm (600 mg/m^3)	72 ppm (270 mg/m^3)	44 ppm (170 mg/m^3)	20 ppm (76 mg/m^3)

8. SUMMARY OF AEGL VALUES

8.1. AEGL Values and Toxicity End Points

AEGL values for epichlorohydrin are presented in Table 4-15. The AEGL-1 value was derived from a no-effect level for irritation in humans. The AEGL-2 values were derived by reducing the AEGL-3 values by a factor of 3 and retaining the 30-min value for the 10-min value. AEGL-3 values for the 10-min, 30-min, and 1-h exposures were derived from a 1-h lethality study in rats; the 4- and 8-h values were derived from a 6-h lethality study in rats.

8.2. Other Standards and Guidelines for Epichlorohydrin

Standards and guidelines established for epichlorohydrin are presented in Table 4-16. The AEGL-1 value of 1.7 ppm is lower than the emergency response planning guideline 1 (ERPG-1) value of 5 ppm. The ERPG-1 value is based on an irritation threshold of 10 ppm (AIHA 2013). The ERPG documentation cites Diechmann and Gerarde (1969) as the source of the threshold, but the citation appears to be in error because that publication makes no mention of effects or lack of effects at 10 ppm.

The AEGL-2 value of 24 ppm for 1 h is similar to the ERPG-2 value of 20 ppm for 1 h. The ERPG-2 value (AIHA 2013) was based on the observation that epichlorohydrin at 20 ppm for 1 h resulted in burning of eyes and nose that was not expected to impair escape; it appears that this observation is based on the anecdotal information in Wexler (1971 [originally reported by Lefaux 1968]). As noted in Section 2.2.2, data supporting these anecdotal statements were not found in the available literature, so this information was not considered adequate to serve as the basis for AEGL values.

TABLE 4-15 AEGL Values for Epichlorohydrin

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)
AEGL-2 (disabling)	53 ppm (200 mg/m^3)	53 ppm (200 mg/m^3)	24 ppm (91 mg/m^3)	14 ppm (53 mg/m^3)	6.7 ppm (25 mg/m^3)
AEGL-3 (lethal)	570 ppm (2,200 mg/m^3)	160 ppm (600 mg/m^3)	72 ppm (270 mg/m^3)	44 ppm (170 mg/m^3)	20 ppm (76 mg/m^3)

TABLE 4-16 Standards and Guidelines for Epichlorohydrin

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)
AEGL-2	53 ppm (200 mg/m^3)	53 ppm (200 mg/m^3)	24 ppm (91 mg/m^3)	14 ppm (53 mg/m^3)	6.7 ppm (25 mg/m^3)
AEGL-3	570 ppm (2,200 mg/m^3)	160 ppm (600 mg/m^3)	72 ppm (270 mg/m^3)	44 ppm (170 mg/m^3)	20 ppm (76 mg/m^3)
ERPG-1 (AIHA)[a]	–	–	5.0 ppm (7.6 mg/m^3)	–	–
ERPG-2 (AIHA)	–	–	20 ppm (76 mg/m^3)	–	–
ERPG-3 (AIHA)	–	–	100 ppm (380 mg/m^3)	–	–
IDLH (NIOSH)[b]	–	75 ppm (280 mg/m^3)	–	–	–
TLV-TWA (ACGIH)[c]	–	–	–	–	0.5 ppm (1.9 mg/m^3)
PEL-TWA (OSHA)[d]	–	–	–	–	5 ppm (19 mg/m^3)
MAC-TGG (The Netherlands)[e]	–	–	–	–	0.5 ppm (1.9 mg/m^3)

[a] ERPG (emergency response planning guidelines, American Industrial Hygiene Association) (AIHA 2013). The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.

The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action.

The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing lifethreatening health effects. [b] IDLH (immediately dangerous to life or health, National Institute for Occupational Safety and Health) (NIOSH 1994) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms, or any irreversible health effects. NIOSH considers epichlorohydrin to be a potential occupational carcinogen.

[c] TLV-TWA (threshold limit value – time-weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 2001, 2012) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. The TLV for epichlorohydrin includes a skin notation.

[d] PEL-TWA (permissible exposure limit – time-weighted average, Occupational Health and Safety Administration) (29CFR Part 1910.1000 [2012]) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week. The PEL for epichlorohydrin includes a skin designation.

[e] MAC (maximaal aanvaaarde concentratie [maximal accepted concentration], Dutch Expert Committee for Occupational Standards, The Hague, The Netherlands) (MSZW 2004) is defined analogous to the ACGIH TLV-TWA.

The 1-h AEGL-3 value of 72 ppm is in the same range as the ERPG-3 value of 100 ppm. The ERPG-3 derivation used an LC_{50} estimate of about 2,000 ppm in multiple species (citing Gage 1959; Kimmerle 1967; and Dietz et al. 1985) as the starting point to derive the guideline of 100 ppm; no further information was given on how the guideline was derived.

The immediately dangerous to life for health (IDLH) value of 75 ppm (NIOSH 1994) is based in part on the statements of Lefaux (1968 [repeated by NIOSH 1976]) that 100 ppm is intolerable and potentially causes pulmonary edema and renal lesions, and on a Russian study (Pet'ko et al. 1966 [cited in NIOSH 1976]) reporting no apparent adverse effects in workers exposed to epichlorohydrin at 4.9-54.9 ppm. Animal data were also referenced to support the IDLH value.

The AEGL-1 value of 1.7 ppm is higher than the American Conference of Governmental Industrial Hygienists threshold limit value–time-weighted average (TLV-TWA) of 0.5 ppm (ACGIH 2001). That value is based on a NOAEL of 5 ppm for fertility in male rats exposed for 10 weeks (John et al. 1983b), as well as a NOAEL of 9 ppm for upper respiratory tract irritation (the LOAEL was 16 ppm in rabbits and 17 ppm in rats) in a repeated exposure study (Gage 1959). The 8-h AEGL-1 of 1.7 ppm is intended to protect against discomfort from a single exposure.

The Occupation Safety and Health Administration permissible exposure limit–time-weighted average (PEL-TWA) for epichlorohydrin is 5 ppm. The

Netherlands has established a maximal accepted concentration of 0.5 ppm for epichlorohydrin. German MAK values have not been established for epichlorohydrin; however, Germany has a skin designation for this compound.

8.3. Data Quality and Research Needs

A robust animal toxicity database was available for deriving AEGL values for epichlorohydrin. However, many animal studies were conducted in a static environment using epichlorohydrin aerosols generated with the use of other substances (alcohol and lutrol). Data were not available for corroborating the nonlethal effects observed in humans. Only studies conducted with epichlorohydrin vapor in which animals were exposed in a dynamic chamber were considered suitable for deriving AEGL values. There are a number of uncertainties concerning some of the AEGL values derived, particularly the 8-h value for AEGL-3.

The time-frame extrapolation procedure seems to break down after 4 h, suggesting that dose fractionation may not be applicable for the longer inhalation exposure durations. Additional studies to investigate dose fractionation for acute exposure would be helpful for relating exposure concentration and duration with toxic effects. It was not possible to ascertain the relative thresholds for respiratory tract irritation and systemic toxicity (renal or hepatic damage) from the available studies. Therefore, additional animal studies in which clinical signs and gross and histopathologic changes in the respiratory tract and systemic organs are evaluated in the same animals would provide helpful information to determine the most sensitive end point.

9. REFERENCES

ABC-Thailand (Aditya Birla Chemicals Thailand, Ltd). 2013. Epichlorohydrin [online]. Available: http://www.adityabirlachemicals.com/products/chlorine_derivatives/epichlorohydrin.html [accessed April 4, 2014].

ACGIH (American Conference of Governmental Industrial Hygienists). 2001. Epichlorohydrin (CAS Reg. No. 106-89-8). Documentation of the Threshold Limit Values and Biological Exposure Indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists .

ACGIH (American Conference of Governmental Hygienists). 2012. Epichlorohydrin (CAS Reg. No. 106-89-8). P. 29 in TLVs and BEIs Based on the Documentation of the Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

AIHA (American Industrial Hygiene Association). 1989. P. 18 in Odor Thresholds for Chemicals with Established Occupational Health Standards. Fairfax, VA: AIHA.

AIHA (American Industrial Hygiene Association). 2013. Current ERPG Values. 2013

ERPG/WEEL Handbook. American Industrial Hygiene Association Guideline Foundation, Fairfax, VA [online]. Available: https://www.aiha.org/get-involved/AIHAGuidelineFoundation/EmergencyResponsePlanningGuidelines/Documents/2013ERPGValues.pdf [accessed Mar. 25, 2014].

Alibaba. 2013. Epochlorohydrin [online]. Available: http://www.alibaba.com/countrysearch/CN-suppliers/Epichlorohydrin_Manufacturers.html [accessed June 17, 2013].

Amoore, J.E., and E. Hautala. 1983. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J. Appl. Toxicol. 3(6):272-290.

Au, W.W., J.B. Ward, Jr., V.M.S. Ramanujam, B.L. Harper, M.T. Moslen, and M.S. Legator. 1988. Genotoxic effects of a sub-acute low-level inhalation exposure to a mixture of carcinogenic chemicals. Mutat. Res. 203(2):103-115.

Barbone, F., E. Delzell, H. Austin, and P. Cole. 1992. A case-control study of lung cancer at a dye and resin manufacturing plant. Am. J. Ind. Med. 22(6):835-849.

Barbone, F., E. Delzell, H. Austin, and P. Cole. 1994. Exposure to epichlorohydrin and central nervous system neoplasms at a resin and dye manufacturing plant. Arch. Environ. Health 49(5):355-358.

Berdasco, N.A.M., and J.M. Waechter. 2012. Epoxy compounds: Aromatic diglycidyl ethers, polyglycidyl ethers, glycidyl esters, and miscellaneous epoxy compounds. Pp. 491-528 in Patty's Industrial Hygiene and Toxicology[online]. Available: http://onlinelibrary.wiley.com/doi/10.1002/0471435139.tox083.pub2/abstract [accessed Apr. 4, 2014].

Buckley, L.A., X.Z. Jiang, R.A. James, K.T. Morgan, and C.S. Barrow. 1984. Respiratory tract lesions induced by sensory irritants at the RD_{50} concentration. Toxicol. Appl. Pharmacol. 74(3):417-429.

Crump, K.S., and R.B. Howe. 1984. The multistage model with a time-dependent dose pattern: Applications to carcinogenic risk assessment. Risk Anal. 4(3):163-176.

Deichmann, W.B., and H.W. Gerarde, eds. 1969. Epichlorohydrin. P. 241 in Toxicology of Drugs and Chemicals. New York: Academic Press.

de Jong, G., N.J. van Sittert, and A.T. Natarajan. 1988. Cytogenetic monitoring of industrial populations potentially exposed to genotoxic chemicals and of control populations. Mutat. Res. 204(3):451-464.

Dietz, F.K., M. Grandjean, and J.T. Young. 1985. Epichlorohydrin: 1-Hour LC_{50} Determination in Fischer-344 Rats. Lake Jackson Research Center, Health and Environmental Sciences - Texas, Dow Chemical, Freeport, TX.

Enterline, P.E., V. Henderson, and G. Marsh. 1990. Mortality of workers potentially exposed to epichlorohydrin. Br. J. Ind. Med. 47(4):269-276.

EPA (U.S. Environmental Protection Agency). 1994. Epichlorohydrin (CAS Reg. No. 106-89-8). Carcinogenicity Assessment. Integrated Risk Information System (IRIS). U.S. Environmental Protection Agency, Washington, DC [online]. Available: http://www.epa.gov/iris/subst/0050.htm [accessed June 2013].

Finell, T.R. 1996. Biomarkers of exposure and susceptibility: Application to ethylene oxide. CIIT Activities 16:2-6.

Formin, A.P. 1966. Biological effects of epichlorohydrin and its hygienic significance as an atmospheric pollutant. Hyg. Sanit. 31(9):357-363.

Freuder, E., and C.D. Leake. 1941. The toxicity of epichlorohydrin. U. Calif. Publ. Pharmacol. 2(5):69-78.

Gage, J.C. 1959. The toxicity of epichlorohydrin vapour. Br. J. Ind. Med. 16(1):11-14.

Gardner, R.J., B.A. Burgess, and G.L. Kennedy, Jr. 1985. Sensory irritation potential of selected nasal tumorigens in the rat. Food Chem. Toxicol. 23(1):87-92.

Giri, A.K. 1997. Genetic toxicology of epichlorohydrin: A review. Mutat. Res. 386(1):2538.

Grigorowa, R., G.M. Muller, R. Rothe, and R. Gholke. 1974. Combined action of epichlorohydrin and elevated ambient temperature in acute and subacute animal experiments [in German]. Int. Arch. Arbeitsmed. 33(4):297-314.

Haskell Laboratory. 1980. Rat Sensory Irritation Study using Epichlorohydrin. Submitted to EPA, Washington, DC, by Du Pont de Nemours & Co., Wilmington, DE with Cover Letter Dated December 3, 1982. EPA Document No. 878220379. Microfiche No.OTS0215158.

HSDB (Hazardous Substance Data Bank). 2009. Epichlorohydrin (CAS Reg. No. 106-898). TOXNET, Specialized Information Services, U.S. National Library of Medicine, Bethesda, MD [online]. Available: http://toxnet.nlm.nih.gov [accessed May, 2013].

HSE (Health and Safety Executive). 1991. Toxicity Review 24, Part 2. 1-Chloro-2,3epoxypropane (Epichlorohydrin). Sheffield: Health and Safety Executive.

IARC (International Agency for Research on Cancer). 1999. Epichlorohydrin. Pp. 603-628 in Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide. IARC Monograph on the Evaluation of Carcinogenic Risk to Humans, Vol. 71 (Part 2). Lyon, France: IARC Press. [online]. Available: http://monographs.iarc.fr/ENG/ Monographs/vol71/mono71-26.pdf [accessed April 2, 2014].

Industrial Bio-Test Laboratories. 1977a. Repeated Dose Inhalation Study with AlphaEpichlorohydrin (CO7001) in F344 Rats, October 13, 1977. Submitted to EPA, Washington, DC, by Monsanto, St. Louis, MO with Cover Letter Dated January 17, 1983. EPA Document No. 878211476. Microfiche No. OTS0206230.

Industrial Bio-Test Laboratories. 1977b. Repeated Dose Inhalation Study with AlphaEpichlorohydrin (CO7001) in B6C3F$_1$, October 13, 1977. Submitted to EPA, Washington, DC by Monsanto, St. Louis, MO with Cover Letter Dated January 17, 1983. Document No. 878211478. Microfiche No. OTS0206230.

Industrial Bio-Test Laboratories. 1977c. Repeated Dose Inhalation Study with AlphaEpichlorohydrin (CO7001) in Golden Syrian Hamsters, October 13, 1977. Submitted to EPA, Washington, DC by Monsanto, St. Louis, MO with Cover Letter Dated January 17, 1983. EPA Document No. 878211477. Microfiche No. OTS0206230.

Ito, A., K. Ito, M. Hoshida, M. Watabe, and F.Y. Qiu. 1995. Experimental studies and renal lesions induced by epichlorohydrin inhalation exposure: Glutathione metabolism and apoptosis. Toho Igakkai Zasshi 42(4):321-330.

Itoh, A., T. Oguchi, M. Watabe, and M. Shimada. 1994. Toxicity profile of epichlorohydrin. Hochudoku 12(2):148-149.

John, J.A., T.S. Gushow, J.A. Ayres, T.R. Hanley, J.F. Quast, and K.S. Rao. 1983a. Teratologic evaluation of inhaled epichlorohydrin and allyl chloride in rats and rabbits. Fundam. Appl. Toxicol. 3(5):437-442.

John, J.A., J.F. Quast, F.J. Murray, L.G. Calhoun, and R.E. Staples. 1983b. Inhalation toxicity of epichlorohydrin: Effects on fertility in rats and rabbits. Toxicol. Appl. Pharmacol. 68(3):415-423.

Kane, L.E., C.S. Barrow, and Y. Alarie. 1979. A short-term test to predict acceptable levels of exposure to airborne sensory irritants. Am. Ind. Hyg. Assoc. J. 40(3):207229.

Kauppinen, T., J. Toikkanen, D. Pedersen, R. Young, M. Kogevinas, W. Ahrens, P. Boffetta, J. Hansen, H. Kromhout, J.M. Blasco, D. Mirabelli, V. de la Orden-Rivera, N. Plato, B. Pannett, A. Savela, H. Veulemans, and R. Vincent. 1998. Occupational Exposure to Carcinogens in the European Union in 1990-93. Carex. International Information System on Occupational Exposure to Carcinogens. Finnish Institute of Occupational Health, Helsinki [online]. Available: http://www.ttl.fi/en/chemical_safety/carex/countries/pages/default.aspx [accessed February 12, 2012].

Kimmerle, G. 1967. Toxicological Studies with Epichlorohydrin, October 20, 1967. Report No. 479/7. Farbenfabriken Bayer AC, Wuppertal-Elberfeld, Germany. Submitted to EPA, Washington, DC, by Mobay Chemical Corporation, Stilwell, KS with Cover Letter Dated January 28, 1983. EPA Document No. 878211473. Microfiche No. OTS0206022.

Kobernick, J.L., J.H. Nair, III, U.C. Pozzani, L.D. Roger, Jr., and J.S. West. 1983. Epichlorohydrin: Repeated Inhalation Preliminary Metabolic Studies, Revision of Acute Toxicity Data, and Human Sensory Response. Special Report 33-41. Mellon Institute, January 28, 1983. Submitted to EPA, Washington, DC, by Union Carbide Corporation, Danbury, CT with Cover Letter Dated December 9, 1983. Document No. 878212138. Microfiche No. OTS0206066.

Kučerová, M., V.S. Zhurkov, Z. Polívková, and J.E. Ivanova. 1977. Mutagenic effect of epichlorohydrin. II. Analysis of chromosomal aberrations in lymphocytes of persons occupationally exposed to epichlorohydrin. Mutat. Res. 48(3-4):355-360.

Laskin, S., A.R. Sellakumar, M. Kuschner, N. Nelson, S. La Mendola, G.M. Rusch, G.V. Katz, N.C. Dulak, and R.E. Albert. 1980. Inhalation carcinogenicity of epichlorohydrin in noninbred Sprague-Dawley rats. J. Natl. Cancer Inst. 65(4):751-757.

Lawrence, W.H., M. Malik, J.E. Turner, and J. Autian. 1972. Toxicity profile of epichlorohydrin. J. Pharm. Sci. 61(11):1712-1717.

Lawrence, W.H., M. Malik, and J. Autian. 1974. Development of a toxicity evaluation program for dental materials and products. II. Screening for systemic toxicity. J. Biomed. Mater. Res. 8(1):11-34.

Lefaux, R. 1968. Epichlorohydrin. P. 108 in Practical Toxicology of Plastics, P.P. Hopf, ed. Cleveland, OH: CRC Press.

Milby, T.H., M.D. Whorton, H.A. Stubbs, C.E. Ross, R.E. Joyner, and R.I. Lipshultz. 1981. Testicular function among epichlorohydrin workers. Br. J. Ind. Med. 38(4):372-377.

MSZW (Ministerie van Sociale Zaken en Werkgelegenheid). 2004. Nationale MAC-lijst 2004. Den Haag: SDU Uitgevers [online]. Available: http://www.lasrook.net/lasrookNL/maclijst2004.htm [accessed Jan. 3, 2014].

NIOSH (National Institute for Occupational Safety and Health). 1976. Criteria for a Recommended Standard. Occupational Exposure to Epichlorohydrin. NIOSH 76-206. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control and Prevention, National Institute for Occupational Safety and Health, Atlanta, GA [online]. Available: http://www.cdc.gov/niosh/docs/1970/76206.html [accessed on February 9, 2012].

NIOSH (National Institute for Occupational Safety and Health). 1994. Documentation for Immediately Dangerous To Life or Health Concentrations (IDLHs): Epichlorohydrin. National Institute for Occupational Safety and Health [online]. Available: http://www.cdc.gov/niosh/idlh/106898.html [accessed July 2013].

NIOSH (National Institute for Occupational Safety and Health). 2003. National Occupational Exposure Survey (NOES) Conducted from 1981-1983 [online]. Available: http://www.cdc.gov/noes/ [accessed July 2013].

NIOSH (National Institute for Occupational Safety and Health). 2011. NIOSH Pocket Guide to Chemical Hazards: Epichlorohydrin. National Institute for Occupational Safety and Health [online]. Available: http://www.cdc.gov/niosh/npg/npgd0254.html [accessed May, 2013].

NRC (National Research Council). 1986. EEGLS for carcinogens. Pp. 25-27 in Criteria and Methods for preparing Emergency Exposure Guidance Level (EEGL), Shortterm Public Emergency Guidance Level (SPEGL), and Continuous Exposure Guidance Level (CEGL) Documents. Washington, DC: National Academy Press.

NRC (National Research Council). 1993. Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. Washington, DC: National Academy Press.

NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. Washington, DC: National Academy Press.

NRC (National Research Council). 2004. Hydrogen chloride. Pp. 77-122 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 4. Washington, DC: The National Academies Press.

NRC (National Research Council). 2010. Ethylene oxide. Pp. 46-135 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 9. Washington, DC: The National Academies Press.

Olsen, G.W., S.E. Lacy, S.R. Chamberlin, D.L. Albert, T.G. Arceneaux, L.F. Bullard, B.A. Stafford, and J.M. Boswell. 1994. Retrospective cohort mortality study of workers with potential exposure to epichlorohydrin and allyl chloride. Am. J. Ind. Med. 25(2):205-218.

Pet'ko, L.I., E.S. Gronsberg, L.N. Chernova, and V.I. Filina. 1966. Some data on the conditions of work and status of health of workers in the production of epichlorohydrin [in Russian]. Gig. Tr. Prof. Zabol. 10(11):52-54.

Picciano, D. 1979. Cytogenetic investigation of occupational exposure to epichlorohydrin. Mutat. Res. 66(2):169-173.

Pilny, M.K., T.S. Lederer, J.S. Murray, M.S. Deacon, R.R. Hanley, J.F. Quast, and J.A. John. 1979. Epichlorohydrin B Subchronic Studies. IV. The Effects of Maternally Inhaled Epichlorohydrin on Rat and Rabbit Embryonic and Fetal Development. Submitted to EPA, Washington, DC, by Dow Chemical Co., Midland, MI with Cover Letter Dated December 20, 1982. EPA Document No. 878210751. Microfiche No. OTS0206139.

Quast, J.F., J.W. Henck, B.J. Postma, D.J. Schuetz, and M.J. McKenna. 1979a. Epichlorohydrin - Subchronic Studies. I. A 90-Day Inhalation Study in Laboratory Rodents (Fischer 344 Rats, Sprague-Dawley Rats, and B6C3F$_1$ Mice. Submitted to EPA, Washington, DC, by Dow Chemical Co., Midland, MI with Cover Letter Dated December 20, 1982. EPA Document No. 878210756. Microfiche No. OTS0206139.

Quast, J.F., T.S. Lederer, B.J. Postma, D.J. Schuetz, and M.J. McKenna. 1979b. Epichlorohydrin B Subchronic Studies. II. A 12-Day Inhalation Study in Laboratory Rodents (Fischer 344 Rats, Sprague-Dawley Rats and B6C3F1 Mice). Submitted to EPA, Washington, DC, by Dow Chemical Co., Midland, MI with Cover Letter Dated December 20, 1982. EPA Document No.878210753. Microfiche No. OTS0206139.

Robinson, B.L., D.E. Guinnup, J.E. Andrews, J.W. Allis, A. McDonald, J.C. Seely, T.J. Mohin, and J.E. Simmons. 1995. Hepatic and renal assessment of acute exposure to inhaled epichlorohydrin: Toxicological evaluation and exposure modeling. Inhal. Toxicol. 7(2):289-301.

Ruijten, M.W.M.M., R. von Doorn, and A.P. van Harreveld. 2009. Assessment of Odour Annoyance in Chemical Emergency Management. RIVM Report 609200001. National Institute for Public Health and the Environment, Bilthoven, The Netherlands [online]. Available: http://www.rivm.nl/bibliotheek/rapporten/609200001.pdf [accessed August 2, 2010]

Ruth, J.H. 1986. Odor thresholds and irritation levels of several chemical substances: A review. Am. Ind. Hyg. Assoc. J. 47(3):A142-A151.

Santodonato, J., S.S. Lande, P.H. Howard, D. Orzel, and D. Bogyo, 1980. Investigation of Selected Potential Environmental Contaminants: Epichlorohydrin and Epibromohydrin. EPA-560/11-80-006. Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC.

Schaper, M. 1993. Development of a database for sensory irritants and its use in establishing occupational exposure limits. Am. Ind. Hyg. Assoc. J. 54(9):488-544.

Schultz, V.C. 1964. Fatty liver and chronic asthma-like bronchitis after inhalation of a paint solvent (epichlorohydrin) [in German]. Dtsch. Med. Wochenschr. 89(28):1342-4344.

Shell Oil Co. 1977. Epichlorohydrin Toxicity and Safety Bulletin 6-76. Submitted to EPA, Washington, DC, by Rhone-Poulenc Inc., Cranbury, NJ with Cover Letter Dated October 27, 1992. EPA Document No. 88-920009884. Microfiche No. OTS0571537.

Shell Oil Co. 1994. Initial Submission: Letter from Shell Co. to EPA Regarding Genotoxicity Studies of Ethylene Oxide, Epichlorohydrin and 1,3-Butadiene with Attachments Dated 05/06/94. EPA Document No. 88-940000277. Microfiche No. OTS0556235.

Shumskaya, N.I., N.M. Karamzina, and M.Y. Savina. 1971. Evaluation of the sensitivity of integral and specific indices during acute epichlorohydrin poisoning [in Russian]. Tokiskol. No. Prom. Khim. Vesh. 12:33–44.

Sienel, G., R. Rieth, and K.T. Rowbottom. 2000. Epoxides. Ullmann's Encyclopedia of Industrial Chemistry [online]. Available: http://onlinelibrary.wiley.com/doi/10.1002/14356007.a09_531/abstract [accessed May 9, 2013].

Slott, V.L., J.D. Suarez, J.E. Simmons, and S.D. Perreault. 1990. Acute inhalation exposure to epichlorohydrin transiently decreases rat sperm velocity. Fundam. Appl. Toxicol. 15(3):597-606.

Smith, F.A., P.W. Langvardt, and J.D. Young. 1979. Pharmacokinetics of Epichlorohydrin Administered to Rats by Gavage or Inhalation, January 15, 1979. Submitted to EPA, Washington, DC by Dow Chemical Company, Midland, MI with Cover Letter Dated December 20, 1983. EPA Document No. 878210754. Microfiche No. OTS 0206139.

Solvay. 2011. Epichlorohydrin. Solvay Chemicals. Tavaux, France [online]. Available:

http://www.solvaychemicals.com/EN/products/chlorinated/Allylicproducts/Epichlorohydrin.aspx [accessed July 2013].

Sram, R.J., Z. Zudova, and N.P. Kuleshov. 1980. Cytogenetic analysis of peripheral lymphocytes in workers occupationally exposed to epichlorohydrin. Mutat. Res. 70(1):115-120.

Sram, R.J., M. Cerna, J. Fernandez, J. Kocisova, I. Kodytkova, J. Novakaova, P. Rossner, A. Siskova, and E. Topinkova. 1981. Mutagenic activity of inhaled epichlorohydrin in mice and rats. Mutat. Res. 85(4):287-288.

Sram, R.J., L. Landa, and I. Samkova. 1983. Effect of occupational exposure to epichlorohydrin on the frequency of chromosome aberrations in peripheral lymphocytes. Mutat. Res. 122(1):59-64.

Stott, W.T., and M.J. McKenna. 1984. The comparative absorption and excretion of chemical vapors by the upper, lower, and intact respiratory tract of rats. Fundam. Appl. Toxicol. 4(4):594-602.

ten Berge, W.F., A. Zwart, and L.M. Appelman. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Hazard. Mater. 13(3):301-309.

Tsai, S.P., S.R. Cowles, D.L. Tackett, M.T. Barclay, and C.E. Ross. 1990. Morbidity prevalence study of workers with potential exposure to epichlorohydrin. Br. J. Ind. Med. 47(6):393-399.

Tsai, S.P., E.L. Gilstrap, and C.E. Ross. 1996. Mortality study of employees with potential exposure to epichlorohydrin: A 10 year update. Occup. Environ. Med. 53(5):299304.

Venable, J.R., C.D. McClimans, R.E. Flake, and D.B. Dimick. 1980. A fertility study of male employees engaged in the manufacture of glycerine. J. Occup. Med. 22(2):87-91.

Weil, C.S., N. Condra, C. Haun, and J.A. Striegel. 1963. Experimental carcinogenicity and acute toxicity of representative epoxides. Am. Ind. Hyg. Assoc. J. 24:305-325.

Wexler, B. 1971. Determination of epichlorohydrin contamination in an industrial facility for the manufacturing of epoxy resins [in Romanian]. Mater. Plast. (Bucharest) 8:322-323.

WHO (World Health Organization). 1984. Epichlorohydrin. Environmental Health Criteria 33. Geneva: World Health Organization, Geneva. [online]. Available: http://www.inchem.org/documents/ehc/ehc/ehc33.htm [accessed Apr. 3, 2014].

ZSITC (Zhongshun Scientific Industrial and Trading Co., Ltd). 2013. Epichlorohydrin [online]. Available http://www.mpresinscn.com/ [accessed June 2013].

APPENDIX A

DERIVATION OF AEGL VALUES FOR EPICHLOROHYDRIN

Derivation of AEGL-1 Values

Key study:	Kobernick J.H., Nair, III., U.C. Pozzani, L.D. Roger, Jr., and J.S. West1983. Epichlorohydrin Repeated Inhalation, Preliminary Metabolic Studies, Revision of Acute Toxicity Data, and Human Sensory Response. Special Report 33-41. Mellon Institute, January 28, 1983. Submitted to EPA, Washington, DC, by Union Carbide Corporation, Danbury, CT with Cover Letter Dated December 9, 1983.EPA Document No. 878212138. Microfiche No. OTS0206066.
Toxicity end point:	Irritation in humans; no-effect level was 17 ppm for 2 min; exposure at 68 ppm for 2 min was associated with irritation of the pharynx, and exposure at 136 ppm for 2 min was associated with irritation to the eyes and pharynx.
Time scaling:	Not applicable
Uncertainty factors:	10 for intraspecies variability
Calculations:	
For all AEGL-1 durations:	17 ppm ÷ 10 = 1.7 ppm

Derivation of AEGL-2 Values

Data on epichlorohydrin were inadequate for deriving AEGL-2 values. Because epichlorohydrin has been shown to have a steep concentration-response curve, AEGL-2 values were estimated by dividing the AEGL-3 values by 3.

Calculations:	1/3 AEGL-3 values (30-min, 1-, 4-, and 8-h)
10-min AEGL-2:	53 ppm; set equal to the 30-min value, because reducing the 10-min AEGL-3 value by a factor of 3 yields an AEGL value of 188 ppm for a 10-min exposure. Anecdotal information provided by Lefaux (1968) suggested that concentrations

	greater than 100 ppm for short intervals might result in pulmonary edema and renal damage. Support for those effects comes from a study of rats exposed to epichlorohydrin at 150 ppm for 1 h that exhibited evidence of severe renal damage (Ito et al. 1995). Thus, the 10-min value was set equal to the 30-min value to protect against pulmonary and renal effects.
30-min AEGL-2:	160 ppm ÷ 3 = 53 ppm
60-min AEGL-2:	72 ppm ÷ 3 = 24 ppm
4-h AEGL-2:	44 ppm ÷ 3 = 14 ppm
8-h AEGL-2:	20 ppm ÷ 3 = 6.7 ppm

Derivation of AEGL-3 Values

10-min, 30-min, 1-h AEGL-3:

Key study:	Dietz, F.K., M. Grandjean, and J.T. Young. 1985. Epichlorohydrin: 1-Hour LC50 Determination in Fischer-344 Rats. Lake Jackson Research Center, Health & Environmental Sciences - Texas, Dow Chemical, Freeport, TX. .
Toxicity end point:	1-h rat LC_{01} of 721 ppm
Time scaling:	$C^n \times k = t$; n = 0.87, based on regression analysis of rat lethality data (1-, 4-, 6-, and 8-h LC_{50} values); C = 721 ppm ÷ 10 = 72.1 ppm; t = 60 min, n = 0.87 $k = 72.1^{0.87}$ ppm × 60 min = 2,480.6 ppm-min
Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability
10- min AEGL-3:	$C = (k/t)^{1/0.87} = (2{,}480.6 \text{ ppm-min} \div 10)^{1/0.87}$ C = 570
30-min AEGL-3:	$C = (k/t)^{1/0.87} = (2{,}480.6 \text{ ppm-min} \div 30)^{1/0.87}$

	C = 160
1-h AEGL-3:	721 ppm ÷ 10 = 72.1 ppm (rounded to 72 ppm)

4- and 8-h AEGL-3:

Key study:	Laskin, S., A.R. Sellakumar, M. Kuschner, N. Nelson, S. La Mendola, G.M. Rusch, G.V. Katz, N.C. Dulak, and R.E. Albert. 1980. Inhalation carcinogenicity of epichlorohydrin in noninbred Sprague-Dawley rats. J. Natl. Cancer Inst. 65(4):751-757.
Toxicity end point:	6-h rat LC_{01} of 274 ppm
Time scaling:	$C^n \times k = t$; n = 0.87; C = 274 ppm ÷ 10 = 27.4 ppm; t = 360 min $k = 27.4^{0.87}$ ppm × 360 min = 6,414.2 ppm-min
Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability
4-h AEGL-3:	$C = (k/t)^{1/0.87} = (6{,}414.2 \text{ ppm-min} \div 240 \text{ min})^{1/0.87}$ C = 44 ppm
8-h AEGL-3:	$C = (k/t)^{1/0.87} = (6{,}414.2 \text{ ppm-min} \div 480 \text{ min})^{1/0.87}$ C = 20 ppm

APPENDIX B

CARCINOGENICITY ASSESSMENT FOR EPICHLOROHYDRIN

The unit risk or q_1* for inhalation exposure to epichlorohydrin is 1.2×10^{-6} $(\mu g/m^3)^{-1}$ (EPA 1994). That value was derived from a carcinogenicity study in which rats developed nasal tumors after exposure to epichlorohydrin at 0, 10, or 30 ppm for 6 h/day, 5 days/week for a lifetime (Laskin et al. 1980). This study was summarized in Section 3.4.

Data summary: Groups of 100 male Sprague-Dawley rats were exposed to epichlorohydrin at 10 or 30 ppm for 6 h/day, 5 days/week for a lifetime. A total of 150 sham-exposed or untreated animals served as controls. One of 100 rats in the 30ppm group developed squamous cell carcinomas of the nasal cavity; none of the 10ppm or control animals developed nasal tumors.

The unit risk (q_1*) derived from the linearized multistage model is $(1.2 \times 10^{-6}$ $\mu g/m^3)^{-1}$.

The calculations for AEGL values following the method presented by NRC (1986) are presented below.

To calculate a virtually safe dose (VSD of d) at a cancer risk of 10^{-6}:

$d = 10^{-6} \div (1.2 \times 10^{-6}\ \mu g/m^3)^{-1} = 8.3 \times 10^1\ g/m^3$

To calculate the total cumulative dose for a total lifetime exposure of 70 years, which is equivalent to 25,600 days:

$$\text{total } d = d \times 25{,}600 = (8.33 \times 10^1\ \mu g/m^3) \times 25{,}600 = 2.13 \times 10^6\ \mu g/m^3.$$

Adjustment to allow for uncertainties in assessing potential cancer risks due to short-term exposure under the multistage model (Crump and Howe 1984), the total dose is divided by a factor of 6:

$$2.13 \times 10^6\ \mu g/m^3 \div 6 = 3.56 \times 10^5\ \mu g/m^3 = 3.56 \times 10^2\ mg/m^3 = 94\ ppm$$

Therefore, a 24-h exposure concentration associated with a 10^{-4} risk is 94 ppm. The 10^{-4} cancer risk associated with exposures for 10, 30, 60, 240, and 480 min can be calculated from the following equation:

$PC \times t = k$, where c = concentration, t = time, and k is a constant.

The AEGL values are compared with cancer risk-based values associated with risks of 10^{-4}, 10^{-5}, and 10^{-6} below:

Risk	10 min	30 min	1 h	4 h	8 h
AEGL values (ppm)					
AEGL-1	1.7	1.7	1.7	1.7	1.7
AEGL-2	53	53	24	14	6.7
AEGL-3	570	160	72	44	20
Cancer risk-based values (ppm)					
10^{-6}	140	45	23	5.6	2.8
10^{-5}	1,400	450	230	56	28
10^{-4}	14,000	4,500	2,300	560	280

APPENDIX C

DERIVATION OF THE LEVEL OF DISTINCT ODOR AWARENESS FOR EPICHLOROHYDRIN

The level of distinct odor awareness (LOA) represents the concentration above which it is predicted that more than one-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. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception. The LOA derivation follows the guidance given by Ruijten et al. (2009).

The odor detection threshold (OT_{50}) for epichlorohydrin is calculated from the odor threshold of 10 ppm (50% of unconditioned personnel) reported by Shell Oil Co. (1977) and adjusted by Ruijten et al. (2009):

$$10 \text{ ppm} \times 40 \text{ ppm} \div 100 \text{ ppm} = 4.0 \text{ ppm}$$

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

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

For the Fechner coefficient, the default $k_w = 2.33$ will be used because of the lack of chemical specific data.

$$3 = 2.33 \times \log (C \div 4.0) + 0.5, \text{ which can be rearranged to}$$
$$\log (C/4.0) = (3 - 0.5) \div 2.33 = 1.07, \text{ and results in } C =$$
$$(10^{1.07}) \times 4.0 = 34.4 \text{ ppm}$$

The resulting concentration is multiplied by an empirical field correction factor. It takes into account that in everyday life factors, such as sex, age, sleep, smoking, upper airway infections, and allergy, as well as distractions, may increase the odor detection threshold by a factor of 4. In addition, it takes into account that odor perception is very fast (about 5 seconds), which leads to the perception of concentration peaks. On the basis of current knowledge, a factor of 1/3 is applied to adjust for peak exposure. Adjustments for distraction and peak exposure lead to a correction factor of 4/3 = 1.33.

$$LOA = C \times 1.33 = 34.4 \text{ ppm} \times 1.33 = 46 \text{ ppm (Ruijten et al. [2009])}$$

Therefore, the LOA for epichlorohydrin is 46 ppm.

APPENDIX D

ACUTE EXPOSURE GUIDELINE LEVELS FOR EPICHLOROHYDRIN

Derivation Summary

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)	1.7 ppm (6.4 mg/m^3)

Key reference: Kobernick, J.L., J.H. Nair, III., U.C. Pozzani, L.D. Roger, Jr., and J.S. West. 1983. 1983. Epichlorohydrin Repeated Inhalation, Preliminary Metabolic Studies, Revision of Acute Toxicity Data, and Human Sensory Response. Special Report 33-41. Mellon Institute, January 28, 1983. Submitted to EPA, Washington, DC, by Union Carbide Corporation, Danbury, CT with Cover Letter Dated December 9, 1983 EPA Document No. 878212138, Microfiche No. OTS0206066.

Test species/Strain/Number: Humans

Exposure route/Concentration/Durations: Inhalation; 17, 68, or 136 ppm for 2 min.

Effects:
17 ppm: 2/4 detected odor, 0/4 experienced irritation
68 ppm: 2/4 had pharyngeal irritation; 4/4 detected odor
136 ppm: 2/4 had pharyngeal irritation and ocular irritation

End point/Concentration/Rationale: Irritation (no-effect level); none of the four subjects experienced irritation.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 1, human study
Intraspecies: 10, although irritation would likely be confined to the eyes and nasal passage (portal of entry), and variability in this response is expected to be limited to variability in pharmacodynamics, a factor of 10 was applied to provide sufficient protection for asthmatic persons.

Modifying factor: 1

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: Not applicable

Data adequacy: The subjects were exposed for only 2 min; however, the irritating properties of epichlorohydrin are not expected to vary considerably in an exposed human population.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
53 ppm (200 mg/m^3)	53 ppm (200 mg/m^3)	24 ppm (91 mg/m^3)	14 ppm (53 mg/m^3)	6.7 ppm (25 mg/m^3)

Data adequacy: The animal and human data on epichlorohydrin pertaining to nonlethal end points were not adequate.

for deriving AEGL-2 values. Therefore, AEGL-3 values were divided by a factor of 3 to estimate the AEGL-2 values. Because of the steepness of the dose-response curve, this method should provide a reasonable estimate of the values and provide an adequate margin of safety relative to lethality and adequate protection against pulmonary edema. Further, long-term studies showed that high concentrations for shorter durations are more effective than lower concentrations for longer durations; therefore, the 3-fold reduction should provide adequate protection against disabling or serious effects. The 10-min value was set equal to the 30-min AEGL-2 value because human and animal data suggested that pulmonary edema and renal damage could occur at concentrations greater than 100 ppm for short intervals.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
570 ppm (2,200 mg/m^3)	160 ppm (600 mg/m^3)	72 ppm (270 mg/m^3)	44 ppm (170 mg/m^3)	20 ppm (76 mg/m^3)

Key reference: Dietz, F.K., M. Grandjean, and J.T. Young. 1985. Epichlorohydrin: 1-Hour LC_{50} Determination in Fischer-344 Rats. Lake Jackson Research Center, Health & Environmental Sciences - Texas, Dow Chemical, Freeport, TX.	Key reference: Laskin, S., A.R. Sellakumar, M. Kuschner, N. Nelson, S. La Mendola, G.M. Rusch, G.V. Katz, N.C. Dulak, and R.E. Albert. 1980. Inhalation carcinogenicity of epichlorohydrin in noninbred Sprague‐Dawley rats. J. Natl. Cancer Inst. 65(4): 751-757.
Test species/Strain/Sex/Number: Rats; Fischer-344; males and females; 6/group.	Test species/Strain/Sex/Number: Rats; Sprague-Dawley; male; 20/group.
Exposure route/Concentration/Duration: Inhalation; 552, 1,008, 1,970, or 3,995 ppm (male and female) and 2,865 and 3,275 ppm (male only) for 1 h.	Exposure route/Concentration/Duration: Inhalation; 283, 303, 339, 369, 421, or 445 ppm for 6 h.

Effects: Weight loss (all concentrations); and nasal irritation, respiratory difficulty, and secretion of porphyrin-like material, corneal cloudiness (~1,970 ppm); central nervous system effects and cyanosis (~3,275 ppm); mortality: 0/12, 0/12, 2/12, 0/6, 0/6, 12/12, respectively.	Effects: Acute respiratory irritation; ocular pulmonary hemorrhage and edema; elevated lung:body weight at ~339 ppm; mortality: 0/20, 1/20, 1/20, 15/20, 16/20, and 17/20, respectively.
Point of departure: 1-h rat LC_{01} of ppm.	Point of departure: 6-h rat LC_{01} of 274 ppm. 721

(Continued)

AEGL-3 VALUES Continued

Uncertainty factors:

Total uncertainty factor: 10

Interspecies: 3, LC_{50} values for rats, mice, guinea pigs, and rabbits were 573-820 ppm for a 4-h exposure. Humans appear to be more sensitive than rats but are within a factor of about 2.5. A concentration of 50 ppm for 66-262 min caused squinting, hypoactivity, and salivation in animals; 20 ppm for 1 h caused burning of eyes and nose in humans. Epichlorohydrin is an epoxide and direct alkylating agent and effects are not expected to differ by more than a factor of 3.

Intraspecies: 3, the irritation and systemic toxicity caused by epichlorohydrin are likely to involve its alkylating activity. Therefore, the concentrations causing severe pulmonary irritation are not expected to vary considerably in the population. The systemic toxicity may be modulated by the detoxification enzymes, most likely epoxide hydrolase or glutathione-S-transferase. The structural similarity of epichlorohydrin to ETO suggests that metabolism involves glutathione-S-transferase, which is genetically polymorphic in human. This similarity in structure provides additional support for a factor of 3. The use of an intraspecies uncertainty factor of 3 is also supported by data on human exposures to epichlorohydrin. Use of higher total uncertainty factor of 30 would result in an 8-h AEGL-3 value of 6.6 ppm; however, occupational exposures as high as 15-54 ppm have occurred (Pet'ko et al. 1966 [cited in NIOSH 1976]; de Jong et al. 1988) and were apparently not life-threatening.

Time scaling: $C^n \times t = k$, where n = 0.87 (derived from LC_{50} data for the rat exposed for 1, 4, 6, or 8 h).

APPENDIX E

CATEGORY PLOT FOR EPICHLOROHYDRIN

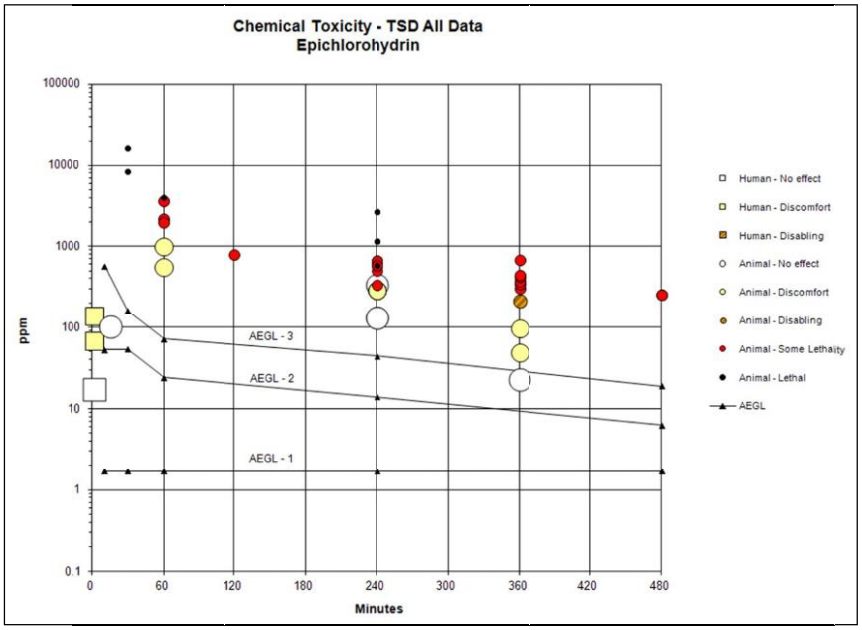

FIGURE E-1 Category plot of toxicity data and AEGL values for epichlorohydrin.

TABLE E-1 Data Used in Category Plot for Epichlorohydrin

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
AEGL-1				1.7	10	AEGL	
AEGL-1				1.7	30	AEGL	
AEGL-1				1.7	60	AEGL	
AEGL-1				1.7	240	AEGL	
AEGL-1				1.7	480	AEGL	
AEGL-2				53	10	AEGL	
AEGL-2				53	30	AEGL	
AEGL-2				24	60	AEGL	
AEGL-2				14	240	AEGL	
AEGL-2				6.7	480	AEGL	
AEGL-3				570	10	AEGL	
AEGL-3				160	30	AEGL	
AEGL-3				72	60	AEGL	
AEGL-3				44	240	AEGL	
AEGL-3				20	480	AEGL	
Kobernick et al. 1983	Human		1	17	2	0	
	Human		1	68	2	1	Throat irritation.
	Human		1	136	2	1	Ocular, throat and nasal irritation.
Berdasco and Waechter 2012	Rat	Males	1	2,165	60	SL	LC_{50}
	Rat	Females	1	3,617	60	SL	LC_{50}
	Rat		1	500	240	SL	LC_{50}
	Rat		1	250	480	SL	LC_{50}
Dietz et al. 1985	Rat	Both	1	552	60	1	
	Rat	Both	1	1,008	60	1	
	Rat	Both	1	1,970	60	SL	Mortality (2/12)
	Rat	Both	1	3,995	60	3	Mortality (12/12)

Grigorowa et al. 1974	Rat	Males	1	635	240	SL	LC_{50}
	Rat	Males	1	582	240	SL	LC_{50}
Kimmerle 1967	Rat		1	132	240	0	
	Rat		1	331	240	0	
	Rat		1	661	240	SL	Mortality (5/10), moderate irritation to mucus membranes.
	Rat		1	2,646	240	3	Mortality (10/10)
Kobernick et al. 1983	Rat	Both	1	580	240	3	Mortality (12/12)
	Rat	Both	1	580	240	SL	Mortality (15/30)
Slott et al. 1990	Rat	Both	1	1,160	240	3	Mortality (6/6)
Laskin et al. 1980	Rat	Males	1	100	240	0	
	Rat	Males	1	303	360	SL	Mortality (1/20)
	Rat	Males	1	339	360	SL	Mortality (1/20), acute respiratory irritation with hemorrhage and severe edema.
	Rat	Males	1	369	360	SL	Mortality (15/20), acute respiratory irritation with hemorrhage and severe edema.
	Rat	Males	1	421	360	SL	Mortality (16/20), acute respiratory irritation with hemorrhage and severe edema.

(Continued)

TABLE E-1 Continued

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
	Rat	Males	1	445	360	SL	Mortality (17/20), acute respiratory irritation with hemorrhage and severe edema.
Weil et al. 1963	Rat		1	250	480	SL	Mortality (4/6)
Freuder and Leake 1941	Mouse		1	8,300	30	3	100% mortality
	Mouse		1	16,600	30	3	100% mortality

Grigorowa et al. 1974	Mouse	Males	1	794	120	SL	LC_{50}
Kobernick et al. 1983	Mouse	Males	1	1,160	240	3	Irritation of mucous membranes, increased respiration, lethargy, and labored breathing.
Kimmerle 1967	Mouse	Males	1	132	240	0	
	Mouse	Males	1	331	240	0	
	Mouse	Males	1	661	240	SL	Mortality (1/20)
	Mouse	Males	1	2,646	240	3	Mortality (20/20)
Buckley et al. 1984	Mouse		1	687	360	SL	
Kobernick et al. 1983	Guinea pig	Males	1	290	240	1	Irritation of mucous membranes.
	Guinea pig	Males	1	580	240	SL	Mortality (2/6), irritation of mucous membranes.
	Guinea pig	Males	1	1,160	240	3	Mortality (4/4)
Kimmerle 1967	Guinea pig	Males	1	132	240	0	
	Guinea pig	Males	1	331	240	SL	Mortality (4/5)
	Guinea pig	Males	1	661	240	SL	Mortality (4/5)
	Guinea pig	Males	1	2,646	240	3	Mortality (5/5)
Kobernick et al. 1983	Rabbit	Males	1	290	240	1	Irritation of mucous membranes.
	Rabbit	Males	1	580	240	SL	Mortality (2/3), irritation of mucous membranes.
	Rabbit	Males	1	1,160	240	3	Mortality (3/3)
Kobernick et al. 1983	Dog		1	290	240	1	Irritation of mucous membranes.
	Dog		1	580	240	3	Mortality (1/1)
	Dog		1	1,160	240	3	Mortality (1/1)
	Monkey		1	290	240	1	Irritation of mucous membranes.
Industrial Bio-Test Laboratories 1977a	Rat	Both	1	9.7	360	0	
	Rat	Both	1	23	360	0	
	Rat	Both	1	48.8	360	1	

	Rat	Both	1	97.3	360	1
	Rat	Both	1	209.8	360	2
Gardner et al. 1985	Rat		1	101	15	0

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