INTERIM
ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
HYDROGEN BROMIDE (CAS Reg. No. 10035-10-6)
and
HYDROGEN IODIDE (CAS Reg. No. 10034-85-2)

HBr and HI

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 to 8 hours. Three levels — AEGL-1, AEGL-2 and AEGL-3 — are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory 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, non-sensory 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 unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

TABLE OF CONTENTS

LIST OF TABLES

EXECUTIVE SUMMARY

The hydrogen halides, hydrogen bromide (HBr) and hydrogen iodide (HI), are colorless, corrosive, non-flammable gases. Hydrogen bromide 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. Hydrogen bromide is used both as a reagent and a catalyst in a variety of organic reactions; it is also used for the preparation of numerous bromide compounds. Anhydrous HBr is shipped in high pressure steel cylinders. Hydrogen iodide is unstable at room temperatures and above, slowly decomposing to hydrogen and iodine. It is extremely soluble in water, forming a strong fuming acid, hydriodic acid. The acid is decomposed by light.

Hydrogen bromide 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 two species of mammals, the rat and the mouse, were available for development of AEGL values. Although the data base for HBr is sparse, additional data on the toxicity of HBr relative to those of hydrogen fluoride (HF) and hydrogen chloride (HCl) were available for comparison purposes. The data bases for HCl and HF are robust. For the endpoint of lethality, the relative toxicities to the rat and mouse are in the order HF>HBr>HCl (MacEwen and Vernot 1972). When considering sublethal concentrations, the severity and extent of lesions to the upper respiratory tract were in the order HF>HCl$HBr, although the severity and extent of lesions were very similar among the three chemicals (Kusewitt et al. 1989; Stavert et al. 1991). The data also showed that all three chemicals are well scrubbed in the upper respiratory passages.

No empirical data were available for HI. In the absence of data, the HI values were set equal to the HBr values. Based on the studies of Kusewitt et al. (1989) and MacEwen and Vernot (1972), HI is predicted to be less toxic than the other hydrogen halides. Being the most water soluble hydrogen halide, it is better scrubbed in the upper nasal passages than the other hydrogen halides. For highly scrubbed chemicals, higher concentrations are necessary to reach the lungs. Thus, setting the HI values equal to the HBr values, with support from the entire data base of hydrogen halides is appropriate.

The AEGL-1 was based on a study with six human volunteers exposed to 2, 3, 4, 5, or 6 ppm HBr for several minutes (Connecticut State Department of Health 1955). No nose, throat, or eye irritation was reported at 2 ppm. One of 6 subjects reported nose and throat irritation (severity not defined) but no eye irritation at 3 ppm. Nose irritation was reported by all six subjects at 5 and 6 ppm, but only one of the subjects reported throat irritation at these concentrations and none reported eye irritation. The concentration of 3 ppm was considered a NOAEL for notable discomfort. This concentration was divided by an uncertainty factor of 3 to protect sensitive individuals; time-scaling was not applied as humans adapt to the slight sensory irritation that defines the AEGL-1. The 1 ppm concentration across time is supported by the AEGL-1 values of 1 and 1.8 ppm developed for HF and HCl, respectively (NRC 2004). The 1 ppm concentration may 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 a no-effect concentration in exercising asthmatics. In the absence of empirical data for HI, the AEGL-1 for HI was set equal to the AEGL-1 for HBr.

The AEGL-2 values for the 30-minute, 1-, 4-, and 8-hour time points were based on severe nasal histopathology in rats exposed to 1300 ppm HCl or HBr for 30 minutes (Stavert et al.1991). For both chemicals, changes in the nasal passages were limited to the most anterior region. Lesions consisted of severe necrohemorrhagic rhinitis and necrosis of the mucosa and submucosa. Although the lungs were unaffected, there was 8% mortality with HBr and 6% mortality with HCl. Derivation of the values followed the reasoning for derivation of values for the related chemical, HCl, which had similar effects but a more robust data base (NRC 2004). A modifying factor of 3 was applied to account for the sparse database of effects defined by AEGL-2 and because the effects observed at the concentration used to derive AEGL-2 values were somewhat severe. An uncertainty factor of 3 was applied for interspecies variability because the test species (rodents) were 2-3 times more sensitive to the effects of HCl than primates. An uncertainty factor of 3 was applied for intraspecies extrapolation since the mechanism of action is direct irritation and the subsequent effect or response is not expected to vary greatly among individuals (NRC 2001). Furthermore, application of the default intraspecies uncertainty factor of 10 would lower the longer-term AEGL-2 values to close to the longer-term AEGL-1 values. Thus, the total uncertainty and modifying factor adjustment is 30-fold. The resulting value (43 ppm) was then time-scaled to the 1-hour AEGL exposure period using the $C^n \times t = k$ relationship, where n=1 based on regression analysis of combined rat and mouse LC_{50} data (1 to 100 minutes) for HCl (ten Berge et al. 1986). The 4- and 8-hour values were derived by applying a modifying factor of 2 to the 1-hour AEGL-2 value, because time-scaling would yield a 4-hour value of 5.4 ppm and an 8-hour value of 2.7 ppm, close to the HCl concentrations tolerated by exercising asthmatic subjects (NRC 2004).

The 10-minute AEGL-2 value for HBr and HI was also based on HCl, and was derived by dividing the mouse HCl RD_{50} of 309 ppm (Barrow et al. 1977) by a factor of 3 to obtain a concentration causing irritation. The human response to sensory irritants can be predicted on the basis of the mouse RD_{50}. Alarie (1981) has shown that the RD_{50} multiplied by 0.1 corresponds to "some sensory irritation;" whereas the RD_{50} is "intolerable." Schaper (1993) validated that for many chemicals, 0.03 times the RD_{50} corresponds to the ACGIH TLV, a concentration that generally prevents sensory irritation in humans. The 0.03 represents the half-way point between 0.1 and 0.01 on a logarithmic scale. Thus, it is reasonable that one-third of the RD_{50}, a value half-way between 0.1 and 1 on a logarithmic scale, might cause significant irritation to humans. Furthermore, one-third of the mouse RD_{50} for HCl (99 ppm) corresponds to an approximate decrease in respiratory rate in the mouse of 30% (Barrow et al. 1977), and decreases in the range of 20 to 50% correspond to moderate irritation (ASTM 1991) which is within the definition of an AEGL-2.

The benchmark dose approach, specifically the $BMCL_{05}$, was used to develop AEGL-3 values for HBr and HI. The basis for the values was the 1-hour lethality data for HBr in Sprague-Dawley rats (MacEwen and Vernot 1972). The 1-hour $BMCL_{05}$ was 1239 ppm. A total uncertainty factor of 10 was applied: 3 for interspecies differences and 3 for differences in human sensitivity. The interspecies uncertainty factor of 3 is sufficient as additional uncertainty or modifying factors would lower the AEGL-3 values to the AEGL-2 values. The basis for time-

scaling was data for the slightly more toxic chemical, HCl. The resulting 30-minute value of 120 ppm was time scaled to shorter and longer time periods using an n value of 1 (where $C^n \times t = k$). Because all three chemicals (HBr, HF, and HCl) are well scrubbed in the upper respiratory tract at moderately high concentrations, the 8-hour AEGL-3 for HBr and HI was set equal to the 4-hour AEGL-3, as was done for HF and HCl (NRC 2004).

The calculated values are listed in the tables below.

Summary of AEGL Values for Hydrogen Bromide

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (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)	Nasal irritation (Connecticut State Dept. of Health 1955)
AEGL–2 (Disabling)	100 ppm (330 mg/m^3)	43 ppm (142 mg/m^3)	22 ppm (73 mg/m^3)	11 ppm (36 mg/m^3)	11 ppm (36 mg/m^3)	Analogy with hydrogen chloride; respiratory tract lesions - rat (Stavert et al. 1991); mouse RD_{50} (Barrow et al. 1977)[a]
AEGL–3 (Lethal)	740 ppm (2442 mg/m^3)	250 ppm (825 mg/m^3)	120 ppm (396 mg/m^3)	31 ppm (102 mg/m^3)	31 ppm (102 mg/m^3)	Benchmark dose - rat (MacEwen and Vernot 1972)

Summary of AEGL Values for Hydrogen Iodide

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1 (Nondisabling)	1.0 ppm (5.2 mg/m^3)	1.0 ppm (5.2 mg/m^3)	1.0 ppm (5.2 mg/m^3)	1.0 ppm (5.2 mg/m^3)	1.0 ppm (5.2 mg/m^3)	Nasal irritation - HBr (Connecticut State Dept. of Health 1955)
AEGL–2 (Disabling)	100 ppm (523 mg/m^3)	43 ppm (225 mg/m^3)	22 ppm (115 mg/m^3)	11 ppm (58 mg/m^3)	11 ppm (58 mg/m^3)	Analogy with hydrogen chloride; respiratory tract lesions - rat (Stavert et al. 1991); mouse RD_{50} (Barrow et al. 1977)[a]
AEGL–3 (Lethal)	740 ppm (3870 mg/m^3)	250 ppm (1307 mg/m^3)	120 ppm (628 mg/m^3)	31 ppm (162 mg/m^3)	31 ppm (162 mg/m^3)	Benchmark dose for HBr- rat (MacEwen and Vernot 1972)

[a] The 10-minute AEGL-2 was based on the RD_{50} for HCl in male Swiss-Webster mice (Barrow et al. 1977). The 30-minute and 1-hour AEGL-2 values were based on nasal lesions in the rat exposed to HCl or HBr (Stavert et al. 1991). The 4- and 8-hour AEGL-2 values were adjusted by applying a modifying factor of 2 to the 1-hour AEGL-2 value.

1. INTRODUCTION

Both hydrogen bromide (HBr) and hydrogen iodide (HI) are colorless nonflammable gases that fume strongly in moist air. Both are highly water soluble. HBr is one of the strongest mineral acids, with a reducing action stronger than that of hydrogen chloride (HCl) (Jackisch 1992). Hydrogen iodide is unstable at room temperatures and above, slowly decomposing to hydrogen and iodine. In water, it forms a mixture of constant minimum and maximum boiling

points and distilling off without decomposition and in a fixed ratio. HI dissolves in water at 10EC and 1 atmosphere pressure to the extent of 70 weight percent to form hydriodic acid. The acid is decomposed by light. In aqueous solution, hydrogen iodide is one of the strongest acids as it is wholly in the ionic form (Braker and Mossman 1980; Lauterbach and Ober 1991; O'Neil et al. 2001; Teitelbaum 2001). Chemical and physical properties for HBr and HI are listed in Table 1.

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. 2001).

HI is prepared by the catalytic reaction of iodine and hydrogen, or by treating concentrated hydriodic acid solutions with phosphorus pentoxide. It is used in the manufacture of hydroiodic acid and organic iodio compounds (Lauterbach and Ober 1991; O'Neil et al. 2001). Hydriodic acid has been used as an expectorant (HSDB 2003).

TABLE 1. Chemical and Physical Properties

Parameter	HBr	HI	Reference
Synonyms	anhydrous bromic acid hydrobromic acid	anhydrous hydriodic acid	O'Neil et al. 2001; NIOSH 2002
Chemical formula	HBr	HI	O'Neil et al. 2001
Molecular weight	80.91	127.93	O'Neil et al. 2001
CAS Reg. No.	10035-10-6	10034-85-2	O'Neil et al. 2001; Lauterbach and Ober 1991
Physical state	colorless gas	colorless gas	O'Neil et al. 2001
Solubility in water	freely soluble, 600:1 v:v, gas to water	extremely soluble, 234 g/100 g at 10EC	O'Neil et al. 2001
Vapor pressure	>760 torr @ 20EC 335 psia @21EC	5670 mm Hg at 21EC	ACGIH 2002 Braker and Mossman 1980
Vapor density (air =1)	2.71	4.46	O'Neil et al. 2001
Density (water =1)	1.48 g/mL @ 25EC	5.23 g/L @ 25EC	Jackisch 1992; O'Neil et al. 2001
Melting point	-87EC	-50.8EC	O'Neil et al. 2001
Boiling point	-67EC	-35.1E	O'Neil et al. 2001
Flammability limits	nonflammable	nonflammable	Jackisch 1992; O'Neil et al. 2001

Conversion factors	1 ppm = 3.3 mg/m^3 1 mg/m^3 = 0.30 ppm	1 ppm = 5.23 mg/m^3 1 mg/m^3 = 0.19 ppm	ACGIH 2002; Calculated

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data on concentrations lethal to humans were located.

2.2. Nonlethal Toxicity

Hydrogen bromide 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 (1955) addressed responses of human subjects to HBr vapors. Six volunteers inhaled HBr ranging from 2 to 6 ppm for durations of several minutes (Table 2). The odor was detectable by all subjects at all concentrations. None of the subjects experienced eye irritation. Only one subject experienced nose and throat irritation at 3 ppm. One subject experienced throat irritation at the higher concentrations, and all subjects experienced nose irritation at 5 and 6 ppm. Although exposure to 5 ppm caused nose and throat irritation in a majority of the subjects, the report authors stated that, "it was considered unlikely that noticeable disturbances will occur if peak concentrations do not exceed this value for brief periods."

TABLE 2. Human Responses to Hydrogen Bromide Vapor[a]

Response	2 ppm	3 ppm	4 ppm	5 ppm	6 ppm
Detectable odor	6	6	6	6	6
Nose irritation	0	1	3	6	6
Throat irritation	0	1	1	1	1
Eye irritation	0	0	0	0	0

[a] Adapted from ACGIH 2002.
0 indicates no subjective irritation in any subject.
Numbers other than 0 indicate number of subjects responding (out of six); responses range from slight, stinging sensation to a definite feeling of irritation.

Amoore and Hautala (1983) reported an odor threshold for HBr of 2 ppm. This is the lowest concentration used in the Connecticut study above; all six subjects detected the odor of HBr at this concentration.

The sharp, penetrating odor of HI is readily detectable (Braker and Mossman 1980), but no information on the odor threshold was located. HI causes irritation of the skin, eyes, and upper respiratory tract. According to Braker and Mossman (1980), concentrations of hydrogen halides of approximately 35 ppm cause irritation of the throat after short exposure. Concentrations of 1000-2000 ppm are lethal to humans on brief exposures and concentrations in the range of 1000-

1300 ppm are dangerous if breathed for 30-60 minutes. This data appears to be taken from Henderson and Haggard (1943) and applies to HCl.

2.3. Neurotoxicity

No information on neurotoxicity in humans was located.

2.4. Developmental/Reproductive Toxicity

No data on developmental or reproductive effects in humans was located.

2.5. Genotoxicity

No data on genotoxicity in humans was located.

2.6. Carcinogenicity

No data on carcinogenicity in humans was located.

2.7. Summary

The only human data involved exposure of six volunteers to 2 to 6 ppm HBr for several minutes (Connecticut State Department of Health 1955). The threshold for subjective irritation involving the nose and throat was 3 ppm. No information on neurotoxicity, developmental/ reproductive effects, genotoxicity, or carcinogenicity of either chemical was located.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

As part of a series of inhalation toxicity studies performed at Wright-Patterson 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 ranging from 2205 to 3822 ppm for 1 hour (Table 3). 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 postexposure. The 1-hour LC_{50} was 2858 ppm (95% confidence limits of 2581-3164 ppm) (Table 4). Responses of the animals during the exposures were dose-related and followed a sequence of nose and eye irritation, labored breathing, gasping, and convulsions. The fur turned orange-brown during the exposures with the intensity of the color related to the concentration. The authors attributed a smoky haze around the animals during exposure to the reaction of the 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 to the lowest concentration returned to a normal weight gain by the end of the postexposure period. Gross examination at necropsy showed severe lung and liver congestion with pulmonary edema in rats that had inhaled 3822 ppm. Rats exposed to the lower concentration had necrotic lesions

on their feet and tails for up to 14 days. Opacity of the cornea, observed immediately following exposure, disappeared within 24 hours. Other than the above observations, specific observations were not described for specific concentrations.

Table 3. Results of One-Hour Inhalation Studies with the Rat and Mouse (HBr)[a]

Species	Concentration (ppm)	Mortality Ratio
Rat	2205	1/10
	2328	4/10
	2759	4/10
	3253	6/10
	3711	7/10
	3822	10/10
Mouse	507	0/10
	875	7/10
	1036	9/10
	1163	10/10

[a] Data from MacEwen and Vernot 1972.

Groups of 5-8 male Fischer 344 rats inhaled approximately 1300 ppm HBr for 30 minutes (Stavert et al. 1991). Rats were placed into whole body flow plethysmographs for measurement of ventilatory rates. Body weight and respiratory tract histology were investigated 24 hours later. The mortality rate was 8% (Table 4). Rats exposed to HBr experienced an immediate and persistent drop in minute ventilatory rate of 25%. A small (<10%) reduction in body weight compared to non-exposed rats occurred by 24 hours post exposure.

As part of the same study, Stavert et al. (1991) compared the toxicities of the three hydrogen halides: HF, HCl, and HBr following inhalation of 1300 ppm for 30 minutes. Mortalities were 0%, 6%, and 8%, respectively. Damage to the respiratory tract was assessed 24 hours after the exposure. The nasal cavity was divided into four regions which were examined microscopically. For all three hydrogen halides, tissue injury was confined to the nasal cavity. Tissue injury in the nasal cavity was similar following exposures to HF and HCl and involved moderate to severe fibrinonecrotic rhinitis in nasal region 1 (most anterior region). The mucosa and submucosa in this region were necrotic, with necrosis extending to the turbinate bone. Thrombosis of vessels, hemorrhage, fibrin and fluid were observed in the nasal passages and polymorphonuclear cells were observed in the submucosa and in the lumen. For HF and HCl, the lesions extended into region 2, but regions 3 and 4 were essentially normal in appearance as was the trachea (showing that all three chemicals were well scrubbed). Table 5 summarizes the extent of necrosis in region 2 of the nasal cavities of eight rats. No lung or tracheal injury was evident for any of the chemicals, although accumulations of inflammatory cells and exudates in the trachea and lungs following the exposure to HCl indicated that this chemical may not be as well scrubbed in the nasal passages as HF and HBr. However, this possibility is modified by the authors' observation of lower minute volumes in the HF- and HBr-exposed rats, so that greater amounts of HCl were breathed. The study authors concluded that respiratory tract injury caused by exposure to the three hydrogen halides is quantitatively similar. Lesions consisted of severe necrohemorrhagic

rhinitis, either bilateral or unilateral. The posterior three-quarters of the nasal cavity and the trachea were free of lesions. There was no change in lung weight. Necrotic lesions were less severe following exposure to HBr compared with exposure to HF or HCl.

TABLE 4. Summary of Acute Lethal Inhalation Data in Rats and Mice (HBr)

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Rat	1000 1300 2858	30 minutes 30 minutes 1 hour	no deaths 8% mortality LC_{50}	Kusewitt et al. 1989 Stavert et al. 1991 MacEwen and Vernot 1972
Mouse	507 814	1 hour 1 hour	no deaths LC_{50}	MacEwen and Vernot 1972

Table 5. Severity of Lesions of Region 2 of the Nasal Cavity of Rats Following Inhalation of 1300 ppm HF, HCl or HBr for 30 Minutes

Necrotic lesion	HF	HCl	HBr
Epithelial	2.0*	2.0*	0.9
Submucosal	0.3	0.4	0.0
Bone	0.0	0.0	0.0
Gland	0.0	0.0	0.0

Data from Stavert et al. 1991.
Based on eight rats/exposure group.
Severity index ranged from 1 to 4 with 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe.
*Statistically significant compared to air-exposed controls, $p<0.05$.

In the same study (Stavert et al. 1991), groups of male Fischer 344 rats were exposed to 1300 ppm HBr for 30 minutes via a tracheal cannula. This procedure bypasses the scrubbing of the nasal passages. Within 24 hours after exposure, 19% of these rats died. Mean lung weight was not significantly different from that of non-cannulated rats or that of rats exposed to air. Microscopically, fibrinonecrotic tracheitis, necrosis of the mucosa of the major bronchus, and polymorphonuclear neutrophils in scattered alveoli were observed. However, quantitatively, the lung lesions 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) also subjected groups of 10 CF1 (ICR derived) mice weighing 20-30 grams to concentrations of HBr ranging from 507 to 1163 ppm for 1 hour (Table 3). The LC_{50} was 814 ppm (95% confidence limits of 701-947 ppm) (Table 4). Responses during the exposures were the same as those of rats above. No deaths occurred in mice inhaling 507 ppm, and these 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 pathology was 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 lower concentrations. Fischer-344 rats (number not specified) inhaled HF, HCl, or HBr at concentrations of 100 to1000 ppm for 30 minutes and were sacrificed 8 and 24 hours later. There was no mortality within the postexposure period (Table 4) and the lesions, consisting of necrosis and inflammation, were restricted to the nasal region. Histopathologic examinations and gravimetric measurements revealed no damage to the lungs. No further details were reported in the available abstract, i.e., specific injury was not described for specific concentrations.

Toxicity data on the related chemical, HCl, are relevant. 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 minutes. 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.

3.3. Neurotoxicity

No information on neurotoxicity in animals was located.

3.4. Developmental/Reproductive Toxicity

No information on developmental/reproductive effects in animals was located.

3.5. Genotoxicity

No information on genotoxicity in animals was located.

3.6. Chronic Toxicity/Carcinogenicity

No information on chronic toxicity/carcinogenicity in animals was located.

3.7. Summary

The data base for animal studies consisted of two studies with HBr. In the first study (MacEwen and Vernot 1972), groups of rats and mice inhaled a range of concentrations for 1 hour. The one-hour LC_{50} values in rats and mice were 2858 and 814 ppm, respectively. All tested concentrations resulted in lethality in rats during the 14 day postexposure period. No deaths occurred in mice exposed to 507 ppm for one hour. In the second study, reported in two publications (Kusewitt et al. 1989; Stavert et al. 1991), no deaths occurred in rats inhaling 1000 ppm for 30 minutes. In rats inhaling 1300 ppm for 30 minutes, mortality was 8% (presumably one of 12 rats) and lesions were confined to the anterior nasal passages. Animals in the latter studies were sacrificed 24 hours after exposure. It should be noted that only one of ten rats exposed to 2205 ppm died in the MacEwen and Vernot (1972) study.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No data on metabolism and deposition of HBr were located. Hydrogen bromide is a site of contact irritant. As such, uptake and metabolism are not relevant to development of AEGL guidelines. 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).

Iodine is an essential nutrient required for development and functioning of the thyroid gland. No information on the metabolism of HI was located. Ingested iodine is readily absorbed from the gastrointestinal tract into the blood. Approximately one-third of normally ingested iodine, 1 mg/week, is taken up by the thyroid gland. The remaining two-thirds is rapidly cleared by the kidneys. The kidney clearance rate of iodide ion is 35 mL/minute, far greater than the 1 mL/minute clearance of chloride ion. Excess iodine absorbed from the blood into the thyroid is synthesized into the thyroid hormones thyroxine and triiodothyronine which are stored as a hormone-thyroglobulin complex (Guyton 1976). Ingested amounts of 2 to 4 mg of iodine have been fatal (O'Neil 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. The same should be true for HI which is more water soluble than HBr. At high concentrations, e.g., 3822 ppm for one hour, 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 a level below what would cause serious respiratory effects. In the studies summarized in Tables 3 and 4, the tissues of the respiratory tract as well as the exposed dermal surfaces, sustained the impact of an acute exposure. Therefore, the concentration of HBr (or HI) in the inhaled air and not the absorbed dose is the primary determinant of effects for acute exposures.

4.3. Structure-Activity Relationships

Hydrogen iodide is the least stable of the hydrogen halides, dissociating into its constituents at room temperature. Chlorine and bromine vapor displace the iodine from hydrogen iodide (Braker and Mossman 1980).

Because the data base for HBr is sparse, and there are no data for HI, it is important to consider the relative toxicities of HBr and other structurally similar chemicals. The group of compounds most closely related to HBr are the other hydrogen halides, HF and HCl. It may be anticipated that some relationships exist in this chemical class between structure and their respective toxicities in animals and humans. However, because of differences in size and electron configuration of the various halogen atoms, substantial differences exist with respect to their chemical and physical properties, which in turn are responsible for their toxicological properties (atomic weights of fluorine, chlorine, and bromine are 19, 35.5, and 80, respectively). This is particularly true in the case of acutely toxic effects resulting from inhalation exposure.

For example, HCl and HBr have considerably higher ionization constants than HF, and are therefore classified as stronger acids. Consequently, higher concentrations of proton-donor hydronium ions are generated from HCl and HBr in aqueous solutions under the same conditions. The protons readily react with cells and tissues resulting in irritant and corrosive properties. On the other hand, the fluoride ion from dissociated HF is a strong nucleophile or Lewis base that is highly reactive with various organic and inorganic electrophiles that are biologically important substances, also resulting in irritation and tissue damage.

In addition to these differences in chemical properties, differences in the water solubilities may be a significant factor in acute inhalation toxicity of these substances. HI is characterized as extremely soluble in water. HF and HBr are characterized as infinitely and freely soluble in water, respectively, and the solubility of HCl although high, is lower, 67 g/100 g of water at 30EC (O'Neil et al. 2001). Thus, it is likely that HBr and HI are more effectively scrubbed in the nasal cavity than HCl, resulting in less penetration to the lungs and less severe toxicity there. The effectiveness of the scrubbing mechanism is demonstrated in the study by Kusewitt et al. (1989) and Stavert et al. (1991) (Section 3 and Table 5). Kusewitt et al. (1989) reported that at concentrations of 100 to 1000 ppm for 30 minutes, all three hydrogen halides were well scrubbed with lesions confined to the nasal passages. The severity of injury increased with increasing concentrations and the relative toxicities of the hydrogen halides were reported as HF>HCl$HBr. For the endpoint of lethality, the relationship was similar, HF>HCl>HBr (Stavert et al. 1991). The relative toxicities for the endpoint of lethality are summarized in Table 6. HI is predicted to be the least toxic.

TABLE 6. Relative Toxicities [LC_{50} Values (ppm)] of HF, HCl, and HBr

Species	Exposure Duration	HF	HCl	HBr	Reference
Rat Mouse	5 minutes	18,200 6247	41,000 13,750		Higgins et al. 1972

Rat Mouse	30 minutes	2042	4700 2644		Rosenholtz et al. 1963 (HF); MacEwen and Vernot 1972 (HCl)
Rat Mouse	1 hour	1395 342	3124[a] 1108		Wohlslagel et al. 1976
Monkey Rat Mouse	1 hour	1774 1278 501		 2858 814	MacEwen and Vernot 1970 MacEwen and Vernot 1972

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

4.4. Other Relevant Information

4.4.1. Species Variability

HBr toxicity data, available for only the rat and mouse, showed that mice were more susceptible to the toxicity of HBr than the rat. 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 susceptible to the lethal effects of HCl than other rodents or baboons" (NRC 1991). "To some extent, this increased susceptibility may be due to less effective scrubbing of HCl in the upper respiratory tract." 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 6 show species susceptibility to HF of mouse>rat>monkey.

4.4.2. Susceptible Populations

Individuals with asthma may respond to exposure to respiratory irritants such as HBr and HI with increased bronchial responsiveness. No information on the relative susceptibility of asthmatic and normal individuals to HBr or HI was located. In a study with HCl, 1.8 ppm for 45 minutes 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 experience greater HBr or HI deposition and pulmonary irritation than individuals at rest.

4.4.3. Concentration-Exposure Duration Relationship

No information on the relationship between concentration and exposure for a single endpoint was located. When no data for time-scaling are available, time scaling is based on $C^n \times t = k$, where n = 3 for shorter exposure durations and n = 1 for longer exposure durations (NRC 2001). Based on lethality data, the n values for time scaling for the similar chemicals, HF and HCl, were 2 and 1, respectively (NRC 2004).

4.4.4. Concurrent Exposure Issues

No information on concurrent exposure issues was located.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

Reliable human data on HBr are limited to the exposure of six volunteers to 2 to 6 ppm for several minutes (Connecticut State Department of Health 1955). At 2, 3, 4, 5, or 6 ppm, nose irritation was reported by 0, 1, 3, 6, and 6 individuals respectively. Throat irritation did not appear to be concentration dependent and no eye irritation was reported. Therefore, the threshold for subjective irritation involving the nose is 3 ppm.

5.2. Summary of Animal Data Relevant to AEGL-1

No data relevant to notable discomfort in animals was located.

5.3. Derivation of AEGL-1

The threshold for nose irritation in human subjects inhaling 3 ppm HBr for several minutes (Connecticut State Department of Health 1955), was selected as the basis for the AEGL-1. This concentration was considered a NOAEL for notable discomfort. The 3 ppm was divided by an intraspecies uncertainty factor of 3 because the threshold for sensory irritation is not expected to vary greatly among individuals (NRC 2001). The intraspecies uncertainty factor of 3 was considered sufficient because the effect of slight irritation is below the definition of AEGL-1. Because adaptation to slight irritation occurs, the resulting 1 ppm concentration was used for all exposure durations (Tables 7 and 8). Calculations are in Appendix A and a category graph of the toxicity data in relation to AEGL values is in Appendix B.

TABLE 7. AEGL-1 Values for Hydrogen Bromide

10-minute	30-minute	1-hour	4-hour	8-hour
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)

TABLE 8. AEGL-1 Values for Hydrogen Iodide

10-minute	30-minute	1-hour	4-hour	8-hour
1.0 ppm (5.2 mg/m^3)	1.0 ppm (5.2 mg/m^3)	1.0 ppm (5.2 mg/m^3)	1.0 ppm (5.2 mg/m^3)	1.0 ppm (5.2 mg/m^3)

The 1 ppm value is considered protective of asthmatics. At low concentrations, HBr is well scrubbed in the upper nasal passages. The 1 ppm concentration for all exposure durations is supported by the AEGL-1 values of 1.0 and 1.8 ppm developed for HF and HCl, respectively (NRC 2004). The AEGL-1 of 1.8 ppm for HCl was based on a no-adverse-effect in exercising asthmatics exposed for 45 minutes. AEGL values for HF and HCL are shown in Table 9.

Table 9. AEGL Values for HF and HCl (ppm)

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1					
HF	1.0	1.0	1.0	1.0	1.0
HCl	1.8	1.8	1.8	1.8	1.8
AEGL-2					
HF	95	34	24	12	12
HCl	100	43	22	11	11
AEGL-3					
HF	170	62	44	22	22
HCl	620	210	100	26	26

Source: NRC (2004).

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No human data relevant to development of AEGL-2 values were located.

6.2. Summary of Animal Data Relevant to AEGL-2

The only data on HBr that addresses effects that meet the definition of an AEGL-2 are the combined studies of Kusewitt et al. (1989) and Stavert et al. (1991) on the hydrogen halides. Following inhalation of 1300 ppm HBr or HCl for 30 minutes, male F-344 rats exhibited severe necrotic lesions of the anterior nasal passages (mortality for HBr was 8%, and mortality for HCl was 6%) (Stavert et al. 1991). Tissue injury was similar for all three hydrogen halides.

6.3. Derivation of AEGL-2

The AEGL-2 values for the 30-minute, 1-, 4-, and 8-hour time points were based on severe nasal histopathology in rats exposed to 1300 ppm HBr or HCl for 30 minutes (Stavert et al. 1991). Because the data base for HCl is more robust than that for HBr, development of AEGL-2 values followed the reasoning for development of HCl AEGL-2 values (NRC 2004). A modifying factor of 3 was applied to account for the sparse database of effects defined by AEGL-2 and because the effects observed at the concentration used to derive AEGL-2 values were somewhat severe. An uncertainty factor of 3 was applied for interspecies variability because the test species (rodents) were 2-3 times more sensitive to the effects of HCl than primates. An uncertainty factor of 3 was applied for intraspecies extrapolation because the mechanism of action is direct irritation and the subsequent effect or response is not expected to vary greatly among individuals (NRC 2001). Application of an interspecies uncertainty factor of 10 would generate longer-term values that are inconsistent with the longer-term AEGL-1 values which were based on a clinical study (Connecticut State Department of Health 1955). Thus, the total uncertainty and modifying factor adjustment is 30-fold. The resulting value (43 ppm) was then time-scaled to 1-hour AEGL exposure period using the $C^n \times t = k$ relationship, where n=1 based on regression analysis of combined rat and mouse LC_{50} data (1 to 100 minutes) for HCl (ten Berge et al. 1986). The 4- and 8-hour values were derived by applying a modifying factor

of 2 to the 1-hour AEGL-2 value, because time-scaling would yield a 4-hour value of 5.4 ppm and an 8-hour value of 2.7 ppm, close to the HCl concentrations tolerated by exercising asthmatic subjects (NRC 2004). The same values were applied to HI.

The 10-minute AEGL-2 value for HBr and HI was also based on HCl, and was derived by dividing the mouse HCl RD_{50} of 309 ppm (Barrow et al. 1977) by a factor of 3 to obtain a concentration causing irritation. As described in NRC (2004), the human response to sensory irritants can be predicted on the basis of the mouse RD_{50}. Alarie (1981) has shown that the RD_{50} multiplied by 0.1 corresponds to "some sensory irritation;" whereas the RD_{50} is "intolerable." Schaper (1993) validated that for many chemicals, 0.03 times the RD_{50} corresponds to the ACGIH TLV, a concentration that generally prevents sensory irritation in humans. The 0.03 represents the half-way point between 0.1 and 0.01 on a logarithmic scale. Thus, it is reasonable that one-third of the RD_{50}, a value half-way between 0.1 and 1 on a logarithmic scale, might cause significant irritation to humans. Furthermore, one-third of the mouse RD_{50} for HCl (99 ppm) corresponds to an approximate decrease in respiratory rate in the mouse of 30% (Barrow et al. 1977), and decreases in the range of 20 to 50% correspond to moderate irritation (ASTM 1991) which is within the definition of an AEGL-2. Values are summarized in Tables 10 and 11. Calculations are in Appendix A and a category graph of the toxicity data in relation to AEGL values is in Appendix B.

TABLE 10. AEGL-2 Values for Hydrogen Bromide

10-minute	30-minute	1-hour	4-hour	8-hour
100 ppm (330 mg/m^3)	43 ppm (142 mg/m^3)	22 ppm (73 mg/m^3)	11 ppm (36 mg/m^3)	11 ppm (36 mg/m^3)

TABLE 11. AEGL-2 Values for Hydrogen Iodide

10-minute	30-minute	1-hour	4-hour	8-hour
100 ppm (523 mg/m^3)	43 ppm (225 mg/m^3)	22 ppm (115 mg/m^3)	11 ppm (58 mg/m^3)	11 ppm (58 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human data relevant to development of AEGL-3 values were located.

7.2. Summary of Animal Data Relevant to AEGL-3

Lethality data for HBr were available for the rat and mouse. One-hour LC_{50} values for the rat and mouse were 2858 and 814 ppm, respectively (MacEwen and Vernot 1972). Data are summarized in Table 3. From the MacEwen and Vernot data for the rat, a 1-hour LC_{01} of 1350 ppm can be calculated by probit analysis. The $BMCL_{05}$ is 1239 ppm. No deaths occurred in rats exposed to 1000 ppm for 30 minutes (Kusewitt et al. 1989) or in mice exposed to 507 ppm for 1 hour (MacEwen and Vernot 1972).

7.3. Derivation of AEGL-3

The benchmark dose approach, specifically the $BMCL_{05}$, was used to develop AEGL-3 values for HBr and HI. The basis for the values was the 1-hour lethality data for Sprague-Dawley rats exposed to HBr (MacEwen and Vernot 1972). The mouse data were not chosen because mice may be more susceptible than other rodents to respiratory irritants. The 1-hour $BMCL_{05}$ was 1239 ppm (Appendix C) and the BMC_{01} was 1456 ppm (data not shown). The more conservative 1-hour $BMCL_{05}$ of 1239 ppm was chosen as the point of departure. A total uncertainty factor of 10 was applied: 3 for interspecies differences and 3 for differences in human sensitivity. Action of a direct-acting irritant is not expected to vary greatly among species or between individuals (NRC 2001). The interspecies uncertainty factor of 3 is sufficient as additional uncertainty or modifying factors would lower the longer-term AEGL-3 values to the AEGL-2 values. The basis for time-scaling was data for the slightly more toxic chemical, HCl. The resulting 30-minute value of 100 ppm was time scaled to shorter and longer time periods using an n value of 1 (where $C^n \times t = k$) (Tables 12 and 13). Because all three chemicals (HBr, HF, and HCl) are well scrubbed in the upper respiratory tract at moderately high concentrations, the 8-hour AEGL-3 was set equal to the 4-hour AEGL-3, as was done for HF and HCl (NRC 2004). Calculations are in Appendix A and a category graph of the toxicity data in relation to AEGL values is in Appendix B.

Table 12. AEGL-3 Values for Hydrogen Bromide

10-minute	30-minute	1-hour	4-hour	8-hour
740 ppm (2442 mg/m^3)	250 ppm (825 mg/m^3)	120 ppm (396 mg/m^3)	31 ppm (102 mg/m^3)	31 ppm (102 mg/m^3)

Table 13. AEGL-3 Values for Hydrogen Iodide

10-minute	30-minute	1-hour	4-hour	8-hour
740 ppm (3870 mg/m^3)	250 ppm (1307 mg/m^3)	120 ppm (628 mg/m^3)	31 ppm (162 mg/m^3)	31 ppm (162 mg/m^3)

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity Endpoints

The AEGL values for HBr and HI are summarized in Table 14. Derivation summaries are in Appendix D.

TABLE 14. Summary of AEGL Values for Hydrogen Bromide and Hydrogen Iodide

Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm
AEGL-2 (Disabling)	100 ppm	43 ppm	22 ppm	11 ppm	11 ppm
AEGL-3 (Lethal)	740 ppm	250 ppm	120 ppm	31 ppm	31 ppm

8.2. Comparison with Other Standards and Guidelines

Available standards and guidelines for HBr are summarized in Table 15. Except for the OSHA permissible exposure limit (PEL), ceiling or peak limits rather than 8-hour time-weighted averages (TWA) have been derived for the workplace. The AEGL-1 for HBr is below these workplace guidelines. The IDLH is based on analogy with HCl (NIOSH 2002). The IDLH for HCl is 50 ppm which is ten times the NIOSH REL. Therefore, the IDLH for HBr was set at ten times the NIOSH REL of 3 ppm. The 30-minute AEGL-2 is similar to the IDLH. No guidelines were found for HI.

TABLE 15. Extant Standards and Guidelines for Hydrogen Bromide

Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm
AEGL-2	100 ppm	43 ppm	22 ppm	11 ppm	11 ppm
AEGL-3	740 ppm	250 ppm	120 ppm	31 ppm	31 ppm
OSHA PEL-TWA (NIOSH)[a]					3 ppm
IDLH (NIOSH)[b]		30 ppm			
REL-Ceiling (NIOSH)[c]	3 ppm				
TLV-Ceiling (ACGIH)[d]	3 ppm				
MAK Peak Limit (Germany)[e]	2 ppm (15-minutes, 4 times/shift)				
MAC Peak Limit (The Netherlands)[f]	2 ppm (15-minute duration)				

[a]**OSHA PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits - Time Weighted Average)** (NIOSH 2002) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[b]**IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** (NIOSH 2002) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

[c]**NIOSH REL-Ceiling (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** (NIOSH 2002) is defined analogous to the ACGIH-TLV-Ceiling.

[d]**ACGIH Ceiling** (ACGIH 2002) is a limit that should not be exceeded during the working day.

[e]**MAK Spitzenbegrenzung (Peak Limit)** (German Research Association 2000) constitutes the maximum average concentration to which workers can be exposed for a period of 15 minutes with no more than 4 excursions/work shift and with an interval of 1 hour between excursions.

[f]**MAC - Peak Limit** (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is a 15-minute peak limit.

8.3. Data Adequacy and Research Needs

Only one study that utilized human subjects was available for development of AEGL-1 values (Connecticut State Department of Health 1955). The study was old and used short exposure durations, but an adequate number of subjects was used, a range of concentrations was used, and irritant levels were clearly described. Animal data were limited to the rat and mouse. The well-conducted studies with rats from two different laboratories (MacEwen and Vernot 1972; Stavert et al. 1991), showed reasonable agreement. One of these studies (MacEwen and Vernot 1972) also addressed the relative toxicities of HBr, HF, and HCl to the rat. Therefore, based on the available data as well as structure-activity relationships, data were available to derive both AEGL-2 and AEGL-3 values.

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APPENDIX A: Time-Scaling Calculations

Derivation of AEGL-1

Key Study:	Connecticut Department of Health (1955)
Toxicity Endpoint:	Nose and throat irritation in one of six subjects at 3 ppm for several minutes
Time Scaling:	No time scaling, there is adaptation to the slight irritation that defines the AEGL-1
Uncertainty factors:	3 for intraspecies - irritation from a direct-contact irritant should not vary greatly among individuals (NRC 2001)
Calculation:	3 ppm/3 = 1 ppm

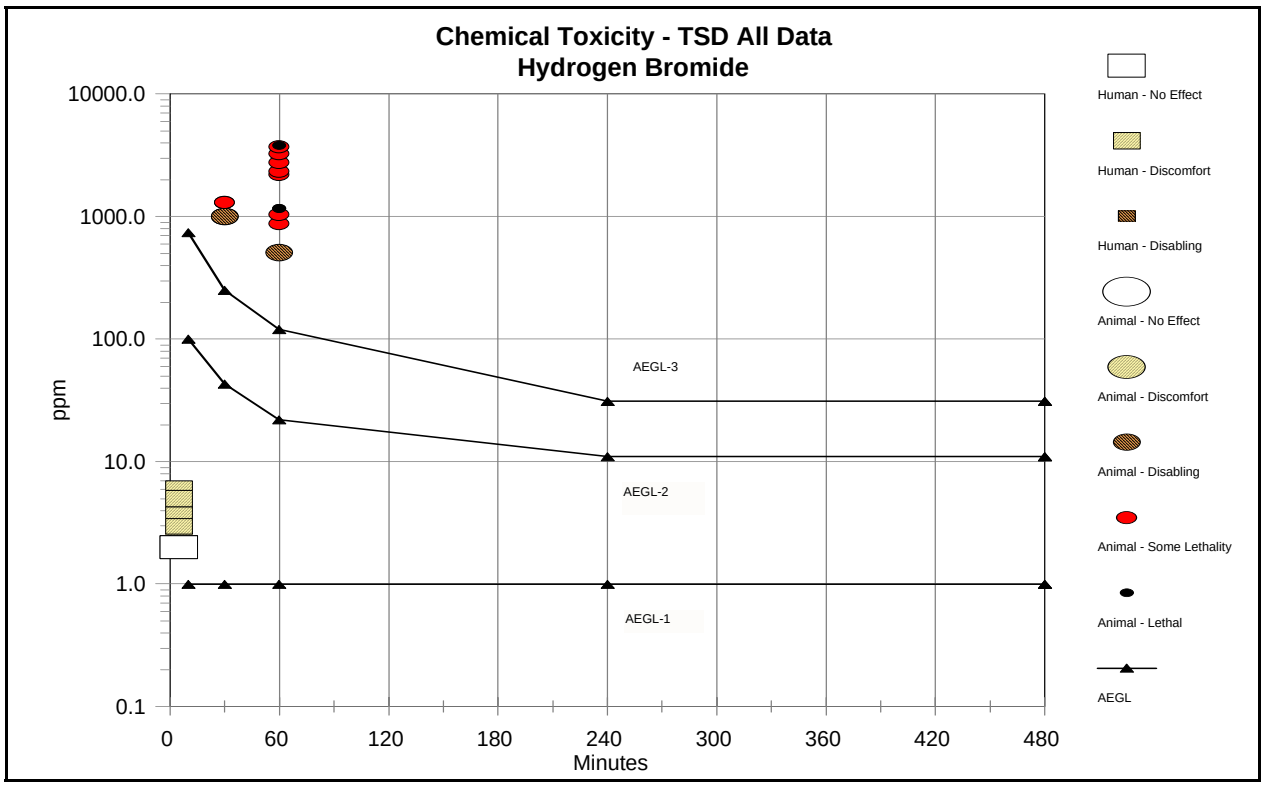
Derivation of AEGL-2

Key Studies:	Values based on analogy with hydrogen chloride (HCl)
HCl key studies:	Stavert et al. (1991); Barrow et al. (1977). The Stavert et al. (1991) study also included data on HBr.
Toxicity Endpoint:	Stavert et al. (1991): Respiratory tract lesions in rats breathing 1300 ppm HCl for 30 minutes Barrow et al. (1977): 10-minute RD_{50} of 309 ppm
Time scaling:	10-minute value based on 10-minute RD_{50} 30 minutes to 4 hours; used values for HCl: $C^1 \times t = k$ 8-hour values set equal to the 4-hour value because hydrogen halides are well scrubbed in the upper respiratory tract.
Uncertainty factors:	10-minute value: RD_{50} divided by 3 30 minutes and 1 hour: (3 for interspecies and 3 for intraspecies) Effects from direct-contact irritants do not vary greatly between species or among individuals (NRC 2001). 4- and 8-hour values: 1 hour value divided by 2
Modifying factor:	3 for sparse data base and severe effect, applied to 30 minutes to 8 hours
Calculations:	
10-min AEGL-2:	309 ppm/3 = 100 ppm
30-min AEGL-2:	$C^1 \times 0.5$ hr = 650 ppm•hr C = 1300 ppm 30 min AEGL-2 = 1300 ppm/30 = 43 ppm
1 hr AEGL-2:	$C^1 \times 1$ hr = 650 ppm•hr C = 650 ppm 1 hr AEGL-2 = 650 ppm/30 = 21.6 ppm
4 hr AEGL-2:	1-hr AEGL-2 ÷ 2 = 11 ppm
8 hr AEGL-2:	1-hr AEGL-2 ÷ 2 = 11 ppm

Derivation of AEGL-3:

Key Study:	MacEwen and Vernot (1972).
Toxicity endpoint:	The point of departure was the Benchmark Dose ($BMCL_{05}$) of 1238.95 ppm for rats exposed for one hour.
Time scaling:	$C^1 \times t = k$, based on rat lethality data with HCl
Uncertainty factors:	Total uncertainty factor:10 Interspecies: 3 - response to 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) Application of default inter- or intraspecies uncertainty factors of 10 would lower the longer-term AEGL-3 values to close to the longer-term AEGL-2 values.
Calculations:	$C^1 \times t = k$ (1238.95 ppm/10) x 60 minutes = 7433.7 ppm•minutes
10-min AEGL-3:	7433.7 ppm•minutes/10 minutes = 740 ppm
30-min AEGL-3:	7433.7 ppm•minutes/30 minutes = 250 ppm
1-hr AEGL-3:	1239 ppm•minutes/10 minutes = 120 ppm
4-hr AEGL-3:	7433.7 ppm•minutes/240 minutes) = 31 ppm
8-hr AEGL-3:	Set equal to 4-hour values of 31 ppm

APPENDIX B: Category Graph of Toxicity Data and AEGL Values



Note: All toxicity data pertain to hydrogen bromide.

APPENDIX C: Benchmark Concentration Calculation

Hydrogen bromide $BMCL_{05}$

```
 ================================================================
         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[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(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

Parameter Estimates

Variable	Estimate	Std. Err.	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

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Analysis of Deviance Table

Model	Log (likelihood)	# Param's	Deviance	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				

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled 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 d.f. = 5 P-value = 0.4134

Benchmark Dose Computation

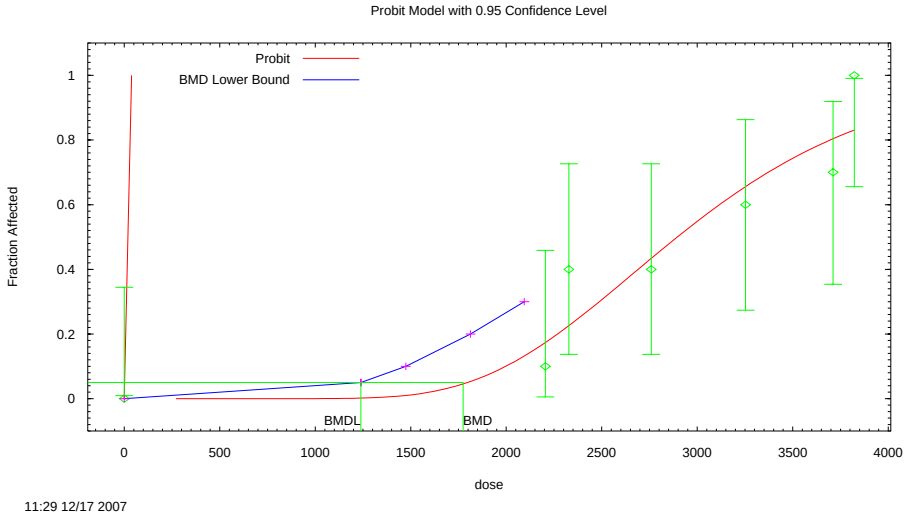
Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95

BMC = 1774.18

BMCL = 1238.95



APPENDIX D: Derivation Summary

ACUTE EXPOSURE GUIDELINE LEVELS FOR HYDROGEN BROMIDE (CAS Reg. No. 10035-10-6) and HYDROGEN IODIDE (CAS Reg. No. 10034-85-2) DERIVATION SUMMARY

AEGL-1 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
1.0 ppm	**1.0 ppm**	**1.0 ppm**	**1.0 ppm**	**1.0 ppm**

Key Reference: Connecticut State Department of Health. 1955. Unpublished data. Occupational Health Section, Connecticut State Department of Health, Hartford, CT.

Test Species/Strain/Number: Human subjects/6

Exposure Route/Concentrations/Durations: Inhalation/2, 3, 4, 5, 6 ppm/several minutes

Effects: Odor detectable for all 6 subjects at all concentrations
2 ppm: no nose, throat, or eye irritation
3 ppm: nose and throat irritation in 1 of 6 subjects; no eye irritation
4 ppm: nose irritation in 3 of 6 subjects; throat irritation in 1 of 6 subjects; no eye irritation
5 ppm: nose irritation in 6 of 6 subjects; throat irritation in 1 of 6 subjects; no eye irritation
6 ppm: nose irritation in 6 of 6 subjects; throat irritation in 1 of 6 subjects; no eye irritation

Endpoint/Concentration/Rationale: 3 ppm is a NOAEL for notable discomfort

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: not relevant
Intraspecies: 3; the threshold for irritancy does not differ greatly among humans (NRC 2001)

Modifying Factor: Not applied

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: Not applied; humans adapt to the slight sensory irritation that defines the AEGL-1

Data Adequacy: Old, but well-conducted study with human subjects. The value is supported by the similar values for other chemicals in this class, HF and HCl. The data base for these latter two chemicals is robust.

AEGL-2 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
100 ppm	**43 ppm**	**22 ppm**	**11 ppm**	**11 ppm**

Key References: **References are for HCl:**
(1) Barrow, C.S., Alarie, Y., Warrick, M., and Stock, M.F. 1977. Comparison of the sensory irritation response in mice to chlorine and hydrogen chloride. Arch. Environ. Health. 32:68-76.
(2) Stavert, D.M., D.C. Archuleta, M.J. Behr, and B.E. Lehnert. 1991. Relative acute toxicities of hydrogen fluoride, hydrogen chloride, and hydrogen bromide in nose- and pseudomouth-breathing rats. Fundam. Appl. Toxicol. 16:636-655.

Test Species/Strain/Number: (1) Mouse RD_{50} study; male F-344 rats, 6-9/exposure group; (2) Rat/F-344/5-8

Exposure Route/Concentrations/Durations: Inhalation: (1) 10-minute mouse RD_{50} for HCl; (1) 30-minute inhalation exposure to 1300 ppm HCl or HBr.

Effects: (1) Depression of the respiratory rate by 50%; (2) severe necrotic lesions of the anterior nasal passages; no deaths in study with HCl; one death in study with HBr.

Endpoint/Concentration/Rationale: (1) Mouse HCl RD_{50} of 309 ppm; (2) 30-minute exposure to 1300 ppm

Uncertainty Factors/Rationale:
Total uncertainty factor for 1-hour value: 10
Interspecies: 3 - the rat was more sensitive than primates in a companion study with HCl
Intraspecies: 3 - HBr is a direct-acting irritant; individual variation should not be more than three-fold (NRC 2001); 10-minute value: the 10-minute mouse RD_{50} was divided by 3 to obtain a concentration that causes irritation

Modifying Factor for 1-hour value: 3 - based on small data set and effects more severe than those defined by the AEGL-2; the 4- and 8-hour values were adjusted by applying a modifying factor of 2 to the 1-hour value to be consistent with the entire data set.

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling to the 1-hour value: $C^n \times t = k$ where $n = 1$ was derived based on regression analysis of rat and mouse LC_{50} data in a study with the chemically-similar HCl.

Data Adequacy: The data base for HBr and HI is sparse, but the empirical data with support from studies on the relative toxicities of the hydrogen halides are adequate for derivation of AEGL-2 values.

AEGL-3 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
740 ppm	**250 ppm**	**120 ppm**	**31 ppm**	**31 ppm**

Key Reference: MacEwen, J.D. and E.H. Vernot. 1972. Toxic Hazards Research Unit Annual Technical Report: 1974. AMRL-TR-74-78, Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH; available from National Technical Information Service, Springfield, VA.

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

Exposure Route/Concentrations/Durations: Inhalation/2205-3822 ppm/1 hour

Effects: Lethality:
2205 ppm: 1/10
2328 ppm: 4/10
2759 ppm: 4/10
3253 ppm: 6/10
3711 ppm: 7/10
3822 ppm: 10/10

Endpoint/Concentration/Rationale: Calculated 1-hour $BMCL_{05}$ of 1239 ppm

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3 - Sufficient, based on differences in sensitivity among species
Intraspecies: 3 - Sufficient; higher factors would result in values inconsistent with the AEGL-2

Modifying Factor: Not applied

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling: $C^1 \times t = k$, based on mouse lethality data for the more toxic chemical HCl

Data Adequacy: Although there were only two well-conducted studies with the rat and mouse, the values are consistent with those for the related chemicals, HF and HCl. The data bases for HF and HCl are robust.