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 the toxicities 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 (MacEwen and Vernot 1972), the relative toxicities to the rat and mouse are in the order HF>HCl≈HBr. 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 in the anteriormost region 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. HI is predicted to be less toxic than the other hydrogen halides. As the most water soluble hydrogen halide, HI may be 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 considered to be appropriate and reasonably conservative.

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 irritation is concentration related and humans adapt to the slight sensory irritation that defines the AEGL-1. The 1.0 ppm concentration across time is supported by the AEGL-1 values of 1.0 and 1.8 ppm developed for HF and HCl, respectively (NRC 2004). The 1.0 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 point of departure for derivation of AEGL-2 values for HBr is the exposure of male rats to 1000 ppm for 30 minutes which resulted in lesions of the nasal passages. It could not be ascertained if the lesions were reversible. Because the severity of the lesions may exceed the definition of AEGL-2 and because this concentration is close to the calculated $BMCL_{05}$ of 1239 ppm used as the point of departure for the AEGL-3, the 1000 ppm concentration was divided by a modifying factor of 2. An uncertainty factor of 3 was applied for interspecies variability because the test species (rodents) were 2-3 times more sensitive than primates to the effects of the related chemical HCl. 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). Furthermore, the intraspecies uncertainty factor of 3 is consistent with that used for other hydrogen halides. The intraspecies uncertainty factor of 3 for HCl was supported by the steep-dose response curve, "which indicates little inter-individual variability" and by the fact that larger uncertainty factors would not be supported by the total data set including the data on exercising asthmatics. It is assumed that the action of all hydrogen halides on the respiratory tract is the same (shown by the data of Stavert et al. 1991), and that protection of exercising asthmatics for one chemical would be protective of asthmatics at a similar concentration of another hydrogen halide. Thus, the total modifying and uncertainty factor adjustment is 20. A time scaling value ($C^n \times t = k$) of n = 1 was used as was done for HCl. Because all three chemicals (HBr, HF, and HCl) are well scrubbed in the upper respiratory tract at moderately high concentrations, the 4- and 8-hour AEGL-2 value for HBr were set equal as was done for HF and HCl (NRC 2004). The 4- and 8-hour values were derived by dividing the 1-hour AEGL-2 value by 2, because time scaling would yield 4- and 8- hour values of 6.3 and 3.1, respectively, close to the AEGL-1 concentrations tested in the Connecticut Department of Health (1955) study. The same values were applied to HI which is predicted to be less toxic than HBr.

The $BMCL_{05}$ of 1239 ppm, calculated from 1-hour lethality data for Sprague-Dawley rats exposed to HBr (MacEwen and Vernot 1972), was selected as the point of departure to develop AEGL-3 values for HBr. A total uncertainty factor of 10 was applied: 3 for interspecies differences and 3 for differences in human sensitivity. Interspecies and intraspecies uncertainty factors of 3 each are considered to be sufficient because the action of a direct-acting irritant is not expected to vary greatly among species or between individuals (NRC 2001). In addition, higher uncertainty factors or the inclusion of modifying factors would lower the longer-term AEGL-3 values to the AEGL-2 values. The 60-minute point of departure was time-scaled to the 10-minute, 30-minute, and 4-hour time periods using a value of 1 for n (where $C^n \times t = k$). The value of 1 was selected based on data for the related compound HCl, for which regression analysis of combined rat and mouse LC_{50} data resulted in a value of n (see NRC, 2004). Consistent with the approach used for HF and HCl (NRC 2004), the 8-hour AEGL-3 for HBr was set equal to the 4-hour AEGL-3, reflecting uncertainty in extrapolating from 1 hour to 8 hours.

The calculated values are listed in the tables below.

S 1. Summary of AEGL Values for Hydrogen Bromide						
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**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)	150 ppm (500 mg/m^3)	50 ppm (170 mg/m^3)	25 ppm (83 mg/m^3)	13 ppm (43 mg/m^3)	13 ppm (43 mg/m^3)	lesions - rat (Kusewitt et al., 1989; Stavert et al. 1991);
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 ($BMCL_{05}$) - rat (MacEwen and Vernot 1972)

S 2. Summary of AEGL Values for Hydrogen Iodide						
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**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)	Analogy with hydrogen bromide
AEGL-2 (Disabling)	150 ppm (780 mg/m^3)	50 ppm (260 mg/m^3)	25 ppm (130 mg/m^3)	13 ppm (68 mg/m^3)	13 ppm (68 mg/m^3)	Analogy with hydrogen bromide
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)	Analogy with hydrogen bromide

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 10°C 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, HBr to water	Extremely soluble, 234 g/100 g at 10°C	O'Neil et al. 2001
Vapor pressure	>760 torr @ 20°C 335 psia @21°C	5670 mm Hg at 21°C	ACGIH 2002 Braker and Mossman 1980
Vapor density (air =1)	2.71	4.46	O'Neil et al. 2001
Density	1.48 g/mL @ 25°C	5.23 g/L @ 25°C	Jackisch 1992; O'Neil et al. 2001
Melting point	-87°C	-50.8°C	O'Neil et al. 2001
Boiling point	-67°C	-35.1°C	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

Amoore and Hautala (1983) reported an odor threshold for HBr of 2 ppm. 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 vapor. 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 (presumably the same one) experienced throat irritation at all of the higher concentrations, and all subjects experienced nose irritation at 5 and 6 ppm. Although exposure to

5 ppm caused nose irritation in all 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

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

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

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. These data appear to be taken from Henderson and Haggard (1943) and apply 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). All six volunteers detected HBr at 2 ppm, and one individual experienced subjective irritation involving the nose and throat at 3 ppm. At higher concentrations, at least half of subjects experienced nose and/or throat irritation. 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)

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

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%. The effect on ventilatory rate was similar with HF exposure, while exposure to HCl caused a much smaller decrease in ventilation. 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 (where region 1 was anterior and region 4 was posterior) which were examined microscopically. For all three hydrogen halides, tissue injury was confined to the nasal cavity. Tissue injury in the anterior nasal cavity was similar following exposures to all three compounds 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. Blood clots were observed in nasal blood vessels; hemorrhage, fibrin and fluid were observed in the nasal passages; and polymorphonuclear cells were observed in the submucosa and in the lumen. For HF and HCl, but not HBr, the lesions extended into region 2. After exposure to all three halogen halides, 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. The study authors concluded that respiratory tract injury caused by exposure to the three hydrogen halides was 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 in the deeper submucosal tissues of region 1 and in all tissues of region 2 (see Table 5) 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	30 min	No deaths	Kusewitt et al. 1989
	1300	30 min	8% mortality	Stavert et al. 1991
	2858	1 hr	LC_{50}	MacEwen and Vernot 1972
Mouse	507	1 hr	No deaths	MacEwen and Vernot 1972
	814	1 hr	LC_{50}	

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 (used to simulate mouth breathing). 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. Lung lesions observed in treated animals were not significantly different from those of the cannulated control group.

3.1.2. Mice

MacEwen and Vernot (1972) (see also Back et al. 1972) 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. In a study in which the ventilatory rate of rats inhaling 1000 ppm HCl for 30 minutes was increased by the addition of CO_2 to the exposure chamber, no deaths occurred, and histopathology lesions were confined to the upper respiratory tract and (Lehnert and Stavert 1991). Barrow et al. (1977) exposed groups of four male Swiss-Webster mice to HCl at concentrations of 40, 99, 245, 440, or 943 ppm for 10 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, (Kusewitt et al. 1989), no deaths occurred in rats inhaling 1000 ppm HBr 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 an irritant at the site of contact. 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).

No information on the metabolism of HI was located. Iodine is an essential nutrient required for development and functioning of the thyroid gland.

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

Differences in size and electron configuration of the various halogen atoms result in substantial differences with respect to their chemical and physical properties, which in turn affect their toxicological properties (atomic weights of fluorine, chlorine, bromine, and iodine are 19, 35.5, 80, and 127 respectively). Hydrogen iodide is the least stable of the hydrogen halides, dissociating into its constituents at room temperature. As the most soluble hydrogen halide, HI may be better scrubbed in the nasal passages than the other compounds, and thus may be less toxic.

Data on the relative toxicities of HF, HCl, and HBr for the endpoint of lethality are available. As can be seen from the data in Table 6, three rodent studies utilizing different exposure durations show that HF is more lethal than HCl (Higgins et al. 1972; Rosenholtz et al. 1963; MacEwen and Vernot 1972; Wohlslagel et al. 1976). For both the rat and mouse, HF is also more lethal than HBr (MacEwen and Vernot 1972). Data from the same laboratory (Wohlslagel et al. 1976; MacEwen and Vernot 1972) show that HCl and HBr have similar 1-hour LC_{50} values, 3124 ppm and 2858 ppm, respectively. Data on the nonlethal toxicity of the three hydrogen halides (Stavert et al., 1991) suggest that HF and HCl cause more severe nasal lesions than HBr, and, unlike HBr, cause damage extending deeper into the nasal cavity under the same exposure conditions. Hydrogen bromide and HF exposure resulted in similar decreases in ventilation rate (~25%), while the decrease associated with HCl exposure was smaller (Stavert et al., 1991).

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

Species	Exposure Duration	HF	HCl	HBr	Reference
Rat	5 min	18,200	41,000		Higgins et al. 1972
Mouse		6247	13,750		
Rat	30 min	2042	4700		Rosenholtz et al. 1963 (HF);
Mouse			2644		MacEwen and Vernot 1972 (HCl)
Rat	1 hr	1395	3124		Wohlslagel et al. 1976
Mouse		342	1108		
Monkey	1 hr	1774			MacEwen and Vernot 1970
Rat		1278		2858	MacEwen and Vernot 1972
Mouse		501		814	

The data of Wohlslagel et al. (1976) and MacEwen and Vernot (1972) were generated in the same laboratory. Therefore, the values for HCl (Wohlslagel et al. 1976) can be compared with those for HF and HBr 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>nonhuman primate (rhesus 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 likely experience increased penetration of HBr or HI into the lower respiratory tract due to increased minute volumes, with the potential for increased irritant response, compared with 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). Chemically, HBr is more similar to HCl than to HF.

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 HBr for several minutes (3 ppm, Connecticut State Department of Health 1955), was selected as the basis for the AEGL-1. This concentration was considered to be a threshold for notable discomfort, as only one individual was affected at this concentration. The 3 ppm point of departure was divided by an intraspecies uncertainty factor of 3, because response to sensory irritation is not expected to vary greatly among individuals (NRC 2001). The intraspecies uncertainty factor of 3 was considered sufficient because the effect of slight irritation is below the definition of AEGL-1. In addition, an intraspecies UF of 3 was used previously in the AEGL derivations for hydrogen chloride (HCl) and hydrogen fluoride (HF), related compounds whose mode of action is the same as HBr (NRC, 2004). It is reasonable to use the same uncertainty factors for a class of chemicals whose mode of action is the same. Finally, the uncertainty factor used to derive the AEGL-1 values for HBr is believed to be protective for asthmatic individuals based on a comparison of the AEGL-1 value for HBr (1.0 ppm) with the AEGL-1 value for HCl (1.8 ppm), which is based on a no-effect level for irritation in exercising asthmatics. There is evidence that HBr is of similar toxicity to HCl; thus, the lower HBr AEGL-1 values derived with an intraspecies UF of 3 are considered to be protective for asthmatics based on the data available for HCl.

Because irritation is dependent on concentration rather than time, and adaptation to slight irritation occurs (Dalton 2001), the resulting 1.0 ppm concentration was used as the HBr AEGL-1 for all exposure durations (Tables 7 and 8). The same values were applied to HI. 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-min	30-min	1-hr	4-hr	8-hr
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-min	30-min	1-hr	4-hr	8-hr
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 AEGL-1 values for HBr and HI are comparable to the AEGL-1 values for HF and HCL, shown in Table 9 below.

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

Classification	10-min	30-min	1-hr	4-hr	8-hr
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). No rats died following exposure to 1000 ppm HBr for 30 minutes (Kusewitt et al. 1989). Lesions consisting of necrosis and inflammation were restricted to the nasal region; the lungs appeared unaffected. Sacrifice took place 24 hours after exposure and no judgment could be made as to whether the lesions were reversible. The authors (Kusewitt et al. 1989; Stavert et al. 1990) noted that nasal lesions were similar in severity and location for all three hydrogen halides when tested at the same concentration, with HF being slightly more toxic than HCl which was similar in toxicity to HBr.

6.3. Derivation of AEGL-2

The point of departure for derivation of AEGL-2 values for HBr is the exposure of male rats to 1000 ppm for 30 minutes which resulted in lesions of the nasal passages. It could not be ascertained if the lesions were reversible. Because the severity of the lesions may exceed the definition of AEGL-2 and because this concentration is close to the calculated $BMCL_{05}$ of 1239 ppm used as the point of departure for the AEGL-3 (Section 7.3), the 1000 ppm concentration was divided by a modifying factor of 2. An uncertainty factor of 3 was applied for interspecies variability because the test species (rodents) were 2-3 times more sensitive than primates to the effects of the related chemical HCl. 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). Furthermore, the intraspecies uncertainty factor of 3 is consistent with that used for other hydrogen halides. The intraspecies uncertainty factor of 3 for HCl was supported by the steep concentration-response curve, which indicates little inter-individual variability and by the fact that larger uncertainty factors would not be supported by the total data set including the data on exercising asthmatics. The concentration-response curve for HBr is also steep (Table 3). It is assumed that the action of all hydrogen halides on the respiratory tract is the same (shown by the data of Stavert et al. 1991), and that protection of exercising asthmatics for

one chemical would be protective of asthmatics at a similar concentration of another hydrogen halide. Thus, the total uncertainty and modifying factor adjustment is 20. A time scaling value (C^n x t = k) of n = 1 was used; this value was derived from the analysis of rat and mouse LC_{50} data for HCl (see NRC, 2004). Because all three chemicals (HBr, HF, and HCl) are well scrubbed in the upper respiratory tract at moderately high concentrations, the 4- and 8-hour AEGL-2 values were set equal as was done for HF and HCl (NRC 2004). The 4- and 8-hour values were derived by dividing the 1-hour AEGL-2 value by 2, because time scaling would yield 4- and 8- hour values of 6.3 and 3.1, respectively, close to the AEGL-1 concentrations tested in the Connecticut Department of Health (1955) study. The same values were applied to HI. AEGL-2 values for HBr and HI are listed in Tables 10 and 11, respectively.

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-min	30-min	1-hr	4-hr	8-hr
150 ppm (500 mg/m^3)	50 ppm (170 mg/m^3)	25 ppm (83 mg/m^3)	13 ppm (43 mg/m^3)	13 ppm (43 mg/m^3)

TABLE 11. AEGL-2 Values for Hydrogen Iodide

10-min	30-min	1-hr	4-hr	8-hr
150 ppm (780 mg/m^3)	50 ppm (260 mg/m^3)	25 ppm (130 mg/m^3)	13 ppm (68 mg/m^3)	13 ppm (68 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 (Appendix C) and the BMC_{01} is 1456 ppm (data not shown). 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). As indicated by a National Research Council report (NRC 1991) and noted in Section 4.4.1, Species Variability, mice are not considered to be an appropriate species for setting lethality values for hydrogen halides, as this species is more susceptible to the lethal effects of HCl than rats or non-human primates (NRC 1991).

7.3. Derivation of AEGL-3

The $BMCL_{05}$ of 1239 ppm, calculated from 1-hour lethality data for Sprague-Dawley rats exposed to HBr (MacEwen and Vernot 1972), was selected as the point of departure to develop AEGL-3 values for HBr. This value was more conservative than the BMC_{01} of 1456 ppm calculated from the same data. A total uncertainty factor of 10 was applied: 3 for interspecies differences and 3 for differences in human sensitivity. Interspecies and intraspecies uncertainty factors of 3 each are considered to be sufficient because the action of a direct-acting irritant is not expected to vary greatly among species or between individuals (NRC 2001). In addition, higher uncertainty factors or the inclusion of modifying factors would lower the longer-term AEGL-3 values to the AEGL-2 values.

The 60-minute point of departure was time-scaled to the 10-minute, 30-minute, and 4-hour time periods using a value of 1 for n (where $C^n \times t = k$). The value of 1 was selected based on data for the related compound HCl, for which regression analysis of combined rat and mouse LC_{50} data resulted in an estimate of n=1 (see NRC, 2004). Consistent with the approach used for HF and HCl (NRC 2004), the 8-hour AEGL-3 for HBr was set equal to the 4-hour AEGL-3, reflecting uncertainty in extrapolating from 1 hour to 8 hours. The same values were applied to HI. The AEGL-3 values for HBr and HI are shown in Tables 12 and 13, respectively. 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-min	30-min	1-hr	4-hr	8-hr
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-min	30-min	1-hr	4-hr	8-hr
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-min	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-1 (Nondisabling)	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm
AEGL-2 (Disabling)	150 ppm	50 ppm	25 ppm	13 ppm	13 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 min	**30 min**	**1 hr**	**4 hr**	**8 hr**
AEGL-1	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm	1.0 ppm
AEGL-2	150 ppm	50 ppm	25 ppm	13 ppm	13 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 tested, 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. Tthese studies also addressed the relative toxicities of HBr, HF, and HCl to the rat. Although the data on HBr were sparse, supporting information on related hydrogen halides and information on relative toxicity are available; thus, the data were considered adequate to derive AEGL values for HBr. The toxicity of HI is predicted to be lower than that of the other hydrogen halides based on its greater water solubility and the likelihood that it may be better scrubbed in the nasal passages; the AEGLs for this compound were set equal to those for HBr.

9. REFERENCES

ACGIH (American Conference of Government and Industrial Hygienists). 2002. Threshold Limit Values (TLVs) for Chemical and Physical Agents and Biological Exposure Indices (BEIs). Cincinnati, OH: ACGIH.

Alarie, Y. 1981. Dose-response analysis in animal studies: Prediction of human responses. Environ. Health Persp. 42:9-13.

Amoore, J.E. and E. Hautala. 1983. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J. Appl. Toxicol. 3:272-289.

ASTM. (American Society for Testing and Materials). 1991. Standard Test Method for estimating sensory irritancy of airborne chemicals. Method E981, Volume 11.04, p. 610-619. ASTM Philadelphia, PA.

Back, K.C., A.A. Thomas, and J.D. MacEwen. 1972. Reclassification of Materials Listed as Transportation Health Hazards. Report No. TSA-20-72-3; PB 214 270, available from the National Technical Information Service, Springfield, VA.

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.

Braker, W. and A.L. Mossman. 1980. Matheson Gas Data Book, 6th ed. Lyndhurst, NJ: Matheson.

Connecticut State Department of Health. 1955. Unpublished data. Occupational Health Section, Connecticut State Department of Health, Hartford, CT (Summarized in ACGIH 2002).

Dalton, P. 2001. Evaluating the human response to sensory irritation: Implications for setting occupational exposure limits. Am. Ind. Hyg. Assoc. J. 62:723-729.

German Research Association (Deutsche Forschungsgemeinschaft). 2000. List of MAK and BAT Values, 2000. Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Report No. 35. Federal Republic of Germany: Wiley-VCH.

Henderson, Y. and H.W. Haggard 1943. Noxious Gases. New York: Reinhold Publishing Corp. p. 126.

Higgins, E.A., V. Fiorca, A.A. Thomas and H.V. Davis. 1972. Acute toxicity of brief exposures to HF, HCl, NO2 and HCN with and without CO. Fire Technol. 8:120-130.

HSDB (Hazardous Substances Data Base). 2003. National Library of Medicine online data base.

Jackisch, P.F. 1992. Bromine Compounds. Kirk-Othmer Encyclopedia of Chemical Technology, 4th ed., Vol. 4. New York: John Wiley & Sons.

Kusewitt, D.F., D.M. Stavert, G. Ripple, T. Mundie, and B.E. Lehnert. 1989. Relative acute toxicities in the respiratory tract of inhaled hydrogen fluoride, hydrogen bromide, and hydrogen chloride. Toxicologist 9:36.

Lauterbach, A. and G. Ober. 1991. Iodine and iodine compounds. In Kirk-Othmer Encyclopedia of Chemical Technology, Vol 14, 4th Ed. New York: John Wiley & Sons.

Lehnert, B.E. and D.M. Stavert. 1991. The Acute Inhalation Toxicity of Pyrolysis Products of Halon 1301. AD-A246 031, Annual Report, Los Alamos National Laboratory, Los Alamos, NM; sponsored by the U.S. Army Medical Research and Development Center, Fort Detrick, Frederick, MD.

MacEwen, J.D. and E.H. Vernot. 1970. Toxic Hazards Research Unit Annual Technical Report: 1970. AMRL-TR-70-77, AD 714694, Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, Ohio.

MacEwen, J.D. and E.H. Vernot. 1972. Toxic Hazards Research Unit Annual Technical Report: 1972. AMRL-TR-72-62, AD 755 358, Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH; available from National Technical Information Service, Springfield, VA.

Ministry of Social Affairs and Employment (SDU Uitgevers). 2000. Nationale MAC list, 1999. The Hague, The Netherlands.

NIOSH. 2002. Hydrogen bromide: IDLH documentation. http://www.cdc.gov/niosh/idlh/10035106.html. Retrieved 6/20/2002.

NRC (National Research Council). 1991. Permissible Exposure Levels and Emergency Exposure Guidance Levels for Selected Airborne Contaminants. Washington, DC: National Academy Press.

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

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

O'Neil, M.J., A. Smith, and P.E. Heckelman, eds. 2001. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals, 13th ed. Whitehouse Station, NJ: Merck & Co., Inc.

Rosenholtz, M.J., T.R. Carson, M.H. Weeks, F. Wilinski, D.F. Ford and F.W. Oberst. 1963. A toxicopathologic study in animals after brief single exposures to hydrogen fluoride. Amer. Ind. Hyg. Assoc. J. 24:253-261.

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

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.

Stevens, B. J.Q. Koenig, V. Rebolledo, Q.S. Hanley, and D.S. Covert. 1992. Respiratory effects from the inhalation of hydrogen chloride in young adult asthmatics. J. Occup. Med. 34:923-929.

Teitelbaum, D.T. 2001. The halogens. pp. 731-825 in Patty's Industrial Hygiene and Toxicology, 5th ed., Vol 3. New York: John Wiley & Sons, Inc.

ten Berge, W.F., A. Zwart and L.M. Appleman. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapors and gases. J. Hazard. Mater. 13:301-310.

Vernot, E.H., J.D. MacEwen, C.C. Haun and E.R. Kinkead. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol. Appl. Pharmacol. 42:417-423.

Wohlslagel, J., L.C. DiPasquale and E.H. Vernot. 1976. Toxicity of solid rocket motor exhaust: effects of HCl, HF, and alumina on rodents. J. Combust. Toxicol. 3:61-69.

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 = 1.0 ppm

Derivation of AEGL-2

Key study: Stavert et al. (1991)

Toxicity Endpoint: Respiratory tract lesions in rats breathing 1000 ppm HBr for 30 minutes

Time scaling: 10 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 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: 2 for sparse data base and severe effect

Calculations:
$C^1 \times t = k$
1000 ppm/(10x2) x 30 minutes = 1500 ppm•min

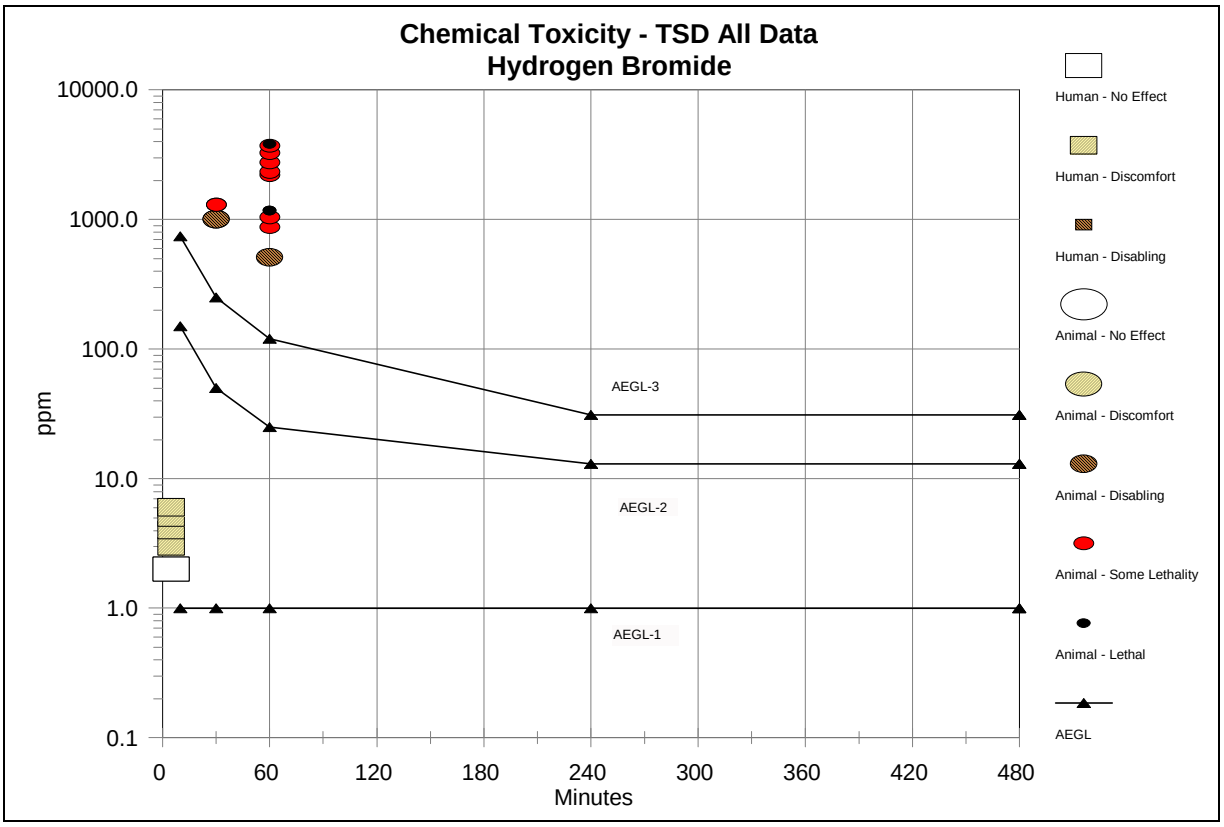
10-min AEGL-2: 1500 ppm•min /10 minutes = 150 ppm
30-min AEGL-2: 1500 ppm•min /30 minutes = 50 ppm
1 hr AEGL-2: 1500 ppm•min /60 minutes = 25 ppm
4 hr AEGL-2: 1-hour AEGL-2/2 = 13 ppm
8 hr AEGL-2: 1-hour AEGL-2/2 = 13 ppm

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:	7433.7 ppm•minutes/60 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.



Data:

For Category: 0 = No effect, 1 = Discomfort, 2 = Disabling, SL = Some Lethality, 3 = Lethal				
Source	**Species**	**ppm**	**Minutes**	**Category**
NAC/AEGL-1		1.0	10	AEGL
NAC/AEGL-1		1.0	30	AEGL
NAC/AEGL-1		1.0	60	AEGL
NAC/AEGL-1		1.0	240	AEGL
NAC/AEGL-1		1.0	480	AEGL
NAC/AEGL-2		150	10	AEGL
NAC/AEGL-2		50	30	AEGL
NAC/AEGL-2		25	60	AEGL
NAC/AEGL-2		13	240	AEGL
NAC/AEGL-2		13	480	AEGL
NAC/AEGL-3		740	10	AEGL
NAC/AEGL-3		250	30	AEGL
NAC/AEGL-3		120	60	AEGL
NAC/AEGL-3		31	240	AEGL
NAC/AEGL-3		31	480	AEGL
CT State Dept. Health 1955	Human	2	5	0, No irritation
	Human	3	5	1, Nose and throat irritation, 1 subject
	Human	4	5	1, Nose and throat irritation, 3 subjects
	Human	5	5	1, Nose and throat irritation, 6 subjects
	Human	6	5	1, Nose and throat irritation, 6 subjects
MacEwen and Vernot 1972	Rat	2205	60	SL, 10% mortality
		2328	60	SL, 40% mortality
		2759	60	SL, 40% mortality
		3253	60	SL, 60% mortality
		3711	60	SL, 70% mortality
		3822	60	3, 100% mortality
MacEwen and Vernot 1972	Mouse	507	60	2, no mortality
		875	60	SL, 70% mortality
		1036	60	SL, 90% mortality
		1163	60	3, 100% mortality
Stavert et al. 1991	Rat	1300	30	SL, 8% mortality
Kusewitt et al. 1989	Rat	1000	30	2, Necrosis and inflammation of the nasal passages

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

                                          95.0% Wald Confidence Interval
    Variable       Estimate       Std. Err.    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.
```

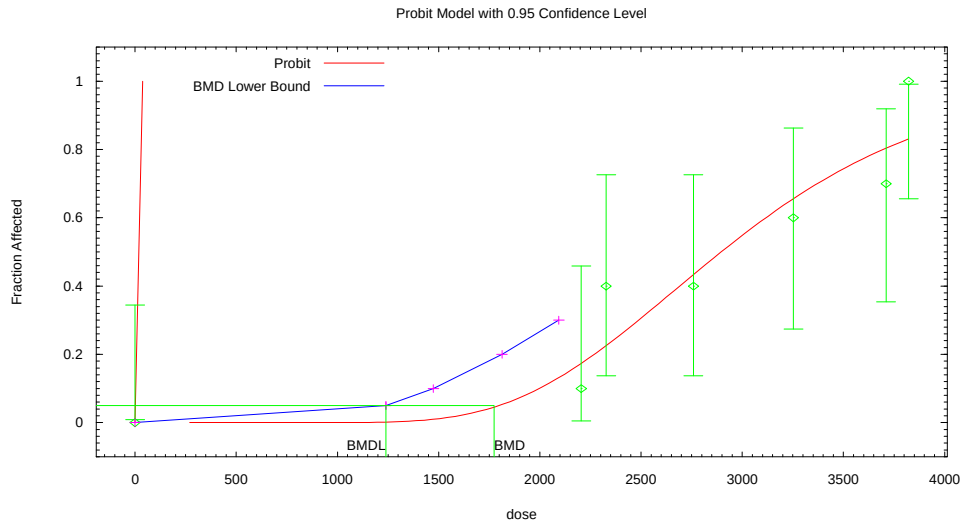
Analysis of Deviance Table

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
$BMCL_{05}$ =1238.95



13:14 12/11 2007

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-min	**30-min**	**1-hr**	**4-hr**	**8-hr**
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 considered to be a threshold for notable discomfort

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: not relevant
Intraspecies: 3; the response to a direct irritant is not expected to differ greatly among humans (NRC 2001), and the resulting AEGL-1 value appears protective for asthmatics based on data available for HCl (NRC, 2004).

Modifying Factor: Not applied

Animal to Human Dosimetric Adjustment: Not applicable

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

1

AEGL-2 VALUES				
10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**
150 ppm	**50 ppm**	**25 ppm**	**13 ppm**	**13 ppm**

Key References:

(1) Kusewitt, D.F., D.M. Stavert, G. Ripple, T. Mundie, and B.E. Lehnert. 1989. Relative acute toxicities in the respiratory tract of inhaled hydrogen fluoride, hydrogen bromide, and hydrogen chloride. Toxicologist 9:36. (abstract).

(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: Rat/F-344/not reported

Exposure Route/Concentrations/Durations: 30-minute inhalation exposure to 1000 ppm HBr.

Effects: Lesions of the anterior nasal passages.

Endpoint/Concentration/Rationale: 30-minute exposure to 1000 ppm with supporting data at 1300 ppm (Stavert et al., 1991)

Uncertainty Factors/Rationale:

Total uncertainty factor: 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);

Modifying Factor for 1-hour value:2, - based on small data set and effects more severe than those defined by the AEGL-2.

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling to the 1-hour value: For 10-minute and 60-minute values, time scaling was applied: $C^n \times t = k$ where n = 1 was derived based on regression analysis of rat and mouse LC_{50} data in a study with the chemically-similar HCl. The 4- and 8-hour values were estimated by dividing the 60-minute value by 2 to be consistent with the entire data set for hydrogen halides.

Data Adequacy: The data base for HBr 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.

1

AEGL-3 VALUES				
10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**
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: $C^1 \times t = k$ for extrapolation to the 10-minute, 30-minute, and 4-hour values, based on rat and mouse lethality data for; 8-hour value set equal to 4-hour value based on uncertainty in extrapolation to 8 hours and consistency with the approach used for HCl and HF.

Data Adequacy: Although there were only two well-conducted studies of HBr 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.

2