

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 guideline 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 *volxiv 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
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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

VOLUME 17

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/m³ [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/m³) 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/m³) 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 non disabling odor, taste, and sensory irritation or certain asymptomatic nonsensory adverse effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

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(NRC 2001a), the first step in establishing AEGLs for a chemical is to collect and review all relevant published and unpublished information.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

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

For most chemicals, actual human toxicity data are not available or critical information on exposure is lacking, so toxicity data from studies conducted in laboratory animals are extrapolated to estimate the potential toxicity in humans. Such extrapolation requires experienced scientific judgment. The toxicity data for animal species most representative of humans in terms of pharmacodynamic and pharmacokinetic properties are used for determining AEGLs. If data are not available on the species that best represents humans, data from the most sensitive animal species are used. Uncertainty factors are commonly used when animal data are used to estimate risk levels for humans. The magnitude of uncertainty factors depends on the quality of the animal data used to determine the 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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Appendix

8

Hydrogen Bromide⁴

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/m³]) 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 Sylvia Talmage (Oak Ridge National Laboratory), Lisa Ingerman (SRC, Inc.), Chemical Manager Susan Ripple (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/m³) 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/m³) 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

Hydrogen bromide (HBr) is a colorless, corrosive, and non-flammable gas. HBr fumes strongly in moist air. It is one of the strongest mineral acids, with a reducing action stronger than that of hydrogen chloride (HCl). It is extremely soluble in water, forming a strong acid that is available as 48% or 68% solutions. HBr is used both as a reagent and as a catalyst in a variety of organic reactions; it is also used in the preparation of numerous bromide compounds. Anhydrous HBr is shipped in high-pressure steel cylinders.

HBr is a severe irritant to the eyes, skin, and nasal passages; high concentrations may penetrate to the lungs resulting in edema and hemorrhage. Data on irritant effects in humans and lethal and sublethal effects in rats and mice were available for developing AEGL values. Although the database for HBr is sparse, data on the toxicity of HBr relative to that of hydrogen fluoride (HF) and HCl were available for comparison purposes. The databases for HCl and HF are robust. On the basis of lethality data from studies of rats and mice, HF is more potent than HCl and HBr; HCl and HBr have similar potencies (MacEwen and Vernot 1972). At sublethal concentrations, the severity and extent of lesions to the upper respiratory tract were greatest for HF, followed by HCl and then HBr, although the severity and extent of lesions in the anterior most region of the respiratory tract were similar among the three chemicals (Kusewitt et al. 1989; Stavert et al. 1991). The data also show that all three chemicals are well scrubbed in the upper respiratory passages.

The AEGL-1 values for HBr are based on a study of six human volunteers exposed at 2, 3, 4, 5, or 6 ppm for several minutes (CT Department of Health, unpublished data, 1955, as cited in ACGIH 2002). No nasal, throat, or ocular irritation was reported at 2 ppm. One subject reported nasal and throat irritation (severity not defined) but no ocular irritation at 3 ppm. Nasal irritation was reported by all six subjects at 5 and 6 ppm, but only one reported throat irritation and none reported ocular irritation. The concentration of 3 ppm was considered a no-observed-adverse-effect level (NOAEL) for notable discomfort. This point of departure was divided by an uncertainty factor of 3 to protect sensitive individuals; time-scaling was not performed, because irritation is concentration related and humans adapt to the slight sensory irritation that defines the AEGL-1. A concentration of 1.0 ppm across the AEGL exposure durations is supported by the AEGL-1 values for HF and HCl of 1.0 and 1.8 ppm, respectively (NRC 2004). The AEGL-1 value might be conservative, as only one of six subjects reported any sensory irritation and the value is the same as that of HF, a slightly more toxic chemical. It is also below the AEGL-1 value of 1.8 ppm for HCl, which was based on a no-effect concentration in exercising asthmatics.

There are limited data on AEGL-2 effects from exposure to HBr. Stavert et al. (1991) reported severe necrohemorrhagic rhinitis in rats exposed to HBr at 1,300 ppm for 30 min; however, 8% mortality was also reported at that concentration. In the absence of suitable data, the AEGL-3 values for HBr were divided by 3 to derive AEGL-2 values.

A $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) of 1,239 ppm was calculated from 1-h lethality data from studies of Sprague-Dawley rats exposed to HBr (MacEwen and Vernot 1972). The $BMCL_{05}$ is an estimate of the threshold for lethality, and was used as the point of departure for calculating AEGL-3 values for HBr. A total uncertainty factor of 10 was applied: 3 for interspecies differences and 3 for human variability. Those individual factors are considered sufficient because the action of a directacting irritant is not expected to vary greatly among species or between individuals (NRC 2001). The 60-min point of departure was time-scaled to the other AEGL durations using the equation $C^n \times t = k$. The value of n was 1, on the basis of data for the related compound HCl, for which regression analysis of combined rat and mouse LC_{50} (lethal concentration, 50% lethality) data resulted in a value of 1 for n (see NRC 2004).

The AEGL values for HBr are presented in Table 8-1.

1. INTRODUCTION

Hydrogen bromide (HBr) is a colorless nonflammable gas that fumes strongly in moist air. It is highly water soluble. HBr is one of the strongest mineral acids, with a reducing action stronger than that of hydrogen chloride (HCl) (Jackisch 1992). Chemical and physical properties for HBr are presented in Table 8-2.

TABLE 8-1 AEGL Values for Hydrogen Bromide

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	1.0 ppm (3.3 mg/m ³)	1.0 ppm (3.3 mg/m ³)	1.0 ppm (3.3 mg/m ³)	1.0 ppm (3.3 mg/m ³)	1.0 ppm (3.3 mg/m ³)	Threshold for nasal irritation in humans (CT Department of Health, unpublished data 1955).
AEGL-2 (disabling)	250 ppm (830 mg/m ³)	83 ppm (270 mg/m ³)	40 ppm (130 mg/m ³)	10 ppm (33 mg/m ³)	5 ppm (17 mg/m ³)	One-third of AEGL-3 values.
AEGL-3 (lethal)	740 ppm (2400 mg/m ³)	250 ppm (830 mg/m ³)	120 ppm (400 mg/m ³)	31 ppm (100 mg/m ³)	15 ppm (50 mg/m ³)	Threshold for lethality in rats (MacEwen and Vernot 1972)

TABLE 8-2 Chemical and Physical Properties

Parameter	Value	Reference
Synonyms	Anhydrous bromic acid, hydrobromic acid	HSDB 2008
Chemical formula	HBr	HSDB 2008
Molecular weight	80.91	HSDB 2008
CAS registry no.	10035-10-6	HSDB 2008
Physical state	Colorless gas	HSDB 2008
Boiling point	-67°C	HSDB 2008
Melting point	-87°C	HSDB 2008
Density	3.307 g/L	Jackisch 1992; HSDB 2008
Solubility in water	Freely soluble 600:1 v:v, HBr to water	HSDB 2008
Vapor density (air = 1)	2.71	HSDB 2008
Vapor pressure	>760 torr at 20°C 335 psia at 21°C	ACGIH 2004; Braker and Mossman 1980
Flammability limits	Nonflammable	Jackisch 1992; HSDB 2008
Conversion factors	1 ppm = 3.3 mg/m ³ 1 mg/m ³ = 0.30 ppm	NIOSH 2011

HBr is produced by burning a mixture of hydrogen and bromine vapor. Platinized asbestos or silica gel may be used as catalysts. The vapor is passed

through hot, activated charcoal or iron to remove the free bromine. The vapor is then either liquefied by cooling for shipment in cylinders or is absorbed in water. Technical HBr, a colorless to light-yellow liquid, is available as 48% or 62% acids in drums, 15,140-L tank trailers, and 37,850-L tank cars. Anhydrous HBr is available in high-pressure steel cylinders (Braker and Mossman 1980; Jackisch 1992). HBr is used in the manufacture of organic and inorganic bromides, hydrobromic acid, as a reducing agent, as a catalyst in controlled oxidation reactions, in the alkylation of aromatic compounds, and in the isomerization of conjugated diolefins (O'Neil et al. 2006).

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data on concentrations of HBr lethal to humans were found.

2.2. Nonlethal Toxicity

Amoore and Hautala (1983) reported an odor threshold of 2 ppm for HBr. HBr liquid and vapor are highly corrosive to tissues. Symptoms of over exposure include coughing, choking, burning in the throat, wheezing, and asphyxia. Skin contact may cause severe burns, and contact of the eyes with the liquid or vapor may result in permanent damage (Jackisch 1992).

One report by the Connecticut State Department of Health (unpublished data, 1955, as cited in ACGIH 2002⁵) addressed responses of human subjects to HBr vapor. Six volunteers inhaled HBr at concentrations of 2-6 ppm for several minutes (Table 8-3). The odor was detected by all subjects at all concentrations. None of the subjects experienced ocular irritation. Only one subject experienced nasal and throat irritation at 3 ppm. One subject (presumably the same one) experienced throat irritation at all of the higher concentrations, and all subjects experienced nasal irritation at 5 and 6 ppm. Responses ranged from slight, stinging sensations to a definite feeling of irritation. Although exposure at 5 ppm caused nasal irritation in all of the subjects, the authors stated that "it was considered unlikely that noticeable disturbances will occur if peak concentrations do not exceed this value for brief periods."

According to Braker and Mossman (1980), hydrogen halides at concentrations of approximately 35 ppm cause irritation of the throat after short exposures. Concentrations of 1,000-2,000 ppm are lethal to humans from brief

⁵ A detailed description of this study was provided in ACGIH's 2002 documentation of threshold limit values and biological exposure indices for HBr. In its update of the documentation in 2004, ACGIH omitted the study description and did not consider the data in its recommendations. The information from the study by the Connecticut Department of Health is retained here because it provides the only quantitative information on human exposure to HBr.

exposures and concentrations of 1,000-1,300 ppm are dangerous if breathed for 3060 min. Those data appear to be from the study by Henderson and Haggard (1943) and apply to HCl.

TABLE 8-3 Human Responses to Hydrogen Bromide Vapor

Number of Subjects (n = 6) Reporting Responses					
Response	2 ppm	3 ppm	4 ppm	5 ppm	6 ppm
Detectable odor	6	6	6	6	6
Nasal irritation	0	1	3	6	6
Throat irritation	0	1	1	1	1
Ocular irritation	0	0	0	0	0

Source: Adapted from ACGIH 2002.

2.3. Neurotoxicity

No information on the neurotoxicity of HBr in humans was found.

2.4. Developmental and Reproductive Toxicity

No data on the developmental or reproductive effects of HBr in humans was found.

2.5. Genotoxicity

No data on the genotoxicity on HBr in humans was found.

2.6. Carcinogenicity

No data on the carcinogenicity of HBr in humans was found.

2.7. Summary

The only human data on HBr involved six volunteers exposed at 2-6 ppm for several minutes (CT Department of Health, unpublished data, 1955, as cited in ACGIH 2002). All six volunteers detected HBr at 2 ppm, and one individual experienced subjective irritation involving the nose and throat at 3 ppm. At higher concentrations, at least half of subjects experienced nasal and throat irritation. No information on neurotoxicity, developmental or reproductive effects, genotoxicity, or carcinogenicity of HBr was found.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

As part of a series of inhalation toxicity studies performed at WrightPatterson Air Force Base, MacEwen and Vernot (1972; also reported in Back et al. 1972 and Vernot et al. 1977) subjected groups of 10 male Sprague-Dawley-derived rats to HBr at 2,205-3,822 ppm for 1 h (Table 8-4). Exposures took place in a modified Rochester chamber and concentrations were monitored with a bromide ion-specific electrode. The rats were monitored for mortality for 14 days. The 1-h LC₅₀ was 2,858 ppm (95% confidence limits of 2,581-3,164 ppm) (Table 8-5). Responses of the animals during the exposures were dose-related and had the following a sequence: nasal and ocular irritation, labored breathing, gasping, and convulsions. The fur turned orange-brown during the exposures, and the color intensity was related to the concentration. The authors attributed a smoky haze around the animals during exposure to the reaction of HBr with the fur or moisture on the fur. During the 14-day postexposure period, the surviving animals were prostrate and most lost weight. Delayed deaths were observed. Burns accompanied by autolysis were observed on exposed areas of the skin. Rats exposed at the lowest concentration (2,205 ppm) returned to a normal weight gain by the end of the postexposure period. Gross examination at necropsy showed severe pulmonary and hepatic congestion and pulmonary edema in rats exposed at 3,822 ppm. The investigators noted that rats exposed at the lower concentration (not specified) had necrotic lesions on their feet and tails for up to 14 days. Opacity of the cornea, observed immediately following exposure, disappeared within 24 h.

Groups of 5-8 male Fischer 344 rats were exposed to HBr at approximately 1,300 ppm for 30 min (Stavert et al. 1991). Rats were placed into whole body flow plethysmographs to measure ventilatory rates. Body weight and respiratory-tract histology were investigated 24 h later. The mortality rate was 8% (Table 8-5). Rats exposed to HBr experienced an immediate and persistent drop in minute ventilatory rate of 25%. The effect on ventilatory rate was similar with HF exposure, whereas exposure to HCl caused a much smaller decrease in ventilation. A small (<10%) reduction in body weight compared to nonexposed rats occurred by 24 h postexposure.

TABLE 8-4 Results of One-Hour Inhalation Studies of Hydrogen Bromide in Rats and Mice

Species	Concentration (ppm)	Mortality Ratio
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Rat	2,205	2,328	1/10
	2,759		4/10
	3,253		4/10
	3,711		6/10
	3,822		7/10
			10/10
Mouse	507	875	0/10
	1,036		7/10
	1,163		9/10
			10/10

Source: Adapted from MacEwen and Vernot 1972.

TABLE 8-5 Summary of Acute Lethality Data on Hydrogen Bromide in Rats and Mice

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Rat	1,300	30 min	8% mortality	Stavert et al. 1991
	2,858	1 h	LC ₅₀	MacEwen and Vernot 1972
Mouse	507	1 h	No deaths	MacEwen and Vernot 1972
	814	1 h	LC ₅₀	

As part of the same study, Stavert et al. (1991) compared the toxicities of three hydrogen halides (HF, HCl, and HBr) in rats exposed at 1,300 ppm for 30 min. Mortalities were 0% for HF, 6% for HCl, and 8% for HBr. Damage to the respiratory tract was assessed 24 h after the exposure. For all three hydrogen halides, tissue injury was confined to the nasal cavity. Tissue injury in the anterior nasal cavity was similar for all three compounds and involved moderate to severe fibrinonecrotic rhinitis. The mucosa and submucosa were necrotic, with necrosis extending to the turbinate bone. Blood clots were observed in nasal blood vessels; hemorrhage, fibrin, and fluid were observed in the nasal passages; and polymorphonuclear cells were observed in the submucosa and in the lumen. The severity of these lesions is summarized in Table 8-6. Exposure to HBr resulted in bilateral or unilateral severe necrohemorrhagic rhinitis in the anterior quarter of the nasal cavity, and necrosis of the mucosa and submucosa that extended to the nasal turbinate bone. For HF and HCl, but not HBr, the lesions were also observed in the second anterior quarter of the nasal cavity. After exposure to all three halogen halides, the posterior half of the nasal cavity (including the ethmoid region) was essentially normal in appearance, showing that all three chemicals were well scrubbed. No pulmonary or tracheal injury was evident for any of the chemicals. The authors concluded that respiratory-tract injury caused by exposure to the three hydrogen halides was quantitatively similar. There was no change in pulmonary weight.

In the same study (Stavert et al. 1991), groups of male Fischer 344 rats were exposed to HBr at 1,300 ppm for 30 min via a tracheal cannula (to simulate mouth breathing). This procedure bypasses the scrubbing of the nasal passages. Within

24 h after exposure, 19% of the rats died. Mean pulmonary weight was not significantly different from that of noncannulated rats or of rats exposed to air. Pulmonary lesions observed in treated animals were not significantly different from those of the cannulated control group.

3.1.2. Mice

MacEwen and Vernot (1972) (see also Back et al. 1972) exposed groups of 10 CF1 (ICR-derived) mice (20-30 g) to HBr at concentrations ranging from 507 to 1,163 ppm for 1 h (Table 8-4). The LC_{50} was 814 ppm (95% confidence limits of 701-947 ppm) (Table 8-5). Responses during exposure were the same as those described for rats (see Section 3.1.1). No deaths occurred in mice exposed at 507 ppm, and the mice had a normal weight gain during the 14-day recovery period. Mice surviving the 14-day postexposure period had necrotic lesions of their tails. No other gross pathologic changes were apparent in surviving mice.

3.2. Nonlethal Toxicity

As part of the Stavert et al. (1991) study, Kusewitt et al. (1989) reported on exposures to three hydrogen halides at lower concentrations. Fischer 344 rats (number not specified) were exposed to HF, HCl, or HBr at concentrations of 100-1,000 ppm for 30 min and were killed 8 and 24 h later. Tissue damage was restricted to the nasal region and consisted of necrosis and inflammation; the severity of the damage increased with concentration. HF was the most toxic, and that the toxicities of HCl and HBr were similar. Histopathologic examinations and gravimetric measurements revealed no damage to the lungs. No further details were reported in the available abstract.

Toxicity data on the related chemical, HCl, are relevant to evaluating the toxicity of HBr. In a study in which the ventilatory rate of rats exposed to HCl at 1,000 ppm for 30 min was increased by the addition of CO_2 to the exposure chamber, no deaths occurred and histopathologic lesions were confined to the upper respiratory tract and (Lehnert and Stavert 1991). Barrow et al. (1977) exposed groups of four male Swiss-Webster mice to HCl at concentrations of 40, 99, 245, 440, or 943 ppm for 10 min. An RD_{50} (a 50% decrease in the respiratory rate) of 309 ppm was calculated. At 99 ppm, approximately one-third of the RD_{50} , the decrease in respiratory rate was 25-30%. Additional studies summarized in NRC (2004) showed that primates were less sensitive to the toxic effects of HCl than rodents.

TABLE 8-6 Severity of Lesions in the Anterior Region of the Nasal Cavity of Rats Following Exposure to Hydrogen Fluoride, Hydrogen Chloride, or Hydrogen Bromide at 1,300 ppm for 30 Minutes

Necrotic Lesion	HF	HCl	HBr
Epithelial	3.3 ^a	3.8 ^a	3.3 ^a
Submucosal	2.6 ^a	3.0 ^a	2.6 ^a
Bone	0.3	2.4 ^a	1.6 ^a
Gland	1.8 ^a	2.4 ^a	1.4 ^a

Severity index: 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe (n = 8).

^a Statistically significant compared to air-exposed controls, p < 0.05.

Source: Adapted from Stavert et al. 1991.

3.3. Neurotoxicity

No information on the neurotoxicity of HBr in animals was found.

3.4. Developmental and Reproductive Toxicity

No information on the developmental or reproductive effects of HBr in animals was found.

3.5. Genotoxicity

No information on the genotoxicity of HBr in animals was found.

3.6. Chronic Toxicity and Carcinogenicity

No information on the chronic toxicity or carcinogenicity of HBr in animals was found.

3.7. Summary

Two studies of HBr in animals were available. In the first study (MacEwen and Vernot 1972), groups of rats and mice were exposed by inhalation to a range of concentrations for 1 h. The 1-h LC₅₀ value was 2,858 in rats and 814 ppm in mice. All tested concentrations resulted in lethality in rats during the 14-day postexposure period. No deaths occurred in mice exposed at 507 ppm for 1 h. In rats exposed at 1,300 ppm for 30 min, mortality was 8% (presumably one of 12 rats) and lesions were confined to the anterior nasal passages (Stavert et al. 1991). Nasal lesions were also observed in rats exposed at up to 1,000 ppm for 30 min (Kusewitt et al. 1989). Animals in the Kusewitt et al. (1989) and Stavert et al. (1991) studies were killed 24 h after exposure. Only one of 10 rats exposed at 2,205 ppm died in the MacEwen and Vernot (1972) study.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No data on the metabolism and deposition of HBr were found. Data on soluble bromides are available from their medical use as oral sedatives, diuretics, and antiepileptics. An oral dose of 3 g (30-60 mg/kg for an adult) is considered a "no-ill effect" dose (Teitelbaum 2001).

4.2. Mechanism of Toxicity

The available studies indicate that the hydrogen halides are severe irritants to the skin, eyes, and respiratory tract, particularly the anterior nasal passages where, depending on concentration, they appear to be effectively scrubbed from the inhaled air. For HBr, deposition in the anterior nasal passages may be attributed to its high solubility and reactivity. At high concentrations (e.g., 3,822 ppm for 1 h), penetration into the lungs occurs as evidenced by pulmonary hemorrhage, edema, and death. Although HBr is absorbed, serious systemic effects are unlikely to occur at concentrations below those that would cause serious respiratory effects. In the studies summarized in Tables 8-4 and 8-5, the tissues of the respiratory tract and exposed dermal surfaces sustained the impact of an acute exposure. Therefore, the concentration of HBr in the inhaled air and not the absorbed dose is the primary determinant of the effects from acute exposures.

4.3. Structure-Activity Relationships

Differences in size and electron configuration of the various halogen atoms result in substantial differences with respect to their chemical and physical properties, which in turn affect their toxicologic properties. The atomic weights of fluorine, chlorine, bromine, and iodine are 19, 35.5, 80, and 127, respectively.

Data on the relative toxicities of HF, HCl, and HBr on the basis of lethality are available. As can be seen from the data in Table 8-7, three rodent studies using different exposure durations show that HF is more lethal than HCl (Rosenholtz et al. 1963; Higgins et al. 1972; MacEwen and Vernot 1972; Wohlslagel et al. 1976). For both the rat and mouse, HF is also more lethal than HBr (MacEwen and Vernot 1972). Data from the same laboratory (Wohlslagel et al. 1976; MacEwen and Vernot 1972) show that HCl and HBr have similar 1-h LC₅₀ values of 3,124 and 2,858 ppm, respectively. Data on the nonlethal toxicity of the three hydrogen halides (Stavert et al. 1991) suggest that HF, HCl, and HBr are similarly toxic to the nasal cavity following acute exposure. HBr and HF exposure resulted in similar decreases (by about 25%) in the ventilation rate of cannulated rats (simulation of mouth breathing), whereas the decrease associated with HCl exposure was smaller (Stavert et al. 1991).

4.4. Other Relevant Information

4.4.1. Species Variability

HBr toxicity data, available for only the rat and mouse, showed that mice are more susceptible than rats. However, when considering lethal concentrations of respiratory irritants (such as HCl), the mouse “may not be an appropriate model for extrapolation to humans,” because “mice appear to be much more

TABLE 8-7 Relative Toxicities of Hydrogen Fluoride, Hydrogen Chloride, and Hydrogen Bromide

Species	Exposure Duration	LC ₅₀ Values (ppm)			Reference
		HF	HCl	HBr	
Rat	5 min	18,200	41,000	–	Higgins et al. 1972
Mouse	5 min	6,247	13,750	–	
Rat	30 min	2,042	4,700		Rosenholtz et al. 1963; MacEwen and Vernot 1972
Mouse	30 min	–	2,644	–	MacEwen and Vernot 1972
Rat	1 h	1,395	3,124	–	Wohlslagel et al. 1976
Mouse	1 h	342	1,108	–	
Monkey	1 h	1,774	–	–	MacEwen and Vernot 1970
Rat	1 h	1,278	–	2,858	MacEwen and Vernot 1972
Mouse	1 h	501	–	814	MacEwen and Vernot 1972

The data of Wohlslagel et al. (1976) and MacEwen and Vernot (1972) were generated in the same laboratory. Therefore, the values for HCl (Wohlslagel et al. 1976) can be compared with those for HF and HBr (MacEwen and Vernot 1972).

susceptible to the lethal effects of HCl than other rodents or baboons. To some extent, this increased susceptibility may be due to less effective scrubbing of HCl in the upper respiratory tract” (NRC 1991). The same principle reasonably holds true for HF and HBr. The respiratory rate of mice is also higher than that of rats. The data in Table 8-7 show species that mice are the most susceptible to HF, followed by the rat and nonhuman primate (rhesus monkey).

4.4.2. Susceptible Populations

Individuals with asthma may respond to exposure to respiratory irritants, such as HBr, with increased bronchial responsiveness. No information on the relative susceptibility of asthmatic and normal individuals to HBr was found. In a study with HCl, exposure at 1.8 ppm for 45 min was a no-effect level for exercising asthmatics (Stevens et al. 1992).

Individuals under stress, such as those involved in emergency situations and individuals engaged in physical activity, will likely experience increased penetration of HBr into the lower respiratory tract due to increased minute volumes, with the potential for increased irritant response, as compared to individuals at rest.

4.4.3. Concentration-Exposure Duration Relationship

No information on the relationship between concentration and exposure for a single end point was found. When no data are available, time scaling is based on the equation $C^n \times t = k$, with default values of $n = 3$ for extrapolation to shorter exposure durations and $n = 1$ for extrapolation to longer exposure durations (NRC 2001). However, information on relevant chemicals HF and HCl are available. On the basis of lethality data, the n values for time scaling was 2 for HF and 1 for HCl (NRC 2004). HBr is more similar chemically to HCl than HF.

4.4.4. Concurrent Exposure Issues

No information on concurrent exposure issues for HBr was found.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Reliable human data on HBr are available from a study of six volunteers exposed at 2-6 ppm for several minutes (CT Department of Health, unpublished data, 1955, as cited in ACGIH 2002). Nasal irritation was reported by 0, 1, 3, 6, and 6 individuals at 2, 3, 4, 5, and 6 ppm, respectively. Throat irritation did not appear to be concentration dependent and no ocular irritation was reported. Therefore, the threshold for subjective nasal irritation is 3 ppm.

5.2. Animal Data Relevant to AEGL-1

No data on HBr relevant to notable discomfort in animals was found.

5.3. Derivation of AEGL-1 Values

The threshold for nasal irritation of 3ppm in human subjects exposed to HBr for several minutes (CT Department of Health, unpublished data, 1955, as cited in ACGIH 2002) was selected as the basis for the AEGL-1 values. That concentration was considered to be a threshold for notable discomfort, as only one individual was affected at that concentration. The 3 ppm point-of-departure was divided by an intraspecies uncertainty factor of 3, because response to sensory irritation is not expected to vary greatly among individuals (NRC 2001). A factor of 3 was considered sufficient because the effect of slight irritation is below the definition of AEGL-1. In addition, an intraspecies uncertainty factor of 3 was used to derive AEGL values for the related compounds HCl and HF, which have the same mode of action as HBr (NRC 2004). It is reasonable to use the same

uncertainty factors for a class of chemicals whose mode of action is the same. Finally, the uncertainty factor used to derive the AEGL-1 values for HBr is believed to be protective of asthmatic individuals on the basis of comparison of the AEGL-1 value for HBr (1.0 ppm) with the AEGL-1 value for HCl (1.8 *Acute Exposure Guideline Levels*

ppm); the latter is based on a no-effect level for irritation in exercising asthmatics. There is evidence that HBr is of similar toxicity to HCl; thus, the lower AEGL-1 values for HBr are considered to be protective of asthmatics on the basis of data on HCl.

Because irritation depends on concentration rather than time, and adaptation to slight irritation occurs (Dalton 2001), 1.0 ppm was used for all of the AEGL-1 exposure durations (see Table 8-8). Derivation of the AEGL-1 values for HBr are presented in Appendixes A and D, and a category plot of the toxicity data for HBr in relation to AEGL values is presented in Appendix B.

Although the AEGL-1 values for HBr are based on data presented in a secondary source, the values obtained from the data are supported by comparison with the related compounds HF and HCl. The AEGL-1 values for HF (1.0 ppm) and HCl (1.8 ppm) are equal to or higher than the values obtained for HBr using data from Connecticut State Department of Health (unpublished data, 1955, as cited in ACGIH 2002). Thus, if AEGL-1 values for HBr were obtained by analogy to these related compounds, the same or higher AEGL-1 values would be derived.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data on HBr relevant to development of AEGL-2 values were found.

6.2. Animal Data Relevant to AEGL-2

The only study of HBr that addresses effects that meet the definition of an AEGL-2 was a study on hydrogen halides by Stavert et al. (1991). Following inhalation of HBr, HCl, or HF at 1,300 ppm for 30 min, male F-344 rats exhibited severe necrotic lesions of the anterior nasal passages and 8% of the rats died (Stavert et al. 1991). Lesions consisting of necrosis and inflammation were restricted to the nasal region; the lungs appeared unaffected. Rats were killed 24 h after exposure and no judgment could be made about whether the lesions were reversible. The authors noted that the nasal lesions were similar in severity and location for all three hydrogen halides when tested at the same concentration.

6.3. Derivation of AEGL-2 Values

The Stavert et al. (1991) study was not considered a suitable basis for derivation of AEGL-2 values because 8% of the animals died after exposure to HBr at 1,300 ppm. Additionally, the study only tested a single concentration and the number of animals tested was not specified. In the absence of suitable data, the **TABLE 8-8 AEGL-1 Values for Hydrogen Bromide**

10 min	30 min	1 h	4 h	8 h
1.0 ppm (3.3 mg/m ³)				

AEGL-3 values for HBr were divided by 3 to estimate AEGL-2 values. This approach is supported by the steep concentration-response curve demonstrated in the MacEwen and Vernot (1972) lethality studies. The AEGL-2 values for HBr are presented in Table 8-9, and the calculations are presented in Appendixes A and D. A category plot of the toxicity data on HBr in relation to AEGL values is presented in Appendix B.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data on HBr relevant to development of AEGL-3 values were found.

7.2. Animal Data Relevant to AEGL-3

Lethality data on HBr were available for the rat and mouse. One-hour LC₅₀ values for the rat and mouse were 2,858 and 814 ppm, respectively (MacEwen and Vernot 1972). The data are summarized in Table 8-4. A 30-min exposure to HBr at 1,300 ppm resulted in 8% mortality in rats (Stavert et al. 1991). From the MacEwen and Vernot study in the rat, a 1-h LC₀₁ of 1,350 ppm was calculated by probit analysis. The BMCL₀₅ was 1,239 ppm (see Appendix C) and the BMC₀₁ was 1,456 ppm (data not shown). No deaths occurred in rats exposed at 1,000 ppm for 30 min (Kusewitt et al. 1989) or in mice exposed at 507 ppm for 1 h (MacEwen and Vernot 1972). As noted in Section 4.4.1 (Species Variability), mice are not considered an appropriate species for setting lethality values for hydrogen halides, because mice are more susceptible to the lethal effects of HCl than rats or non-human primates (NRC 1991).

7.3. Derivation of AEGL-3 Values

The BMCL₀₅ of 1,239 ppm, calculated from 1-h lethality data from studies in Sprague-Dawley rats exposed to HBr (MacEwen and Vernot 1972), is an estimate of the threshold for lethality and was selected as the point of departure to develop AEGL-3 values for HBr. This value was more conservative than the BMC₀₁ of 1,456 ppm calculated from the same data. A total uncertainty factor of 10 was applied: 3 for interspecies differences and 3 for intraspecies variability.

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TABLE 8-9 AEGL-2 Values for Hydrogen Bromide

10 min	30 min	1 h	4 h	8 h
250 ppm (830 mg/m ³)	83 ppm (270 mg/m ³)	40 ppm (130 mg/m ³)	10 ppm (33 mg/m ³)	5 ppm (17 mg/m ³)

The individual factors are considered to be sufficient because the action of a direct-acting irritant is not expected to vary greatly among species or between individuals (NRC 2001).

The 60-min point of departure was time-scaled to the other AEGL-3 durations using the equation $C^n \times t = k$. The value of n was 1, on the basis of data on the related compound HCl, for which regression analysis of combined LC₅₀ data from rats and mice resulted in an estimate of $n = 1$ (see NRC 2004). The AEGL3 values for HBr are presented in Table 8-10. The use of the BMCL₀₅ as the point-of-departure for the AEGL-3 values is supported by the finding that the point-of-departure for the 30-min AEGL-3 is an estimate of the threshold for lethality of 155 ppm and is approximately 10-fold lower than the concentration which resulted in 8% mortality (1,300 ppm) (Stavert et al. 1991). The AEGL-3 calculations are presented in Appendices A and D, and a category plot of the toxicity data on HBr in relation to the AEGL values is presented in Appendix B.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

The AEGL values for HBr are presented in Table 8-11. The AEGL-1 values were based on the concentration that did not result in nasal irritation in subjects exposed to HBr for several minutes. AEGL-2 values were derived by taking one-third the AEGL-3 values, and the AEGL-3 values were based on the BMCL₀₅ estimated from rat lethality data.

A comparison of the AEGL values for HBr, HCl, and HF is presented in Table 8-12. The AEGL-1 values for the three hydrogen halides are similar, as are the longer-term AEGL-2 values. The AEGL-3 values for HBr and HCl are similar and the HF values are generally lower; this is consistent with the findings

presented in Table 8-7, which showed that lethality was observed at lower concentrations of HF, as compared to HBr and HCl.

8.2. Comparison with Other Standards and Guidelines

Other standards and guidelines for HBr are presented in Table 8-13. Except for the Occupational Safety and Health Administration's permissible exposure limit, ceiling or peak limits rather than 8-h time-weighted averages (TWA) have been derived for the workplace. The AEGL-1 for HBr is below the workplace guidelines. The immediately dangerous to life or health (IDLH) value is based on analogy with HCl (NIOSH 1994). The IDLH for HCl is 50 ppm which is 10 times the recommended exposure limit (REL) of the National Institute for Occupational Safety and Health (NIOSH). Therefore, the IDLH for HBr was set at 10 times the NIOSH REL of 3 ppm. The 30-min AEGL-2 is similar to the IDLH.

TABLE 8-10 AEGL-3 Values for Hydrogen Bromide

10 min	30 min	1 h	4 h	8 h
740 ppm (2,400 mg/m ³)	250 ppm (830 mg/m ³)	120 ppm (400 mg/m ³)	31 ppm (100 mg/m ³)	15 ppm (50 mg/m ³)

TABLE 8-11 AEGL Values for Hydrogen Bromide

Classification	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1 (non-disabling)	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm
AEGL-2 (disabling)	250 ppm	83 ppm	40 ppm	10 ppm	5 ppm
AEGL-3 (lethal)	740 ppm	250 ppm	120 ppm	31 ppm	15 ppm

TABLE 8-12

Hydrogen Fluoride

(ppm) AEGL Values for Hydrogen Bromide, Hydrogen Chloride, and

Classification	10 min	30 min	1 h	4 h	8 h
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AEGL-1					
HBr	1.0	1.0	1.0	1.0	1.0
HCl	1.8	1.8	1.8	1.8	1.8
HF	1.0	1.0	1.0	1.0	1.0
AEG-2					
HBr	250	83	40	10	5
HCl	100	43	22	11	11
HF	95	34	24	12	12
AEGL-3					
HBr	740	250	120	31	15
HCl	620	210	100	26	26
HF	170	62	44	22	22

Source of the HCl and HF values: NRC 2004.

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TABLE 8-13 Standards and Guidelines for Hydrogen Bromide

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm
AEGL-2	250 ppm	83 ppm	40 ppm	10 ppm	5 ppm
AEGL-3	740 ppm	250 ppm	120 ppm	31 ppm	15 ppm
IDLH (NIOSH) ^b	–	30 ppm	–	–	–
PEL-TWA (OSHA) ^b	–	–	–	–	3 ppm
TLV-C (ACGIH) ^c	2 ppm	2 ppm	2 ppm	2 ppm	2 ppm
REL-C (NIOSH) ^d	3 ppm	3 ppm	3 ppm	3 ppm	3 ppm
MAK peak limit (Germany) ^e	2 ppm (15 min, 4 times/shift)	–	–	–	–

^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 limits – time-weighted average, Occupational Health and Safety Administration) (29CFR 1910.1045 [2006]) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/wk.

^c TLV-C (threshold limit value – ceiling, American Conference of Governmental Industrial Hygienists) (ACGIH 2012) is a limit that should not be exceeded during the working day. ^d REL-C (recommended exposure limit – ceiling, National Institute for Occupational Safety and Health) (NIOSH 2011) is defined analogous to the ACGIH TLV-ceiling.

^e MAK Spitzenbegrenzung (peak limit) (German Research Association (DFG 1999) constitutes the maximum average concentration to which workers can be exposed for a period of 15 min with no more than four excursions per work shift and with an interval of 1 h between excursions.

8.3. Data Adequacy and Research Needs

Only one study of human subjects was available for development of AEGL-1 values (CT Department of Health, unpublished data, 1955, as cited in ACGIH 2002). The study was unpublished and available only in a secondary source. Although the study used short exposure durations, an adequate number of subjects was used, a range of concentrations was tested, and irritant levels were clearly described. Animal data on HBr were available from studies of two species, the rat and mouse. The well-conducted studies with rats from two different laboratories (MacEwen and Vernot 1972; Stavert et al. 1991) had reasonable agreement in results. Those studies also addressed the relative toxicities of HBr, HF, and HCl in the rat. Although the data on HBr were sparse, supporting information on related hydrogen halides and information on relative toxicity are available; thus, the data were considered adequate to derive AEGL-1 and 3 values for HBr. The database was not considered suitable for AEGL-2 values; the AEGL-3 values were divided by 3 to derive AEGL-2 values for HBr.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR HYDROGEN BROMIDE

Derivation of AEGL-1 Values

Key study:	CT Department of Health, unpublished data (1955, as cited in ACGIH 2002)
Toxicity end point:	Nasal and throat irritation in one of six subjects to HBr at 3 ppm for several minutes
Time scaling:	No time scaling, because there is adaptation to slight irritation.
Uncertainty factors:	3 for intraspecies variability; irritation from a direct-contact irritant should not vary greatly among individuals (NRC 2001).

Calculation: $3 \text{ ppm} \div 3 = 1.0 \text{ ppm}$ (applied to all AEGL durations)

Derivation of AEGL-2 Values

Because data on HBr were inadequate, AEGL-2 values were derived by taking one-third of the respective AEGL-3 values.

Calculations:

10-min AEGL-2: $740 \text{ ppm} \div 3 = 250 \text{ ppm}$

30-min AEGL-2: $250 \text{ ppm} \div 3 = 83 \text{ ppm}$

1-h AEGL-2: $110 \text{ ppm} \div 3 = 40 \text{ ppm}$

4-h AEGL-2: $31 \text{ ppm} \div 3 = 10 \text{ ppm}$

8-h AEGL-2: $15 \text{ ppm} \div 3 = 5 \text{ ppm}$

Derivation of AEGL-3 Values

Key study: MacEwen and Vernot (1972)

Toxicity end point: Lethality in rats exposed for 1 h, BMCL_{05} of 1,238.95 ppm.

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Time scaling: $C^n \times t = k$; $n = 1$ on the basis of lethality data on HCl in rats
 $(1,238.95 \text{ ppm} \div 10) \times 60 \text{ min} = 7,433.7 \text{ ppm-min}$

Uncertainty factors: 3 for interspecies differences; a direct-contact irritant is not expected to vary greatly between species (NRC 2001)
3 for intraspecies variability; response to a directcontact irritant is not expected to vary greatly among humans (NRC 2001)

Calculations:

10-min AEGL-3: $7,433.7 \text{ ppm-min} \div 10 \text{ min} = 740 \text{ ppm}$

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30-min AEGL-3: $7,433.7 \text{ ppm-min} \div 30 \text{ min} = 250 \text{ ppm}$

1-h AEGL-3: $7,433.7 \text{ ppm-min} \div 60 \text{ min} = 120 \text{ ppm}$

4-h AEGL-3: $7,433.7 \text{ ppm-min} \div 240 \text{ min} = 31 \text{ ppm}$

8-hAEGL-3: $7,433.7 \text{ ppm-min} \div 480 \text{ min} = 15 \text{ ppm}$

APPENDIX B

CATEGORY PLOT FOR HYDROGEN BROMIDE

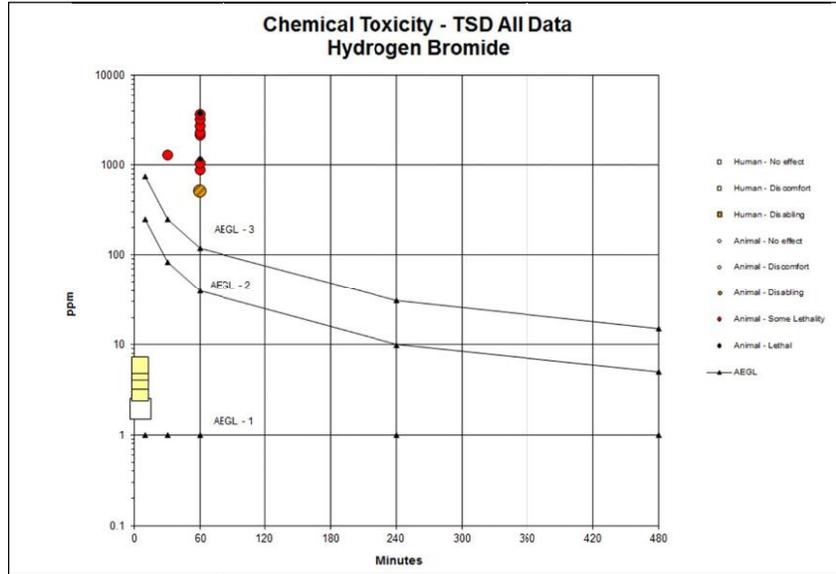


FIGURE B-1 Category plot of toxicity data and AEGL values for hydrogen bromide.

Source

TABLE B-1 Data Used in the Category Plot for Hydrogen Bromide

	Species	ppm	Minutes	Category
AEGL-1		1.0	10	AEGL
AEGL-1		1.0	30	AEGL
AEGL-1		1.0	60	AEGL
AEGL-1		1.0	240	AEGL
AEGL-1		1.0	480	AEGL
AEGL-2		250	10	AEGL
AEGL-2		83	30	AEGL
AEGL-2		40	60	AEGL
AEGL-2		10	240	AEGL
AEGL-2		5	480	AEGL
AEGL-3		740	10	AEGL
AEGL-3		250	30	AEGL
AEGL-3		120	60	AEGL
AEGL-3		31	240	AEGL
AEGL-3		15	480	AEGL
CT State Dept. Health 1955	Human	2	5	0, no irritation
CT State Dept. Health 1955	Human	3	5	1, nasal and throat irritation, 1 subject
CT State Dept. Health 1955	Human	4	5	1, nasal and throat irritation, 3 subjects
CT State Dept. Health 1955	Human	5	5	1, nasal and throat irritation, 6 subjects
CT State Dept. Health 1955	Human	6	5	1, nasal and throat irritation, 6 subjects

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MacEwen and Vernot 1972	Rat	2,205	60	SL, 10% mortality
MacEwen and Vernot 1972	Rat	2,328	60	SL, 40% mortality
MacEwen and Vernot 1972	Rat	2,759	60	SL, 40% mortality
MacEwen and Vernot 1972	Rat	3,253	60	SL, 60% mortality
MacEwen and Vernot 1972	Rat	3,711	60	SL, 70% mortality
MacEwen and Vernot 1972	Rat	3,822	60	3, 100% mortality
MacEwen and Vernot 1972	Mouse	507	60	2, no mortality
MacEwen and Vernot 1972	Mouse	875	60	SL, 70% mortality
MacEwen and Vernot 1972	Mouse	1,036	60	SL, 90% mortality
MacEwen and Vernot 1972	Mouse	1,163	60	3, 100% mortality
Stavert et al. 1991	Rat	1,300	30	SL, 8% mortality

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

APPENDIX C

BENCHMARK CONCENTRATION CALCULATION

Hydrogen bromide BMCL₀₅

Probit Model. (Version: 2.8; Date: 02/20/2007)
 Input Data File: C:\BMDS\HBR05.(d)
 Gnuplot Plotting File: C:\BMDS\HBR05.plt Mon
 Dec 17 11:29:37 2007

BMDS MODEL RUN

The form of the probability function is:

$P[\text{response}] = \text{Background} + (1 - \text{Background}) * \text{CumNorm}(\text{Intercept} + \text{Slope} * \text{Log}(\text{Dose}))$, where CumNorm(.) is the cumulative normal distribution function

Dependent variable = COLUMN3
 Independent variable = COLUMN1
 Slope parameter is not restricted

Total number of observations = 7
 Total number of records with missing values = 0
 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
 background = 0 intercept
 = -29.967
 slope = 3.76563

Asymptotic Correlation Matrix of Parameter Estimates

(**The model parameter(s) - background have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix.)

	Intercept	Slope
Intercept	1	-1
Slope	-1	1

Analysis of Deviance Table

Model	Log (likelihood) No. Parameters	Deviance Test	Test d.f.	P-value
-------	---------------------------------	---------------	-----------	---------

Full model	-29.5498	7			
Fitted model	-32.7425	2	6.38533	5	0.2705
Reduced model	-48.2628	1	37.426	6	<.0001

AIC: 69.485

Hydrogen Bromide 455

Parameter Estimates

Variable	Estimate	Standard Error	95.0% Wald Confidence Interval	
			Lower Conf. Limit	Upper Conf. Limit
Background	0	NA		
Intercept	-27.4619	7.00164	-41.1848	-13.7389
Slope	3.45097	0.877253	1.73158	5.17035

and thus has no standard error. a bound implied by :

Goodness of Fit

Scaled					
Dose	Estimated Probability	Expected	Observed	Size	Residual
0.0000	0.0000	0.000	0	10	0.000
2205.0000	0.1855	1.855	1	10	-0.696
2328.0000	0.2397	2.397	4	10	1.188
2759.0000	0.4518	4.518	4	10	-0.329
3253.0000	0.6727	6.727	6	10	-0.490
3711.0000	0.8164	8.164	7	10	-0.951
3822.0000	0.8422	8.422	10	10	1.369

Chi Sq. = 5.02; DF = 5; P-value = 0.4134

Benchmark Dose Computation

Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95 BMC

= 1774.18

BMCL₀₅ = 1238.95

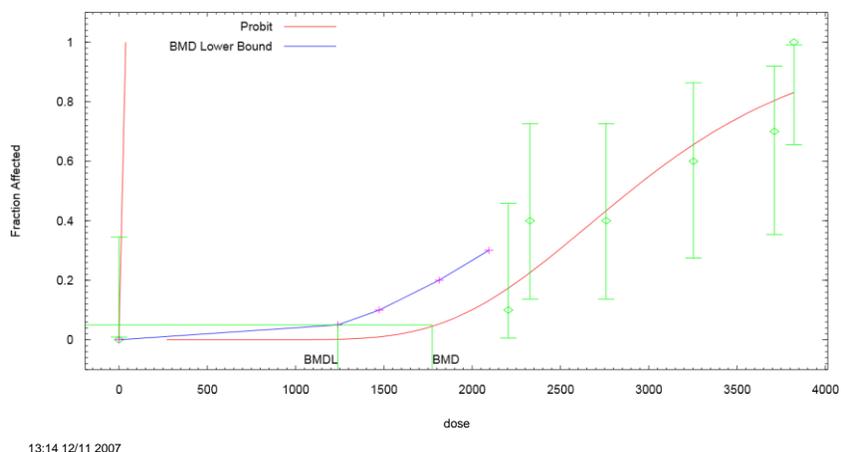


FIGURE C-1 Probit model with 0.95 confidence level.

APPENDIX D

**ACUTE EXPOSURE GUIDELINE LEVELS
FOR HYDROGEN BROMIDE**

Derivation Summary

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
1.0 ppm				

Key reference: Connecticut State Department of Health. 1955. Unpublished data. Occupational Health Section, CT Department of Health, Hartford, CT (as cited in ACGIH 2002)

Test species/Strain/Number: Humans, six subjects

Exposure route/Concentrations/Durations: Inhalation; 2, 3, 4, 5, or 6 ppm for several minutes

Effects: Odor detectable for all six subjects at all concentrations 2 ppm: No nasal, throat, or ocular irritation.
3 ppm: Nasal and throat irritation in one of six subjects; no ocular irritation. 4 ppm: Nasal irritation in three of six subjects; throat irritation in one of six subjects; no ocular irritation.
5 ppm: Nasal irritation in all six subjects; throat irritation in one of six subjects; no ocular irritation.

6 ppm: Nasal irritation in all six subjects; throat irritation in one of six subjects; no ocular irritation. 6 ppm: Nasal irritation in all six subjects; throat irritation in one of six subjects; no ocular irritation.

End point/Concentration/Rationale: 3 ppm is considered a threshold for notable discomfort

Uncertainty factors/Rationale:

Total uncertainty factor: 3

Intraspecies: 1, because key study is in human subjects

Intraspecies: 3; the response to a direct irritant is not expected to differ greatly among humans (NRC 2001), and the resulting AEGL-1 value appears protective for asthmatics on the basis of data on HCl (NRC 2004).

Modifying factor: Not applied

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: Not applied; humans adapt to the slight sensory irritation.

Data adequacy: Old but well-conducted study with human subjects. AEGL-1 value is supported by similar AEGL values for other chemicals in this class, HF and HCl. The databases on HF and HCl are robust.

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AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
250 ppm	83 ppm	40 ppm	10 ppm	5 ppm

Data adequacy: The database on HBr is inadequate, so AEGL-2 values were derived by dividing the AEGL-3 values by 3. This is supported by the steep concentration-response curve observed in the lethality studies by MacEwen and Vernot (1972).

AEGL-3 VALUES

10-min	30-min	1-hr	4-hr	8-hr
740 ppm	250 ppm	120 ppm	31 ppm	15 ppm

Key reference: MacEwen, J.D., and E.H. Vernot. 1972. Toxic Hazards Research Unit Annual Technical Report: 1972. AMRL-TR- 72-62. AD 755-358. Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH.

Test species/Strain/Number: Rat, Sprague-Dawley, 10 per group

Exposure route/Concentrations/Durations: Inhalation; 2,205-3,822 ppm for 1 h

Effects:

Lethality:

2,205 ppm: 1/10

2,328 ppm: 4/10 2,759

ppm: 4/10

3,253 ppm: 6/10

3,711 ppm: 7/10

3,822 ppm: 10/10

End point/Concentration/Rationale: 1-h BMCL₀₅ of 1,239 ppm

Uncertainty factors/Rationale:

Total uncertainty factor: 10

Interspecies: 3, a direct-contact irritant is not expected to vary greatly between species (NRC 2001)

Intraspecies: 3, response to a direct-contact irritant is not expected to vary greatly among humans (NRC 2001)

Modifying factor: Not applied

Animal-to-human dosimetric adjustment: Insufficient data

Time scaling: $C^n \times t = k$; $n = 1$ on the basis of rat and mouse lethality data on HCl.

Data adequacy: Although there were only two well-conducted studies of HBr in the rat and mouse, the values are consistent with those for the related chemicals, HF and HCl. The databases for HF and HCl are robust.
