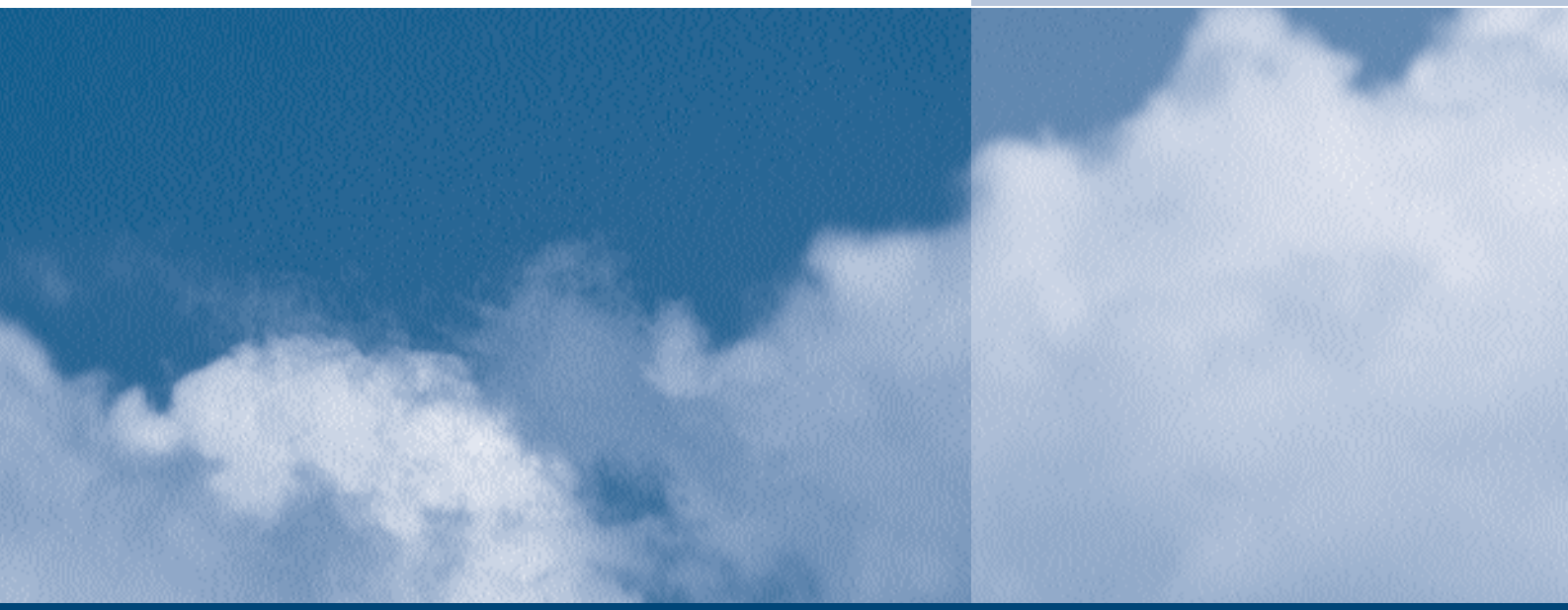

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A Review of the Toxicity and Environmental Behaviour of Hydrogen Bromide in Air

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Professor Mike Depledge Head of Science

EXECUTIVE SUMMARY

Hydrogen bromide is a colourless, readily water soluble gas which dissolves to form hydrobromic acid. Hydrogen bromide is used for organic syntheses, for dissolving certain ores, in the manufacture of bromides, and as an alkylating catalyst (ACGIH, 2001).

In the past ethylene dibromide was added to leaded petrol as a scavenger. Hydrogen bromide was therefore released until recently from mobile sources. Emissions of hydrogen bromide are likely to have decreased considerably over the past 10 years as a result of the reduction in leaded petrol and coal use, the installation of flue gas desulphurisation at some power stations and the closure or abatement of emissions from waste incineration plants.

There are limited data on national atmospheric emissions, as hydrogen bromide is not included in the National Atmospheric Emissions Inventory or the Environment Agency's Pollution Inventory. The major anthropogenic sources of hydrogen bromide are coal combustion, waste combustion and metal recycling, in which bromine containing compounds present in the feed stock are likely to be emitted as hydrogen bromide. The use of hydrogen bromide in the chemical industry may also lead to releases.

Open path monitoring methods appear to be available which may have sufficient sensitivity and response time to detect short-term fluctuations in concentration however these methods have generally not been demonstrated in routine use. These methods have not been used routinely and are generally regarded as research methods suitable for short-term campaigns rather than continuous measurement networks. However if cost was not a significant barrier then it is likely that they could be used.

The possibility exists for the natural formation of hydrogen bromide from bromide present in sea salt particles in the lower atmosphere. The bromide in the sea salt aerosol may react with acidic species such as nitric acid or nitrogen pentoxide to form hydrogen bromide. Hydrogen bromide is also formed in the stratosphere from the degradation of bromine containing compounds.

Ambient concentrations of hydrogen bromide are not regularly measured in the UK. Particulate-associated bromide was until recently measured at three sites in the UK. Levels at these sites have decreased significantly since the 1970s. The lead to bromine ratio at the Chilton site near a busy main road has generally been close to that found in leaded petrol. The particle associated bromide concentrations at a site in the Lake District appear dominated by sea salt.

Data on the toxicity of hydrogen bromide following inhalation exposure in humans or laboratory animals are limited. Toxicity reviews including the inhalation route of exposure, have been published by the American Conference of Governmental Industrial Hygienists and Garlanda and Basilico (1993). The discussion in this dossier is largely based on these reviews. Particular mention is made of those studies that have been used to derive the inhalation limits.

An odour threshold of 6.7 mg/m^3 (1.86 ppm) has been reported for hydrogen bromide.

There is a dose-response of ocular, nasal, or throat irritation in human volunteers after inhalation for "several minutes" of hydrogen bromide at concentrations of 2, 3, 4 5 or 6 ppm (7, 10, 13, 17 or 20 mg/m^3) although an odour was detected by all volunteers.

All volunteers reported nose irritation at hydrogen bromide concentrations of 6 ppm (20 mg/m^3), but the incidence of throat irritation remained unchanged at concentrations up to 6 ppm. No eye irritation was observed at hydrogen bromide concentrations of up to 6 ppm. Based on these results, the No Observed Adverse Effect Level (NOAEL) was considered to be 2 ppm (7 mg/m^3).

In the one case report in the literature, a 60-year old female laboratory technician developed pulmonary infiltrates suggestive of chemical pneumonitis following accidental exposure to a mixture containing hydrogen bromide and phosphorous trifluoride.

The respiratory tissue damage as a result of inhalation of hydrogen bromide vapours is thought to arise from the hydrobromic acid that is formed, which causes tissue necrosis as a result of oedema, laryngeal spasm or inflammation of the upper respiratory system.

Toxicity data for hydrogen bromide following inhalation exposure in laboratory animals are limited to a single study. Male nose-breathing rats exposed to hydrogen bromide vapour at 1,300 ppm (4.4 g/m^3) for 30 minutes, exhibited severe, necrotising rhinitis characterised by necrosis of the mucosa, submucosa, and turbinate bone; thrombosis and haemorrhage of the nasal blood vessels; and fibrin and fluid in the nasal passages. The pseudo-mouth breathers had variable degrees of fibronecrotic tracheitis.

Contents

1 INTRODUCTION

The Environment Agency of England and Wales is responsible for the authorisation of releases of a wide range of chemicals from industrial processes. As part of the permitting process the Environment Agency requires soundly based information on the levels of particular substances which are likely to lead to no significant harm to human health and the natural environment. These Environmental Assessment Levels (EALs) are published by the Environment Agency in a guidance document H1 (Horizontal Guidance Note; IPPC H1: Integrated Pollution Prevention and Control: Environmental Assessment and Appraisal of BAT, Environment Agency 2003) in order to make transparent to industry and other stakeholders the values being used within the Agency and to assist applicants with judging the acceptability of alternative process options.

The present approach within H1 uses a hierarchy of values. Where accepted UK or international ambient air quality standards are available either from the UK's Expert Panel on Air Quality Standards (EPAQS), EU directives or the World Health Organization these values are used. However, the great majority of substances for which release permits are sought are not covered by these published reviews. As a result H1 presently makes use of UK occupational exposure limits (OELs) set by the HSE corrected for the longer exposure and the potential greater range of sensitivities of the wider population.

There is however a number of limitations with applying this approach uncritically. For example, some OELs may take into account technological considerations, such as levels that were achievable in industrial settings at the time the standard was derived, which are neither health-based nor relevant to ambient air concentrations. Others may not be based on the toxicological endpoint, which would be the critical endpoint for the population at large, including sensitive sub-populations.

The Environment Agency has set in place a strategy of measures to improve the basis for the setting of EALs. Part of this has involved developing a work programme, in consultation with Defra and the devolved administrations, for EPAQS to develop Guidelines that may be used for the purposes of H1. EPAQS has been asked initially to look at six substances;

- hydrogen fluoride,
- hydrogen chloride,
- hydrogen bromide,
- hydrogen iodide,
- chlorine
- bromine.

A series of six reports, one on each substance, has been produced on behalf of the Environment Agency to support the work of EPAQS. Each report reviews the sources of release to the atmosphere, a summary of monitoring methods used in the UK, UK ambient concentrations and the literature on human toxicology and health effects. The present report addresses hydrogen bromide.

Hydrogen bromide (HBr) is a gas at environmental conditions. The CAS number is 10035-10-6. It has a boiling point of –67°C and is readily water-soluble. On dissolution in water it forms hydrobromic acid.

1.1 Anthropogenic Sources of Hydrogen Bromide

The UK's National Atmospheric Emissions Inventory does not estimate emissions of hydrogen bromide. Within England and Wales, the majority of major industrial plants are regulated by the Environment Agency. The Environment Agency's Pollution Inventory does not require the reporting of HBr releases, however some sources do report releases to the Environment Agency. In other parts of the UK similar regulatory controls are in place. The principal sites that reported releases in 2002 are given in Table 1.1. Most of these emission estimates, specifically those from combustion sources, were made by measuring the bromine content of the coal and then calculating the emissions.

Table 1.1 - The Main Point Source Releases of Hydrogen Bromide reported to the Environment Agency and SEPA

Operator	Site	Process	HBr Emission 2001 Tonnes	HBr Emission 2002 Tonnes	SO_2 Emission 2002 kg	SO_2/HBr Ratio 2002
EDF Energy (Cottam Power) Ltd	Cottam Power Station, Retford, Nottinghamshire	Coal fired power station	112	130	70500	542
AEP Energy Services UK Generation Ltd	Ferrybridge C Power Station, Knottingley, West Yorkshire	Coal fired power station	114	115	48144	419
Scottish Power PLC	Longannet Power Station, Kincardine-on- Forth, Fife	Coal fired power station	137 (90-222)	113[1] (68-220)	67100	594 (303-984)
EDF Energy (West Burton Power) Ltd	West Burton Power Station, Retford, Nottinghamshire	Coal fired power station	146	112	68461	611
AEP Energy Services UK Generation Ltd	Fiddlers Ferry Power Station, Warrington, Cheshire	Coal fired power station	130	93	28200	303
Powergen UK PLC	Ironbridge Power Station, Telford, Shropshire	Coal fired power station	37	64	31600	494
TXU Europe Power Ltd	High Marnham Power Station, Newark, Nottinghamshire	Coal fired power station	36	44	33290	757
Powergen UK PLC	Drakelow B Power Station, Burton-on-Trent, Staffordshire	Coal fired power station		35	22529	644
Scottish Power PLC	Cockenzie Power Station, Cockenzie, East Lothian	Coal fired power station	-	33[1] (20-65)	19700	594 (303-984)
Powergen UK PLC	Ratcliffe-on-Soar Power Station, Nottingham, Nottinghamshire	Coal fired power station	13	16.2	15924	984
Blue Circle Industries PLC	Hope Works, Hope, Derbyshire	Cement works	-	7.8	-	-
Lafarge Lime Ltd	Thrislington Works, Ferryhill, County Durham	Lime Works	-	2.1	-	-
British Sugar PLC	Cantley, Norfolk	Sugar factory	-	1.1	-	-

Note 1 HBr emissions for Cockenzie and Longannet power stations were calculated from the release of sulphur oxides as sulphur dioxide reported to SEPA and the average, maximum and minimum ratio of SO_2 to HBr for the power stations with reported releases of both pollutants in the relevant year.

It is likely that the emissions of hydrogen bromide can be divided into two categories; (i) those which are as a result of combustion in which the concentrations are likely to be low, but the flue gas volumes are high and emission is continuous leading to possibly significant mass emissions of hydrogen bromide; and (ii), those from chemical processes, where the concentrations will be high, but release may be infrequent and the quantity of gas released during each event small.

No measurements have been identified of bromine in coal or hydrogen bromide in power station emissions. However Table 1 indicates that coal fired power stations are a major source of hydrogen bromide. In those power stations with flue gas desulphurisation (FGD) a large fraction of the hydrogen bromide formed will not be emitted. Two coal-fired power stations have presently fitted FGD and others will be fitting FGD over the next decade.

Burning waste in incinerators is likely to lead to hydrogen bromide emissions because many materials are treated with brominated flame-retardants. We have however found no reported measurements of hydrogen bromide in waste incinerator emissions. All modern waste incinerators have acid gas abatement systems. Before 1996 there was a greater quantity of waste burnt, as the incinerators did not have acid gas abatement equipment. It is likely that hydrogen bromide emissions from waste incineration decreased greatly in 1996 and are now very small. Emissions from the burning of waste on bonfires or open hearths in the home are likely to occur and will be unabated.

It is possible that some of the plastics treated with brominated flame-retardants enter the metal recycling chain and in consequence there may be emissions from secondary metal plants and electric arc furnaces, however this has not been documented.

Chemical processes that use hydrogen bromide may lead to releases to the atmosphere. This may occur from either leakage from values and seals around reactors, reactor venting or failure of control systems. No information is available on the likely size of these releases.

1.2 Atmospheric Chemistry of Hydrogen Bromide

Hydrogen bromide is not photolysed in the troposphere, as it does not significantly adsorb ultraviolet light at wavelengths greater than 290 nm. As such it's environmental fate is either reaction with hydroxyl radicals (OH) or deposition to surfaces.

Experiments on the atmospheric chemistry of bromine species have shown that hydrogen bromide may be formed in the upper atmosphere. The route comes indirectly from organic bromine compounds such as CH_3Br via the reaction of BrO with hydroxyl, OH, which then contributes to the depletion of ozone. Balloon measurement experiments have also found hydrogen bromide in the stratosphere. There is also some suggestion of the involvement of bromine compounds in depleting ozone in the arctic environment (Finlayson-Pitts and Pitts 2000) with a correlation between low ozone concentrations and high filter collected bromide. While the chemistry of the proposed reaction scheme involves hydrogen bromide the source of the bromine in this situation is thought to be either biologically produced bromoform or sea salt aerosol.

1.3 Deposition Mechanisms

As a result of the high solubility of hydrogen bromide both wet and dry deposition of the compound is likely to be rapid.

1.4 Methods of Measurement

Measurements of hydrogen bromide can be carried out by a number of methods, including denuders, diffusion tube monitoring and use of bubbler methods. There is however little evidence that these methods have been used for this purpose.

The Environment Agency (Environment Agency 2000) recently published a review of methods for measuring pollutants in ambient air. This suggests that methods available for hydrogen chloride can be easily adapted for hydrogen bromide analysis.

The methods discussed by the Agency include the use of continuous flow analysers using ion selective electrodes to measure the bromide dissolving out of air. These have the advantage of giving near continuous response to the atmospheric signal. Another continuous measurement method is open path spectroscopy however no evidence of its application to hydrogen bromide monitoring has been found.

1.4.1 Bubbler methods

A method using midget impingers has been used for hydrogen chloride determination. The air is passed through a pre–filter to exclude particulate bound halides and then the impingers at a flow rate of 2.5 l/min. The impingers contain 10ml of a 0.1 M sodium hydroxide solution. It is recommended that an air volume of 10–200 l be sampled. No detection limit is quoted (Environment Agency 2000). This method would not provide suitable time resolution.

1.4.2 Denuder methods

Rupprecht and Pasternick market a denuder system for hydrogen chloride and fluoride measurement, which can probably be adapted to hydrogen bromide measurement. The air is sampled at 15 l min^{-1} through two denuder tubes which are coated with sodium carbonate in glycerol. Following exposure for between 1 and 24 hours the denuders are extracted with a small volume of deionised water. The bromide ion is measure by ion chromatography. The gas can be passed through a polytetrafluoroethylene (PTFE) filter following the denuder to collect bromide associated with particles. The detection limit can be as low as 5 ng m^{-3} for a daily sample. However the time resolution at typical environmental levels needs to be around 24 hours.

Lodge (1989) describes a denuder system which consists of a sodium bicarbonate coated 1220 mm by 7mm glass tube to collect gaseous halides followed by a filter to collect particulate halides. The halide collected on the coating is removed with water or buffer and analysed for halide by ion selective electrode. For a 12-hour sample at 14

l/min, the method range is about 100 μg/ m^3 but this can be modified by altering the sample volume. Precision is quoted to be better than ±10%.

1.4.3 Diffusion tube

Diffusion tubes are marketed for the measurement of hydrogen bromide. They appear to be subject to considerable uncertainty.

1.4.4 DIAL

Differential Adsorption LIDAR uses a laser to shine two nearby wavelengths into the air. The wavelengths are selected so that one is adsorbed actively by the species of interest and the other is not. The backscattered light is measured at the two frequencies and the difference between them represents the adsorption by the component of interest. The technique suffers when high aerosol concentrations decrease the intensity of the backscattered light returned to the detector. The technique can give rapid sensitive concentration measurements across a section of the atmosphere. Evidence has not been found for this technique being applied to HBr.

1.4.5 DOAS

Differential Optical Absorption Spectroscopy uses a light emitter to project a beam of light with wavelengths between visible and ultra violet. The light beam passes through a known distance to a receiver. The monitoring path is usually between 300 and 800 metres. As the beam of light passes through the air the different molecules absorb different wavelengths depending on their spectra. The light is then returned through a fibre optic cable to a spectrometer. The spectrometer measures the intensity of the different wavelengths compared to the original beam and then calculates the air concentrations of the particular gases. A detection limit has not been quoted for HBr.

1.4.6 DLSIOS

Diode laser single ion optical spectroscopy is a high-resolution spectroscopy technique that can detect HBr in the parts per million range. Response times are reported to be as low as 1 second.

1.5 UK Measurements

No reported measurements of the ambient concentration of hydrogen bromide in the UK were found.

Since 1972, measurements of bromide associated with particles have been made at three rural sites as part of the Department for Environment Food and Rural Affairs' Rural Trace Elements Network. Results of the quarterly concentrations are shown in Table 2. The annual mean concentrations are presented in Table 3. The reports presenting these

figures suggest that at Chilton, until recently the lead to bromine ratio, near to a busy dual carriageway, is close to the ratio between lead and bromine in leaded petrol. This suggests that the largest source of both lead and particle associated bromide at that vicinity is leaded petrol. At Wraymires, a site in the Lake District, the major influence on the bromide to lead ratio appears to be sea salt. At Styrupp, while the air concentrations of bromine and lead are higher than the other sites, the ratios of their concentrations are intermediate, perhaps suggesting the influence of the coal fired power stations of the Trent valley. The trends in measured concentrations between 1996 and 2001 are shown in Figure 2. Figure 3 shows the average concentration in each quarter over the same period showing that the concentrations vary seasonally with higher concentrations in winter. Figure 4 shows the lead to bromine ratio.

It is noticeable that in the 30 years between the network commencing and finishing, concentrations of particle-associated bromine had decreased at all sites but most markedly at Styrupp in the East Midlands.

Table 1.2 - Quarterly Mean Air Concentrations of particle associated bromide (ng/m^3) at three rural sites in the Defra Rural Trace Elements Network 1996-2002

Quarter	Chilton	Styrupp	Wraymires
1996 Q1	12.1	17.5	8.9
1996 Q2	7.4	8.5	3.3
1996 Q3	5.0	9.4	<2
1996 Q4	10.2	16.9	4.0
1997 Q1	11.3	18.0	12.8
1997 Q2	6.9	9.6	3.3
1997 Q3	5.5	8.1	5.6
1997 Q4	10.0	19.7	7.2
1998 Q1	8.7	14.4	9.8
1998 Q2	5.2	7.5	3.7
1998 Q3	4.7	5.7	4.1
1998 Q4	8.3	14.6	8.1
1999 Q1	4.0	13.4	8.7
1999 Q2	4.5	6.5	5.7
1999 Q3	3.8	7.7	4.7
1999 Q4	4.6	13.1	8.6
2000 Q1	12	15	13
2000 Q2	8.1	6.5	3.7
2000 Q3	4.7	7.1	3.4
2000 Q4	8.6	21	7.1
2001 Q1	7.4	11.6	7
2001 Q2	5.4	6.9	3.3
2001 Q3	4.2	5.5	3.1
2001 Q4	3.7	6.6	6
2002 Q1	7.8	11	8.5
2002 Q2	5.1	6	5
2002 Q3	5.5	5.9	2.7

Quarter	Chilton	Styrupp	Wraymires
2002 Q4	6.5	6.3	4.9

Measurements of bromide in rainwater were also made at the same sites between 1972 and 1981. The average total annual bromide deposition during the period 1972-1981 was 2.0, 2.9 and 4.6 μg cm^{-2} $year^{-1}$ at Chilton, Styrrup and Wraymires (Baker S., personal communication).

Table 1.3 - Annual Mean Air Concentrations of particle associated bromide (ng/m^3) at three rural sites in the Defra Rural Trace Elements Network 1972 -74 and 1996 - 2002.

Year	Chilton	Styrupp	Wraymires
1972	47	160	19
1973	110	280	53
1974	35	89	25
1996	8.7	13.1	4.6
1997	8.4	13.9	7.2
1998	6.7	10.6	6.4
1999	4.2	10.2	6.9
2000	8.4	12.3	6.8
2001	5.2	7.7	4.9
2002	6.0	7.3	5.2

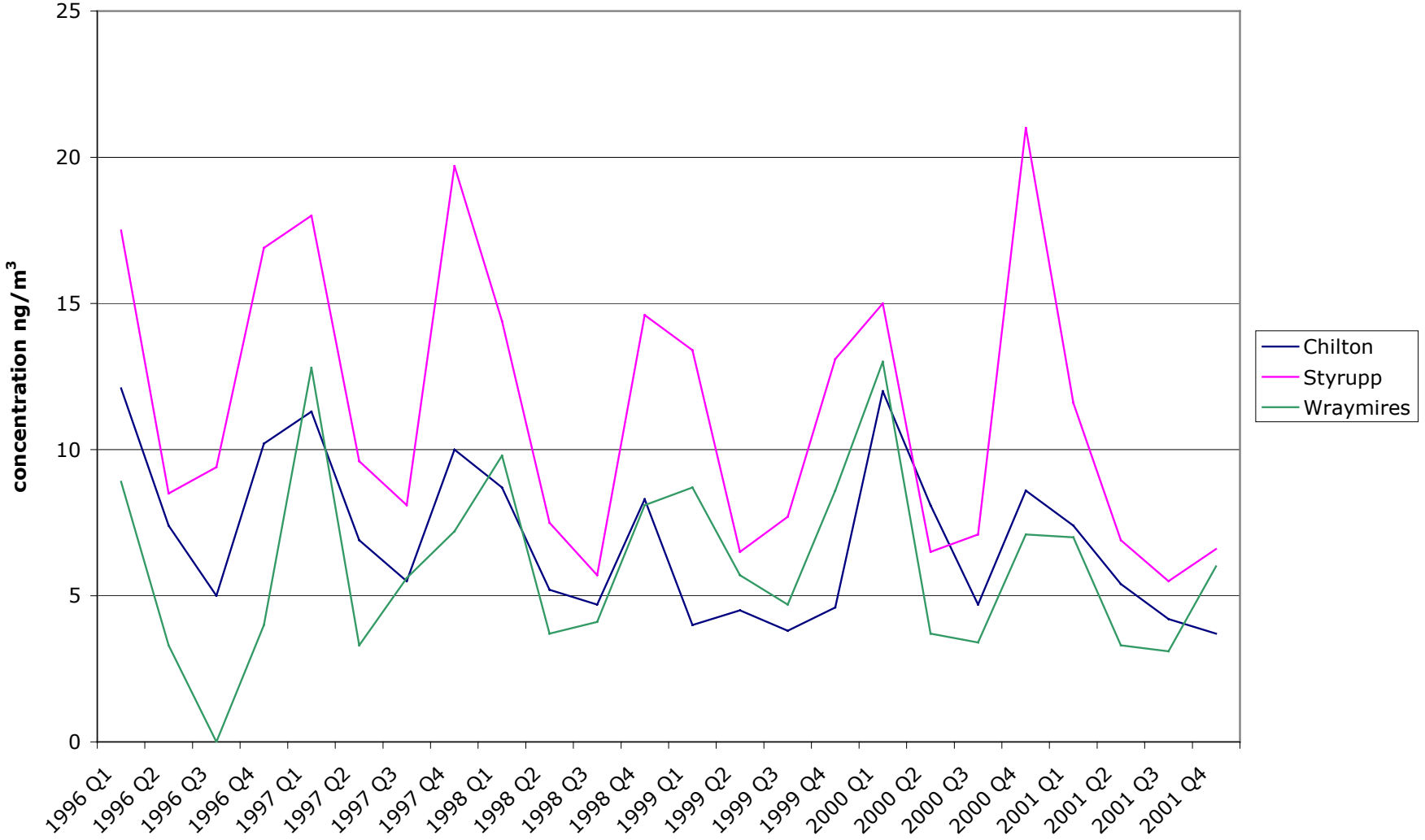

Figure 1.1 - Quarterly Mean Air Concentrations of particle associated bromide (ng/m^3) at three rural sites in the Defra Rural Trace Elements Network

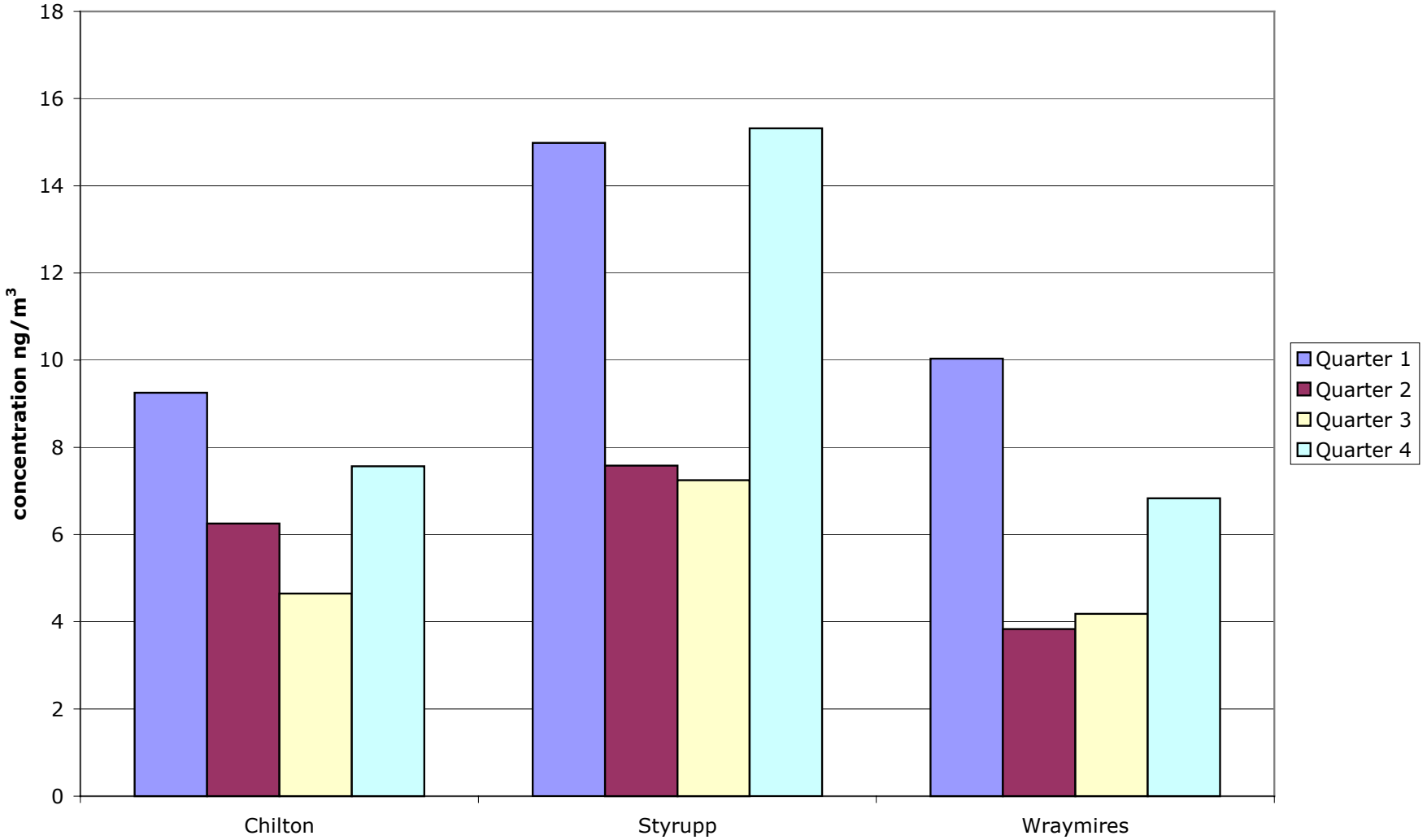

Figure 1.2 - Mean Concentration of particle associated bromide (ng/m^3) averaged over each quarter 1996-2001

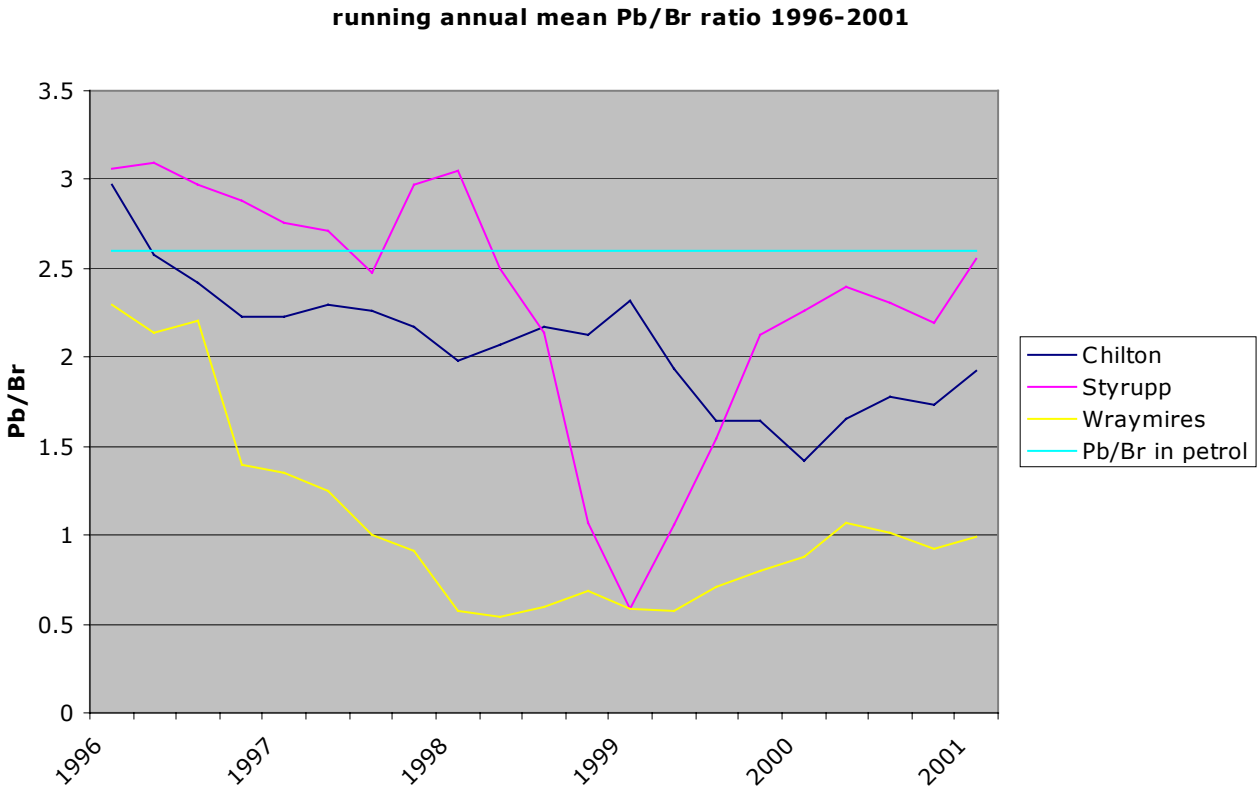

Figure 1.3 - Recent trends in the ratio of lead to particle associated bromide at three rural sites

2 INTRODUCTION TO TOXICOLOGY OF HYDROGEN BROMIDE

Hydrogen bromide gas will dissolve in water to exist as hydrobromic acid. At low concentrations of exposure to hydrobromic acid, the lung will ensure that the acid is neutralised to its corresponding salts. Therefore, there exists the potential for exposure to the bromide ion following exposure to hydrogen bromide. Several groups and organizations have examined the toxicity of the bromide ion including the World Health Organization, the Joint WHO/FAO Meeting on Pesticide Residues and the International Programme on Chemical (IPCS).

In medicine, inorganic bromide was introduced in the second half of last century as a sedative and antilibido agent. Bromide was introduced as an anti-epileptic drug and many other bromide-containing drugs were intensively used as sedatives and anticonvulsants until the beginning of the 20th century when they were gradually replaced by barbiturates and other anti-epileptics such as phenytoin. The use of bromides is now obsolete due to the availability of more selective drugs with a higher therapeutic index. As a result the incidence of chronic bromide intoxication known as bromism has been drastically reduced.

The World Health Organisation's (WHO) IPCS reviewed the data available for methyl bromide, which was used extensively as a fumigant, in their Environmental Health Criteria No.166. In addition, in combination with the Food and Agricultural Organization of the United Nations (FAO) as the Joint Expert Committee on Food Additives (JECFA) and the Joint Meeting on Pesticide Residues (JMPR), the WHO has established an Acceptable Daily Intake (ADI) for bromide of 0-1 mg/kg body weight. Van Leeuwen and Sangster have also reviewed the toxicology of the bromide ion. These reviews consider the systemic toxicity of the bromide ion in detail.

In 2003, the UK Committee on Toxicity (COT) considered the dietary intake of bromine and the evaluation by JECFA and JMPR (which established an ADI of 0-1 mg/kg body weight (as bromide)). COT stated that the upper boundary of 1 mg/kg body weight was an exposure below which intakes are unlikely to pose a risk to health. The estimated UK dietary intake from the 1997 total diet study was 3.6 mg/person per day (equivalent to 0.06 mg/kg body weight per day), which is well below the ADI and allows for significant exposure from other routes.

The rat is an obligate nose-breather and has a complex nasal turbinate structure that will filter out many relatively fine particles that would normally be expected to penetrate to the alveoli. Thus, whereas 7 μm is considered to represent the upper size limit for particles to reach alveolar regions in man, this is more likely to be in the region of 3-4 μm in the rat. Differences in action with gases have not been described. One of the studies described in this dossier reports the results of exposure using a rodent pseudo-mouth breathing model in comparison with nose breathing with resultant differences in local effects.

In general, inhalation studies have limited applicability to humans where mouth breathing dominates. Therefore, human studies are likely to provide most relevant information on the nature and extent of toxicity. However, consideration of the animal

studies may be important in the identification of hazard and the type of lesion to be anticipated and where there are insufficient appropriate human studies.

The policy of the UK HSE is to take into consideration both human and animal data. If there is a good database of human studies, assessments would be primarily based on this. However, in the absence of such data, an assessment would be on the basis of animal (usually rodent) studies. In these studies, more weight is given to the presence of tissue damage. Uncertainty factors may be applied to NOAEL or Lowest Observed Adverse Effect Level (LOAEL) for pathological findings in rodent studies to suggest appropriate exposure levels. It is difficult to draw quantitative extrapolations from the results of animal studies and in particular, HSE tend not to use such extrapolation from RD50 values (concentration capable of producing a 50% decrease in breathing rate) obtained in the ALARIE test. Data suggesting changed breathing patterns in rodents would encourage assessors to examine the human database for evidence of similar effects in humans (Personal communication, Elanor Ball, HSE).

3 ANIMAL TOXICITY DATA

3.1 Absorption, Distribution, Metabolism, and Excretion

No data are available concerning the metabolism or kinetics of hydrogen bromide in laboratory animals.

3.2 Acute Toxicity

The 60-minute LC_{50} value for hydrogen bromide is 2,860 ppm (9620 mg/m^3) and 815 ppm (2710 mg/m^{-3}) in the rat and mouse, respectively (OSHA, 2003; ACGIH, 2001). Garlanda and Basilico (1993) reported an LC_{50} value for hydrogen bromide of 76 mg/kg following intraperitoneal administration in the rat.

Stavert *et al*. (1991) exposed groups of male Fischer 344 anaesthetised rats to filtered air or 1,300 ppm (4400 mg/m^3) of hydrogen bromide vapour for 30 minutes. Each treatment had a nose-breathing group and a pseudo-mouth-breathing group. Twenty-four hours after the exposure, body, lung, and right cranial lobe weights were measured, mortality was recorded, and histopathology of the nasal passages, trachea, and lung was conducted.

In the nose-breathers, mean body weight was statistically reduced compared to the controls in the hydrogen bromide-treated group. Mean absolute body weights were not provided. Mean absolute lung weights or right cranial lobe weights were not statistically different compared to controls. Nose breathers exhibited severe, necrotising rhinitis, necrosis of the mucosa, submucosa, and turbinate bone, and thrombosis and haemorrhage of the nasal blood vessels in the upper respiratory tract. The presence of fibrin and fluid in the nasal passages was also reported. These effects were not observed in other lower regions of the respiratory tract. Approximately 8% of nose-breathers died by 24 hours post-exposure.

In the pseudo-mouth-breathers after 24 hours, mean body weight was reduced in the controls by approximately 13 g compared to 17 g in the hydrogen bromide-treated group, but the difference was not statistically significant. Mean absolute body weights were not provided. Mean absolute lung weights or right cranial lobe (wet and dry) weights were not statistically different compared to controls. Mouth breathers had variable degrees of fibronecrotic tracheitis. Approximately 19% of mouth-breathers died within 24 hours. The authors concluded that the adverse effects on the upper respiratory tract, as a response to hydrogen bromide inhalation is dependent upon the route (i.e. nose or mouth) by which they are inhaled. It should be noted that the doses in this study are relatively high and may not be relevant to environmental exposure levels.

3.3 Chronic Toxicity/Carcinogenicity

No chronic toxicity or carcinogenicity data in laboratory animals were identified in the available literature.

3.4 Genotoxicity

No data concerning the genotoxic potential of hydrogen bromide in laboratory animals were identified in the available literature.

3.5 Reproductive/Developmental

No reproductive or developmental toxicity data in laboratory animals were identified in the available literature.

4 HUMAN STUDIES

4.1 Summary

Data on the toxicity of hydrogen bromide following inhalation exposure in humans or laboratory animals are limited. The respiratory tissue damage as a result of inhalation of hydrogen bromide vapours is thought to arise from the hydrobromic acid that is formed, which causes tissue necrosis as a result of oedema, laryngeal spasm or inflammation of the upper respiratory system (Garlanda and Basilico, 1993). A volunteer study cited in ACGIH (2001) reported that the inhalation of hydrogen bromide vapour at 2 ppm (7 mg/m^3) for "several minutes" did not result in any ocular, nasal, or throat irritation, although volunteers detected an odour. Inhalation at 3 ppm (10 mg/m^3) for several minutes resulted in nose and throat irritation in 1/6 volunteers. Nose irritation was present in fifty percent of the volunteers at 4 ppm (13 mg/m^3).

4.2 Absorption, Distribution, Metabolism and Excretion

No data are available concerning the metabolism or kinetics of hydrogen bromide in humans.

4.3 Mechanism of Toxicity

Hydrobromic acid is corrosive to the eyes, skin, and mucous membranes. The acid formed from inhalation of hydrogen bromide vapour cause respiratory tissue necrosis as a result of oedema, laryngeal spasm or inflammation of the upper respiratory system (Garlanda and Basilico, 1993).

4.4 Acute Toxicity in Humans

ACGIH (2001) reported that inhalation of hydrogen bromide vapour at 2 ppm (7 mg/m^3) for "several minutes" did not result in ocular, nasal, or throat irritation, although an odour was detected by volunteers (CSDH, 1955). Inhalation of hydrogen bromide vapour at 3 ppm (10 mg/m^3) for several minutes resulted in nose and throat irritation in 1/6 volunteers. At 4 and 5 ppm (13 and 17 mg/m^3), the incidence of nose irritation increased to 3/6 and 6/6, respectively. All 6 volunteers reported nose irritation at hydrogen bromide concentrations of 6 ppm (20 mg/m^3), but the incidence of throat irritation remained unchanged (1/6) at concentrations up to 6 ppm (20 mg/m^3). No eye irritation was observed at hydrogen bromide concentrations of up to 6 ppm (20 mg/m^3). Based on these results, the NOAEL was considered to be 2 ppm (7 mg/m^3).

Inhalation of approximately 35 ppm (118 mg/m^3) hydrogen bromide for a short period was reportedly associated with irritation of the throat, while "more severe exposures" resulted in pulmonary oedema, which was at times accompanied by laryngeal spasm (Garlanda and Basilico, 1993). Concentrations of hydrogen bromide from 1,400-2,100 ppm (4710- 7100 mg/m^3) were reported to be lethal in an exposure lasting a few minutes.

Occupational

A case report by Kraut and Lilis (1988) identified a 60-year old female laboratory technician who developed pulmonary infiltrates suggestive of chemical pneumonitis following accidental exposure to an unknown amount of a mixture containing hydrogen bromide and phosphorous trifluoride. A protracted illness ensued, and the infiltration did not completely resolve, such that a relapse occurred 1 and 3 months later. Another relapse occurred seven months later, possibly following exposure to other unspecified respiratory irritants. Ten months after the initial exposure, the chest X-ray returned to normal, but diffusion abnormalities suggestive of interstitial pulmonary fibrosis was observed on a transbronchial biopsy. The study authors suggested that the recurrence of respiratory symptoms without resolution of the initial pneomonitis was suggestive of bronchiolitis obliterans, a potentially fatal complication of toxic irritant gas exposure. However, the possibility of other mechanisms could not be excluded.

There have been several reports of inadvertent hydrogen bromide exposures caused by the pyrolysis of methyl bromide released as a home fumigant agent and of bromotrifluoromethane, bromochlorodifluoromethane, and bromochloro-methane released from fire extinguishers (ACGIH, 2001).

4.5 Chronic Toxicity / Carcinogenicity

Alexandrov (1983) reported that chronic exposure to hydrogen bromide was associated with upper respiratory catarrh and dyspepsia, slight reflex modifications, reduced erythrocyte counts, and possibly reduced olfactory sensitivity. No further information, including the exposure concentration or exposure duration was specified. According to OSHA (2003), Sittig (1991) reported that long-term exposure may cause chronic nasal and bronchial discharge and indigestion. No other data concerning chronic toxicity or carcinogenicity in humans has been found in the available literature.

4.6 Genotoxicity

No data concerning the genotoxic potential of hydrogen bromide in humans were identified in the available literature.

4.7 Reproductive/Developmental

No reproductive or developmental toxicity data in humans were identified in the available literature.

5 EVALUATIONS AND RECOMMENDATIONS BY OTHER ORGANISATIONS

5.1 Summary

3 ppm is set as a short-term occupational exposure standard in most countries for which information was found (Austria, Australia, Belgium, Denmark, Finland, Netherlands, Norway, Philippines and the UK). Exceptions are Germany (5ppm), Poland (2.1 ppm) and Turkey (5 ppm). In the US the present ACIGH value of 3 ppm may be revised down to 2 ppm by analogy with hydrogen chloride.

Table 5.1 - Summary table of the existing Occupational Standards/Guideline levels for hydrogen bromide in various international organisations (Note: averaging times are provided where available)

Country	Organisation	Occupational Exposure Standard/ Guideline	Concentration	Averag-ing time
USA	**ACGIH**	**TLV-Ceiling**	3 ppm (9.9 mg/m^3)	
USA	**OSHA**	**PEL**	3 ppm (10 mg/m^3)	8 hours
USA	**US EPA**	**AEGL - 1**	1 ppm (proposed)	30 mins
USA	**US EPA**	**AEGL - 1**	1 ppm (proposed)	1 hour
USA	**US EPA**	**AEGL - 1**	1 ppm (proposed)	4 hour
USA	**US EPA**	**AEGL - 1**	1 ppm (proposed)	8 hour
EC		**OES**	2 ppm (7 mg/m^3)	
EC		**STEL**	3 ppm (10 mg/m^3)	
USA	**NIOSH**	**REL**	3 ppm (10 mg/m^3)	
USA		**IDLH**	30 ppm (100 mg/m^3)	
Germany		**MAK**	5 ppm (17 mg/m^3)	
Germany		**STEL**	10 ppm	
Australia		**MAK**	3 ppm (10 mg/m^3)	
Denmark		**OES**	3 ppm (9.9 or 10 mg/m^3)	
Norway		**OES**	3 ppm (9.9 or 10 mg/m^3)	
Philippines		**OES**	3 ppm (9.9 or 10 mg/m^3)	
UK	**HSE**	**STEL**	3 ppm (10 mg/m^3,)	10 minutes
Belgium		**STEL**	3 ppm (9.9 mg/m^3)	
Finland		**STEL**	3 ppm (10 mg/m^3)	
Austria		**MAK**	3 ppm (10 mg/m^3)	
Austria		**MAC**	3 ppm (10 mg/m^3)	
Poland		**MAC**	2.1 ppm (7 mg/m^3)	
Poland		**MAC-STEL**	6.3 ppm (21 mg/m^3)	
Switzerland		**MAK-week**	3 ppm (10 mg/m^3)	
Turkey		**OES**	5 ppm (17 mg/m^3)	

In 2001, the ACGIH set a Threshold Limit Value- Ceiling (TLV-Ceiling) of 3 ppm (9.9 mg/m^3) for hydrogen bromide which is not to be exceeded during any part of the working exposure. This was based on an unpublished study from the Connecticut State Department, the details of which appears to be no longer available. This value is based

on primary irritation with no known chronic effects observed in a study of–human volunteers, in which a NOAEL of 2 ppm was identified after inhalation of hydrogen bromide at concentrations up to 6 ppm (ACGIH, 2001). ACGIH have issued a Notice of Intention to change the TLV-Ceiling to 2 ppm, based on primary irritation and analogy to hydrogen chloride (ACGIH 2003).

The Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL) for hydrogen bromide is 3 ppm (10 mg/m^3) as an 8-hour time weighted average (OSHA, 1997). The value applies to general industry, the construction and shipyard industries, and federal contractors (RTECS, 2003).

The USEPA Office of Pollution Prevention and Toxics is responsible for setting Acute Exposure Guideline Levels (AEGLs). There are three types of guidelines: AEGL-1, AEGL-2 and AEGL-3. The AEGL-1 is the airborne concentration (expressed as ppm or mg/m^3) of a substance at or above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain sub-clinical non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure. For hydrogen chloride there are currently only proposed AEGLs of 1ppm for each averaging time; these values are yet to be finalised.

The Commission of the European Communities (Garlanda and Basilico, 1993) recommend an Indicative Occupational Exposure Limit Value (IOELV) of 2 ppm (7 mg/m^3) (time-weighted average, not to exceed 3 ppm) and a Short-Term Exposure Limit of 3 ppm (10 mg/m^3) for hydrogen bromide. These values were based on occupational exposure data in humans, which demonstrate nasal and throat irritation at 3 ppm.

The National Institute for Occupational Safety and Health (NIOSH, 1997) has determined a Recommended Exposure Limit: Ceiling Value of 3 ppm (10 mg/m^3), which is not to be exceeded during any part of the working exposure. This value is based on the risk of eye, mucous membrane, and skin irritation. An IDLH (Immediately Dangerous To Life Or Health) value of 30 ppm (100 mg/m^3) was also determined for hydrogen bromide.

In Germany, the MAK (Maximale Arbeitplatz-Konzentration – or maximum workplace concentration) for hydrogen bromide is 5 ppm (17 mg/m^3) and the 5-minute Short-Term Exposure Level is 10 ppm for a maximum of 8 times per shift (HSDB, 2003; RTECS, 2003).

The peak limitation MAK for hydrogen bromide in Australia is 3 ppm (10 mg/m^3) as a time-weighted average (HSDB, 2003; RTECS, 2003).

In Denmark, Norway, and the Philippines, the occupational exposure limit for hydrogen bromide is 3 ppm (9.9 or 10 mg/m^3) as a time-weighted average (RTECS, 2003).

In the UK, the 15-minute Short-Term Exposure Limit (STEL) for occupational exposure to hydrogen bromide is 3 ppm (10 mg/m^3, respectively) (RTECS, 2003; HSDB, 2003).

The UK Committee on Toxicity considered the dietary intake of bromine in 2003. The committee reviewed an evaluation by JECFA and JMPR (which established an ADI of 0-1 mg/kg body weight (as the bromide ion). They considered the upper boundary of 1 mg/kg body weight as an intake below which intakes are unlikely to pose a risk to

health. The estimated dietary intake from the 1997 total diet study was 3.6 mg/person per day (equivalent to 0.06 mg/kg body weight per day), which is well below the acceptable level and allows for significant exposure from other routes.

In Belgium, the Short-Term Exposure Limit (STEL) for occupational exposure to hydrogen bromide is 3 ppm (9.9 mg/m^3) (RTECS, 2003).

In Finland, the Short-Term Exposure Limit (STEL) for dermal occupational exposure to hydrogen bromide is 3 ppm (10 mg/m^3) (RTECS, 2003).

The MAK for occupational exposure to hydrogen bromide is 3 ppm (10 mg/m^3) in Austria (RTECS, 2003).

In the Netherlands, the maximum allowable concentration MAC-TGG for hydrogen bromide is 3 ppm (10 mg/m^3) (RTECS, 2003).

In Poland, the maximum allowable concentration (MAC) as a time-weighted average for hydrogen bromide is 7 mg/m^3 (2.1 ppm) and the maximum allowable concentration for a short-term exposure (MAC-STEL) is 21 mg/m^3 (6.3 ppm) (RTECS, 2003).

In Switzerland, the MAK-week for hydrogen bromide is 3 ppm (10 mg/m^3) and the KZG-Week is 6 ppm (20 mg/m^3) (RTECS, 2003).

In Turkey, the occupational exposure limit as a time-weighted average for hydrogen bromide is 5 ppm (17 mg/m^3) (RTECS, 2003).

6 CONCLUSIONS

The irritant effects and respiratory tissue damage as a result of inhalation of hydrogen bromide vapours is thought to arise from the hydrobromic acid that is formed, which causes tissue necrosis as a result of oedema, laryngeal spasm or inflammation of the upper respiratory system. However, there does exist the possibility of systemic effects consequent to absorption of the bromide anion. Following exposure to low concentrations of hydrogen bromide the buffering capacity of the physiological fluids will neutralise its acidifying effects on dissolution. The bromide ion concentration however will increase. This could potentially lead to systemic effects if exposure to a high enough dose occurs. The likelihood is however, that other routes of exposure present more of a realistic hazard than inhalation. Systemically, bromides are toxic only at concentrations much higher than can be realistically achieved by inhalation. This localised damage to the respiratory tract is likely to differ in location between animals and man, reflecting different breathing patterns and the possibility of mouth breathing by human subjects, but the animal studies indicate the type of lesion to be expected. There is insufficient data to classify the carcinogenic potential of hydrogen bromide.

There is a very limited range of experimental studies on hydrogen bromide. The study by Stavert *et al* makes a direct comparison of the response to various hydrogen halides in rodent species. In this study, damage in the nose-breathing rats was confined to the nasal region with both hydrogen bromide and hydrogen chloride. The pseudo-mouth-breathing rats showed tracheal damage in the form of large areas of epithelial necrosis accompanied by accumulation of inflammatory exudates. However, the exposures were to a relatively high level of 1300ppm for 30 minutes and thus have a limited applicability to environmental exposures. There was less histological damage with hydrobromic acid than with hydrochloric acid but the minute volume was 30% reduced with hydrogen bromide and this was not seen with hydrogen chloride. This latter response is relevant to nose breathing rats, and has limited human applicability. Overall, this study is useful in that it confirms that local epithelial damage is the primary response to hydrogen bromide, as it is with the other halogen acids.

The evaluation by the American Conference of Government Industrial Hygienists (ACGIH) (2001): Hydrogen bromide, refers to an unpublished study from Connecticut State Department of Health (1955). Six volunteer subjects inhaled hydrogen bromide in a test chamber at concentrations ranging from 2-6ppm for several minutes. Irritation was experienced by a majority of subjects at 5ppm, though this was considered a tolerable exposure. The NOAEL was considered to 2 ppm (7 mg/m^3). In the absence of further data, this can be regarded as indicative only.

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List of Figures

List of Tables

Appendix A – Key References

The members of EPAQs will be provided with copies of the key references identified from the toxicological review listed below.

American Conference of Government Industrial Hygienists (ACGIH) (2001): Hydrogen bromide

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Appendix B - Medical Glossary

adenoma	a benign tumour of *epithelial origin that is derived from glandular tissue or exhibits clearly defined glandular structures; may undergo malignant change.
atelactasis	failure of part of the lung to expand
barbiturates	a group of drugs, derived from barbituric acid that depress activity of the central nervous system and formally used as sedatives.
blepharospasm	involuntary tight contraction of the eyelids
bronchiolitis obliterans	also known as BOOP (bronchiolitis obliterans organising pneumonia); a disease entity characterised by a flu-like illness with cough, fever, shortness of breath and late inspiratory crackles
bronchopneumonia	pneumonia infection which starts in a number of small bronchi and spreads in a patchy manner into the alveoli.
cardiovascular system	the circulatory system – the heart together with the two networks of blood vessels
cheilitis	inflammation on the lips
chorioamnionitis	Infection, of the chorionic and amniotic membranes caused by bacteria. These membranes enclose the amniotic fluid and when infection is present in the membranes, the mother and foetus are at increased risk for severe infection.
choliangiocarcinoma	a malignant tumour of the bile ducts
chromatolysis	the dispersal or disintegration of the microscopic structures within the nerve cells that normally produce proteins (part of the cell's response to injury)
cilia	hair-like structures, large numbers of which found on certain epithelial cells; particularly characteristic of the epithelium that lines the upper respiratory tract, where their beating serves to remove particles of dust and other foreign material
clastogen/clastogenic	causing chromosomal aberrations
cyanosis	a bluish discoloration of the skin and mucous membranes resulting from an inadequate amount of oxygen in the blood
desquamation	the process where the outer layer of the epidermis of the skin is removed by scaling
diuresis	increased secretion of urine by the kidneys
emphysema (related to the lung)	a disease where the air sacs of the lungs are enlarged and damaged, which reduces the surface area for the exchange of oxygen and carbon dioxide
endomitotic	chromosome replication without mitosis, leading to polyploidy.
epithelium	the tissue that covers the external surface of the body and lines hollow structures.
erythrocyte	blood cell containing the red pigment haemoglobin, the principal function of which is the transport of oxygen
fenestration	creation on an opening (surgical or due to disease)
fibrin	the final product of the process of blood coagulation, produced by the action of the enzyme thrombin on a soluble precursor *fibrinogen
fibrinogen	a substance present in blood plasma, that is acted upon by the

	enzyme thrombin to produce the insoluble protein *fibrin in the final stage of blood coagulation
tracheitis	inflammation of the trachea
follicle-stimulating hormone (FSH)	a hormone synthesised and released by the pituitary gland; stimulates ripening of the follicles in the ovary and formation of sperm in the testes
goblet cell	a column shaped secretory cell found in the epithelium of the respiratory and intestinal tracts; secretes the principal constituents of mucous
haemorrhage	bleeding: the escape of blood from a ruptured blood vessel, externally or internally
hepatic	relating to the liver
hepatocyte	the principle cell type in the liver; a large cell with metabolic functions
hilar	refers to the area where nerves and blood vessels attach to an organ
histology (histological)	study of the structure of tissues by means of special staining techniques combined with light and electron microscopy
hyaline membrane disease	also known as respiratory distress syndrome. the condition in a newborn infant in which the lungs are imperfectly expanded
hypercapnia	the presence in the blood of an abnormally high concentration of carbon dioxide
hyperplasia	the increased production and growth of normal cells in a tissue or organ; the infected part becomes larger but retains its normal form.
hypertension	high blood pressure
hypertrophy	increase in the size of a tissue or organ brought about by the enlargement of its cells rather than by cell multiplication (i.e. muscles undergo this change in response to increased work).
hypotension	where arterial blood pressure is abnormally low
hypotonia	a state of reduced tension in muscle
hypoxaemia	reduction of the oxygen concentration in the arterial blood, recognised clinically by the presence of central and peripheral *cyanosis
hypoxia	a deficiency of oxygen in the tissues
lacrimation	the production of excess tears; crying
lesion	a zone of tissue with impaired function as a result of damage by disease or wounding
leucopoiesis	the process of production of white blood cells (leucocytes)
luteinising hormone (LH)	a hormone synthesised and released by the pituitary gland that stimulates ovulation, corpus luteum formation, progesterone synthesis by the ovary and androgen synthesis by the interstitial cells of the testes
macrophage	a large scavenger cell present in connective tissue and major organs and tissues
meatus	a passage or opening
acidosis	a condition in which the acidity of body fluids and tissues is abnormally high
mediastinum	area at the centre of the chest which contains the heart, windpipe (trachea), gullet (oesophagus) large main blood vessels and the lymph nodes that surround the heart.

metaplasia	an abnormal change in the nature of a tissue
microphthalmia	a congenitally small eye, usually associated with a small eye socket
mucosa	also known as mucous membrane; the moist membrane lining many tubular structures and cavities, including the nasal sinuses, respiratory tract, gastrointestinal tract, biliary and pancreatic systems.
myocardium	the middle of the three layers forming the wall of the heart
dystrophy	a disorder of an organ or tissue, usually muscle, due to an impaired nourishment of the affected part
nares	the nasalis muscles (nares) are used as accessory muscles of respiration during times of respiratory distress; they are partially responsible for 'nasal flaring'.
nasopharynx	the part of the *pharynx that lies above the soft palate
necropsy	autopsy
necrosis	the death of some or all of the cells in an organ or tissue
ocular	related to the eye and vision
oedema	excessive accumulation of fluid in the body tissues
olfactory	relating to the sense of smell and nose
oligozoospermia	condition where the sperm concentration is low, less than 20 million per ml.
parenchyma	the functional part of an organ, as opposed to the supporting tissue (*stroma*)
pathology	study of disease processes with the aim of understanding their nature and causes
peritoneal mesothelioma	a tumour of the *peritonium
peritoneum	the *serous membrane of the abdominal cavity
pharyngitis	inflammation of the part of the throat behind the soft palate; produces a sore throat and associated with tonsillitis
pharynx	the muscular tube, lined with mucosa, that extends from the beginning of the oesophagus up to the base of the skull.
plethysmograph	a record of the changes in the volume of a limb caused by alterations on blood pressure
pneumomediastatinum	air in the mediastinum
pneumonitis	inflammation of the lung that is confined to the walls of the air sacs
polymorphonuclear leucocyte	same as polymorph and neutrophil – variety of white blood cell that is capable of ingesting and killing bacteria and provides an important defence against infection.
proteinuria	the presence of protein in the urine; may indicate the presence of damage or disease of the kidneys
pseudomembrane	a false membrane, consisting of a layer of exudate on the surface of the skin or mucous membrane
pulmonary	relating to the lung
renal	relating to the kidneys
rhinitis	inflammation of the mucous membrane of the nose
rhinorrhea	a persistent watery mucous discharge from the nose, as in the common cold
septal	partition between the left and right halves of the chest
serous membrane	a smooth transparent membrane, consisting of mesothelium and underlying elastic fibrous connective tissue lining certain large cavities of the body

squamous cell	an epithelial cell that is flat like a plate and forms a single layer of epithelial tissue
squamous metaplasia	a change in the nature of tissue into *squamous epithelium; may be an early sign of malignant change
submucosa	the layer of loose connective tissue underlying a mucous membrane
synctial	made up of a mass of *protoplasm containing several nuclei, e.g, muscle fibres are *synctia*
tachypneoa	rapid breathing
thrombosis	a condition in which the blood changes from a liquid to a solid state and produces a blood clot
protoplasm	the material of which living cells are made, which includes the cytoplasm and nucleus
trigeminal nerve	the fifth and largest cranial nerve; controls the muscles involved in chewing and relaying information about temperature, pain and touch from the whole frond half of the head
turbinate bone	any of the three thin scroll-like bones that form the sides of the nasal cavity (also known as nasal concha)

Appendix C – Glossary of Terms and Acronyms

Acceptable Daily Intake (ADI): The amount of a chemical a person can be exposed to on a daily basis over an extended period of time (usually a lifetime) without suffering deleterious effects.

Ambient Air Level Goals (AALGs): The term used by Calabrese and Kenyon to describe the numerical values derived using their methodology. The values are described as goals because the values are based only on health effects and do not include consideration of technical, economic, and analytical feasibility or any other issues that are within the realm of risk management.

Average Daily Dose (ADD): Dose rate averaged over a pathway-specific period of exposure expressed as a daily dose on a per-unit-body-weight basis. The ADD is usually expressed in terms of mg/kg-day or other mass-time units.

Benchmark Dose (BMD) or Concentration (BMC): A statistical lower confidence limit on the dose that produces a predetermined change in response rate of an adverse effect (called the benchmark response or BMR) compared to background.

Best Available Techniques (BAT): The meaning of this term can depend on the context within which it is used. When used in the context of IPPC or PPC it is defined as the most effective and advanced technique for the prevention, or where that is not practicable, the minimisation of emissions and impact on the environment as a whole. It includes consideration of the availability of the technique for the type of process concerned and cost. However, the term BAT may also be applied in the context of the IPC regime where it has a similar meaning to that under IPPC or PPC except that costs are not taken into consideration. See also Integrated Pollution Prevention and Control, Integrated Pollution Control and Pollution Prevention and Control.

Best Practicable Environmental Option (BPEO): The Royal Commission on Environmental Pollution (RCEP) in their Twelfth Report defined the BPEO as;

"the option which provides the most benefit or least damage to the environment as a whole, at acceptable cost, in the long term as well as the short term."

The determination of the BPEO was intended to be wide ranging and include assessment of, for example, alternative ways of undertaking the activity in different locations. Impacts were also to be considered broadly and include not only the direct impact of a process on the natural environment or human health but also issues such as visual intrusion, the effects of additional traffic or the production and delivery of raw materials. The term was also applied to the Integrated Pollution and Control regime, which required operators to use the Best Available Techniques Not Entailing Excessive Cost to achieve the Best Practical Environmental Option *in relation to releases from the process*. This definition, therefore, prescribes the scope of the BPEO when used in the context of IPC and specifically excludes consideration of effects other than those arising directly from the process releases. The term BPEO is not specifically mentioned in Integrated Pollution Prevention and Control. However, the directive does refer to the need to protect the environment as a whole, which is taken to be a similar concept to BPEO.

Carcinogen: An agent capable of inducing cancer.

Carcinogenesis: The origin or production of a benign or malignant tumour. The carcinogenic event modifies the genome and/or other molecular control mechanisms of the target cells, giving rise to a population of altered cells.

Case-control study: An epidemiological study contrasting those with the disease of interest (cases) to those without the disease (controls). The groups are then compared with respect to exposure history, to ascertain whether they differ in the proportion exposed to the chemical(s) under investigation.

Chronic Exposure: Multiple exposures occurring over an extended period of time, or a significant fraction of the animal's or the individual's lifetime.

Chronic Study: A toxicity study designed to measure the (toxic) effects of chronic exposure to a chemical.

Chronic Toxicity: The capacity of a substance to cause adverse human health effects as a result of chronic exposure.

Cohort Study (or Prospective Study): An epidemiological study comparing those with an exposure of interest to those without the exposure. These two cohorts are then followed over time to determine the differences in the rates of disease between the exposure subjects.

Confounder (or Confounding Factor): A condition or variable that is both a risk factor for disease and associated with an exposure of interest. This association between the exposure of interest and the confounder (a true risk factor for disease) may make it falsely appear that the exposure of interest is associated with disease.

Control Group (or Reference Group): A group used as the baseline for comparison in epidemiological studies or laboratory studies. This group is selected because it either lacks the disease of interest (case-control group) or lacks the exposure of concern (cohort study).

Dose-Response Relationship: The relationship between a quantified exposure (dose), and the proportion of subjects demonstrating specific, biological changes (response).

Environmental Assessment Level: Environmental Assessment Levels (EALs) are benchmarks in a particular environmental media which denote the concentration of a chemical that should have no adverse effects on the natural environment or human health. By comparison with the predicted environmental concentrations arising from releases, they are intended to enable the significance of releases to be assessed, the need for further pathway modelling to be determined and the relative impact of pollutants released to different environmental media to be compared.

Horizontal Guidance Note (H1): The name of the guidance note issued by the Environment Agency which describes how operators should assess the environmental impact of processes and appraise the Best Available Techniques when applying for a permit under the Pollution Prevention and Control (PPC) regime. The term 'Horizontal' refers to the fact that the guidance can be applied across all the sectors covered by PPC.

Indicative Occupational Exposure Limit Values (IOELVs): European Community limit values, which are health based and are set under the EU Chemical Agents Directive (98/24/EC) (earlier Directives referred to the as ILVs). They indicate levels of exposure to hazardous substances considered to provide protection from ill health caused by work. IOELVs are similar to the British OELs system under COSHH.

Integrated Pollution Control (IPC): Prior to the PPC regulations coming into force, many industrial sectors covered by the IPPC Directive were regulated under Part I of the Environmental Protection Act 1990. This introduced the systems of Integrated Pollution Control (IPC), which controlled releases to all environmental media, and Local Air Pollution Control (LAPC), that controlled releases to air only. Processes regulated under IPC were controlled by the Environment Agency in England and Wales and were potentially the most polluting or technically complex. LAPC was operated by local authorities. Similar but separate arrangements were applied to Scotland and Northern Ireland. The objective of IPC was to use the Best Available Techniques Not Entailing Excessive Cost (BATNEEC) to prevent releases or where that was not practicable to minimise and render them harmless.

Integrated Pollution Prevention and Control (IPPC): The system of Integrated Pollution Prevention and Control (IPPC) applies an integrated environmental approach to the regulation of certain industrial activities. This means that emissions to air, water (including discharges to sewer) and land, plus a range of other environmental effects, must be considered together. It also means that regulators must set permit conditions so as to achieve a high level of protection for the environment as a whole. These conditions are based on the use of the Best Available Techniques. (BAT), which balances the costs to the operator against the benefits to the environment. IPPC aims to prevent emissions and waste production and where that is not practicable, reduce them to acceptable levels. IPPC also takes the integrated approach beyond the initial task of permitting, through to the restoration of sites when industrial activities cease. IPPC was introduced by the European Community (EC) Directive 96/61/EC on Integrated Pollution Prevention and Control (the IPPC Directive). The Directive is implemented by the Pollution Prevention and Control (England and Wales) Regulations 2000, SI 2000/1973. Separate systems have been introduced to apply the IPPC Directive to Scotland, Northern Ireland and the offshore oil and gas industries. Industrial activities are being brought under the control of the regulations on a sector by sector basis according to a timetable set out in the regulations and the Directive will not be fully implemented until 2007. See also Pollution Prevention and Control and Integrated Pollution Control.

Integrated Risk Information System (IRIS). IRIS is an on-line database established by the US Environmental Protection Agency (EPA) which provides information related to; substance identification, chemical and physical properties, hazard identification and dose response assessments. EPA working groups then review the available studies and develop reference doses based on assessment of lifetime exposure for non-carcinogenic endpoints or unit risk estimates for carcinogenicity. Information is also given on relevant EPA regulatory actions, standards and guidelines. The data included within IRIS is extensively peer reviewed and represents EPA consensus on risk. Selected studies from the primary literature are referenced.

Maximum Exposure Limit (MEL): Maximum Exposure Limits (MELs) are one of the two types of Occupational Exposure Limits (OELs) the UK Health and Safety Commission (HSC) sets. A MEL is proposed for substances, which may cause the most serious health effects, such as cancer and occupational asthma. These are substances for which no threshold level of exposure for the key health effect can be determined or for which exposure thresholds may be identified but at a concentration that is not yet routinely achievable in the workplace. The Control of Substances Hazardous to Health (COSHH) regulations 1999 require that exposure should be reduced as far below the MEL as reasonably practicable. See also Occupational Exposure Standard (OES).

Minimum Risk Level (MRL): An estimate of daily exposure to a substance that is likely to be without an appreciable risk of adverse effects (other than cancer) over a specified duration of exposure. The ATSDR develops MRLS for acute, intermediate and chronic duration exposures by the oral and inhalation routes. The concept, definition and derivation of MRLs are consistent with those of EPA's RfC and RfD. ATSDR publishes MRLs as part of its toxicological profile documents for each substance.

No-Observed-Adverse-Effect Level (NOAEL): A highest exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered adverse, nor precursors to adverse effects.

No-Observed-Effect Level (NOEL): An exposure level at which there are no statistically or biologically significant increases in the frequency or severity of any effect between the exposed population and its appropriate control.

Occupational Exposure Level (OEL): This is the collective term used in America to describe American occupational levels; those typically referred to are Recommended Exposure Limits (RELs), Permissible Exposure Limits (PELs) and Threshold Limit Values (TLVs).

Occupational Exposure Limit (OEL): The UK Health and Safety Commission (HSC) sets occupational exposure limits (OELs) which are concentrations of substances in the air at or below which occupational exposure is considered to be adequate. The HSC sets two types of occupational exposure limits – Maximum Exposure Limits (MELs) and Occupational Exposure Standards (OES). See also Occupational Exposure Level.

Occupational Exposure Standard (OES): Occupational Exposure Standards (OES) are one of the two types Occupational Exposure Limits (OELs) the UK Health and Safety Commission (HSC) sets. An OES is proposed at a level at which based on current scientific knowledge, there is no indication of risk to the health of workers who breathe it in daily. If exposure to a substance that has an OES is reduced to at least that level, then adequate control has been achieved.

Permissible Exposure Limits (PELs). Occupational exposure limit issued by the US Occupational Safety and Health Administration (OSHA). PELs are time-weighted average concentrations that must not be exceeded during any 8 hour work shift of a 40 hour week. May consider economic and technical feasibility in addition to health effects.

Pollution Prevention and Control (PPC): The Pollution Prevention and Control (England and Wales) Regulations 2000, SI 2000/1973 implement the requirements of the European Community (EC) Directive 96/61/EC on Integrated Pollution Prevention and Control (the IPPC Directive), in so far as it relates to installations in England and Wales. Separate systems have been introduced to apply the IPPC Directive to Scotland, Northern Ireland and the offshore oil and gas industries. The regulatory regime established by the regulations is often known as the PPC regime. See also Integrated Pollution Prevention and Control and Integrated Pollution Control.

Recommended Exposure Limits (RELs). Occupational exposure limit developed by the US National Institute of Occupational Safety and Health (NIOSH). RELs are time-weighted average concentrations for up to a 10-hour work day during a 40-hour work week, that should not be exceeded at any time during a work day.

Reference Concentration (RfC): An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark concentration, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in EPA's non-cancer health assessments.

Relative Source Contribution (RSC). The RSC is an assessment of the proportion of total exposure to a substance that may be allowed to arise from a specific exposure route, in this context inhalation. This may be calculated, where exposure routes are quantified, on the basis of the scale of exposure from other routes compared to the allowable exposure. However in many cases assumptions need to be made as to the relative importance of inhalation. In some circumstances use of an RSC may not be relevant such as where the endpoint is non-cumulative, e.g. irritation, or the adverse effect is specific to inhalation and would not occur via other routes of exposure.

Threshold Limit Values (TLVs). These values are established by the American Conference of Governmental Industrial Hygienists (ACGIH). They are the concentration in air of a substance to which, it is believed that, most workers can be exposed daily without adverse effect. Quoted as time weighted concentrations for a 7 or 8 hour workday and a 40 hour working week. For most substances the value may be exceeded, to a certain extent, provided there are compensating periods of exposure below the value during the workday, or in some cases working week. A limited number of substances are given ceiling concentrations that should never be exceeded.

Uncertainty Factor (UF): (also known as a safety factor) one of several, generally 10-fold factors, used in operationally deriving the RfD and RfC from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, i.e., interhuman or intraspecies variability; (2) the uncertainty in extrapolating animal data to humans, i.e., interspecies variability; (3) the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure to lifetime exposure, i.e., extrapolating from subchronic to chronic exposure; (4) the uncertainty in extrapolating from a LOAEL rather than from a NOAEL; and (5) the uncertainty associated with extrapolation from animal data when the data base is incomplete.