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

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

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

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

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

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

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

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

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

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

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

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

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

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

REVIEW OF AEGL REPORTS

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

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

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

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

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

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Appendixes

5

Ethylene Chlorohydrin[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

[4] This document was prepared by the AEGL Development Team composed of Robert Young (Oak Ridge National Laboratory), Heather Carlson-Lynch (SRC, Inc.), Julie Klotzbach (SRC, Inc.), Chemical Manager George Rusch (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).

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 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

Ethylene chlorohydrin is used in the manufacture of pesticides, plasticizers, plant-protection agents, and dye intermediates. It is generally manufactured with a purity of greater than 99% with some being produced as an anhydrous grade. It is also used as a precursor in the production of ethylene oxide. An odor threshold of 0.4 ppm has been reported for ethylene chlorohydrin but data are not available from which to determine an acute level of odor awareness.

Data on ethylene chlorohydrin were insufficient for deriving AEGL-1 values. There were neither human nor animal data on AEGL-1 severity effects following exposure to ethylene chlorohydrin vapor.

Data on AEGL-2 severity effects in humans were not available. Because animal data involved either no lethality or 100% lethality, the concentrationresponse relationship for ethylene chlorohydrin vapor exposure is unknown. No data pertaining to AEGL-2 effects were available. Data in mice (Goldblatt 1944) showed there to be less than a four-fold difference between the concentration associated with a nonlethal response (280 ppm for 120 min) and the concentration producing 100% lethality (1,090 ppm for 120 min), which suggests a steep exposure-response relationship. In accordance with NRC (2001) guidance,

the AEGL-2 values were estimated as a three-fold reduction of the AEGL-3 values.

The point-of-departure for deriving AEGL-3 values was 280 ppm for 120 min, which was the concentration that did not produce lethality in mice (Goldblatt 1944). Values were scaled across time using the equation $C^n \times t = k$. Default values for n of 3 for extrapolating to shorter durations and 1 when extrapolating to longer durations were used to derive values protective of human health (NRC 2001). Two uncertainty factors of 10 were applied; one to account for interspecies differences and one to account for intraspecies variability. Ethylene chlorohydrin does not appear to be a direct-contact irritant and death in animals does not appear to be a function of damaged epithelial tissue of the respiratory tract; however, the available data are not sufficient to conclusively describe the mechanism of toxicity.

The AEGL values for ethylene chlorohydrin are presented in Table 5-1.

1. INTRODUCTION

Ethylene chlorohydrin may be used in the manufacture of pesticides, plasticizers, plant-protection agents, and dye intermediates (HSDB 2005). It is generally manufactured with a purity greater than 99% with some being produced as an anhydrous grade. It is a precursor in the production of ethylene oxide. Production volumes of $1.6\text{-}2.0 \times 10^7$ kg have been reported (HSDB 2005).

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

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Goldblatt and Chiesman (1944) described two cases originally reported by Koelsch (1927) involving acute exposure to ethylene chlorohydrin. In one case, a worker was exposed to ethylene chlorohydrin while cleaning a machine with a rag soaked in the chemical (dermal and inhalation exposure) for 2.5 h. Exposure concentrations were not measured and there was no report of the use of protective equipment. He became nauseous and vomited and experienced a violent headache and giddiness. He died the next day, and autopsy showed inflammatory detachment of mucous membranes in the respiratory passages and pulmonitis of the right lung. The other case concerned one of four men involved in staining oil-cloth with dye mixed with ethylene chlorohydrin. Exposure concentrations were not measured and there was no report of the use of protective equipment. The man experienced nausea and narcosis and stopped working. The duration of exposure

was not specified. He died in the evening after suffering from dyspnea, and autopsy showed cerebral and pulmonary edema, acute gastrointestinal catarrh, renal degeneration, disease of the cardiac valves and aorta, and arterial calcification.

TABLE 5-1 AEGL Values for Ethylene Chlorohydrin

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Insufficient data.
AEGL-2 (disabling)	2.1 ppm (6.9 mg/m^3)	1.5 ppm (4.9 mg/m^3)	1.2 ppm (3.9 mg/m^3)	0.47 ppm (1.5 mg/m^3)	0.23 ppm (0.76 mg/m^3)	One-third of the AEGL-3 values (NRC 2001).
AEGL-3 (lethal)	6.4 ppm (21 mg/m^3)	4.4 ppm (14 mg/m^3)	3.5 ppm (12 mg/m^3)	1.4 ppm (4.6 mg/m^3)	0.70 ppm (2.3 mg/m^3)	Nonlethal exposure of mice at 280 ppm for 120 min (Goldblatt 1944).

[a] Not recommended. Absence of an AEGL-1 value does not imply that exposures at concentrations below the AEGL-2 value are without effect.

TABLE 5-2 Chemical and Physical Data for Ethylene Chlorohydrin

Parameter	Value	Reference
Synonyms	2-chloroethanol; 2-chloro ethyl alcohol	HSDB 2005
CAS registry no.	107-07-3	HSDB 2005
Chemical formula	C_2H_5ClO	HSDB 2005
Molecular weight	80.52	HSDB 2005
Physical state	Liquid	HSDB 2005
Melting point	-67°C	HSDB 2005
Boiling point	128-130°C	HSDB 2005
Density/specific gravity	1.197 at 20°C	HSDB 2005
Solubility in water	1×10^6 mg/L	HSDB 2005
Relative vapor density	2.78	HSDB 2005
Vapor pressure	4.9 mm Hg at 20°C	HSDB 2005
Saturated vapor concentration	645 ppm	Calculated according to Perez and Solderholm (1991)
Conversion factors in air	1 ppm = 3.29 mg/m^3 1 mg/m^3 = 0.30 ppm	NIOSH 2011

Goldblatt and Chiesman (1944) also reported a fatality following exposure to ethylene chlorohydrin vapor. In one case, a worker became ill after exposure for about 1.5 h to vapors of ethylene chlorohydrin and ethylene dichloride while performing maintenance in an ethylene chlorohydrin tower. Exposure concentrations were not measured and there was no report of the use of protective equipment. He experienced repeated vomiting 1 h after the exposure, unsteadiness at 2 h, weak pulse and restlessness at 4 h, and low blood pressure and rales between 4 and 11.5 h after exposure. He deteriorated rapidly and died 14 h after exposure. Autopsy showed congestion of the tracheal mucous membranes, marked and extensive collapse of the lungs, pulmonary edema, and cerebral congestion.

Dierker and Brown (1944) reported a fatal case in which a man was exposed for 2 h to ethylene chlorohydrin and petroleum solvents during a cleaning operation. The worker wore rubber gloves to prevent dermal contact, but was exposed to solvent vapors by inhalation. He experienced nausea and vertigo and was later sent to a hospital for treatment. He was cyanotic with labored breathing and a slightly irregular pulse and died from respiratory failure that night. Autopsy showed congested lungs and kidneys, edema of the liver, and cloudy swelling of the renal tubules. Post-exposure estimates of the concentration of petroleum solvents and ethylene chlorohydrin were determined by resuming the cleaning operation and measuring the exposure concentration at the breathing level. The petroleum solvent concentration was 150-400 ppm and the average ethylene chlorohydrin concentration was estimated to be 305 ppm.

Agricultural exposure to ethylene chlorohydrin during treatment of seed potatoes to enhance germination resulted in one death (Bush et al. 1949). The inhalation exposure concentration estimated by field and laboratory tests was 300-500 ppm. Dermal contact also occurred during the treatment process. The use of protective equipment was not reported. The worker experienced nausea, vomiting, dizziness, abdominal pain, weakness, and diminished vision after working several hours. He eventually returned to work, but collapsed several hours later and was transported to a hospital in a comatose condition where he died that night. Autopsy findings revealed fatty infiltration of the liver, edema of the brain and lungs, dilation of the heart chambers, degeneration of the myocardium, congestion of the spleen, cloudy swelling and hyperemia of the kidneys, petechial hemorrhages of the skin and conjunctiva, ascites, and hydrothorax.

2.2. Nonlethal Toxicity

An odor threshold for ethylene chlorohydrin of 0.4 ppm has been reported (ACGIH 2001).

Several nonfatal case reports of exposure to ethylene chlorohydrin vapor were summarized by Goldblatt and Chiesman (1944). These cases occurred during

a time period where the average exposure concentration was 18 ppm. There was also likely concurrent exposure to ethylene dichloride. The exposure duration was not specified and the use of protective equipment was not reported. A qualitative summary of signs and symptoms by organ system was provided: digestive system (nausea, epigastric pain, and vomiting); cardiovascular system (shock and depressed circulation); nervous system (headache, giddiness, incoordination, confusion, and mild narcotic effects); respiratory system (cough and rhonchi); and skin (erythema on arms and trunk in severe cases).

In addition to the fatality described in Section 2.1, Bush et al. (1949) also reported nonlethal toxicity in five agricultural workers exposed intermittently to ethylene chlorohydrin at 300-500 ppm (estimated by field and laboratory tests). The exposure duration was not specified and the use of protective equipment was not reported. The workers experienced nausea, vomiting, irritation of the eyes, nose, and lungs, dizziness, diminished vision, and numbness of the hands and fingers. Four workers required hospitalization for treatment of symptoms.

2.3. Developmental and Reproductive Effects

Data on the developmental and reproductive toxicity of ethylene chlorohydrin in humans were not available.

2.4. Genotoxicity

No information regarding the genotoxicity of ethylene chlorohydrin in humans was available.

2.5. Carcinogenicity

Greenberg et al. (1990) reported an increased risk of mortality from pancreatic cancer and leukemia in workers at a Union Carbide plant in which ethylene chlorohydrin was manufactured. In a 10-year follow-up of 278 male workers at the plant, Benson and Teta (1993) reported excess deaths from pancreatic cancer (8 observed vs. 1.6 expected, SMR = 492 with 95% confidence interval of 158-1,140) and lymphopoietic and hematopoietic cancers (8 observed vs. 2.7 expected; SMR = 294 with 95% confidence interval of 127-580). Olsen et al. (1997) found no increased risk for these cancers in workers at Dow Chemical facilities.

2.6. Summary

Human data with which to develop AEGL values are not available. Only qualitative information is available regarding the inhalation toxicity of ethylene chlorohydrin in humans. The available reports lack details about exposure and involved concurrent exposure to other chemicals. Case reports failed to provide definitive information regarding target organs or cause of death.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Ambrose (1950) describe experiments in which groups of five adult male rats (strain not specified) were exposed using various exposure regimens and various dilutions of the test material. Various dilutions of ethylene chlorohydrin were placed in a bubbling tower immersed in a 40°C water bath. Air was passed through the tower and into the exposure chamber (neither air temperature nor air flow were specified, but air flow was noted as never exceeding 570 mL/min). No indication (other than the air flow value) was given that the possibility of aerosolization of the test material was considered. The inhalation exposure concentrations associated with specific dilutions of ethylene chlorohydrin in water were not measured or estimated (whether vapor phase, aerosol, or mixed) in the study report. On the basis of the experimental results, the investigators noted that ethylene chlorohydrin was extremely toxic but deaths were delayed from 124 h, depending on the concentration of the chemical in aqueous solution. The inhalation exposure concentrations associated with specific dilutions of ethylene chlorohydrin in water were not measured or estimated. Ambrose (1950) concluded that a 1-h exposure to ethylene chlorohydrin at 7.5 ppm and repeated exposure at 2 ppm was lethal to rats; however, the study did not describe the source of these air concentration values. In addition, the report did not specify the incidence of lethality at each concentration. Qualitatively, rats exhibited no signs of toxicity prior to ethylene chlorohydrin-induced lethality. Necropsy findings included cyanosis, dark blood, and "darker than normal" liver and kidneys. The reporting limitations associated with this study (lack of measured or estimated exposure concentrations, lack of lethality data) preclude the use of these data in deriving AEGL values.

Goldblatt (1944) reported results of single exposure experiments in young adult rats (three animal per, strain and sex not specified) exposed to ethylene chlorohydrin vapor. The exposure apparatus consisted of a gas meter, flow meter, constant dropping apparatus, a suction system, and chambers for vaporization, mixing, and exposure. Air flow was maintained at 8-10 L/min and dropping of the test article was precisely controlled. Although no analytic data were provided, the

investigator noted that the vapor concentration could be calculated within reasonable limits for any air flow or test article drop rate. It was stated that the ethylene chlorohydrin was pure but no data were provided. A 15-min exposure at 0.003 g/L (840 ppm, based on the conversion factor of 0.001 g/L = 280 ppm, v/v, reported by Goldblatt [1944]) and a 120-min exposure at 0.001 g/L (280 ppm) were not lethal whereas a 30-min exposure at 0.004 g/L (1,120 ppm) and 60-min exposure at 0.003 g/L (840 ppm) killed all three rats within 1 day (see Table 5-3). Narcosis was not produced and most exposure-related deaths occurred following the exposure rather than during the exposure. Histologic examinations revealed renal damage (medullary hemorrhage, hemolysis, and swollen and detached convoluted tubules) and areas of collapse in the lungs, but no pulmonary hemorrhage or edema.

Goldblatt (1944) also described a repeated-exposure experiment in which three rats (strain and sex not specified) were exposed for 15 min/day to ethylene chlorohydrin at 0.002-0.005 g/L (about 560-1,400 ppm/day) for 11 days. One rat died on day 3, another on day 6, and a third on day 11. Observed signs included weight loss and lethargy. Urinalysis revealed no signs of renal toxicity although histologic examination of dead rats showed renal “congestion” and hemorrhage and hepatic congestion.

A 4-h LC_{50} (lethal concentration, 50% lethality) value of 32 ppm for rats was reported in a review by Browning (1965).

3.1.2. Mice

Dierker and Brown (1944) exposed six mice (sex not reported) to ethylene chlorohydrin at 365 ppm for 120 min. The atmosphere was maintained by evaporating anhydrous ethylene chlorohydrin in an air stream through the exposure chamber. The animals became ill in less than 1 h. One mouse died 4 h after exposure from a respiratory-related cause. Examination showed pulmonary edema, capillary engorgement, and interstitial hemorrhages in the liver, kidney, and lungs.

Goldblatt (1944) also reported lethality data for groups of three adult mice (strain and sex not specified) following single 15- to 120-min exposures to ethylene chlorohydrin (see Table 5-4). Experimental protocols were the same as those as described for rats in Section 3.1.1.

TABLE 5-3 Lethality in Rats Following Single Exposure to Ethylene Chlorohydrin

Concentration[a]	Duration (min)	Effect
0.003 g/L (840 ppm)	15	Nonlethal
0.004 g/L (1,120 ppm)	30	3/3 dead next day
0.003 g/L (840 ppm)	60	Lethal next day
0.001 g/L (280 ppm)	120	Nonlethal

[a] Three rats/group. Conversion of g/L to ppm based on 0.001 g/L = 280 ppm.
Source: Adapted from Goldblatt 1944.

TABLE 5-4 Lethality in Mice Following Single Exposure to Ethylene Chlorohydrin

Concentration[a]	Duration (min)	Effect
0.001 g/L (280 ppm)	120	Nonlethal
0.003 g/L (840 ppm)	60	3/3 dead next day
0.0032 g/L (896 ppm)	60	3/3 dead next day
0.0039 g/L (1,090 ppm)	15	2/3 dead after 2 days

0.0039 g/L (1,090 ppm)	120	3/3 dead in 140-170 min
0.0045 g/L (1,260 ppm)	30	3/3 dead next day
0.0052 g/L (1,460 ppm)	60	3/3 dead in 100 min to next day
0.007 g/L (1,960 ppm)	120	3/3 dead in 110-129 min

[a] Three mice/group. Conversion of g/L to ppm based on 0.001 g/L = 280 ppm.
Source: Adapted from Goldblatt 1944.

Acute Exposure Guideline Levels

In a toxicity study by Lawrence et al. (1971), duplicate groups of five male Swiss-Webster mice were exposed at various non-specified concentrations of ethylene chlorohydrin (99% pure) for 10-15 min. An LT_{50} (duration resulting in 50% lethality) of 13.3 min reported, but the data were insufficient for calculating an LC_{50}. Although the vapor concentration was not stated, the actual concentration in the chamber was not constant and that equilibrium was likely occurring after 14 min. The data, which appeared to be from five exposure concentrations over the previously noted 10-15 min durations, were insufficient as a basis for any exposure-response estimate.

3.1.3. Guinea Pigs

Lethality data for guinea pigs were reported by Goldblatt (1944) and are summarized in Table 5-5. Although the investigator suggested guinea pigs were less sensitive to the lethal effects of ethylene chlorohydrin, the data are for only one animal per exposure group.

3.1.4. Summary of Animal Lethality Data

In studies of laboratory animals exposed to ethylene chlorohydrin, lethality generally did not occur during exposure but was delayed from approximately 2 h to 1 day postexposure. Both interspecies and intraspecies variability in lethal response is evident, but the guinea pig data are based on a study that used only one animal per concentration.

3.2. Nonlethal Toxicity

3.2.1. Rats

A 1-h exposure to ethylene chlorohydrin at 4 ppm was not lethal to rats (Ambrose 1950). Goldblatt (1944) reported that a single 15-min exposure of rats

(sex and strain not specified) to ethylene chlorohydrin at 0.003 g/L (about 840 ppm) was not lethal. Exposed rats exhibited discomfort, closure of the eyes, and nasal irritation, but it was unclear whether the effects were observed in all of the rats or just those more severely affected.

TABLE 5-5 Lethality in Guinea Pigs Following Single Exposure to Ethylene Chlorohydrin

Concentration[a]	Exposure Duration (min)	Effect
0.003 g/L (840 ppm)	30	Nonlethal
0.003 g/L (840 ppm)	120	Dead next day
0.0039 g/L (1,090 ppm)	108	Dead next day
0.005 g/L (1,400 ppm)	55	Nonlethal

[a] One guinea pig/group. Conversion pf g/L to ppm based on 0.001 g/L = 280 ppm. Source: Adapted from Goldblatt 1944.

3.2.2. Mice

A 120-min exposure of mice (sex and strain not specified) to ethylene chlorohydrin at 0.001 g/L (about 280 ppm) was not lethal (Goldblatt, 1944).

In the experiment by Dierker and Brown (1944), five of six mice survived a 120-min exposure to ethylene chlorohydrin at 365 ppm. The animals became ill less than an hour into the exposure, and displayed increased respiratory rates and minimal activity. Labored respiration was observed 4 h postexposure, and improvement was observed 6-h postexposure. The mice were reported to be normal 24 h after exposure and did not develop any untoward symptoms during a 1-week postexposure observation period.

3.2.3. Guinea Pigs

A single 30-min exposure to ethylene chlorohydrin at 0.003 g/L (about 840 ppm) or a 55-min exposure at 0.005 g/L (about 1,400 ppm) was not lethal to guinea pigs (one animal/exposure) (Goldblatt 1944).

3.2.4. Cats

Goldblatt (1944) reported that cats (number, sex, and breed were not specified) exposed to ethylene chlorohydrin at concentrations of 10-15 mg/L (2,8004,200 ppm) for several hours showed no effects on blood pressure and no signs of respiratory disturbances regardless of whether the exposure was via a tracheal cannula or through the nasal passages.

3.2.5. Rabbits

Goldblatt (1944) reported that rabbits (number, sex, and breed not specified) exposed to ethylene chlorohydrin at concentrations of 10-15 mg/L (2,8004,200 ppm) for several hours showed no effects on blood pressure and no signs of respiratory disturbances regardless of whether the exposure was via a tracheal cannula or through the nasal passages.

3.2.6. Summary of Nonlethal Toxicity in Animals

Available data do not precisely characterize the concentration-response relationship for nonlethal effects of exposure to ethylene chlorohydrin vapor. Most studies were lethality assays and, although identifying some exposures as nonlethal, do not provide detailed information on the nature or severity of the effects (if any) that occurred. Generally, the exposure-response relationship is poorly defined.

3.3. Developmental and Reproductive Effects

No information is available regarding the developmental and reproductive toxicity of ethylene chlorohydrin in animals following inhalation exposure. Results of intravenous studies in CD-1 mice showed that ethylene chlorohydrin increased the incidence of malformed fetuses only at a dose that was associated with an increased maternal mortality (NTP 1983a). Studies in New Zealand white rabbits also intravenously exposed to ethylene chlorohydrin failed to demonstrate fetotoxic or teratogenic effects (NTP 1983b).

3.4. Genotoxicity

NTP (1985) reported that ethylene chlorohydrin was mutagenic in *Salmonella typhimurium* strains TA100 and TA1535 with and without Aroclorinduced hamster or rat liver S9. Ethylene chlorohydrin was not mutagenic in strains TA1537 or TA98 and did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster*. Overall, the compound is considered a weak base-pair substitution mutagen in bacteria. It is essentially negative in other test systems such as fungi, *D. melanogaster*, mammalian cell cultures, and rodents.

3.5. Carcinogenicity

Information regarding the carcinogenicity of ethylene chlorohydrin following inhalation exposure is not available. In dermal studies with rats and mice, NTP (1985) concluded that increases in incidences of lymphomas or leukemias, as well as increased incidences in alveolar/bronchiolar adenomas and carcinomas, were not treatment related.

3.6 Summary

Lethality generally did not occur during inhalation exposure to ethylene chlorohydrin but rather was delayed from approximately 2 h to 1 day after exposure. Nonlethal effects were not well characterized and information was generally not available to describe the nature or severity of the effects. No information is available regarding the developmental and reproductive toxicity or carcinogenicity of ethylene chlorohydrin in animals following inhalation exposure. The chemical is considered a weak base-pair substitution mutagen in bacteria, but is essentially negative in other test systems such as fungi, *D. melanogaster*, mammalian cell cultures, and rodents.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

There is no information on the metabolism and disposition of ethylene chlorohydrin following inhalation exposure. In Wistar rats, up to 80% of an orally administered radiolabeled dose was excreted in the urine although none of the radioactivity represented the parent compound (Grunow and Altmann 1982). Radioactivity in the blood declined by 50% after 4 h. The major urinary metabolites were thiodiacetic acid and thionyldiacetic acid. Radio-labeled carbon dioxide was also detected in expired air, indicating that carbon dioxide is a metabolite of ethylene chlorohydrin. Johnson (1965) hypothesized that ethylene chlorohydrin toxicity may, in part, be a function of increased chloroacetaldehyde resulting from saturation of glutathione conjugation. Results of in vitro and in vivo metabolism studies showed formation of S-carboxymethyl-GSH in livers of rats given ethylene chlorohydrin (Johnson 1967).

4.2. Mechanism of Toxicity

The precise mode of action of ethylene chlorohydrin is not known. Goldblatt and Chiesman (1944) noted the delay between exposure and onset of symptoms in humans, suggesting the absence of warning properties of exposure. Bush et al. (1949) reported autopsy findings of severe liver and brain damage as well as involvement of other organs in an occupational accident. Signs and symptoms in nonfatal exposures suggested multi-organ involvement including gastrointestinal disorders, nervous system effects, and respiratory tract irritation. In animals, Goldblatt (1944) stated that although inhalation exposure to ethylene chlorohydrin appeared to have a depressant effect on the central nervous system and would induce immobility, a typical narcosis was not observed. Additionally, necropsy results from the Goldblatt (1944) experiments did not reveal significant evidence of respiratory-tract tissue damage but did suggest renal involvement. Goldblatt (1944) reported that inhalation exposure of rats (chamber exposure or via a tracheal cannula) produced neither respiratory disturbances nor effects on blood pressure.

4.3. Structure-Activity Relationships

There are no structure activity data from which to develop AEGL values for ethylene chlorohydrin. It has been hypothesized that chloroacetaldehyde is a metabolite of ethylene chlorohydrin (Johnson 1965). AEGL values for ethylene chlorohydrin and chloroacetaldehyde vary by less than two-fold; 10- and 30-min values for ethylene chlorohydrin are somewhat lower than those for

chloroacetaldehyde while the 1-, 4-, and 8-h values for ethylene chlorohydrin values are slightly higher.

4.4. Species Variability

Data are insufficient to accurately assess species variability in the toxic response to inhalation exposure to ethylene chlorohydrin. Goldblatt and Chiesman (1944) suggested that women may be somewhat more liable to develop symptoms than men on the basis of case reports.

4.5. Concurrent Exposure Issues

There are no concurrent exposure issues unique to ethylene chlorohydrin that would be instrumental in developing the AEGL values.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Studies in humans show that nonlethal exposure to ethylene chlorohydrin causes several effects which exceed the definition of both AEGL- 1 and AEGL2 effects, including vomiting, dizziness, diminished vision, shock, depressed circulation, incoordination, confusion, and mild narcotic effects (Goldblatt and Chiesman 1944; Bush et al. 1949). These studies also either include concomitant exposure to other chemicals or do not provide adequate exposure information. Therefore, data in humans are not suitable for derivation of AEGL-1 values.

5.2. Animal Data Relevant to AEGL-1

Studies in animals either identify effects which exceed the AEGL-1 definition or do not identify any effects. Goldblatt (1944) reported signs of discomfort, eye closure, and nasal irritation in rats exposed to ethylene chlorohydrin at 840 ppm for 2 h; however, since eye closure is an AEGL-2 effect, the data are not suitable for derivation of AEGL-1 values. Minimal activity, an AEGL-2 level effect, was reported in mice exposed to ethylene chlorohydrin at 365 ppm for 2 h (Dierker and Brown 1944). Exposure of mice (280 ppm for 2 h), guinea pigs (840 for 30 min or 1,400 ppm for 55 min), cats (2,800-4,200 ppm for "several hours"), and rabbits (2,800-4,200 ppm for "several hours") did not produce adverse effects. Thus, no data are available to define the concentration-response relationship for AEGL-1 effects.

5.3. Derivation of AEGL-1 Values

There are no exposure-response data consistent with AEGL-1 severity effects and estimation of exposures consistent with such minor responses is not possible. Thus, AEGL-1 values are not recommended.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

There are no quantitative human data with which to develop AEGL-2 values for ethylene chlorohydrin. Although nonlethal exposures reportedly resulted in a wide range of effects (Goldblatt and Chiesman 1944; Bush et al. 1949), reliable exposure concentration and duration estimates are lacking.

6.2. Animal Data Relevant to AEGL-2

Animal data appropriate for AEGL-2 derivation are deficient in characterization of the nonlethal effects and do not characterize an exposure-response relationship.

6.3. Derivation of AEGL-2 Values

Exposure-response data for toxic effects consistent with AEGL-2 severity are lacking for ethylene chlorohydrin. Case reports in humans lack adequate exposure descriptions and animal toxicity data focus on lethal response, with most experimental results showing near 100% lethality. In experiments with less than 100% lethality, no information is provided about nonlethal effects.

Following the guidelines in NRC (2001), AEGL-2 values for ethylene chlorohydrin were estimated as one-third of the AEGL-3 values. Data in mice (Goldblatt 1944) showed there to be a less than four-fold difference between a nonlethal response (280 ppm for 120 min) and 100% lethality (1,090 ppm for 120 min), which implies a steep exposure-response relationship. The AEGL-2 values for ethylene chlorohydrin are presented in Table 5-6.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

Reports of human deaths following occupational exposure accidents lack adequate description of the exposures. Estimated exposures of 300 ppm for approximately 2 h and at 500 ppm (unknown duration) were reportedly lethal.

7.2. Animal Data Relevant to AEGL-3

Exposures to ethylene chlorohydrin as low as 1,120 ppm for 30 min (rats) and 1,260 ppm for 30 min (mice) caused 100% lethality (Goldblatt 1944). Results from this study also showed that exposing rats at 840 ppm for 15 min or mice at 280 ppm for 120 min was not lethal. The study was compromised by the small number of animals used (three per group). Although the animal data do not precisely describe the exposure-response relationship for inhalation exposure to ethylene chlorohydrin vapor, the data do differentiate between nonlethal and lethal exposures. Although Ambrose (1950) reported lethality and nonlethal observations, analytic concentrations were not provided and the details of the experiments were insufficient to justify use of the data in deriving AEGL-3 values.

TABLE 5-6 AEGL-2 Values for Ethylene Chlorohydrin

10 min	30 min	1 h	4 h	8 h
2.1 ppm (6.9 mg/m^3)	1.5 ppm (4.9 mg/m^3)	1.2 ppm (3.9 mg/m^3)	0.47 ppm (1.5 mg/m^3)	0.23 ppm (0.76 mg/m^3)

7.3. Derivation of AEGL-3 Values

No data are available with which to definitively assess the exposureresponse relationship for lethality resulting from inhalation exposure to ethylene chlorohydrin. Experiments in animals are compromised by the small numbers of animals tested and by response data showing near 100% lethality or no lethality. Such data do not allow for a valid estimation of a lethality threshold using benchmark dose methods. Therefore, exposure data from the Goldblatt (1944) study showing no lethality were considered were used to estimate a lethality threshold for AEGL-3 development. Data from studies of mice provided both a nonlethal (280 ppm) and 100% lethal (1,090 ppm) estimate for the same exposure duration (120 min) and, therefore, were considered most appropriate for determining a point-of-departure for AEGL-3 derivation.

The exposure concentration-exposure duration relationship for many irritant and systemically acting 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). Data on ethylene chlorohydrin were inadequate to calculate an empirical value of n, so default values of n =3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations were used.

Two uncertainty factors of 10 were applied; one to account for interspecies differences and one to account for intraspecies variability. Ethylene chlorohydrin does not appear to be a direct-contact irritant and death in animals does not appear to be a function of damaged respiratory tract epithelial tissue; however, the available data are not sufficient to conclusively describe a mechanism of toxicity.

The resulting AEGL-3 values are presented in Table 5-7 and their derivation summarized in Appendix A. A comparison of the AEGL-3 values with the human lethality estimate (300 ppm for 2 h) reported by Dierker and Brown (1944) shows that the AEGL-3 values are sufficiently protective (protection of sensitive populations would necessitate an order of magnitude reduction of the 300 ppm exposure to 30 ppm) and serves to justify the interspecies uncertainty factor.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

Data were not available for developing AEGL-1 values for ethylene chlorohydrin. In lieu of AEGL-2 specific data, the AEGL-2 values were estimated as one-third of the AEGL-3 values (NRC 2001). For lethal exposures, deaths occurred both during and up to a day following exposure. Animals exhibited a wide range of effects during exposure, including eye closure, nasal irritation, labored respiration, and decreased activity. Signs and toxicity and limited necropsy findings suggested multiple organ and system involvement (cyanosis, dark blood, renal medullary hemorrhage, hemolysis, detached convoluted tubules, areas of collapse in the lungs, pulmonary congestion, and pulmonary edema) with no definitive mode of action being described. Derivation of the AEGL-3 values was based on a nonlethal exposure of rats as an estimate of a lethal threshold; there was very little margin between exposures causing no lethality and those causing 100% lethality. AEGL values for ethylene chlorohydrin are presented in Table 5-8.

8.2. Other Standards and Guidelines

A summary of available standards and guidelines for ethylene chlorohydrin is presented in Table 5-9. The National Institute of Occupational Safety and Health (NIOSH) recommended exposure limit and the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit have ceiling notations indicating that 1 ppm should not be exceeded at any time. The German maximum concentration and the Dutch maximum allowable concentration are also set at 1ppm, but there is no ceiling notation. The Occupational Safety and Health Administration (OSHA) has a permissible exposure limit of 5 ppm for ethylene chlorohydrin. All of the standards for the chemical have a skin notation recognizing the potential for toxicity from dermal absorption. The NIOSH immediately dangerous to life or health (IDLH) value was set at 7 ppm on the basis of acute inhalation toxicity data in animals (Patty 1963; Browning 1965). The AEGL values are consistent with current standards and guidelines and protective of human health. The AEGL-2 value for 30 min is comparable but less

than the IDLH value, as would be expected from the differences in the target populations. At exposures higher than the AEGL-2, individuals could experience impaired ability to escape or long-lasting health effects.

TABLE 5-7 AEGL-3 Values for Ethylene Chlorohydrin

10 min	30 min	1 h	4 h	8 h
6.4 ppm (21 mg/m^3)	4.4 ppm (14 mg/m^3)	3.5 ppm (12 mg/m^3)	1.4 ppm (4.6 mg/m^3)	0.70 ppm (2.3 mg/m^3)

TABLE 5-8 AEGL Values for Ethylene Chlorohydrin

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2 (disabling)	2.1 ppm (6.9 mg/m^3)	1.5 ppm (4.9 mg/m^3)	1.2 ppm (3.9 mg/m^3)	0.47 ppm (1.5 mg/m^3)	0.23 ppm (0.76 mg/m^3)
AEGL-3 (lethal)	6.4 ppm (21 mg/m^3)	4.4 ppm (14 mg/m^3)	3.5 ppm (12 mg/m^3)	1.4 ppm (4.6 mg/m^3)	0.70 ppm (2.3 mg/m^3)

[a] Not recommended. Absence of AEGL-1 values does not imply that exposures at concentrations below the AEGL-2 values are without effect.

TABLE 5-9 Standards and Guidelines for Ethylene Chlorohydrin

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	2.1 ppm (6.9 mg/m^3	1.5 ppm (4.9 mg/m^3)	1.2 ppm (3.9 mg/m^3)	0.47 ppm (1.5 mg/m^3)	0.23 ppm (0.76 mg/m^3)
AEGL-3	6.4 ppm (21 mg/m^3)	4.4 ppm (14 mg/m^3)	3.5 ppm (12 mg/m^3)	1.4 ppm (4.6 mg/m^3)	0.70 ppm (2.3 mg/m^3)
IDLH (NIOSH)[a]	–	7 ppm (23 mg/m^3)	–	–	–
PEL-TWA (OSHA)[b]	–	–	–	–	5 ppm (16 mg/m^3)
TLV-C (ACGIH)[c]	1 ppm (3.3 mg/m^3)	1 ppm (3.3 mg/m^3)	1 ppm (3.3 mg/m^3)	1 ppm (3.3 mg/m^3)	1 ppm (3.3 mg/m^3)

REL-C (NIOSH)[d]	1 ppm (3.3 mg/m^3)	1 ppm (3.3 mg/m^3)	1 ppm (3.3 mg/m^3)	1 ppm (3.3 mg/m^3)	1 ppm (3.3 mg/m^3)
MAK (Germany)[e]	–	–	–	–	1 ppm (3.3 mg/m^3)
MAC (the Netherlands)[f]	–	–	–	–	1.0 ppm (3 mg/m^3)

[a] 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.

[b] PEL-TWA (permissible exposure limit – time-weighted average, Occupational Health and Safety Administration) (29 CFR 1910.1000 [2013]) is defined as an employee's exposure to any substance that shall not exceed the 8-h TWA given for that substance in any 8-h work shift of a 40-h work week. The PEL for ethylene chlorohydrin includes a skin notation.

[c] TLV-C (threshold limit value – ceiling, American Conference of Governmental Industrial Hygienists) (ACGIH 2001, 2012) is the concentration that should not be exceeded at any time. The TLV-ceiling for ethylene chlorohydrin includes a skin notation.

[d] REL-C (recommended exposure limit – ceiling, National Institute for Occupational Safety and Health) (NIOSH 2011) is defined as the value that should not be exceeded at any time. The REL ceiling for ethylene chlorohydrin includes a skin notation.

[e] MAK (maximale arbeitsplatzkonzentration [maximum workplace concentration], Deutsche Forschungsgemeinschaft [German Research Association], Germany) (DFG 2002) is defined analogous to the OSHA PEL-TWA. The MAK for ethylene chlorohydrin includes a skin notation.

[f] MAC (maximaal aanvaaarde concentratie [maximal accepted concentration]), Dutch Expert Committee for Occupational Standards, The Hague, The Netherlands) (MSZW 2004) is defined analogous to the OSHA PEL-TWA. The MAC for ethylene chlorohydrin includes a skin notation.

8.3. Data Adequacy and Research Needs

Data reported for human exposure to ethylene chlorohydrin demonstrate systemic effects of ethylene chlorohydrin and add support to the toxicologic end points of the animal data. Quantitative animal data are available from a few inhalation studies of rats, mice, guinea pigs, cats, and rabbits. The data demonstrate toxicity outcomes in animals that are similar to those observed in humans. Although the animal data provide information on lethal and nonlethal exposures, data used to derive AEGL-3 values are from a single dose-ranging study that used a small number of animals. Additional data providing information at exposures that are irritating or nonincapacitating would be useful for deriving

AEGL1 values and refining AEGL-2 values. Additional data are needed with respect to the exposure-response relationship and mode of action of ethylene chlorohydrin vapor exposure.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR ETHYLENE CHLOROHYDRIN

Derivation of AEGL-1 Values

Because of insufficient data regarding AEGL-1 severity effects and the overall exposure-response relationship for ethylene chlorohydrin vapor exposure, AEGL-1 values are not recommended. Absence of AEGL-1 values does not imply that exposures below the AEGL-2 values are without effect.

Derivation of AEGL-2 Values

Because of insufficient data on AEGL-2 severity effects, the AEGL-2 values were estimated as one-third of the AEGL-3 values as per guidance in NRC (2001). The lethality data in rats, mice, and guinea pigs indicate a steep exposure-response relationship.

10-min AEGL-2:	6.4 ppm ÷ 3 = 2.1 ppm
30-min AEGL-2:	4.4 ppm ÷ 3 = 1.5 ppm
1-h AEGL-2:	3.5 ppm ÷ 3 = 1.2 ppm
4-h AEGL-2:	1.4 ppm ÷ 3 = 0.47 ppm
8-h AEGL-2:	0.70 ppm ÷ 3 = 0.23 ppm

Derivation of AEGL-3 Values

Key study:	Goldblatt, M.W. 1944. Toxic effects of ethylene chlorohydrin. Part II. Experimental. Br. J. Ind. Med. 1(4):213-223.
Critical effect:	A 120-min nonlethal exposure at 280 ppm in mice was used as an estimated lethality threshold. A 120-min exposure at 1,090 ppm resulted in 100% lethality.
Time scaling:	$C^n \times t = k$, where n = 1 or 3 (NRC 2001)
Uncertainty factors:	10 for interspecies differences 10 for intraspecies variability; ethylene chlorohydrin

	does not appear to be a direct-contact irritant and death in animals does not appear to be a function of damaged respiratory tract epithelial tissue. In the absence of data regarding the mode of action of ethylene chlorohydrin toxicity and because of the small numbers of animals used in the reported studies, an intraspecies uncertainty of 10 is retained. Sensitive populations could not be identified.
Modifying factor:	None applied
Calculation:	$(280 \text{ ppm})^1 \times 120 \text{ min} = 560 \text{ ppm-h}$ $(280 \text{ ppm})^3 \times 120 \text{ min} = 43{,}904{,}000 \text{ ppm-h}$
10-min AEGL-3:	$C^3 \times 10 \text{ min} = 43{,}904{,}000 \text{ ppm-h}$ $C = 637 \text{ ppm}$ $C = 637 \text{ ppm} \div 100 = 6.4 \text{ ppm}$
30-min AEGL-3:	$C^3 \times 30 \text{ min} = 43{,}904{,}000 \text{ ppm-h}$ $C = 444 \text{ ppm}$ $C = 444 \text{ ppm} \div 100 = 4.4 \text{ ppm}$
1-h AEGL-3:	$C^3 \times 60 \text{ min} = 43{,}904{,}000 \text{ ppm-h}$ $C = 353 \text{ ppm}$ $C = 353 \text{ ppm} \div 100 = 3.5 \text{ ppm}$
4-h AEGL-3:	$C \times 240 \text{ min} = 560 \text{ ppm-h}$ $C = 140 \text{ ppm}$ $C = 140 \text{ ppm} \div 100 = 1.4 \text{ ppm}$
8-h AEGL-3:	$C \times 480 \text{ min} = 560 \text{ ppm-h}$ $C = 70.0 \text{ ppm}$ $C = 70.0 \text{ ppm} \div 100 = 0.70 \text{ ppm}$

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR ETHYLENE CHLOROHYDRIN

Derivation Summary

AEGL-1 VALUES

Because of insufficient data regarding AEGL-1 severity effects and the overall exposure-response relationship for ethylene chlorohydrin vapor exposure, AEGL-1 values are not recommended. Absence of AEGL-1 values does not imply that exposures below the AEGL-2 values are without effect.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
2.1 ppm (6.9 mg/m^3)	1.5 ppm (4.9 mg/m^3)	1.2 ppm (3.9 mg/m^3)	0.47 ppm (1.5 mg/m^3)	0.23 ppm (0.76 mg/m^3)

Data adequacy: Data on ethylene chlorohydrin were insufficient for deriving AEGL-2 values. In accordance with NRC (2001) guidance, AEGL-2 values were estimated by dividing the AEGL-3 values by 3. Animal lethality data indicate a steep exposureresponse relationship for ethylene chlorohydrin.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
6.4 ppm (21 mg/m^3)	4.4 ppm (14 mg/m^3)	3.5 ppm (12 mg/m^3)	1.4 ppm (4.6 mg/m^3)	0.70 ppm (2.3 mg/m^3)

Reference: Goldblatt, M.W. 1944. Toxic effects of ethylene chlorohydrin. Part II. Experimental. Br. J. Ind. Med. 1(4):213-223.

Test Species/Strain/Sex/Number: Mouse; strain and gender not specified; 3/group

Exposure route/Concentrations/Durations: Inhalation

Concentration (ppm)	Duration (min)	Effect
280[a]	120	No lethality
1,090	120	3/3 dead at 140-170 min
1,960	120	3/3 dead at 110-129 min

[a] Concentration used as the point-of-departure for AEGL-3 derivation.

Effects: Signs of discomfort and irritation, and incoordination at higher concentrations (group-specific observations were not provided) and death.

End point/Concentration/Rationale: Lowest concentration with no mortality (280 ppm for 120 min)

Uncertainty factors/Rationale:
Interspecies: 10, absence of information available to describe species differences in toxicity.
Intraspecies: 10, ethylene chlorohydrin does not appear to be a direct-contact irritant and

death in animals does not appear to be a function of damaged respiratory tract epithelial tissue. In the absence of data regarding the mode of action of ethylene chlorohydrin toxicity and because of the small numbers of animals used in the studies, a factor of 10 is retained.

Modifying factor: None applied

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: $C^n \times t = k$, where n = 1 for extrapolation to longer durations or n = 3 for extrapolation to shorter durations (NRC 2001)

Data adequacy: Marginal; the exposure-response relationship is not fully defined by the available data; animal data are based on exposures with only three animals per group.

APPENDIX C

CATEGORY PLOT FOR ETHYLENE CHLOROHYDRIN

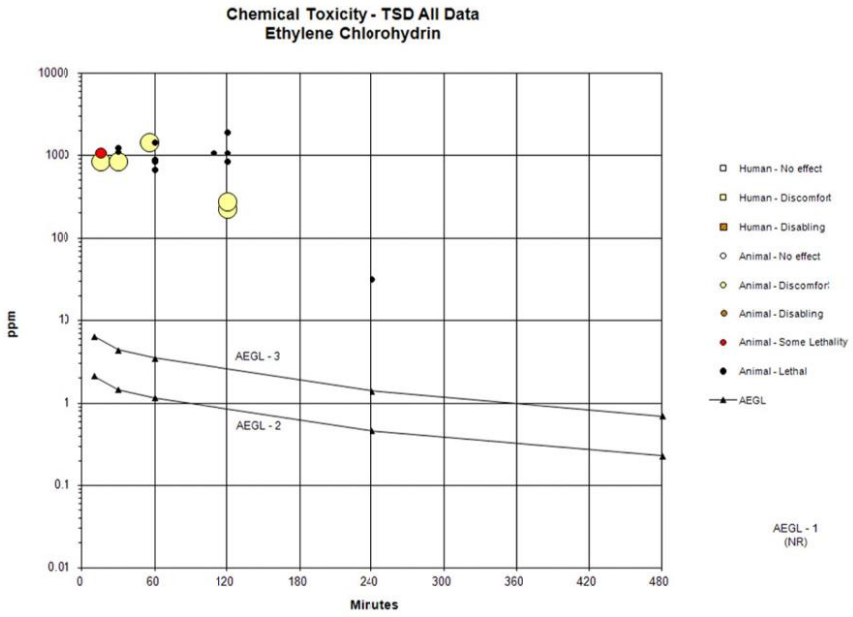

FIGURE C-1 Category plot of toxicity data and AEGL values for ethylene chlorohydrin.

TABLE C-1 Data Used in Category Plot of Ethylene Chlorohydrin

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
AEGL-1				NR	10	AEGL	
AEGL-1				NR	30	AEGL	
AEGL-1 NR 60 AEGL AEGL-1 NR 240 AEGL							
AEGL-1 NR 480 AEGL AEGL-2 2.1 10 AEGL							
AEGL-2				1.5	30	AEGL	
AEGL-2 1.2 60 AEGL AEGL-2 0.47 240 AEGL							
AEGL-2 0.23 480 AEGL AEGL-3 6.4 10 AEGL							
AEGL-3				4.4	30	AEGL	
AEGL-3				3.5	60	AEGL	
AEGL-3				1.4	240	AEGL	
AEGL-3				0.7	480	AEGL	
Goldblatt 1944	Rat		1	840	15	1	Nonlethal; no details but minor effects possible.
	Rat		1	1,120	30	3	100% lethality.
	Rat		1	678	60	3	Lethal
	Rat		1	226	120	1	Nonlethal; no details but minor effects possible.

(Continued)

TABLE C-1 Continued

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
	Mouse		1	280	120	1	Nonlethal; no details but minor effects possible.
	Mouse		1	840	60	3	100% lethality
	Mouse		1	896	60	3	100% lethality
	Mouse		1	1,090	15	SL	Lethal
	Mouse		1	1,090	120	3	Lethal
	Mouse		1	1,260	30	3	Lethal
	Mouse		1	1,460	60	3	Lethal
	Mouse		1	1,960	120	3	Lethal
	Guinea pig		1	840	30	1	Nonlethal; no details but minor effects possible.
	Guinea pig		1	840	120	3	Lethal
	Guinea pig		1	1,090	108	3	Lethal
	Guinea pig		1	1,460	55	1	Nonlethal; no details but minor effects possible.
Patty 1963	Rat		1	32	240	3	LC_{50} no details.
Dierker and Brown 1944	Human		1	300	120	3	Human lethality (estimated exposure concentration).

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