Acute Exposure Guideline Levels for Selected Airborne Chemicals, Volume 9

Committee on Acute Exposure Guideline Levels; Committee on Toxicology; National Research Council

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VOLUME 9

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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 approximately 200 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 ninth volume in

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

the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*. It reviews the AEGLs for bromine, ethylene oxide, furan, hydrogen sulfide, propylene oxide, and xylenes for scientific accuracy, completeness, and consistency with the NRC guideline reports. It also includes a chapter addressing the use of physiologically based pharmacokinetic (PBPK) models to support the derivation of AEGLs.

The committee's review of the AEGL documents involved both oral and written presentations to the committee by the NAC 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 nine 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 nine committee interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for bromine (twelfth and fifteenth interim reports, 2005 and 2008, respectively), ethylene oxide (tenth and fifteenth interim reports, 2004 and 2008, respectively), furan (sixth, eighth, and fifteenth interim reports, 2001, 2002, and 2008, respectively), hydrogen sulfide (third, sixth, seventh, eighth, and ninth interim reports, 2000, 2001, 2002, 2002, and 2003, respectively), propylene oxide (tenth interim report, 2004), xylenes (twelfth and fourteenth interim reports, 2005 and 2006, respectively), and the use of PBPK models to support the derivation of AEGLs (fifteenth interim report, 2008): Deepak Bhalla (Wayne State University), Harvey Clewell (The Hamner Institutes for Health Sciences), Rakesh Dixit (MedImmune/AstraZeneca Biologics, before he became a member of the committee), David Gaylor (Gaylor and Associates, LLC), Sidney Green (Howard University), A. Wallace Hayes (Harvard School of Public Health), Sam Kacew (University of Ottawa), Nancy Kerkvliet (Oregon State University), Florence K. Kinoshita (Hercules Incorporated [retired]), Kenneth Poirier (Toxicology Excellence for Risk Assessment),Charles R. Reinhardt (DuPont Haskell Laboratory [retired]), and Bernard M. Wagner (New York University Medical Center [retired]).

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of this volume before its release. The review of the third interim report, completed in 2000, was overseen by Mary Vore, University of Kentucky Medical Center. The reviews of the sixth interim report (2001), seventh interim report (2002), fourteenth interim report (2006), and fifteenth interim report (2008) were overseen by Robert Goyer, University of Western Ontario (retired). The reviews of the eighth interim report (2002) and tenth interim report (2004) were overseen by David H. Moore, Battelle Memorial Institute. The review of the ninth interim report (2003) was overseen by Judith A. Graham, American Chemistry Council (retired). The review of the twelfth interim report (2005) was overseen by David W. Gaylor, Gaylor and Associates, LLC. 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 the following persons: Ernest Falke, Marquea D. King, Iris A. Camacho, and Paul Tobin (all from EPA); and George Rusch (Honeywell, Inc.). The committee also acknowledges Raymond Wassel and Keegan Sawyer, the project directors for their work this project. Other staff members who contributed to this effort are James J. Reisa (director of the Board on Environmental Studies and Toxicology), Susan Martel (senior program officer for toxicology), Ruth Crossgrove (senior editor), Radiah Rose (manager of editorial projects), Mirsada Karalic-Loncarevic (manager of the Technical Information Center), Orin Luke (senior program assistant), and Tamara Dawson (program associate). Finally, I would like to thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

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

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

This report is the ninth 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 or Health. Although several public and private groups, such as the Occupational Safety and Health Administration and the American Conference of Governmental Industrial Hygienists, have established exposure limits for some substances and some exposures (e.g., workplace or ambient air quality), these limits are not easily or directly translated into emergency exposure limits for exposures at high levels

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

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

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

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

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

[1]NAC is composed of members from EPA, DOD, many other federal and state agencies, industry, academia, and other organizations. The NAC roster is shown on page 9.

upon cessation of exposure.

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

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

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

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

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

For most chemicals, actual human toxicity data are not available or critical information on exposure is lacking, so toxicity data from studies conducted in laboratory animals are extrapolated to estimate the potential toxicity in humans. Such extrapolation requires experienced scientific judgment. The toxicity data

for animal species most representative of humans in terms of pharmacodynamic and pharmacokinetic properties are used for determining AEGLs. If data are not available on the species that best represents humans, data from the most sensitive animal species are used. Uncertainty factors are commonly used when animal data are used to estimate risk levels for humans. The magnitude of uncertainty factors depends on the quality of the animal data used to determine the no-observed-adverse-effect level (NOAEL) and the mode of action of the substance in question. When available, pharmacokinetic data on tissue doses are considered for interspecies extrapolation.

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

REVIEW OF AEGL REPORTS

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

The AEGL draft reports are initially prepared by ad hoc AEGL development teams consisting of a chemical manager, two chemical reviewers, and a staff scientist of the NAC contractor—Oak Ridge National Laboratory. The draft documents are then reviewed by NAC and elevated from "draft" to "proposed" status. After the AEGL documents are approved by NAC, they are published in the *Federal Register* for public comment. The reports are 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 subcommittee is satisfied with the reviews.

Because of the enormous amount of data presented in AEGL reports, the NRC committee cannot verify all of the data used by NAC. The NRC committee relies on NAC for the accuracy and completeness of the toxicity data cited in the

AEGL reports. Thus far, the committee has prepared seven reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009, 2010). This report is the ninth volume in that series. AEGL documents for bromine, ethylene oxide, furan, hydrogen sulfide, propylene oxide, and xylenes are each published as an appendix in this report. This volume also contains a chapter on the use of physiologically based pharmacokinetic models to support the derivation of AEGLs. 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

1

Bromine[1]

Acute Exposure Guideline Levels

PREFACE

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

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL—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 have been defined as follows:

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

[1]This document was prepared by the AEGL Development Team composed of Sylvia Talmage (Oak Ridge National Laboratory) and Chemical Manager Ernest Falke (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances). 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 guideline reports (NRC 1993, 2001).

effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

Airborne concentrations below the AEGL-1 represent exposure levels 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 AEGLs 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

The halogen bromine (Br_2) is a dark reddish-brown volatile liquid at room temperature. Its oxidizing potential lies between that of chlorine and iodine. Bromine is used as a water disinfectant, for bleaching fibers, and in the manufacture of medicinal bromine compounds, dyestuffs, flame retardants, agricultural chemicals, inorganic bromide drilling fluids, and gasoline additives.

Bromine is a skin, eye, and respiratory-tract irritant. Inhalation causes respiratory-tract irritation and pulmonary edema. Although accidental human exposures have occurred, concentrations were either not reported or were judged unreliable. The data on the inhalation toxicity of bromine are sparse and, at times, conflicting. Aside from old and anecdotal information, the database is limited to one study with human subjects and two lethality studies with the mouse as the test species. One of the lethality studies (Bitron and Aharonson 1978) provided data sufficient for derivation of the relationship between concentrations that result in lethality (LC_{50} values [concentration with 50% lethality]) and exposure duration: $C^{2.2} \times t = k$ (chemical concentration in air with a chemical-specific exponent applied to a specific end point × exposure time = response).

The AEGL-1 was based on exposures of 20 healthy human subjects to concentrations of 0.1 to 1.0 ppm for at least 30 min (Rupp and Henschler 1967). Eye irritation, but not nose or throat irritation, occurred during a 30-min exposure at 0.1 ppm. At concentrations of ≥0.5 ppm, there was a stinging and burning sensation of the conjunctiva. The 30-min exposure to 0.1 ppm, which caused

mild irritation, was chosen as the basis for the AEGL-1. The 0.1-ppm concentration was divided by an intraspecies uncertainty factor of 3 to protect susceptible individuals. An intraspecies uncertainty factor of 3 was considered sufficient because workers have been occupationally exposed to 1 ppm with no symptoms other than "excess irritation" (Elkins 1959). The resulting 0.033-ppm concentration is 30-fold lower than the 1-ppm concentration that induced excess irritation in healthy workers. Effects at this low concentration appear to be limited to the eyes and upper respiratory tract; there is likely to be little penetration to the lower respiratory tract. Compared with the 0.5-ppm AEGL-1 concentration for chlorine, a chemical that more readily penetrates to the lower respiratory tract, the intraspecies uncertainty factor of 3 for bromine is considered adequate. An intraspecies uncertainty factor of 1 was applied to the 0.5-ppm test value for chlorine because this concentration failed to elicit an asthmatic response in atopic and asthmatic individuals. The resulting 30-min AEGL-1 value of 0.033 ppm was used for all AEGL-1 exposure durations, as adaptation to mild sensory irritation occurs.

The AEGL-2 was based on the exposure to approximately 1 ppm for 30 min, which the subjects in the above study (Rupp and Henschler 1967) found irritating (stinging and burning sensation of the conjunctiva and nose and throat irritation). The 30-min 1-ppm value was divided by an intraspecies uncertainty factor of 3 to protect susceptible individuals and time-scaled to the other AEGL-2 exposure durations by using the concentration-exposure duration relationship of $C^{2.2} \times t = k$ from the mouse lethality study. An intraspecies uncertainty factor of 3 was considered sufficient, as the symptoms may be below those defining the AEGL-2. Furthermore, compared with the 30-min AEGL-2 value of 2.8 ppm for chlorine, this value may be conservative. The 30-min value for the less well-scrubbed chlorine was based on transient changes in pulmonary parameters (without respiratory symptoms) in asthmatic and atopic individuals. No reliable studies with exposures to higher concentrations were located.

Both lethality studies with the mouse described the inhalation toxicity of both chlorine and bromine. However, both studies reported lower LC_{50} values for chlorine than those reported in more recent well-conducted studies. Nevertheless, the study that reported the lower lethal concentrations for chlorine was used for derivation of the AEGL-3 values for bromine (Schlagbauer and Henschler 1967). The data in this study showed a clear concentration-response relationship; the exposure duration was 30 min. Using probit analysis, a 30-min LC_{50} value of 204 ppm and a 30-min LC_{01} of 116 ppm were calculated. The 30-min LC_{01} of 116 ppm was used as the basis for calculation of AEGL-3 values. The 116-ppm LC_{01} was divided by a combined uncertainty factor of 10 (3 for interspecies differences [the mouse was the most sensitive species for lethal effects in tests with other halogens] and 3 for intraspecies differences [at high concentrations, bromine is corrosive to the mucous membranes of the respiratory system; effects are not expected to differ greatly among individuals]) and

scaled across time using the relationship $C^{2.2} \times t = k$, derived from the Bitron and Aharonson (1978) study.

The calculated values are shown in Table 1-1.

1. INTRODUCTION

Bromine, a halogen, is a dark reddish-brown volatile liquid that vaporizes readily to a red vapor at room temperature. The diatomic state persists in the liquid, gas, and solid phases. Chemically, the electronegativity and oxidizing potential of halogens decrease as the atomic weight increases, thus making bromine intermediate in oxidizing potential between chlorine and iodine. All the halogens form an acid in water, and the reactivity of these acids shows the same relationship as the elemental halogens. The water solubility of bromine is greater than that of chlorine (O'Neil et al. 2001; Teitelbaum 2001). Additional chemical and physical properties are listed in Table 1-2.

The uses of bromine include water disinfection, bleaching fibers and silk, and the manufacture of medicinal bromine compounds and dyestuffs (O'Neil et al. 2001). The global market for bromine-containing compounds includes flame retardants, agricultural chemicals (principally methyl bromide), inorganic bromide drilling fluids such as calcium bromide, and gasoline additives (Glauser 2009). Production of ethylene dibromide, a gasoline antiknock agent for leaded fuels has decreased substantially over the past years. Likewise, the use of brominated fumigants and pesticides, such as ethylene dibromide and methyl bromide, has been restricted in the United States (Teitelbaum 2001). Commercially, bromine is recovered from soluble bromide salts in salt lakes, inland seas, brine wells and seawater. Seawater contains bromine at a concentration of 65 ppm (Teitelbaum 2001).

In 2005, world production was estimated at 587,000 metric tons, most of the bromine being used for brominated flame retardants ((Glauser 2009). Several production plants are located near natural brine sites in Arkansas (Jackisch 1992). Bromine is shipped in bulk quantities in 7,570-liter (L) and 15,140-L lead-lined pressure tank cars or 6,435- to 6,813-L nickel-clad pressure tank trailers filled to at least 92% capacity (Jackisch 1992). Bromine is also shipped in 600-, 1,200-, and 1,800-gallon tank trucks and 2,300- and 4,400-gallon tank cars (Great Lakes Chemical Corporation 1996).

Bromine is a skin, eye, and respiratory tract irritant (Teitelbaum 2001). All of the exposure data on humans and many of the experimental data on animals are extremely old, provide few experimental details, or conflict with more recent information. Therefore, many of the data are considered unreliable. Two inhalation studies with the mouse as the test species and using several concentrations and exposure durations were located. However, both of these studies report values for chlorine that are much lower than those of other researchers.

TABLE 1-1 Summary of AEGL Values for Bromine

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (Nondisabling)	0.033 ppm (0.22 mg/m^3)	0.033 ppm (0.22 mg/m^3)	0.033 ppm (0.22 mg/m^3)	0.033 ppm (0.22 mg/m^3)	0.033 ppm (0.22 mg/m^3)	Eye irritation in humans (Rupp and Henschler 1967)
AEGL-2 (Disabling)	0.55 ppm (3.6 mg/m^3)	0.33 ppm (2.2 mg/m^3)	0.24 ppm (1.6 mg/m^3)	0.13 ppm (0.85 mg/m^3)	0.095 ppm (0.62 mg/m^3)	Conjunctiva and nose and throat irritation in humans (Rupp and Henschler 1967)
AEGL-3 (Lethal)	19 ppm (124 mg/m^3)	12 ppm (78 mg/m^3)	8.5 ppm (55 mg/m^3)	4.5 ppm (29 mg/m^3)	3.3 ppm (21 mg/m^3)	30 min LC_{01} in mice (Schlagbauer and Henschler 1967)

TABLE 1-2 Chemical and Physical Data for Bromine

Parameter	Data	Reference
Synonyms	Dibromine	HSDB 2008
CAS registry number	7726-95-6	O'Neil et al. 2001
Chemical formula	Br_2	O'Neil et al. 2001
Structure	Br-Br	O'Neil et al. 2001
Molecular weight	159.9 (Br_2)	O'Neil et al. 2001
Physical state	Dark, reddish-brown fuming liquid, vaporizes rapidly at room temperature	O'Neil et al. 2001
Melting and boiling point	−7.25ºC/59.47ºC	O'Neil et al. 2001
Solubility	17 g/L in water at 20ºC	Teitelbaum 2001
Vapor pressure	175 mmHg at 20ºC	AIHA 2001
Vapor density (air = 1)	3.5	AIHA 2001
Liquid density (water = 1)	3.1	O'Neil et al. 2001
Flammability	Not flammable; may cause fire on contact with combustibles	DOT 1985
Conversion factors (Br_2)	1 ppm = 6.5 mg/m^3 1 mg/m^3 = 0.15 ppm	AIHA 2001

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Champeix et al. (1970) described the case of a worker exposed to an unknown concentration of vapor during an industrial accident. A postmortem examination revealed bromine burns to 20% of the body, extensive pulmonary and

tracheal damage, and effects on the kidneys and liver. In another industrial accident, eight workers were exposed to an unknown concentration of bromine vapor (Suntych 1953). Three workers developed bronchopneumonia, one developed blepharospasm, and the remainder developed laryngitis. One worker died as the result of sudden circulatory failure associated with bronchopneumonia.

Carel et al. (1992) reported a transportation accident involving a semitrailer truck carrying liquid bromine on an isolated stretch of highway in the Negev Desert, Israel. The driver was pinned in the cabin of the truck and was unable to free himself or reach his protective equipment. He died of bromine intoxication 3 h after the accident occurred.

Using primarily the database on chlorine, the relationship between the toxicity of chlorine and bromine, and the relationship between concentration and time from animal lethality data, Withers and Lees (1986) calculated an LC_{50} for humans exposed to bromine. Their model incorporates the effects of physical activity, inhalation rate, the effectiveness of medical treatment, and the lethal toxic load function (the relationship between lethality, concentration, and time). Concentrations were based on the estimate that bromine is 1.5 times less toxic than chlorine. The estimated 30-min LC_{50} at a standard level of activity (inhalation rate of 12 L/min) for the regular, vulnerable, and average (regular + vulnerable) populations were 375, 150, and 315 ppm, respectively. Estimated LC_{10} values for a 10-min exposure were 325, 130, and 208 ppm, respectively.

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold

The odor threshold for bromine has been variously reported at approximately 0.01 to 3.8 ppm (Rupp and Henschler 1967; Billings and Jonas 1981; Amoore and Hautala 1983; Ruth 1986). Ruth (1986) reported the threshold for irritation at 0.3 ppm, but the source of the data was not stated. Rupp and Henschler (1967) reported that healthy subjects had difficulty distinguishing between the odor of chlorine and the odor of bromine at concentrations up to 1 ppm, the highest concentration tested. The odor has been reported as suffocating by O'Neil et al. (2001) and bleachy and penetrating by Ruth (1986).

2.2.2. General Toxic Effects

The signs and symptoms associated with human exposure to low concentrations include upper airways irritation, inflammation of the eyelids, lacrimation, coughing, nosebleed, and a feeling of oppression, dizziness, and headache (Flury and Zernik 1931; Alexandrov 1983; Teitelbaum 2001). After several hours these symptoms may be followed by abdominal pain and diarrhea and a measles-like eruption on the trunk and extremities. Inhalation of "larger quantities" results in brown coloration of the eyes, tongue, and mucous membranes of

the mouth, catarrh, salivation, coughing, feeling of suffocation, glottis cramps, hoarseness, bronchitis, and bronchial asthma (Flury and Zernik 1931). Bromine was reported to produce a stinging and burning sensation of the conjunctiva at exposures of ≥0.5 ppm (Rupp and Henschler 1967). Chronic exposure to bromine resulting in excessive tissue levels of bromide ions (bromism) may lead to slowing of cerebration, impaired memory, anorexia, skin rash, headache, slurring of speech, confusion, weakness, disturbed reflexes, drowsiness, and mild conjunctivitis (EPA 1988).

Irritant levels for bromine have been reported in several sources. Many of the data are extremely old and are compromised by inadequate descriptions of vapor-generation methods, analytic-measurement methods, and exposure durations. These data and reviews are cited here for completeness.

Henderson and Haggard (1943), relying on older data including Matt (1889) and Flury and Zernik (1931) who cite Lehmann (1887), stated that 40-60 ppm is dangerous for brief exposures, 4 ppm is the maximum concentration that can be tolerated for 0.5 to 1 h, and 0.1 to 0.15 ppm can be tolerated for prolonged periods of time. Flury and Zernik (1931) and Withers and Lees (1986) cited the data of Matt (1889) who exposed human volunteers to bromine vapor (bromine was poured into a room) for 16 min to 7.67 h. Under this exposure scenario, Matt (1889) stated that 1-2 ppm could be tolerated by workers indefinitely, 3.5 ppm is tolerable for 30 min to 1 h, and 4 ppm is intolerable for work conditions.

Workers regularly exposed to bromine concentrations at approximately 0.3 to 0.6 ppm for 1 year experienced headache; pain in the joints, stomach, and chest; irritability; and loss of appetite (Alexandrov 1983). Long-term exposure can lead to nervous system disorders, myocardial degeneration, and thyroid hyperplasia. The source of the Alexandrov (1983) data was not given. Elkins (1959), citing a personal communication, reported that 1 ppm in a Massachusetts plant handling liquid bromine was judged to be excessively irritating. Flury and Zernik (1931) cited the data of Lehmann (1887) who reported that exposure to 0.75 ppm in a workroom caused no symptoms in 6 h. OSHA (unpublished material, 1997) monitoring data taken from January 1, 1985, to January 1, 1997, and involving 22 samples from 10 area offices, showed that workers are currently exposed to concentrations between 0.00 and 0.18 ppm. "Total times" for the 0.18-ppm exposures ranged from 15 min to 7.5 h.

2.2.3. Clinical Study

In a clinical study, Rupp and Henschler (1967) determined the odor threshold and subjective irritation concentrations of both chlorine and bromine. These authors subjected 20 healthy students to "low concentrations" of bromine or chlorine in an 8 m^3 exposure chamber. Bromine gas was generated directly from a heated 2-L flask containing 50 mL of the liquid; dilutions were made

with fresh air. Analytic determinations were made titrimetrically with thiosulfate solution (higher concentrations) or spectrophotometrically (concentrations below 0.1 ppm). Samples were collected in potassium iodide solution (higher concentrations) or by absorption by *o*-toluidine hydrochloride (lower concentrations). The odor threshold for bromine was tested at concentrations of 0.01, 0.02, 0.05, 0.1, 0.2, 0.5, and 1.0 ppm over a 30-min duration. Odor intensity was evaluated with the descriptors: minimal, medium strong, strong, and very strong. Subjective eye, nose, and throat irritation was evaluated as concentrations increased from 0 to 0.9 ppm over a 1-h duration.

A total of 20 students were tested, with 3-4 entering the exposure chamber at one time. Upon chamber entry, odor of bromine was noted by all 20 individuals at a concentration of 0.01 ppm, with an intensity of minimal to medium strong. At 0.2 ppm, most subjects rated odor intensity between medium strong and very strong. In the second part of the study, the subjects recorded their irritation every 5 min over a 60-min period. Eye irritation was first noted at a bromine concentration of 0.1 ppm and occurred within the first 30 min of exposure. At concentrations of 0.2 ppm and higher, distinct nose, eye, and throat irritation occurred, with a rapidly increasing concentration response. Between 0.5 and 0.9 ppm, a 5-min exposure was perceived as uncomfortable (concentrations of 0.5 to 0.9 ppm were irritating to the conjunctiva, nose, and throat.); however, the intensity of effect did not increase above 0.5 ppm. Irritation appeared to be limited to the eyes, nose, and throat; a "compelling cough stimulus" was not attained at concentrations up to 0.9 ppm. At similar concentrations, bromine was found to be more irritating than chlorine. In evaluating their own experiment, the authors noted that the actual concentrations were approximately 40% (range 17-57%) less than the nominal concentrations reported above. Measurements were taken in the vicinity of a wall and not in the immediate area of the subjects. In evaluating the experimental results, Henschler considered the threshold for subjective discomfort to be 0.5 ppm (D. Henschler, Institut for Toxicology, Wurzburg, Germany, personal commun., Dec. 21, 1999).

In the same study, Rupp and Henschler (1967) reported sensory irritation for chlorine at concentrations that proved to be nonirritating in later well-conducted studies (reviewed in 54 Fed. Reg. 2455[1989]). For example, Rupp and Henschler (1967) reported conjunctival pain in several subjects after 15 min of exposure to chlorine at 0.5 ppm, whereas, in a study by Rotman et al. (1983), healthy subjects reported no serious subjective symptoms of irritation from chlorine at a concentration of 1 ppm for 8 h. The lack of controls in the Rupp and Henschler (1967) study as well some methodologic shortcomings in the chlorine part of the study are discussed by OSHA (54 Fed. Reg. 2455 [1989]). The more recent studies of odor thresholds reported higher concentrations than those reported in the Rupp and Henschler (1967) study. It should also be noted that concentration and exposure-duration data reported in the text and figures of the Rupp and Henschler study are conflicting.

2.2.4. Accidents

On the morning of November 8, 1984, an accident at a chemical plant in Geneva, Switzerland, resulted in the release of 550 kg of liquid bromine (Morabia et al. 1988). Bromine in gaseous form was released via the ventilation system with sufficient force to form a dense brown cloud that drifted into the neighborhood. The cloud remained low over the ground and drifted through the center of the town before reaching Lake Geneva where it dissipated. The time elapsed from the release to disappearance of the cloud over the lake was approximately 5 h. An ozone analyzer located at the Ecotoxicological Centre of the Canton of Geneva (location not given) detected an oxidizing substance between 10 and 12 o'clock that morning. At an undefined time, the centre measured bromine concentrations (Draeger tubes equipped with chlorine reactive tubes) to define the outside limits of the potentially contaminated zone. These concentrations were between 0.2 and 0.5 ppm; concentrations were not measured initially or in the vicinity of the plant.

Ninety-one patients were admitted to the casualty, outpatient, and ophthalmology departments of the University Hospital at Geneva (Morabia et al. 1988). These patients reported signs and symptoms of eye irritation (90%), upper airways irritation (68%), cough (47%), expectoration (34%), and headache (46%). One patient, a worker at the plant, was treated for severe acute bronchitis; following hydrocortisone treatment, he rapidly recovered and was discharged the next day. In the remainder of the patients, symptoms were considered moderate and self-limiting. A 1-month follow-up of 62 of the patients indicated that there were no serious late complications.

Following the transportation accident described by Carel et al. (1990, 1992) in Section 2.1 above, several motorists were exposed to bromine vapor when they stopped to assist the driver of the truck. These exposures produced only mild respiratory symptoms and first and second degree burns to exposed areas of the skin. Four persons were treated with steroids because of shortness of breath; one, a heavy smoker, had diffuse lung wheezes. Six to eight weeks after the accident, four of the exposed motorists complained of cough, shortness of breath, chest tightness, eye irritation, headache, dizziness, fatigue, memory disturbances, and sleep and sexual disturbances. Clinical and laboratory examinations, however, revealed no abnormal findings.

2.3. Developmental and Reproductive Effects

No data concerning developmental and reproductive effects of bromine exposure in humans by the inhalation route were identified in the available literature. Chronic bromism has been associated with two cases of developmental problems (EPA 1988). The bromism was a result of ingestion of bromide salts.

2.4. Genotoxicity

No data concerning the genotoxicity of bromine in humans were identified in the available literature.

2.5. Carcinogenicity

No data concerning the carcinogenicity of bromine in humans were identified in the available literature.

2.6. Summary

No inhalation studies on the developmental and reproductive toxicity, genotoxicity, or carcinogenicity of bromine in humans were located in the available literature. Human exposures may cause eye, skin, and mucous membrane irritation as well as headache, abdominal pain, and dyspnea (Teitelbaum 2001). Incidences of human exposures were found, but few clear concentration-exposure durations were reported. Some of these data indicate that concentrations of ≤1.0 ppm are irritating (Elkins 1959; Rupp and Henschler 1967; Alexandrov 1983; Ruth 1986). Other data are quoted from secondary and tertiary sources. A study using human subjects reported eye irritation at a concentration of 0.1 ppm and additional sensory irritation at concentrations of ≥0.2 ppm (Rupp and Henschler 1967). The results of parts of this study do not agree with data or statements of other, more recent investigators (Rotman et al. 1983; Ruth 1986; 54 Fed. Reg. 2455 [1989]).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Several recent sources cited the data of Flury and Zernik (1931), who cited the data of Lehmann (1887). These data are so old that they should be considered unreliable but are reported here for completeness. Lehmann (1887) reported that inhalation exposure of three animal species at 180 ppm (duration not reported) caused severe irritation and corneal clouding, the 7-h LC_{10} was 140 ppm for both the cat and guinea pig, and exposure at 300 ppm for 3 h caused deaths in rabbits and guinea pigs. Observations at the latter concentration-exposure time revealed pulmonary edema, deposits on the trachea and bronchi, and gastric hemorrhage.

Henderson and Haggard (1943) reported that a concentration of 1,000 ppm is rapidly fatal. Their source of data appears to be Hill (1915) who experimented with guinea pigs. The original data were not located.

3.1.1. Rats

Ivanov et al. (1976) reported an LC_{50} of 415 ppm for the rat. Neither the exposure time nor the original citation were stated.

3.1.2. Mice

Ivanov et al. (1976) reported an LC_{50} of 4,46 ppm for the mouse. Neither the exposure time nor the original citation was stated.

Two other acute lethality studies, both using the mouse as the test species, provided details of the exposures. Bitron and Aharonson (1978) exposed 1-month-old male albino mice (28 to 126 mice/group) to concentrations of 240 or 750 ppm for four exposure times at each concentration and calculated 50% mortality as a function of exposure time (median lethal exposure time, or Lt_{50}). Bromine vapor was generated from the liquid, collected in an aqueous solution of potassium iodide, and determined by standard iodometry. Mice were restrained in cylindrical glass exposure chambers. Postexposure observations were made over a 30-day period. The data displayed a clear dose-response relationship and Lt_{50} values for the 240 and 750 ppm exposures were 100 and 9 min, respectively. Mortality at each concentration-exposure duration is listed in Table 1-3. Dose-response curves were presented graphically, and the values listed in Table 1-3 were estimated from the graph. The results of this work were unusual in that many of the deaths were delayed, occurring during the second week of the observation period, rather than during and immediately following exposure. The authors exposed similar groups to chlorine, and it was noted that chlorine is considerably more toxic to mice than bromine.

Using the method of Litchfield and Wilcoxon (1949), Bitron and Aharonson (1978) also computed 0 or 100% mortalities, which they presented graphically. For the 240-ppm concentration, no deaths were calculated to occur following an exposure for 20 min. For the 750-ppm concentration, no deaths were calculated to occur following approximately 5 min of exposure (same as the experimental value).

TABLE 1-3 Mortality in Mice Exposed to Bromine at 240 or 750 ppm

Concentration (ppm)	Exposure Duration (min)	Mortality (%)
240	24	7
	65	27
	120	50
	215	90
750	5	0
	7	44
	13	73
	24	95

Source: Bitron and Aharonson 1978. Reprinted with permission; copyright 1978, American Industrial Hygiene Association.

Schlagbauer and Henschler (1967) exposed groups of 10 female NMRI mice (weight 18-23 g) to various concentrations of bromine for 30 min in order to calculate an LC_{50}. Generation and measurement methods were the same as in a companion study that used human subjects (Rupp and Henschler 1967). The data showed a clear dose-response relationship (Table 1-4). The authors calculated a 30-min LC_{50} of 174 ppm. The 30-min LC_{01} was 116 ppm.

In a second experiment (Schlagbauer and Henschler 1967), mice were exposed to bromine at concentrations of 22 or 40 ppm for 3 or 6 h, and mortalities were determined after 10 days. No deaths occurred at 22 ppm for 3 h; mortality was 70% for the 6-h exposure. At a concentration of 40 ppm, deaths occurred following the 3-h (3/10) and 6-h (8/10) exposures. Again, it was observed that chlorine was more toxic than bromine (the 30-min LC_{50} value of bromine was approximately 1.5 times that of chlorine). The present study did not use a control group. In reviewing the data on chlorine and bromine, Withers and Lees (1986) noted that the chlorine 30-min LC_{50} value of Schlagbauer and Henschler (1967) is lower than values of other researchers.

3.2. Nonlethal Toxicity

Ivanov et al. (1976) reported on exposures of groups of eight rats (a total of 800 rats) to concentrations of bromine ranging from 0.12 to 77 ppm. The exposure time was 4 h. The authors quoted an earlier source, and no details of the exposure methods or vapor generation or analytic techniques were given. A concentration of 1.5 ppm decreased respiratory frequency by 19% (134 respirations/min in the exposed group compared with 165 respirations/min in the controls). "Olfactory sharpness," the ability to react to or detect other compounds, appeared to be decreased, and the number of "free cells" in the upper respiratory pathways was increased. The authors considered this concentration the threshold for irritation, which they defined as "$Lim_{ir.}$" Respiratory, cardiac, vascular, neural ("SPP" and reflexes), and endocrine system (dynamics of ^{131}I accumulation and release by the thyroid) effects developed at 50 mg/m^3 (7.7 ppm), and spermatogenesis was affected at 100 mg/m^3 (15 ppm). No further details were reported.

Ivanov et al. (1976) also reported on subchronic (4 month) exposures of rats at three concentrations: 1.9, 0.2, and 0.02 ppm. A 4-month exposure to bromine at 1.9 ppm produced effects on the respiratory, olfactory, and endocrine systems. Exposure at 0.2 ppm for 4 months led to less pronounced changes, which were reversible after a 1-month recovery period. A concentration of 0.02 ppm had no effect.

In a 28-day feeding study with rats, liquid bromine (38%) administered at 20 mg/kg/day induced clinical signs of salivation and decreased activity; increased red-blood-cell count, hemoglobin and packed cell volume (all reversible in 14 days); increased serum glucose; and increased urinary volume with protein (EPA 2005).

TABLE 1-4 Mortality in Mice Exposed to Bromine at 111 to 315 ppm for 30 Min

Concentration (ppm)	Morality
111	0/10
40	3/10
199	6/10
236	9/10
252	10/10
268	9/10
290	10/10
315	10/10

Source: Schlagbauer and Henschler 1967. Reprinted with permission; copyright 1967, *International Archives of Occupational and Environmental Health*.

3.3. Developmental and Reproductive Effects

No data concerning developmental effects of bromine in animals were found in the available literature. Ivanov et al. (1976) reported that a 4-h exposure to bromine at 15 ppm affected spermatogenesis in male mice; further details were not reported.

3.4. Genotoxicity

Liquid bromine, tested at a concentration of 38.0% and a volume of 10 µg/plate, was positive in the *Salmonella typhimurium* microsome reverse mutation assay with strains TA 1537 and TA 100 in the absence of S9 and with strain TA 1537 in the presence of S9 activation. Bromine was cytotoxic for all strains with and without metabolic activation at more than 3,333 µg/plate (EPA 2002).

3.5. Chronic Toxicity and Carcinogenicity

No data concerning the chronic toxicity or carcinogenicity of bromine in animals were located in the available literature. Potassium bromate ($KBrO_3$) has been shown to be a renal carcinogen in rats. The mechanism of action has been attributed to the generation of oxygen radicals by $KBrO_3$, a strong oxidizer. KBr is not a carcinogen (Kurokawa et al. 1990).

3.6. Summary

Data on the acute inhalation toxicity of bromine are sparse. Most of the older experimental data using animal species are of questionable reliability.

Only two studies provide experimental methods and details adequate for consideration in derivation of AEGLs. Bitron and Aharonson (1978) determined Lt_{50} values for one species, the mouse. The Lt_{50} at a concentration of 750 ppm was 9 min, and the Lt_{50} at a concentration of 240 ppm was 100 min. No deaths occurred or were predicted to occur during a 5-min exposure at 750 ppm or during a 20-min exposure at 240 ppm. The study of Schlagbauer and Henschler (1967) reported much lower lethal values for bromine as well as for chlorine. Their 30-min LC_{50} value for the mouse was 174 ppm. A concentration of 15 ppm for 4 h affected spermatogenesis in male mice (Ivanov et al. 1976). Limited data were located concerning genotoxicity, and no data concerning developmental effects or carcinogenicity were located in the available literature.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No data on the absorption, distribution, metabolism, or excretion of bromine following inhalation exposures in humans or animals were located in the available literature. Alexandrov (1983) stated that bromine may enter the body following inhalation, ingestion, or skin application, but the source of the data was not provided. Bromine gas reacts at the site of contact and metabolic and kinetic considerations are not relevant regarding the determination of AEGL values.

4.2. Mechanism of Toxicity

Bromine, a strong oxidizing agent, is a respiratory irritant and can cause pulmonary edema in humans and animals (Teitelbaum 2001). Reaction with water results in the formation of hypobromous acid, HOBr, which slowly decomposes to hydrobromic acid and oxygen (Downs and Adams 1973).

4.3. Structure-Activity Relationships

The irritating potential of mucus membrane irritants may be related to their water solubility. At 20-25ºC, the water solubility of bromine is 0.214 mol/L, whereas that of chlorine is 0.092 mol/L (Teitelbaum 2001). Water solubility determines the scrubbing capacity or penetration of a gas into the respiratory tract. On the basis of water solubility, bromine would react more intensely in the upper respiratory tract and thus be better scrubbed than chlorine. As a result of being well-scrubbed in the upper nasal passages, bromine may produce a feeling of irritation at a lower concentration than chlorine. Chlorine, on the other hand, would more readily penetrate to the lower respiratory tract, resulting in lethality at concentrations that are lower than those for bromine. This differ-

ence in lethality is substantiated by the study of Rupp and Henschler (1967). Bitron and Aharonson (1978) observed similar results for lethality in studies with the mouse. The 30-min LC_{50} values for chlorine and bromine are listed in Table 1-5. The 30-min Lt_{50} (LC_{50}) values for Bitron and Aharonson (1978) were determined using the relationship between concentration and exposure time as explained in Section 7.2; values for the two concentration-exposure durations were averaged. Because of the 30-day postexposure observation period in this study, the Lt_{50} can be defined as an LC_{50}. For comparison purposes, the 30-min LC_{50} value for fluorine in the mouse is 225 ppm (Keplinger and Suissa 1968).

Bromine is more water soluble than chlorine (Teitelbaum 2001) and would be scrubbed to a greater extent in the nasal passages than chlorine; relatively smaller amounts would reach the lungs. Because of its reactive potential and decomposition in the presence of water (Teitelbaum 2001), the solubility of fluorine has not been defined. In the respiratory tract of the rat, the relative inhalation toxicities of the hydrohalous acids formed is HF > HCl ≥ HBr (Kusewitt et al. 1989).

4.4. Other Relevant Information

4.4.1. Species Differences

No relatively recent data sufficient for comparing differences in species sensitivity for either irritation or lethality were located in the available literature. In the older data, no differences were found in lethality values in two separate exposures between the cat and guinea pig and guinea pig and rabbit (Lehmann 1887). For the halogens fluorine and chlorine, the mouse is the most sensitive tested species (NRC 2004, 2010).

4.4.2. Susceptible Populations

Individuals with asthma or other respiratory diseases may be more susceptible to the effects of respiratory irritants than healthy individuals. No data on bromine and the asthmatic population were located.

TABLE 1-5 Relative Toxicities of Chlorine and Bromine to the Mouse

Chemical	30-Min LC_{50}	Reference
Chlorine	203	Bitron and Aharonson 1978
	127	Schlagbauer and Henschler 1967
Bromine	424	Bitron and Aharonson 1978
	174	Schlagbauer and Henschler 1967

4.4.3. Concentration-Exposure Duration Relationship

ten Berge et al. (1986) used the two Lt_{50} data points from the study by Bitron and Aharonson (1978) to determine the concentration and exposure duration relationship of $C^{2.2} \times t = k$, where C is concentration, t is time, and k is a constant.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

Many of the data on bromine are old, unreferenced, anecdotal, or conflicting (Elkins 1959; Rupp and Henschler 1967; Alexandrov 1983; Ruth 1986; HSDB 2008). Rupp and Henschler (1967) reported that eye irritation occurred at 0.1 ppm. Current monitoring data from the Occupational Safety and Health Administration (OSHA) show that workers are exposed to concentrations up to 0.18 ppm, presumably without irritation. Ruth (1986) reported that the irritation threshold (undefined) was 0.3 ppm; workers exposed to 0.3 to 0.6 ppm for 1 year suffered various symptoms (Alexandrov 1983). Except for the study of Rupp and Henschler (1967), all of these values are either poorly documented or appear unusually low compared with more recent data for other halogens. The only clinical study, Rupp and Henschler (1967), reported eye irritation, but no nose or throat irritation, at a concentration of 0.1 ppm for 30 min. Concentrations of 0.5 to 0.9 ppm were irritating to the conjunctiva, nose, and throat. The intensity of the irritation was not well-described, and their values in related experiments (chlorine) are low in comparison to other researchers.

The more-robust database for chlorine rather than bromine can also be considered when addressing the irritation potential of halogens. In four clinical studies, some with atopic or asthmatic individuals, exposure to chlorine at 0.4 or 0.5 ppm for various periods of time did not produce airway hyper-reactivity or an asthmatic response (Anglen 1981; Rotman et al. 1983; D'Alessandro et al. 1996; Shusterman et al. 1998). Because sensitive individuals were tested, an intraspecies uncertainty factor of 1 was applied to derive an AEGL-1 value for chlorine (NRC 2004).

5.2. Summary of Animal Data Relevant to AEGL-1

No useful data were available. Ivanov et al. (1976) reported that the threshold of irritation for bromine for rats was 1.5 ppm during a 4-h exposure, but they quoted an earlier source and provided few experimental details.

5.3. Derivation of AEGL-1

The AEGL-1 was based on exposures of 20 healthy human subjects to

concentrations of 0.1 to 0.9 ppm for up to 60 min (Rupp and Henschler 1967). Eye irritation, but no nose or throat irritation, occurred during a 30-min exposure at 0.1 ppm. At concentrations ≥0.5 ppm, there was a stinging and burning sensation of the conjunctiva. The 30-min 0.1 ppm concentration, which caused mild irritation, was divided by an intraspecies uncertainty factor of 3 to protect susceptible individuals. This adjustment was considered appropriate for acute exposure to chemicals in which the mechanism of action involves surface contact irritation of ocular or respiratory tract tissue or both rather than systemic activity following absorption and distribution of the parent chemical or a biotransformation product to a target tissue (NRC 2001). An intraspecies uncertainty factor of 3 was also considered sufficient because workers have been occupationally exposed to bromine at 1 ppm with no other symptoms than "excess irritation" (Elkins 1959). The resulting 0.033 ppm concentration is 30-fold lower than the 1 ppm concentration that induced excess irritation in healthy workers. Effects at this low concentration appear to be limited to the eyes and upper respiratory tract; there is likely to be little penetration to the lower respiratory tract. Compared with the AEGL-1 value of 0.5 ppm for chlorine, a chemical that more readily penetrates to the lower respiratory tract, the uncertainty factor of 3 is appropriate. The 0.5-ppm concentration of chlorine, with no uncertainty factor applied, was considered protective of the tested atopic and asthmatic individuals. The 30-min AEGL-1 value of 0.033 ppm for bromine was used across all exposure durations because adaptation occurs to mild sensory irritation (Table 1-6). Calculations for AEGL values are in Appendix A. Appendix B is a graph of the toxicity data in relationship to the AEGL values.

The proposed values are far below the 0.3 ppm threshold for irritation in humans reported by Ruth (1986). The values are 27- to 160-fold below the threshold for irritation in rats, as reported by Ivanov et al. (1976), which was 1.5 ppm for 4-h.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Elkins (1959) quoted 1 ppm as excessively irritating in workers, but these were chronic exposures. Alexandrov (1983) reported severe choking at 1.7-3.5 ppm, but his values were not documented. The healthy subjects in the study of Rupp and Henschler (1967) reported prickling or stinging of the eyes and nose and throat irritation at concentrations of 0.5 to 0.9 ppm (1.0 ppm for 30 min in the odor intensity study). These sensations were reported following exposures of greater than 30 min. The intensity of the symptoms was not well described.

TABLE 1-6 AEGL-1 Values for Bromine

10 min	30 min	1 h	4 h	8 h
0.033 ppm (0.22 mg/m^3)	0.033 ppm (0.22 mg/m^3)	0.033 ppm (0.22 mg/m^3)	0.033 ppm (0.22 mg/m^3)	0.033 ppm (0.22 mg/m^3)

6.2. Summary of Animal Data Relevant to AEGL-2

Ivanov et al. (1976) reported that the threshold for acute effects for a 4-h exposure of rats to bromine was 7.7 ppm, but they quoted an earlier source and provided few details.

6.3. Derivation of AEGL-2

The AEGL-2 was based on the exposure to bromine of 1 ppm (rounded from 0.9 ppm in the odor intensity study) for 30 min, which the subjects in the Rupp and Henschler (1967) study found irritating (stinging and burning sensation of the conjunctiva and nose and throat irritation). The 30-min 1 ppm value was divided by an intraspecies uncertainty factor of 3 to protect susceptible individuals and time-scaled to the other AEGL-2 exposure durations using the concentration-exposure duration relationship of $C^{2.2} \times t = k$ from the mouse lethality study. An intraspecies uncertainty factor of 3 was considered sufficient, as the symptoms may be below those defining an AEGL-2. Furthermore, compared with the 30-min AEGL-2 value of 2.8 ppm for chlorine, this value may be conservative. The 30-min value for the less well-scrubbed chlorine was based on transient changes in pulmonary parameters (without respiratory symptoms) in asthmatic and atopic individuals (Rotman et al. 1983; D'Alessandro et al. 1996). No reliable studies with exposures to higher concentrations were located. The calculated values appear in Table 1-7 and calculations are contained in Appendix A. Appendix B is a category graph of the toxicity data in relation to AEGL values.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No reliable human data relevant to derivation of an AEGL-3 values were located in the available literature.

TABLE 1-7 AEGL-2 Values for Bromine

10 min	30 min	1 h	4 h	8 h
0.55 ppm (3.6 mg/m^3)	0.33 ppm (2.2 mg/m^3)	0.24 ppm (1.6 mg/m^3)	0.13 ppm (0.85 mg/m^3)	0.095 ppm (0.62 mg/m^3)

7.2. Summary of Animal Data Relevant to AEGL-3

Two studies using the mouse provided data on lethality. Both studies provided lethality data on bromine and chlorine. Both studies reported lower LC_{50} values for chlorine than those reported for bromine in more recent well-conducted studies. Bitron and Aharonson (1978) calculated Lt_{50} values for bromine at a concentration of 750 ppm for 9 min in the mouse and at a concentration of 240 ppm for 100 min. The 240 and 750 ppm concentrations can be considered LC_{50} values for the tested times. Using the $C^{2.2} \times t = k$ relationship, these two values can be used to calculate 30-min LC_{50} values. The respective 30-min LC_{50} values are 415 and 434 ppm (average, 424 ppm). No deaths were calculated to occur at 750 ppm for 5 min or 240 ppm for 20 min.

The study by Schlagbauer and Henschler (1967) provided a lower LC_{50} for bromine for the mouse. The lethality data in their study showed a good concentration-response relationship and the exposure time was held constant at 30 min. Using probit analysis, a 30-min LC_{01} of 116 ppm was calculated.

7.3. Derivation of AEGL-3

Both lethality studies with the mouse described the inhalation toxicity of chlorine and bromine. However, both studies reported lower LC_{50} values for chlorine than those reported for bromine in more recent well-conducted studies. Nevertheless, the study that reported the lower lethal concentrations for chlorine was used for derivation of the AEGL-3 values for bromine (Schlagbauer and Henschler 1967). The data in this study showed a clear concentration-response relationship; furthermore, the exposure duration was longer than it was in the Bitron and Aharonson (1978) study. Using probit analysis, a 30-min LC_{50} value of 204 ppm and a 30-min LC_{01} of 116 ppm were calculated. The 30-min LC_{01} of 116 ppm was used as the basis for calculation of AEGL-3 values for bromine. The 116 ppm LC_{01} was divided by a combined uncertainty factor of 10 (3 for interspecies differences [the mouse was the most sensitive species for lethal effects in tests with other halogens] and 3 for intraspecies differences [at high concentrations, bromine is corrosive to the mucous membranes of the respiratory system; effects are not expected to differ greatly among individuals] [NRC 2001]) and scaled across time using the relationship of $C^{2.2} \times t = k$, which was derived from the Bitron and Aharonson (1978) study. Calculations are provided in Appendix A, and values appear in Table 1-8 below. Appendix B is a category graph of the toxicity data in relation to AEGL values.

The calculated AEGL-3 values for bromine are below those of chlorine (NRC 2004) and fluorine (NRC 2010) (Table 1-9). This result indicates that the values for bromine are protective, as chlorine is 1.5 times more toxic than bromine based on lethality in the mouse. As noted, the database for chlorine is extensive. In addition, the mice used by Bitron and Aharonson (1978) were young

and were restrained in glass enclosures during the exposures. Both of these factors increase the sensitivity of the tested species to chemical toxicity.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

The AEGLs for bromine were derived in the following manner. The AEGL-1 and AEGL-2 values were based on a study with 20 human subjects who were exposed to concentrations of 0.1 to 0.9-1.0 ppm (Rupp and Henschler 1967). Eye irritation noted within a 30- min exposure at 0.1 ppm was used as the basis for the AEGL-1. At 0.5 to 0.9 ppm (1.0 ppm), the nose and throat were also irritated. A 30-min exposure at 1 ppm was used as the basis for the AEGL-2 values. An intraspecies uncertainty factor of 3 was considered sufficient because irritation was confined to the eyes during the 0.1-ppm exposure (precluding an asthmatic response), and workers have been occupationally exposed at 1 ppm with no reported symptoms other than "excess irritation." The AEGL-1 values were not time-scaled, as adaptation to mild sensory irritation occurs. Time-scaling for the AEGL-2 was based on a lethality study with the mouse (Bitron and Aharonson 1978).

TABLE 1-8 AEGL-3 Values for Bromine

10 min	30 min	1 h	4 h	8 h
19 ppm (124 mg/m^3)	12 ppm (78 mg/m^3)	8.5 ppm (55 mg/m^3)	4.5 ppm (29 mg/m^3)	3.3 ppm (21 mg/m^3)

TABLE 1-9 Comparison of AEGL Values for Fluorine, Chlorine, and Bromine

Classification	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1					
Fluorine	1.7 ppm	1.7 ppm	1.7 ppm	1.7 ppm	1.7 ppm
Chlorine	0.5 ppm	0.5 ppm	0.5 ppm	0.5 ppm	0.5 ppm
Bromine	0.033 ppm	0.033 ppm	0.033 ppm	0.033 ppm	0.033 ppm
AEGL-2					
Fluorine	20 ppm	11 ppm	5.0 ppm	2.3 ppm	2.3 ppm
Chlorine	2.8 ppm	2.8 ppm	2.0 ppm	1.0 ppm	0.71 ppm
Bromine	0.55 ppm	0.33 ppm	0.24 ppm	0.13 ppm	0.095 ppm
AEGL-3					
Fluorine	36 ppm	19 ppm	13 ppm	5.7 ppm	5.7 ppm
Chlorine	50 ppm	28 ppm	20 ppm	10 ppm	7.1 ppm
Bromine	19 ppm	12 ppm	8.5 ppm	4.5 ppm	3.3 ppm

The AEGL-3 values for bromine were based on a study using the mouse (Schlagbauer and Henschler 1967). Thirty-minute exposures to several concentrations were tested. The data showed a clear concentration-response relationship from which LC_{50} and LC_{01}values could be calculated. The 30-min LC_{01} of 116 ppm, derived by probit analysis, was divided by a total uncertainty factor of 10 (3 each for interspecies and intraspecies differences, as the mouse is the most sensitive species in studies with halogens, and at high concentrations, bromine is corrosive to the respiratory tissues, and effects are not expected to differ greatly among species or between individuals) and scaled to the other exposure times using $C^{2.2} \times t = k$. The resulting values are lower than those for chlorine, which is known to be more toxic than bromine.

The AEGL values for three levels and five exposure periods are summarized in Table 1-10. Data and derivations are summarized in Appendix C.

8.2. Comparisons with Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures are listed in Table 1-11. The 1-h AEGL-1 and AEGL-2 values are below the respective emergency response planning guideline (ERPG) values. The ERPG values were based on an unobjectionable odor, 0.1 ppm (Rupp and Henschler 1967), and mild and transient health effects at slightly higher concentrations (Rupp and Henschler 1967; Morabia et al. 1986; D. Henschler, Institut for Toxicology, Wurzburg, Germany, personal commun., Dec. 21, 1999). The ERPG-2 was based on the same studies that reported that exposure to concentrations above 0.5 ppm caused coughing, dizziness, and intense irritation to the eyes, nose, and throat. The 1-h ERGP-3 was based on the mouse lethality studies of Bitron and Aharonson (1978) and Schlagbauer and Henschler (1967) and on the concentration- time relationship of Withers and Lees (1986). The 1-h AEGL-3 and ERPG-3 values are similar. The same references were used for derivation of all AEGL values.

TABLE 1-10 Summary of AEGL Values for Bromine

Classification	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	0.033 ppm (0.22 mg/m^3)	0.033 ppm (0.22 mg/m^3)	0.033 ppm (0.22 mg/m^3)	0.033 ppm (0.22 mg/m^3)	0.033 ppm (0.22 mg/m^3)
AEGL-2 (Disabling)	0.55 ppm (3.6 mg/m^3)	0.33 ppm (2.2 mg/m^3)	0.24 ppm (1.6 mg/m^3)	0.13 ppm (0.85 mg/m^3)	0.095 ppm (0.62 mg/m^3)
AEGL-3 (Lethal)	19 ppm (124 mg/m^3)	12 ppm (78 mg/m^3)	8.5 ppm (55 mg/m^3)	4.5 ppm (29 mg/m^3)	3.3 ppm (21 mg/m^3)

The immediately dangerous to life and health (IDLH) value is based on several reviews and specifically cites the data of Flury and Zernik (1931) and Henderson and Haggard (1943). Full-day workplace standards are all 0.1 ppm, with short-term allowable exposures at 0.2 and 0.3 ppm. The 8-h AEGL-1 and AEGL-2 values are below workplace standards.

TABLE 1-11 Extant Standards and Guidelines for Bromine

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	0.033 ppm	0.033 ppm	0.033 ppm	0.033 ppm	0.033 ppm
AEGL-2	0.55 ppm	0.33 ppm	0.24 ppm	0.13 ppm	0.095 ppm
AEGL-3	19 ppm	12 ppm	8.5 ppm	4.5 ppm	3.3 ppm
ERPG-1 (AIHA)[a]			0.1 ppm		
ERPG-2 (AIHA)			0.5 ppm		
ERPG-3 (AIHA)			5 ppm		
IDLH (NIOSH)[b]		3 ppm			
REL-TWA (NIOSH)[c]					0.1 ppm
PEL-TWA (OSHA)[d]					0.1 ppm
TLV-TWA (ACGIH)[e]					0.1 ppm
REL-STEL (NIOSH)[f]					0.3 ppm
TLV-STEL (ACGIH)[g]					0.2 ppm
MAK (Germany)[h]					Withdrawn
MAC (The Netherlands)[i]					0.1 ppm

[a]ERPG (emergency response planning guidelines, American Industrial Hygiene Association (AIHA 2001): The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action. The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects.

[b]IDLH (immediately dangerous to life or health, National Institute for Occupational Safety and Health) (NIOSH 1996) represents the maximum concentration from which

escape within 30 min would be possible without any escape-impairing symptoms or any irreversible health effects.

[c]REL-TWA (recommended exposure limits–time-weighted average, National Institute for Occupational Safety and Health) (NIOSH 2005) is analogous to the ACGIH TLV-TWA.

[d]PEL-TWA (permissible exposure limits–time-weighted average, Occupational Safety and Health Administration, OSHA) (29 CFR 1910.1000 [2003]) is analogous to the ACGIH TLV-TWA but is for exposures of no more than 10 h/d, 40 h/wk.

[e]TLV-TWA (Threshold Limit Value–time-weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 1996) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[f]REL-STEL (recommended exposure limits–short-term exposure limit, National Institute for Occupational Safety and Health) (NIOSH 2005) is analogous to the ACGIH TLV-TWA.

[g]TLV-STEL (Threshold Limit Value–short-term exposure limit, American Conference of Governmental Industrial Hygienists) (ACGIH 1996) is defined as a 15-min TWA exposure that should not be exceeded at any time during the workday even if the 8-h TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 min and should not occur more than four times per day. There should be at least 60 min between successive exposures in this range.

[h]MAK (maximale argeitsplatzkonzentration [maximum workplace concentration], Deutsche Forschungsgemeinschaft [German Research Association]) (DFG 2007) is analogous to the ACGIH TLV-TWA. The MAK for bromine was withdrawn in 2007, and bromine was placed in category IIB, substances for which no MAK value can be established at present.

[i]MAC (maximaal aanvaarde concentratie [maximum accepted concentration], SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment, The Hague, The Netherlands]) is analogous to the ACGIH TLV-TWA (MSZW 2004).

8.3. Data Adequacy and Research Needs

The data on the toxic effects of bromine are sparse. Because of the sparse-data, lower values were chosen for the AEGL-1 and AEGL-2 than might have been used in the presence of extensive data. No recent reliable human studies were available. Some of the studies that are quoted and requoted in toxicology books were performed as early as the 1880s; vapor generation and analytic techniques have improved since that time. The clinical study by Rupp and Henschler (1967) tested both bromine and chlorine and reported irritant values for chlorine that are lower than those in other studies. The values for bromine may be correspondingly low. Two lethality studies with the mouse as the test species were available for calculation of the AEGL-3 values. Both the key study, Schlagbauer and Henschler (1967), and the study by Bitron and Aharonson (1978) were noted to have lower lethality values for chlorine than those of many other investigators, and their values for bromine may be correspondingly low. Although bromine is less toxic than chlorine, the interim AEGL-3 values for bromine are less than those for chlorine (NRC 2004).

In the absence of reliable studies that address the end point of irritation, a study to determine the exposure concentration producing a 50% decrease in the respiratory rate (RD_{50}) in the mouse would be of value, particularly as it would confirm the irritation potential of bromine relative to that of chlorine.

9. REFERENCES

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APPENDIX A

DERIVATION OF AEGL VALUES FOR BROMINE

Derivation of AEGL-1

Key study:	Rupp and Henschler 1967
Toxicity end point:	Eye irritation in humans at 0.1 ppm for 30 min
Uncertainty factors:	3 for intraspecies variability
Time-scaling:	Not applied; adaptation to mild sensory irritation
Modifying factor:	None
Calculation:	0.1 ppm/3 = 0.033 ppm

Derivation of AEGL-2

Key study:	Rupp and Henschler 1967
Toxicity end point: for 30 min	Eye, nose, and throat irritation in humans at 1.0 ppm
Time-scaling:	$C^{2.2} \times t = k$, based on mouse lethality study (Bitron and Aharonson 1978)
Uncertainty factors:	3 for intraspecies variability
Modifying factor:	None
Calculations:	(Concentration/uncertainty factors)$^{2.2} \times t = k$ (1 ppm/3)$^{2.2} \times 30$ min = k 2.676 ppm$^{2.2} \times$ min = k
10-min AEGL-2:	(2.676 ppm$^{2.2} \times$ min/10 min)$^{1/2.2}$ = 0.55 ppm
30-min AEGL-2:	0.33 ppm
1-h AEGL-2:	(2.676 ppm$^{2.2} \times$ min/60 min)$^{1/2.2}$ = 0.24 ppm
4-h AEGL-2:	(2.676 ppm$^{2.2} \times$ min/240 min)$^{1/2.2}$ = 0.13 ppm

8-h AEGL-2: $(2.676\ ppm^{2.2} \times min/480\ min)^{1/2.2} = 0.095\ ppm$

Derivation of AEGL-3

Key study:	Schlagbauer and Henschler 1967
Toxicity end point: probit analysis	30-min LC_{01} of 116 ppm in the mouse, calculated by
Time-scaling:	$C^{2.2} \times t = k$, based on mouse lethality study (Bitron and Aharonson 1978)
Uncertainty factors:	3 for intraspecies variability 3 for interspecies variability
Modifying factor:	None
Calculations:	(Concentration/uncertainty factors)$^{2.2} \times t = k$ $(116\ ppm/10)^{2.2} \times 30\ min = k$ $6{,}590.66\ ppm^{2.2} \times min = k$
10-min AEGL-3:	$(6{,}590.66\ ppm^{2.2} \times min/10\ min)^{1/2.2} = 19\ ppm$
30-min AEGL-3:	$116/10 = 12\ ppm$
1-h AEGL-3:	$(6{,}590.66\ ppm^{2.2} \times min/60\ min)^{1/2.2} = 8.5\ ppm$
4-h AEGL-3:	$(6{,}590.66\ ppm^{2.2} \times min/240\ min)^{1/2.2} = 4.5\ ppm$
8-h AEGL-3:	$(6{,}590.66\ ppm^{2.2} \times min/480\ min)^{1/2.2} = 3.3\ ppm$

APPENDIX B

CATEGORY GRAPH OF TOXICITY DATA AND AEGL VALUES

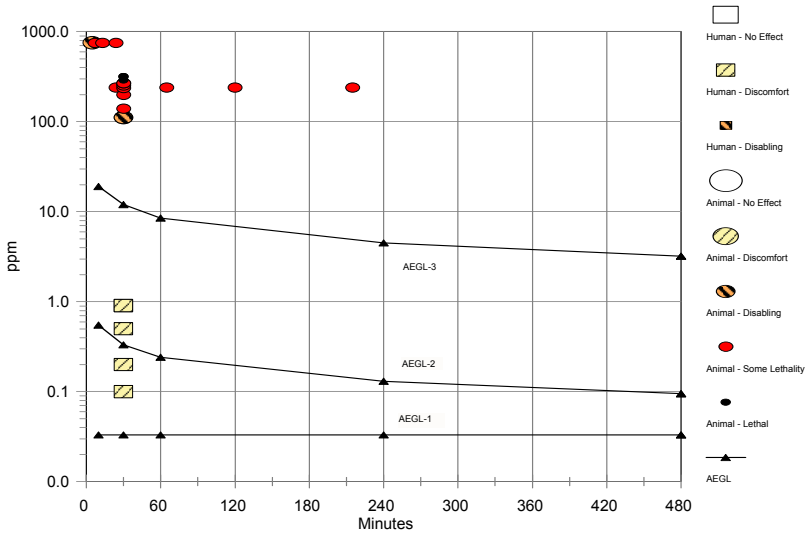

FIGURE B-1 Category graph for bromine.

TABLE B-1 Data Used in Category Graph

Source	Species	ppm	Min	Category[a]
AEGL-1		0.033	10	AEGL
AEGL-1		0.033	30	AEGL
AEGL-1		0.033	60	AEGL
AEGL-1		0.033	240	AEGL
AEGL-1		0.033	480	AEGL
AEGL-2		0.55	10	AEGL
AEGL-2		0.33	30	AEGL
AEGL-2		0.24	60	AEGL
AEGL-2		0.13	240	AEGL
AEGL-2		0.095	480	AEGL

(Continued)

TABLE B-1 Continued

Source	Species	ppm	Min	Category[a]
AEGL-3		19	10	AEGL
AEGL-3		12	30	AEGL
AEGL-3		8.5	60	AEGL
AEGL-3		4.5	240	AEGL
AEGL-3		3.3	480	AEGL
Bitron and Aharonson 1978	Mouse	240	24	SL
	Mouse	240	65	SL
	Mouse	240	120	SL
	Mouse	240	215	SL
	Mouse	750	5	2
	Mouse	750	7	SL
	Mouse	750	13	SL
	Mouse	750	24	SL
Schlagbauer and Henschler 1967	Mouse	111	30	2
	Mouse	140	30	SL
	Mouse	199	30	SL
	Mouse	236	30	SL
	Mouse	252	30	SL
	Mouse	268	30	SL
	Mouse	290	30	3
	Mouse	315	30	3
Rupp and Henschler 1967	Human	0.1	30	1
	Human	0.2	30	1
	Human	0.5	30	1
	Human	0.9	30	1

[a]Category 0, no effect; 1, discomfort; 2, disabling, 3, lethal; SL, some lethality.

APPENDIX C

ACUTE EXPOSURE GUIDELINE LEVELS FOR BROMINE

Derivation Summary for Bromine

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
0.033 ppm	0.033 ppm	0.033 ppm	0.033 ppm	0.033 ppm

Key Reference: Rupp, H., and D. Henschler. 1967. Effects of low concentrations of chlorine and bromine on man [in German]. Int. Arch. Arbeitsmed. 23(1):79-90.

Test Species/Strain/Number: 20 human subjects

Exposure Route/Concentrations/Durations: Inhalation, concentrations of 0.1 to 1.0 ppm for at least 30 min

Effects:
0.1 ppm: eye irritation
0.50 to 1.0 ppm: eye, nose, and throat irritation

End Point/Concentration/Rationale: Eye irritation but not nose or throat irritation at 0.1 ppm for 30 min; meets the AEGL-1 definition of notable discomfort.

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: Not applied, human data used
Intraspecies: 3, Workers have been exposed to concentrations up to 1 ppm with irritation being the only reported symptom. Compared with the 0.5 ppm AEGL-1 for the less well-scrubbed chlorine, the value may be conservative. Chlorine at 0.5 ppm for 4 h failed to elicit an asthmatic response in sensitive subjects.

Modifying Factor: Not applied

Animal to Human Dosimetric Adjustment: Not applied.

Time-Scaling: Not applied, adaptation to mild sensory irritation.

Data Adequacy: Compared with the irritancy data on chlorine, these values may be conservative. Based on the small database for bromine, extra protectiveness was considered appropriate.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.55 ppm	0.33 ppm	0.24 ppm	0.13 ppm	0.095 ppm

Key Reference: Rupp, H., and D. Henschler. 1967. Effects of low concentrations of chlorine and bromine on man [in German]. Int. Arch. Arbeitsmed. 23(1):79-90.

Test Species/Strain/Number: 20 human subjects

Exposure Route/Concentrations/Durations: Inhalation, concentrations of 0.1 to 1.0 ppm for at least 30 min

(Continued)

AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
0.55 ppm	0.33 ppm	0.24 ppm	0.13 ppm	0.095 ppm

Effects:
0.1 ppm: eye irritation
0.5 to 1.0 ppm: eye, nose, and throat irritation

End Point/Concentration/Rationale: Throat irritation at the 1.0 ppm concentration.

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: Not applied, human data used.
Intraspecies: 3. Symptoms are below those defining an AEGL-2, but no reliable studies with exposures to higher concentrations were located. Irritation appeared to be limited to the upper respiratory tract with likely little penetration to the lower respiratory tract. Compared with the 30-min AEGL-2 value of 2.8 ppm for chlorine (which was protective of sensitive subjects) the uncertainty factor of 3 is adequate.

Modifying Factor: Not applied.

Animal to Human Dosimetric Adjustment: Not applied.

Time-scaling: $C^{2.2} \times t = k$, based on a mouse lethality study.

Data Adequacy: Compared with the irritancy data on chlorine, these values may be conservative. But, based on the limited data base for bromine, extra protectiveness was considered appropriate.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
19 ppm	12 ppm	8.5 ppm	4.5 ppm	3.3 ppm

Key Reference: Schlagbauer, M., and D. Henschler. 1967. Inhalation toxicity of chlorine and bromine with single and repeated exposures [in German]. Int. Arch. Arbetsmed. 23(1):91-98.

Test Species/Strain/Number: Mouse/NMRI/10 per exposure group

Exposure Route/Concentrations/Durations: Inhalation, 110.5 to 315 ppm for 30 min

Concentration:	Mortality:
110.5 ppm:	0/10
139.7 ppm:	3/10
198.9 ppm:	6/10
236.0 ppm:	9/10
252.1 ppm:	10/10
267.6 ppm:	9/10
290.3 ppm:	10/10
315.0 ppm	10/10

End Point/Concentration/Rationale: LC_{01} calculated by probit analysis

(Continued)

AEGL-3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
19 ppm	12 ppm	8.5 ppm	4.5 ppm	3.3 ppm

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3; the mouse was the most sensitive species in other studies with halogens
Intraspecies: 3; at high concentrations, the corrosive action of irritants is not expected to differ greatly among individuals.

Modifying Factor: Not applied.

Animal to Human Dosimetric Adjustment: Not applied.

Time-scaling: $C^{2.2} \times t = k$, based on a mouse lethality study.

Data Adequacy: Compared with the lethality data on chlorine, these values may be conservative, but based on the small database for bromine, extra protectiveness was considered appropriate.