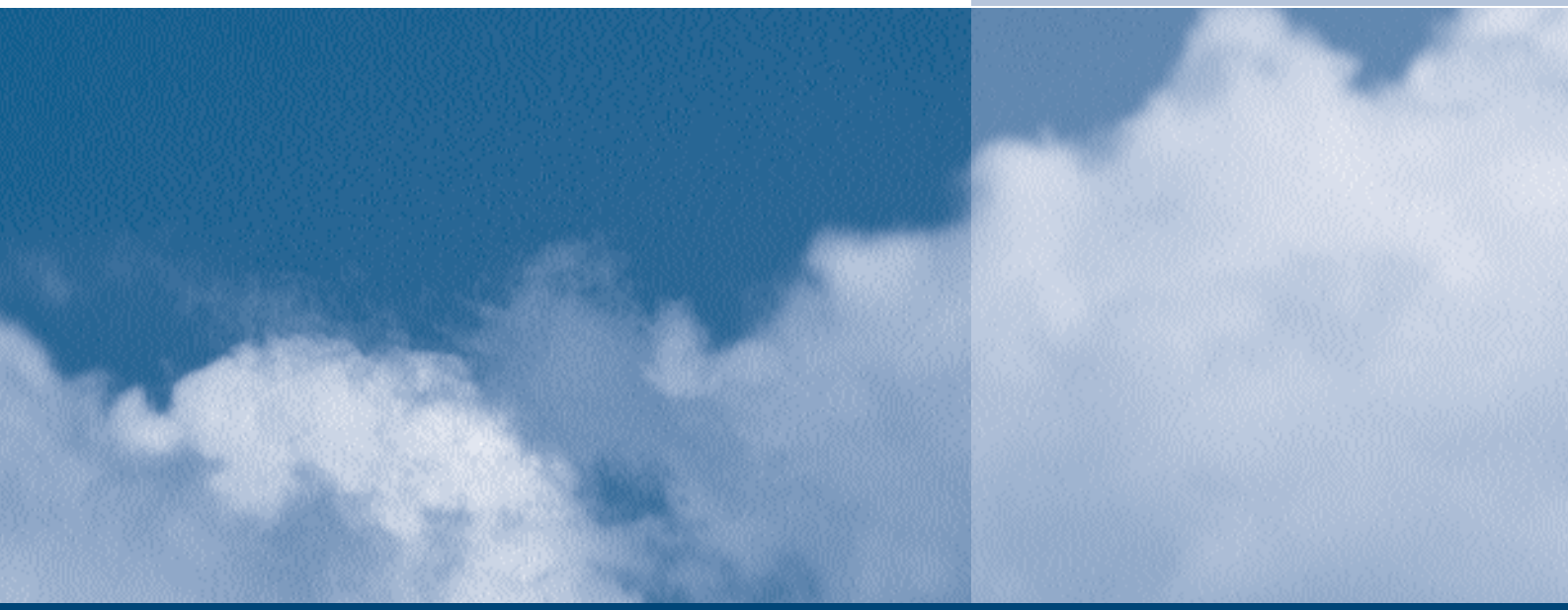

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A Review of the Toxicity and Environmental Behaviour of Bromine in Air

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Professor Mike Depledge Head of Science

EXECUTIVE SUMMARY

Bromine is an oxidising acidic gas with a noxious odour. The principal sources are associated with bromine production and use in the chemical industry. As a result, releases are often of short duration due to batch operations.

A number of measurement methods have been published for bromine but while most are insufficiently sensitive to be of use in other than an occupational setting, some offer the potential for short-term sensitive measurements. These methods are not 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 these measurements could be so used. No UK measurements of bromine in ambient air have been identified. The atmospheric lifetime of bromine is short during day light hours as a result of photodissociation.

Bromine is a volatile liquid that gives off suffocating vapours, is corrosive to the skin, and may cause severe gastroenteritis if ingested. Inhalation of bromine vapours and/or direct contact of bromine liquid or vapour with the skin and mucous membranes will produce direct tissue injury. There is usually a delay in the appearance of clinical signs after exposure. The injury may occur at various levels of the respiratory tract depending on the concentration and duration of exposure. Target organs associated with bromine exposure include the upper and lower respiratory tract, skin, and eyes.

Toxicological reviews for bromine, which include the inhalation route, have been published by the World Health Organization's International Programme on Chemical Safety (ICPS) and the American Conference of Governmental Industrial Hygienists (ACGIH). A review for bromine published by the United States Environmental Protection Agency (US EPA) focuses primarily on the oral route. This discussion on bromine is largely based on these reviews. Particular mention is made of those studies that have been used to derive the inhalation limits.

While there are no reported human volunteer studies, occupational and accidental exposure suggest that exposure to approximately 0.2 ppm (1.3 mg/m^3) and above may be associated with eye and respiratory tract irritation.

Case reports of accidental and occupational exposure to bromine vapours describe skin and eye irritation and damage, some of which is not apparent upon initial medical examination.

The upper airway irritation caused by inhalation of bromine vapours is thought to be due to its water solubility. Bromine reacts with the water present in mucous membranes to liberate nascent oxygen or oxygen free radicals, which are capable of producing tissue damage.

Acute animal studies have reported LC_{50} values in mice of approximately 240 ppm (1600 mg/m3; 2 hour exposure)-750 ppm (5000 mg/m3; 7 min exposure).

Pulmonary oedema, pseudomembranous deposits on the trachea and bronchi, and haemorrhage of the gastric mucosa were observed after guinea pigs and rabbits inhaled bromine vapours at 300 ppm (2000 mg/m^3) for 3 hours. Bronchopneumonia and

evidence of functional disturbances in the central nervous system were observed in animals that died several days after the exposure.

Rats, mice, and rabbits inhaling 0.2 ppm (1.3 mg/m^3) of bromine for four months developed disturbances in the respiratory, nervous, endocrine systems. No adverse effects were observed at 0.02 ppm (0.13 mg/m^3).

In several early studies ranging from three months to one year the effects of oral administration of bromine or sodium bromide in laboratory animals were a reduction in relative prostate weight and secretory activity in males and reduced "thyroid activation" in females. A variety of behavioural effects were observed at higher doses.

Rats fed 0.01 mg/kg bw/day bromine for 6 months experienced changes in their conditioned reflexes and several blood indexes. A No Observed Adverse Effect Level (NOAEL) for sodium bromide of >40 mg/kg-day was identified from a one-year feeding study in rats and 100 mg/kg bw/day from a one-year feeding study in dogs.

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 bromine.

Bromine (Br_2) (CAS Number 7726-95-6) is a liquid at room temperature. Its melting point is -7°C and its boiling point is 59°C. Under environmental conditions it is likely to be present as a vapour. It is water-soluble; up to 3.5g dissolving in 100 g of water at 25°C. On dissolution in water it forms hydrobromous and hydrobromic acids. These acids will further dissociate to produce the bromide ion. This is of particular note as although bromine itself has the potential to cause local adverse effects the bromide ion produced on dissolution may be absorbed leading to systemic effects.

First isolated in 1826, bromine has a characteristic reddish-brown colour and a pungent odour (its name comes from the Greek for 'stench'). Like other halogens it is not found in its elemental form in nature, as it is very reactive. It was traditionally isolated from seawater and the process involved mixing chlorine with the water acidified to pH 3.5. The bromide ions are then oxidised by the chlorine to bromine and the vapour is removed by blowing air through the brine, the bromine being recovered from the air. This method is not widely used today, as there are more concentrated sources of bromide available. The largest producer nation is the USA, where the element is extracted from bromine-rich brine wells in Arkansas and Michigan.

Bromine has a wide range of applications. Historically much of the bromine output was used in the production of ethylene dibromide, a lead scavenger used in making petrol antiknock compounds. However, there has been a large reduction in the production and use of leaded petrol over the last two decades because of legislation on health and environmental issues and concerns surrounding these additives. Bromine is also used indirectly in making the fumigant methyl bromide, but this route has also been restricted through the Montreal Protocol and subsequent legislation on ozone depleting substances. One of its most well known and probably most important uses is in the manufacture of flame-retardants which used 44% of US production in 2002. Bromine is one of the few chemical elements with fire-resistance properties. However, recent declines in the consumer electronics and computer markets have led to decreases in the use of bromine in flame-retardant production (Lyday, 2003).

Bromine also finds use in the following: water treatment, dyes, pesticide synthesis, algal control, photographic films, sedatives, refrigerating agents, analgesics, anaesthetics, hydraulic fluids and pharmaceuticals.

In order to allow comparison of concentrations, conversions have been provided between the concentration value as given in the documents reviewed and either mass concentration or volume fraction as required. This conversion has been based on assumed conditions of 20 °C 101325 Pa. This may not represent the original study conditions and hence may lead to a small uncertainty in the conversion.

1.1 Anthropogenic Sources of Bromine

The main source of bromine emissions to the atmosphere is likely to be from installations where it is produced and subsequently used, usually in the production of other chemical compounds. Other potential emission sources include power station cooling towers and air conditioning services. World wide bromine production in 1997 was 470,000 tonnes, of which the USA produced 247,000, Israel 135,000 tonnes and the UK 28,000 tonnes. One plant in the UK manufactures bromine (Amlwch in Anglesey,

Wales), and this is owned by Great Lakes Chemicals Limited (formerly Associated Octel). Some sources do report releases to the Environment Agency. The largest reported releases are given in Table 1.

Table 1.1 Main Point Source Releases of Bromine reported to the Environment Agency in 2001 and 2002

Operator	Site	Process	Bromine Emission 2001 Kilograms	Bromine Emission 2002 Kilograms
BASF PLC	Cramlington, Northumberland	Chemical Works	410	518
Ineos Fluor Ltd	Runcorn, Cheshire	Chemical Works	200	200
Great Lakes Manufacturing (UK) Ltd	Newton Aycliffe, County Durham	Chemical Works	195	26
Exxonmobil Chemical Ltd	Hythe, Hampshire	Chemical Works	1	0.9
Bayer Cropscience Ltd	Norwich, Norfolk	Chemical Works	0.69	0.7
Rhodia Pharma Solutions Ltd	Cramlington, Northumberland	Chemical Works	3	0.2

1.2 Atmospheric Chemistry of Bromine

1.2.1 Diatomic Bromine

Bromine vapour is rapidly photolysed by UV radiation in sunlight forming bromine atoms. The bromine atoms will subsequently react with other compounds, ultimately depositing possibly via the formation of an aerosol of particulate bromide.

Released bromine molecules Br_2 will dissociate in sunlight to create bromine atoms. However, if the concentration of bromine is very high the photolytic depletion may be delayed. This reaction does not occur at night.

For summer midday conditions in the UK corresponding to a zenith angle of 30 degrees, J1 is approximately 0.03 s^{-1} (based on analysis of absorption cross sections in Finlayson-Pitts) significantly more rapidly than chlorine.

Appendix 3 shows the predicted bromine concentrations down wind of a 1 g/s emission source under stable night-time, neutral and unstable atmospheric conditions. The Figures show model predictions with dispersion only, with dry deposition, with wet and dry deposition and with dry deposition and photolysis. The monatomic bromine formed by photolysis of the diatomic molecule reacts in turn with unsaturated hydrocarbons such as ethane and ethyne to form addition compounds. Bromine, with other saturated hydrocarbons such as methane or ethane will form hydrogen bromide and RH radicals. The monatomic bromine also reacts with ozone in the atmosphere to form the OBr radical. The OBr radical itself dissociates to the constituent atoms under sunlight. These reactions are not likely to be limited by the availability of reactants in the atmosphere. Given the relative rates of the hydrocarbon and ozone reactions the

bromine atom fate is principally to form OBr. The eventual fate of the OBr radical is complex.

1.3 Deposition Mechanisms

Bromine is likely to deposit quite rapidly being a reactive gas. The deposition rate will be limited by physical atmospheric processes, rather than chemical reaction rates at the surface.

1.4 Methods of Measurement

Under accidental release conditions, bromine can be observed through its colour and strong odour. However at more typical ambient air concentrations, other approaches may be used. Frequently these methods detect bromide ions rather than bromine. Some electronic detectors do not distinguish between bromine and chlorine.

1.4.2 Bubbler Methods

A method using midget impingers has been used for bromine determination. The air is passed through a pre–filter to exclude particulate bound material and then a midget impinger at a flow rate of 1.0 l/min. The impingers contain 10 to 15 ml of a 0.003 M sodium bicarbonate ($NaHCO_3$) /0.0024 M sodium carbonate (Na_2CO_3) solution. An air volume of around 30 l are recommended to be sampled. A working range of 0.015 to 0.31 ppm is quoted (OSHA 1990). The detection is of the bromide ion by ion chromatography. A correction is made for the bromate ion formed during dissolution. The bromate ion may also be measured, however, as this chromatographic peak may be subject to interference it is typically used only for confirmation that bromine was present.

1.4.3 Sorbent Tube Sampling

Tube detectors are basic approaches for occupational hygiene monitoring. Air is drawn with a hand pump over a tube containing a chemical that changes colour when exposed to bromine. Some tubes are cross sensitive to chlorine. Concentrations of 0.3-5 ppm bromine can be detected.

1.4.4 Electronic Gas Detectors

Electrochemical gas sensors have been developed for the detection of halogen gases including bromine. These methods are susceptible to interference from other halogens such as chlorine. The sensors can respond to traces as low as 3 ppm (20 mg/m^3). These provide rapid responses to changing concentrations and so are used for system failure detection in chemical plants. They are not sensitive enough for non-industrial settings.

1.4.5 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 and sensitive results.

1.4.6 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 different the 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 this to the original beam and then calculates the air concentrations of the particular gases. A detection limit is not quoted for bromine.

1.4.7 DLSIOS

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

1.5 Ambient Air Measurements

No measurements of ambient bromine concentrations have been identified for the UK. Measurements are not made regularly around the one production plant in the UK.

Measurements of bromide associated with particles sample those with aerodynamic diameters up to approximately 15μm, have been made at three rural sites in England since 1972. This data is given in the hydrogen bromide report associated with this study (Coleman *et al*, 2004).

The measurement methods described above such as DIAL, DOAS and DLSIOS have the capability to measure rapid fluctuations in bromine concentrations in ambient air down to concentrations released around industrial sites. However, presently these techniques are not in use for this purpose at least partly of reasons of cost and perceived practicality.

2 INTRODUCTION TO TOXICOLOGY OF BROMINE

Bromine reacts reversibly with water (although it is often simply considered water-soluble) to form both hydrobromic and hydrobromous acids. According to the Merck index, these are not formed in equimolar concentrations (unlike chlorine). The hypobromous ions may react to form bromide and bromate ions. The extent of this reaction is, however, very limited. At low level exposure to hydrobromic and hypobromous acids, the buffering capacity of the physiological fluids will ensure that the pH is not significantly altered. However, the potential exists for exposure to the bromide and bromate ions following exposure to bromine. Several groups and organizations have examined the toxicity of the bromide ion and also bromate (which is a potential human carcinogen).

In medicine, inorganic bromide was introduced in the second half of last century as a sedative and antilibido agent. Bromides 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. Barbiturates and other anti-epileptics such as phenytoin gradually replaced these. 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 Organization's IPCS reviewed the data available for methyl bromide in their Environmental Health Criteria No.166 which was used extensively as a fumigant (WHO, 1995). In addition, in combination with the Food and Agriculture Organization of the United Nations (FAO) as the Joint Expert Committee on Food Additives (JECFA) and the Joint Meeting on Pesticide Residues (JMPR) they have established an Acceptable Daily Intake (ADI) 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.

The UK's Committee on Toxicity reviewed the use of potassium bromate as a flour improver in 1988, following concerns about its possible carcinogenicity in rodents. The relevant studies carried out in Japan in 1982-1987, involved administration of potassium bromate in the drinking water, thus bromate itself was ingested (Food Advisory Committee 1989). The Committee on Mutagenicity (COM) was also asked in 1988 to comment on the published data. COM concluded that much of the published data on the mutagenicity of potassium bromate at that time, were inadequate as a result of the sparsity of supporting data on results and the lack of use of exogenous metabolic activation systems in *in vitro* studies. However, the available data did suggest that potassium bromate has the ability to produce chromosome damage both *in vitro* and *in vivo*. Hence COM concluded that potassium bromate should be regarded as an *in vivo* mutagen (Department of Health Personal Communication 2003). In 1993, the Committee on Carcinogenicity was asked to comment on the carcinogenicity and genotoxicity of bromate (as an *in vivo* mutagen and a carcinogen), inducing renal adenomas and peritoneal mesotheliomas in rats. The Committee confirmed that bromate was genotoxic and carcinogenic and that there was no evidence of any threshold for these effects (Committee on Carcinogenicity 1993). They recommended that bromate levels in drinking water should be kept as low as possible.

WHO, as part of their rolling revision to the guidelines for drinking water quality, have recently made available a draft document on bromate that sets a provisional guideline value of 10 μg/L. This re-evaluation was based on practical considerations. The health-based number relating to the concentration in drinking water associated with excess lifetime cancer risk of 10^{-5} was 2 μg/litre. Bromates have also been used as oxidising agents in the food industry (although JECFA in 1995 concluded that the use of potassium bromate in food processing was not appropriate and that, as a general principle, bromate should not be present in food as consumed) and therefore exposure to bromate is likely to be greater from other routes of exposure than from the inhalation route.

The UK Committee on Toxicity (CoT) considered the dietary intake of bromine in 2003. The committee reviewed an evaluation by JECFA and JMPR that established an ADI of 0-1 mg/kg body weight. COT considered it inappropriate to recommend a range of intakes for bromine that included zero, as it is not certain that bromine is essential. 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. They estimated the dietary intake from the 1997 total diet study as 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.

3 ANIMAL TOXICITY DATA

3.1 Introduction

The rat is an obligate nose-breather and has a complex nasal turbinate structure that will filter out many relatively fine particles, which 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. Although differences in action with gases have not been widely described, one of the studies described in the report on hydrogen bromide describes the results of exposure using a rodent mouth-breathing model in comparison with nose breathing with resultant differences in local effects.

In general, animal 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, then 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).

There are few inhalation studies in animals and the gaps in data have been filled by a number of experiments conducted using oral administration of bromine, as bromine is readily absorbed through the gastrointestinal tract. The chronic oral studies report a number of systemic effects including neuronal and hormonal toxicity. Data on the metabolism of bromine and longer inhalation effects are not available and so it is unclear whether the systemic effects outlined would be seen with inhalation of bromine gas under any circumstance. There is some evidence of CNC effects following very high lethal concentrations of bromine vapour.

3.2 Summary

The effects of inhalation of bromine vapours have been investigated in laboratory animals. Time and concentration-dependent mortality in mice was observed following inhalation of bromine vapour. The key inhalation animal studies are summarised in the table below and further detail is given in the text.

Table 3.1 - Key Inhalation Animal Studies

Species	Concentration ppm	Exposure Duration	Effect	Reference
Mice	240	2 hours	50% mortality in 30 days	Bitron and Aharonson, 1978
Mice	750	7 minute	50% mortality in 30 days	Bitron and Aharonson, 1978
Guinea pigs and Rabbits	300	3 hours	Pulmonary oedema, pseudomembranous deposits on the trachea and bronchi, haemorrhage of the gastric mucosa	Perry *et al* 1994

3.3 Absorption, Distribution, Metabolism, and Excretion

No data on the metabolism or kinetics of bromine in laboratory animals have been identified.

3.4 Acute Toxicity

Oral LD_{50} values of 3,500 mg/kg and 7,000 mg/kg have been reported for sodium bromide in rats and mice, respectively (USEPA, 1993). Based on acute oral and dermal toxicity data in laboratory animals, sodium bromide has been classified by the USEPA (1993) as Toxicity Category III. Sodium bromide was classified as Toxicity Category IV (the lowest level of acute toxicity) for ocular and dermal irritation, as it was shown not to be a dermal sensitiser.

Van Leeuwen and Sangster (1987) cited a 4-week study by Van Logten *et al*. (1973), in which Wistar rats were fed sodium bromide at 0, 300, 1,200, 4,800 or 19,200 mg/kg. Motor incoordination, reduced grooming activity, and increased mean relative kidney weights were observed in high-dose rats.

Bitron and Aharonson (1978) reported that delayed mortality in male albino mice was observed following inhalation of bromine vapour. Mortality and time of death were measured for several weeks after inhalation of a single dose of bromine at 240 ppm (1600 mg/m^3) for 15 to 270 minutes or 750 ppm (5000 mg/m^3) for 15 to 30 minutes. The time of death depended markedly on exposure duration. The exposure time resulting in 50% lethality (LT_{50}) was 9 minutes at 750 ppm and 100 minutes at 240 ppm. Approximately 50% of mice exposed to bromine at 240 ppm for 2 hours died within 30 days after the exposure. At 750 ppm, a 7-min exposure of mice was lethal to approximately 40% within 30 days.

Post mortem examinations conducted on guinea pigs and rabbits after exposure to bromine vapours at 300 ppm (2000 mg/m^3) for 3 hours revealed pulmonary oedema, pseudomembranous deposits on the trachea and bronchi, and haemorrhage of the gastric mucosa (Perry *et al.,* 1994). Bronchopneumonia and evidence of functional disturbances in the central nervous system were observed in animals that died several days after the exposure.

3.5 Chronic toxicity/Carcinogenicity studies

The effects of chronic inhalation of bromine vapours in laboratory animals were limited to a four-month study reported by NRC (1981). Rats, mice, and rabbits inhaling 0.2 ppm (1.3 mg/m3) bromine for four months developed disturbances in the respiratory, nervous and endocrine systems. No adverse effects were observed after four months at 0.02 ppm (0.13 mg/m3) (NRC, 1981) and this figure could be used as a NOAEL.

The USEPA (1993) has reviewed several early studies ranging from three months to one year, which report the effects of oral administration of bromine or sodium bromide in laboratory animals. In a 90-day feeding study by Van Logten *et al*. (1974), rats were fed sodium bromide at 0, 75, 300, 1,200, 4,800 or 19,200 ppm (0, 3.75, 15, 60, 240, or 960 mg/kg-day, respectively). At 240 mg/kg-day, reduced relative prostate weight and secretory activity was observed in males and reduced "thyroid activation" was observed in females. At the highest dose, lack of grooming, reduced motor coordination, growth retardation, an increased percentage of neutral granulocytes, and "thyroid inactivation" were observed in male and female rats. High-dose males also exhibited increased relative thyroid weights, pituitary gland cysts, reduced relative prostate weight and secretory activity, and reduced spermatogenesis. High-dose females also exhibited reduced corpora lutea. The biological half-life of bromide was estimated to be 3-5 days. The NOAELs in this study were 15 mg/kg-day in females and 60 mg/kg-day in males. This study clearly shows systemic effects with oral exposure to bromine.

The US National Research Council (NRC) (1981) reported that rats fed 0.01 mg/kg bromine for 6 months experienced changes in their conditioned reflexes and several blood indexes.

In a one-year feeding study by Spencer *et al*. (1944), rats were administered sodium bromide at 0.1% (reported to be equivalent to 24.3 to 40.9 mg/kg-day). This level was considered a NOAEL and reportedly resulted in blood bromide levels of 27 to 64 mg/dL.

In a one-year feeding study by Rosenblum *et al.* (1960), dogs were fed sodium bromide at 100 mg/kg-day. Since no effects were observed, this level was identified as the NOEL.

3.6 Genotoxicity

No studies examining the genotoxic potential of bromine were identified in the published literature.

3.7 Neurotoxicity

No studies examining the potential neurotoxic effects of bromine in laboratory animals were identified in the published literature.

3.8 Reproductive/Developmental Toxicity

The USEPA (1993) reported that an early study by Harned *et al*. (1944) administered bromide to pregnant rats through dietary feed at 192 mg/kg on Gestation Days 4 through 12. Reduced learning ability was observed in the offspring.

In a 90-day feeding study by Van Logten *et al*. (1974), rats were fed sodium bromide at 0, 75, 300, 1,200, 4,800 or 19,200 ppm (0, 3.75, 15, 60, 240, or 960 mg/kg/day, respectively). In addition to various systemic effects, high-dose males exhibited reduced spermatogenesis, and high-dose females exhibited reduced corpora lutea.

4 HUMAN STUDIES

4.1 Summary

The upper airway irritation caused by inhalation of bromine vapours is thought to be due to its water solubility (WHO, 1999). Bromine reacts with the water present in mucous membranes to liberate nascent oxygen or oxygen free radicals, which are capable of producing tissue damage. There is usually a delay in the appearance of clinical signs after exposure. Target organs associated with bromine exposure include the upper and lower respiratory tract, skin, and eyes (WHO, 1999).

Data on the toxicity of bromine are limited, but in one key study, Morabia *et al* (1988) reported that following industrial accidental exposure to bromine vapour at 0.2 to 0.5 ppm (1.3 to 3.3 mg/m^3) acute conjunctivitis, upper respiratory tract irritation, cough, and/or headache was observed in 91 patients.

4.2 Absorption, Distribution, Metabolism and Excretion

In living organisms, bromine forms bromide ions on adsorption into physiological fluids (USEPA, 1993). The reactivity of bromine in biological systems makes it difficult to study the pharmacokinetics and to separate the effects of the bromine from those of the bromine compounds and metabolites (WHO, 1999). The physical characteristics of bromine are extremely important in determining the site and depth of lung penetration, the systemic absorption, and the local effects of the exposure (WHO, 1999). It has been suggested that the absorption of bromine vapours by other routes is usually minimal compared with the dose delivered by inhalation (WHO, 1999), but no quantitative data were provided.

Ryan and Baumann (1999), van Leeuwen and Sangster (1987), and Rauws (1983) have reviewed the metabolism and kinetic data for bromide ion in humans. Bromide is rapidly absorbed from the gastrointestinal tract. The maximum plasma concentration occurs in approximately 90 minutes. Bromide ion is distributed almost exclusively in the extracellular fluid throughout the body much like the chloride ion, and can cross the blood-brain barrier. Transplacental distribution has also been reported. The volume of distribution of bromide is 0.3 L/kg. Bromide does not undergo metabolism. Elimination occurs mainly through the kidneys via a slow first-order process. Bromide competes with chloride for tubular reabsorption. A mean renal clearance of 267 mg/kg-day has been reported. The elimination half-life ranges between 10.5 and 14 days. A small amount of bromide ion is excreted in the faeces, perspiration, saliva, breast milk, and tears.

4.3 Mechanism of toxicity

The toxic effects of the bromine vapour on the respiratory tract are primarily due to its water solubility (WHO, 1999). Bromine produces immediate irritation of the upper airways upon contact. The adverse effects of bromine are considered to be similar to

those of chlorine (WHO, 1999). Due to its potent oxidising action, bromine liberates nascent oxygen or oxygen free radicals from the water present in mucous membranes. Nascent oxygen is a potent oxidiser, capable of producing tissue damage (WHO, 1999). The extent of the damage is dependent on the dose of bromine and the availability of water.

On contact with water, hydrobromic and bromic acids are formed and result in secondary irritation. Contact with the respiratory epithelium produces alveolar capillary congestion, which is followed by focal and confluent patches of high-fibrinogen oedematous fluid. This can result in copious frothy, blood-tinged sputum. A granulocyte response may occur several hours after inhalation. Hyaline membrane formation can occur later resulting in clinical deterioration at a time when signs of improvement have occurred. Poor oxygen diffusion, hypoxia, and hypercapnia as a result of atelectasis, emphysema and membrane formation may also result. Acute obstructive ventilatory impairment leads to severe hypoxaemia, metabolic acidosis, and death, usually due to cardiac arrest secondary to the hypoxaemia (WHO, 1999).

4.4 Acute toxicity in humans

Initial irritant symptoms of bromine vapour inhalation on the upper and lower respiratory tract include dyspnoea, coughing, choking, and wheezing (WHO, 1999). Immediate or delayed bronchoconstriction and the development of laryngeal spasm, glottal oedema, asthma and tracheobronchitis may also occur. With increased parenchymal penetration, peribronchiolar abscesses, pulmonary infiltrates consistent with chemical pneumonitis, bronchiolitis obliterans and pulmonary oedema may be observed. More severe respiratory symptoms may be delayed for several hours after the exposure. Acute obstructive ventilatory impairment may lead to severe hypoxaemia, metabolic acidosis, measles-like rash and subsequent death (WHO, 1999).

Bromine has an odour threshold of 0.05 ppm (Calabrese and Kenyon, 1991). This value is a geometric mean of several reported literature values. Bromine is a lacrimator at concentrations less than 1 ppm (7 mg/m^3) (HSDB, 2003). The ACGIH (2001) reported that Alexandrov (1983) found bromine vapour to be extremely irritating to the eyes, skin, and mucous membranes, and that inflammatory lesions of the upper airways were observed after inhalation of bromine vapour. Alexandrov (1983) recommended against prolonged exposure to a bromine concentration of greater than 0.08 ppm (0.5 mg/m^3), and suggested that a respirator be used at concentrations of 0.5 to 0.6 ppm (3 to 4 mg/m^3). In was noted that concentrations from 1.7 to 3.5 ppm (11 to 23 mg/m^3) were associated with severe choking, concentrations around 10 ppm (30 to 60 mg/m^3) were considered extremely dangerous, and concentrations around 30 ppm (200 mg/m^3) proved fatal in a short time. No details are given of the derivation of these levels.

Inhalation of unknown concentrations of bromine vapour has been associated with bronchopneumonia, blepharospasm, and chronic laryngitis after acute exposures (Suntych, 1953). Extensive pulmonary and tracheal damage and effects on the liver and kidney (Champeix *et al*., 1970) or sudden circulatory failure associated with bronchopneumonia (Suntych, 1953) have been reported in cases of fatal exposure.

Based on a review of selected toxicity data, Withers and Lee (1986) proposed a model for the lethal toxicity of inhaled bromine (ACGIH, 2001). The LC_{50} value for a 10-minute exposure was estimated to be 650, 260 and 546 ppm (mg/m^3) for the regular, vulnerable, and average population, respectively. The LC_{50} value for a 30-minute exposure was estimated to be 375, 150, and 315 ppm for the regular, vulnerable, and average population, respectively. Bromine was considered 1.5 times less toxic than chlorine.

4.5 Occupational studies

The ACGIH (2001) reported that a study by Elkins (1959) found that workers exposed to 1 ppm in a plant handling liquid bromine found the level to be excessively irritating. Earlier studies by Flury and Zernick (1931), which were reported by Perry *et al.* (1994), indicated that exposure to 0.75 ppm in a workroom for six hours was reportedly not associated with any clinical symptoms.

Regular occupational exposure to bromine concentrations ranging from 0.3 to 0.6 ppm for one year was associated with headaches, irritability, loss of appetite, dyspepsia, and pain in the joints, stomach, and chest (HSDB, 2003; Alexandrov, 1983). After five or six years, there may be loss of corneal reflexes, pharyngitis, vegetative disorders, and thyroid hyperplasia accompanied by thyroid dysfunction. Myocardial degeneration and hypotension, or functional and secretory disorders of the digestive tract may also occur. Signs of inhibition of leucopoiesis and leucocytosis have been seen in the blood. The blood concentration of bromine varies between 0.15 mg/100 mL to 1.5 mg/100 mL independently of degree of intoxication (HSDB, 2003; Alexandrov, 1983).

In 1984, the accidental release of a cloud of bromine vapour from an industrial plant in Geneva, Switzerland occurred (at measured concentrations between 0.2 to 0.5 ppm). This was associated with acute conjunctivitis, upper respiratory tract irritation, cough, and/or headaches in 91 patients, with approximately 40 % of the population at risk (Morabia *et al*., 1988). The exposure persisted for several hours at concentrations above the maximum allowable concentration of 0.1 ppm and short-term exposure limit (STEL) of 0.3 ppm. It should be noted that the authors indicated that the exposure concentrations were likely to be much higher around the immediate vicinity of the plant during the initial phases of the release, although no measurements were obtained. The main symptoms were acute conjunctivitis (90%), upper respiratory tract irritation (68%), cough (47%), and headache (46%). Symptoms persisted in 20 to 30% of the patients for up to three days (Morabia *et al*., 1988).

A 21-year old male maintenance technician in a chemical company developed a cough with severe bronchospasm and spontaneous pneumomediastinum following an accidental exposure to bromine from a ruptured check valve (Lossos *et al*., 1990). It was not specified whether the initial contents of the valve were bromine liquid or vapour. The man immediately developed a burning sensation on his face and started coughing. The man presented with coughing, choking, tachypnoea, wheezing, and prolonged expiration. A chest radiograph taken after admission was normal, but pneumomediastinum was observed in a chest radiograph taken a few hours later, while coughing was still persistent. No evidence of subcutaneous emphysema or chemical

pneumonitis was observed. The patient was released four days later after normal pulmonary function and chest radiographs were achieved.

The case of a 42-year old man, who developed pulmonary oedema after accidental inhalation of bromine vapours, was reported by Sagi *et al*. (1985). The man, who was previously healthy, was exposed to bromine vapours after a barrel containing bromine exploded in his presence. No signs of skin injury were apparent upon initial examination. A chest radiograph showed signs of pulmonary oedema. One day later, blisters, which required surgical intervention, appeared on the left foot and calf. Skin was autografted to this region, and the man was discharged 20 days later with no apparent local or systemic complications.

Liubchenko and Alekseeva (1991) described a case of accidental exposure to bromine vapours in a pharmaceutical plant operator. Limited details from this Russian publication were available. Bronchitis twenty days after the exposure, myocardial dystrophy, and increased hepatic enzyme activity, reportedly indicative of hepatocyte membrane lesions were observed.

4.6 Chronic toxicity /Carcinogenicity

No chronic data or data concerning the carcinogenic potential of bromine in humans were identified in the available literature.

4.7 Genotoxicity

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

4.8 Neurotoxicity

The bromide ion is a central nervous system depressant producing ataxia, slurred speech, tremor, nausea, vomiting, lethargy, dizziness, visual disturbances, unsteadiness, headaches, impaired memory and concentration, disorientation and hallucinations (WHO, 1999). This has only been documented in the literature with reference to overdoses of bromide-containing medications and the inhalation of bromide-containing fumigants (WHO, 1999).

4.9 Reproductive/Developmental Toxicity

Limited developmental/reproductive toxicity data in humans were identified in the available literature. Spermatogenesis and reproductive performance were evaluated in eight men accidentally exposed to bromine vapour after a truck loaded with liquid bromine over turned, resulting in the formation of a brownish-red well-defined cloud of bromine vapour (Potashnik *et al*., 1992). Although the exposure concentration was not reported, it was said to be above the IDLH (Immediately Dangerous To Life Or Health) value of 3 ppm for bromine. The duration of the exposure ranged from 50 to 240

minutes, depending on the individual. The eight men and their spouses were monitored for up to 40 weeks. Although two cases of oligozoospermia were considered related to the exposure, no apparent effects on reproductive performance resulted, since the spouses of both men became pregnant shortly after the exposure. Plasma levels of the follicle stimulating hormone and luteinising hormone were normal in all men. One first-trimester abortion and one late abortion, reportedly due to chorioamnionitis, occurred among the 5 pregnancies, which were conceived within a year following the accident. The authors suggested that a mild degree of spermatogenic suppression and impaired reproductive performance occurred following paternal exposure to bromine vapour during the accident. However, due to the small study size, a confident cause-result linkage could not be established. The authors also acknowledged that some of the effects could be attributed to physical and/or emotional stress resulting from the exposure.

Few data were identified relating to the developmental effects of bromine exposure in humans. Some limited data were available regarding the developmental effects of exposure to bromides. USEPA (1993) reported that a woman, who had two "normal" children, had two "retarded boys", 1.5 years apart, while taking bromides. The retarded boys had growth retardation and reduced head size. A second case report identified a woman who took high doses of bromide. Her seven-day old nursing infant was found to have bromide intoxication. Blood bromide levels in the mother were 320 mg/dL and her breast milk was found to have 120 mg/dL bromide.

The WHO (1999) identified one report of neonatal bromism, reportedly involving neurological depression and hypotonia secondary to maternal bromide exposure at a photographic laboratory, but no further details were provided.

5 EVALUATIONS AND RECOMMENDATIONS BY OTHER ORGANISATIONS

5.1 Summary

Short-term exposure values have been set at between 0.1 and 0.3 ppm. Long term exposure limits have been set at 0.1 ppm by the UK, Germany, Japan, Poland, Switzerland the USSR and in the US by ACGIH, over 8 hours, and NIOSH, over 10 hours.

Table 5.1 - Summary table of the Occupational Standards/ Guideline levels for Bromine from various international organisations.

Country	Organisation	Occupational Standard/Guideline	Concentration	Averaging time
USA	ACGIH	TLV-TWA	0.1 ppm (0.66 mg/m3)	8 hour
USA	ACGIH	TLV-STEL	0.2 ppm (1.3 mg/m3)	15 minute
USA	NIOSH	REL	0.1 ppm (0.66 mg/m3)	10 hour
USA	NIOSH	STEL	0.3 ppm (2.0 mg/m3)	15 minute
USA	NIOSH	IDLH	3 ppm	
USA	OSHA	PEL	0.1 ppm (0.66 mg/m3)	8 hours
USA		STEL	0.3 ppm (2.0 mg/m3)	15 minutes
USA	US EPA	AEGL - 1	0.033 ppm (interim)	30 minutes
USA	US EPA	AEGL - 1	0.024 ppm (interim)	1 hour
USA	US EPA	AEGL - 1	0.013 ppm (interim)	4 hour
USA	US EPA	AEGL - 1	0.0095 ppm (interim)	8 hour
UK	HSE	OES	0.1 ppm (0.66 mg/m3)	8 hour
UK		STEL	0.3 ppm (2.0 mg/m3)	15 minutes
Australia			0.1 ppm (0.66 mg/m3)	8 hours
Australia			0.3 ppm (2.0 mg/m3)	15 minutes
Belgium			0.1 ppm (0.66 mg/m3)	8 hours
Belgium			0.3 ppm (2.0 mg/m3)	15 minutes
Denmark			0.1 ppm (0.66 mg/m3)	8 hours
Denmark			0.3 ppm (2.0 mg/m3)	15 minutes
Sweden			0.1 ppm (0.66 mg/m3)	8 hours
Sweden			0.3 ppm (2.0 mg/m3)	15 minutes

In 2001, the American Council of Government Industrial Hygienists (ACGIH) set a 8-hour Threshold Limit Value – Time Weighted Average (TLV-TWA) of 0.1 ppm (0.66 mg/m^3) and a 15-minute Threshold Limit Value – Short-Term Exposure Level (TLV-STEL) of 0.2 ppm (1.3 mg/m^3) to minimise the respiratory irritation and pulmonary tissue injury associated with exposure to bromine vapour. These values were based on the observations noted by Henderson and Haggard (1943), Alexandrov (1983), and Morabia *et al*. (1988).

The National Institute for Occupational Safety and Health (NIOSH, 1997) has determined a Recommended Exposure Limit (REL) of 0.1 ppm (0.66 mg/m3) as a 10-hour time-weighted average. This value is based on the risk or respiratory irritation and lung damage associated with inhalation of bromine vapours. The NIOSH 15-minute Short-Term Exposure Limit (STEL) for bromine is 0.3 ppm (2.0 $mg/^{m3}$). An IDLH

(Immediately Dangerous to Life or Health) value of 3 ppm was also determined for bromine.

Although vacated in 1998, the Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL) for bromine was 0.1 ppm (0.66 mg/m3) as an 8-hour time weighted average and the Short-Term Exposure Limit (STEL) is 0.3 ppm (2.0 mg/m^3) (OSHA, 1998). These levels are still enforced in some states (HSDB, 2003).

The USEPA Office of Pollution Prevention and Toxics has responsibility for setting Acute Exposure Guideline Levels (AEGLs) for chemicals. There are three types of guidelines: AEGL-1, AEGL-2 and AEGL-3. 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. The interim values quoted (Table 5.1) are yet to be finalised.

According to WHO (1999), the International Labour Office (ILO, 1991) reported occupational exposure limits and Short-Term Exposure Limit (STEL) values for many European countries. The countries which have adopted the same 0.1 ppm (0.66 mg/m^3) 8-hour time weighted average value and the same 15-minute Short-Term Exposure Limit (STEL) of 0.3 ppm (2.0 mg/m^3) for bromine include Australia, Belgium, Denmark, and Sweden. Although the UK has adopted the same 0.1 ppm (0.66 mg/m^3) 8-hour time weighted average value, the STEL of 0.3 ppm (2.0 mg/m^3) is for a 10-minute exposure (HSDB, 2003).

According to WHO (1999), the International Labour Office (ILO, 1991) reported occupational exposure limits for bromine in Germany, Japan, Poland, Switzerland, the UK, and the USSR of 0.1 ppm (approximately 0.7 mg/m^3) as an 8-hour time weighted average. Germany was cited as not having a STEL due to local irritant effects (WHO, 1999); however, a 5-minute STEL of 0.2 ppm for eight exposures per shift were cited in HSDB (2003).

According to WHO (1999), the International Labour Office (ILO, 1991) reported that Finland, France, and Hungary have a STEL of 0.3 ppm (2.0 mg/m^3) for bromine, but Switzerland has a STEL of 0.2 ppm (1.4 mg/m^3).

The USSR has a dermal Maximum Allowable Concentration-Short-term Exposure Level (MAC-STEL) of 0.5 ppm for bromine (HSDB, 2003; WHO, 1999).

Sticht and Kaferstein (1988) reported that the Acceptable Daily Intake (ADI) for bromide through oral ingestion is 1 mg/kg. No information was available regarding how this value was determined.

The UK Committee on Toxicity considered the dietary intake of bromine in 2003. They reviewed an evaluation by JECFA and JMPR that established an ADI of 0-1 mg/kg body weight. COT considered it inappropriate to recommend a range for intakes of bromine that included zero as it is not certain that bromine is essential. 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.

6 CONCLUSIONS

The most obvious adverse effect arising from human exposure to bromine gas is local irritation of the respiratory tract. There does, however, exist the possibility of systemic effects consequent to absorption of the bromide anion or even potentially bromate produced when bromine reacts in aqueous media. Bromine is a very reactive molecule and a strong oxidising agent, which in its liquid form is corrosive to skin, eyes and the respiratory tract. Vapour pressure at normal temperatures is relatively high and the vapour is moderately soluble in water, to give a mixture of hydrobromic acid and hypobromous acid. At low concentrations the bicarbonate concentration in the lung will ensure that these acids are neutralised to the corresponding salts. 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 achieved by inhalation. It is also likely that any bromate formed will be well below the threshold of acceptability given the established carcinogenicity in animals. Thus, the major toxic effect is likely to be a local response to the presence of the strong oxidising agent, hypobromite. 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 will indicate the type of lesion to be expected. In the case of bromine, lesions are often more extensive than those in response to chlorine, possibly indicating a deeper penetration into the tissue (and to basement membranes) rather than damage being confined to the surface epithelium and therefore, regeneration may take longer. Evidence for a more severe effect on repeated exposure is confined to case reports and is not well established.

There are relatively few primary animal studies with bromine. In particular, chronic inhalation is confined to a study by NRC (1981), in which rats, mice and rabbits were exposed to 1.3 mg/m^3 (0.2ppm) bromine for 4 months. As well as the expected disturbances in the respiratory system, there were also reports of nervous and endocrine systems disruption. These observations would indicate a systemic effect but are difficult to reconcile with contemporary data on the toxicology of bromide ions and therefore conclusions regarding the systemic effects are difficult to draw from this study. However, a no effect level of $0.13mg/m^3$ (0.02ppm) was reported and this is consistent with other data. The lack of further animal data on repeat dose exposure is a concern as the above study does not confirm the localised nature of the lesions which define the NOAEL.

The study by van Logten *et al* (1974) investigating the semi-chronic toxicity of sodium bromide in rats, can be regarded as definitive for the toxicity of the bromide ion in rats. The study is slightly deficient by modern standards in the range of parameters tested and its completion preceded GLP. Nevertheless, it is of sufficient quality to allow satisfactory assessment. The use of the oral rather than the inhalation route raises questions of toxicokinetics but the very high doses used and the continuous nature of the dosing minimise the importance of this difference.

The account by Morabia *et al* (1988) of accidental bromine exposure in an urban population provides useful information on human responses to a bromine cloud where

the concentration was assessed to be in the range of 0.2-0.5ppm. This value probably puts a lower concentration level on the effects described. However, as with most studies of this type the potential presence of pockets of higher concentration or abnormal exposure patterns cannot be eliminated.

The case report by Burns and Linden (1997) on toxicity secondary to bromine exposure and hydrobromic acid exposure, is significant in that it clearly indicates the possibility of human toxicity at levels where there may be no significant sensory irritation. This latter point, is also consistent with the findings of Ruth (1986) which report the lowest and highest odour thresholds for bromine as 0.05ppm and 3.8ppm respectively, with a threshold of irritation given as 0.3ppm. It should be recognised that these values are high, compared to some others in the literature. The lack of primary information and the variability in quoted values leads to difficulties in arriving at a clear definition of the relative concentrations for toxicity and irritation.

The ACGIH (American Conference of Government Industrial Hygienists) 2001 Documentation of the threshold limit value for bromine, is a useful summary review. It summarises some of the less accessible Russian literature. The main disadvantage is that the review is directed mainly to occupational exposure and therefore takes little account of vulnerable sub-groups.

The US EPA (1993) Re-registration eligibility decision - bromine, is also a useful summary of the oral toxicity of bromine and therefore gives a good assessment of the potential no effect levels for bromides, etc. The disadvantage is that there is no significant consideration of inhalation exposure and the potential toxicokinetic differences from oral administration.

The WHO (1999) Poison information monograph on bromine provides a good summary of the potential effects from various routes of exposure. This is recent and comprehensive. However, it suffers from the disadvantage that few details of the material reviewed are provided.

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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.

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Appendix B – Literature Search Strategy

The search of the scientific literature was performed in several stages. Initially a primary search of the full literature to April 2003 was conducted and assessed for content. The search was then refined to look for reviews. Following this, a further search was performed to look for reviews in the time period 01/01/1995 – 30/04/2003. A final search to include the search term toxicity was also made.

The initial search included the following literature sources;

A primary search of PubMed with search term Bromine
World Health Organisation Environmental Health Criteria
INCHEM – WHO database of documents
IARC – International Agency for Research on Cancer
EURAR – European Union Risk Assessment reports
USEPA Integrated Risk Information System
USEPA (2000) Office of Pollution Prevention and Toxics. Acute Exposure Guideline Levels
American Conference of Governmental Industrial Hygienists
Agency for Toxic Substances and Diseases Registry
Occupational Safety and Health Administration
National Institute for Occupational Safety and Health
Office of Environmental Health Hazard Assessment
Health and Safety Executive
Toxicology Excellence for Risk Assessment
Health Canada
NAS (National Academy of Sciences)
International Uniform Chemical Information Database (2000)
Google Search Bromine
Toxnet search Bromine

The later searches looked at the following;

Search with search term Bromine and limited to reviews
Search with search term Bromine and limited to reviews and 01/01/1995 – 30/04/2003
Search of PubMed with search term Bromine and limited to reviews with search terms Bromine and toxicity

Appendix C - Dispersion of Bromine from a Low Level Release

Bromine vapour is rapidly photolysed by the ultraviolet radiation in sunlight forming bromine atoms. The bromine atoms will subsequently react with a range of other compounds present in the atmosphere, ultimately depositing to the ground, possibly via the formation of an aerosol of particulate bromide containing species or as the bromide ion dissolved in rain, fog or snow.

For a release of bromine the 15-minute mean plume centre line concentration can be approximated over relatively short distances of perhaps a few kilometres by the following equation;

$$\frac{dF_i}{dt} = P_i - L_i - \frac{v_{d_i}}{h} F_i - \Lambda_i F_i + E_i + D_i$$

Where:

- F_i is the volume integrated concentration of component i, $=hWc_i$
- P_i is the rate of production of i by reaction
- L_i is the rate of loss of i by reaction
- v_d is the dry deposition velocity~0.05 m s^{-1} for reactive gases
- Λ is the wet scavenging coefficient ~ 0.0001 s^{-1} for reactive gases when raining
- E is the rate of emission
- D is the change in flux resulting from the change in volume of the plume
- h is the height of the plume$=(\pi/2)^{0.5}\sigma_z$
- W is the width of the plume$=2(\pi/2)^{0.5}\sigma_y$
- t is the time since release
- x is the distance from the release point

For stable atmospheric conditions

$$\sigma_z = 10 + 16x(1 + 0.3x)^{-1}$$
$$\sigma_y = 40x(1 + 0.1x)^{-0.5}$$

wind speed u = 2 m/s
h < 100 m
x = ut/1000 km

For neutral atmospheric conditions

$$\sigma_z = 10 + 0.06x(1 + 1.5x)^{-0.5}$$
$$\sigma_y = 0.08x(1 + 0.1x)^{-0.5}$$

wind speed u = 5 m/s
h < 800 m

and for unstable atmospheric conditions;

$$\sigma_z = 10 + 0.12x$$

$$\sigma_y = 0.16x(1 + 0.1x)^{-0.5}$$

wind speed u = 2 m/s

h < 1200 m

Released bromine molecules Br_2 will dissociate in sunlight to create bromine atoms. This reaction will not occur at night. Further if the concentration of bromine is very high the photolytic depletion may be delayed. The predicted concentration of bromine (Br_2) is given by:

$$c = \frac{Q}{uhW}\exp\left((-\frac{v_d}{h} - \Lambda - J_1)\frac{X}{u}\right)$$

Where:

- X=ut
- Q is the rate of emission
- J_1 is the rate of photolysis of Br_2.

For summer midday conditions in the UK corresponding to a zenith angle of 30 degrees, J1 is approximately 0.03 s-1 (representing a time constant of 33 seconds) (based on analysis of absorption cross sections in Finlayson-Pitts) which is significantly more rapid than the photolysis of chlorine.

Figures 3 to 5 show the predicted bromine concentrations down wind of a 1 g/s emission source under stable night-time, neutral and unstable atmospheric conditions. The Figures show model predictions with dispersion only, with dry deposition, with wet and dry deposition and with dry deposition and photolysis.

Formation of Bromine atoms and HBr from the atmospheric release of Bromine

The bromine radical formed by photolysis of the diatomic molecule can then react with ozone, alkanes, alkenes and the hydroperoxy radical or recombine. Table C.1 compares the pseudo first order time constants for each reaction and typical atmospheric background concentrations. Comparison of the background concentrations with those in Figs 1-3 shows that the background concentrations of the co-reactants are generally in excess compared with bromine (at least for a 1g/s emission rate). It is concluded that the reaction is not likely to be limited by the availability of reactants in the atmosphere.

The predicted concentration of hydrogen bromide is then:

$$c = \frac{2Q}{uhW}\exp\left((-\frac{v_d}{h} - \Lambda)\frac{X}{u}\right)\left(1 - \exp(-J_1\frac{X}{u})\right)$$

Table C.1 Reaction Rate Constants and Atmospheric Composition Assumptions

Reaction	Order	Reaction rate	Conditions	Pseudo first order time constant, s^{-1}
$Br+Br+M=Br_2+M$	3	4.25e-33 cm^6 $molecule^{-2}$ s^{-1}	Air 10^9 ppb Br 1 ppb	325
$Br+O_3=BrO+O_2$	2	1.18 e^{-12} cm^3 $molecule^{-1}$ s^{-1}	Ozone 40 ppb	0.8
$Br+HO_2=HBr+O_2$	2	1.54 e^{-12} cm^3 $molecule^{-1}$ s^{-1}	Hydroperoxy radical 0.008 ppb	3000
$Br+C_2H_6=HBr+C_2H_5$	2	3.1e^{-19} cm^3 $molecule^{-1}$ s^{-1}	Ethane 8 ppb	10^7
$Br+C_2H_4$=products	2	1.6 e^{-13} cm^3 $molecule^{-1}$ s^{-1}	Ethene 12 ppb	19.4
$Br+C_3H_6$=products	2	3.6 e^{-12} cm^3 $molecule^{-1}$ s^{-1}	Propene 4 ppb	2.6

The main reaction of the bromine radical is with ozone except at very high concentrations (>10 ppb) when significant recombination occurs. A substantial fraction of the bromine radicals reacts with alkenes.

The main products of the reaction with the alkene compounds are bromoalkene adducts, which redissociate or react with oxygen to form a peroxy radical which will then react further to form a range of brominated aldehydes, acids etc. These brominated compounds may subsequently dissociate back to the Br radical either rapidly directly or during the eventual decomposition of these compounds.

The bromine oxide formed as the product of the reaction with ozone then may react further with nitrogen dioxide to form bromine nitrate or may regenerate bromine atoms as the result of reactions with nitric oxide or by photodissocation. Table C.2 compares the rates of reaction of the bromine oxide with relevant species. The reactions of the BrO with both NO and NO_2 are both relatively fast, with the NO_2 reaction effectively acting as a sink for the bromine because the reaction rate of the photolysis of the $BrONO_2$ is relatively slow.

Table C.2 Rates of some reactions of Bromine Oxide with Nitrogen Oxides

Reaction	Order	Reaction rate	Conditions	Pseudo first order time constant, s^{-1}
$BrO+ NO_2=BrONO_2$	3	5.1e^{-31} cm^6 $molecule^{-2}$ s^{-1}	Air 10^9 ppb NO_2 5 ppb	1.8
BrO=Br+O	Photolysis	0.033 s^{-1}		30
$BrO+NO=Br+NO_2$	2	2.1e^{-11} cm^3 $molecule^{-1}$ s^{-1}	NO 5 ppb	0.35
$BrONO_2$=products	Photolysis	< 0.0015 s^{-1}		>666

If the sequence of reactions from Br_2 to Br to BrO to $BrONO_2$ is considered, the overall rate is limited by the initial photolysis of the bromine molecule; Br_2. Similarly, the rate of photolysis of Br_2 is also likely to limit the rate of reaction of the sequence Br_2 to Br to bromoalkene adducts to brominated peroxy radical to brominated products. Thus it is concluded that the removal of bromine molecules and radicals from the air by reaction to form relatively more stable products is limited by the initial rate of photolysis.

It is unknown whether the reaction products identified represent a greater or lesser risk to human health than bromine.

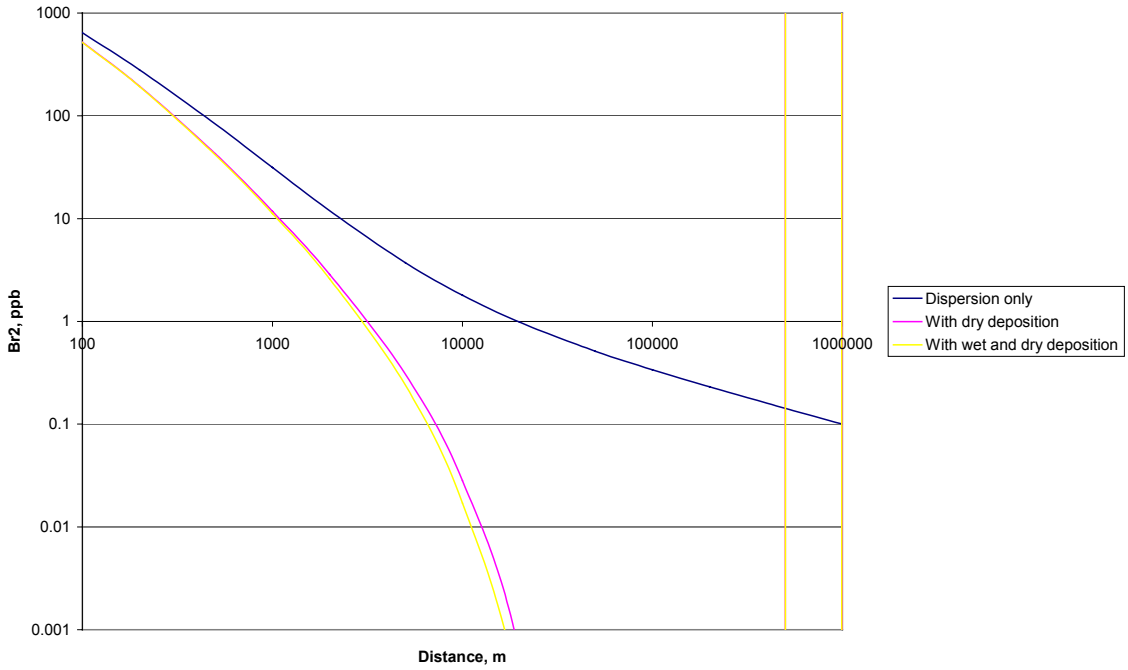

Figure C1 Bromine concentrations under stable night time dispersion conditions (1g/s emission)

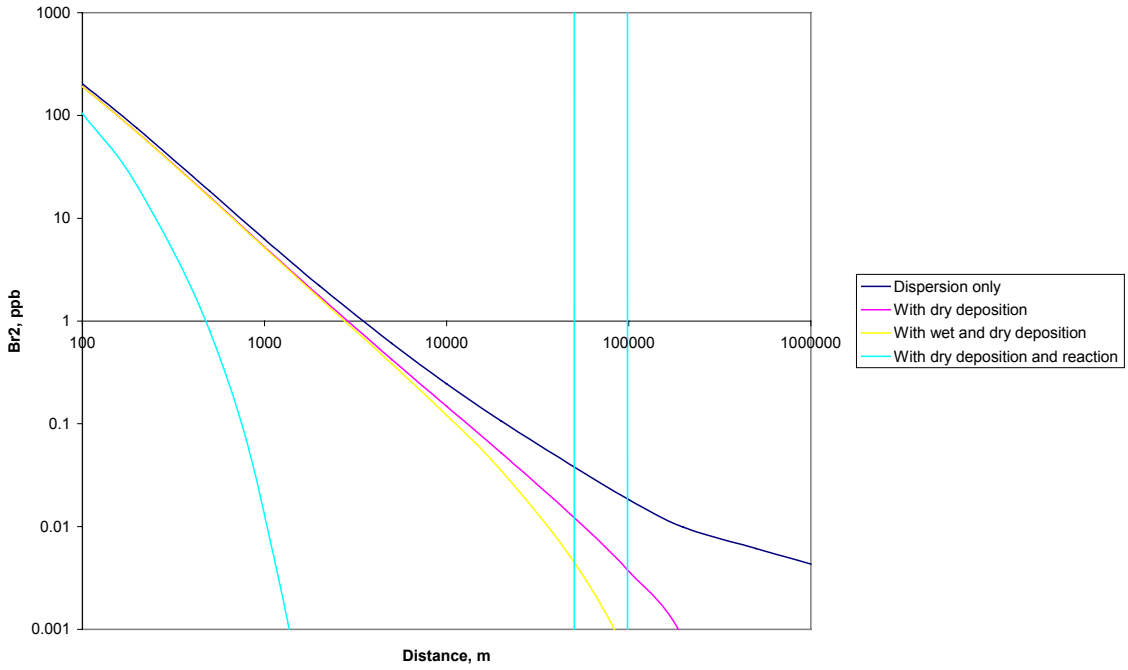

Figure C2 Bromine concentration under neutral daytime dispersion conditions

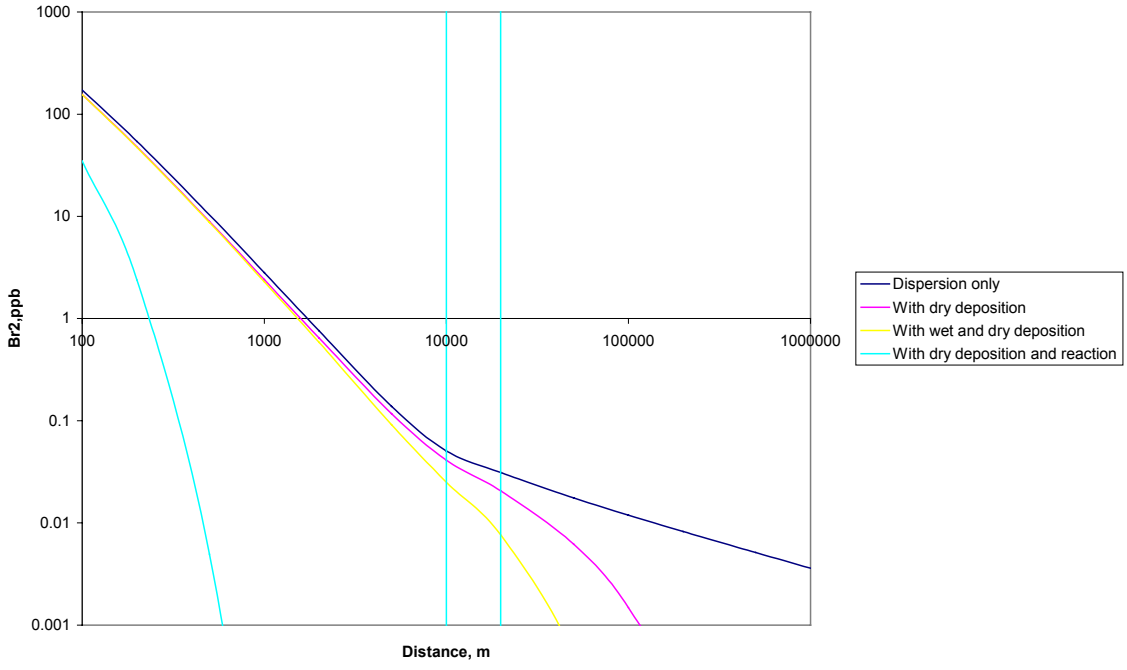

Figure C3 Bromine concentration under unstable daytime dispersion conditions

Appendix D - Equilibrium of Bromate Formation from the Dissolution of Bromine at the lung surface

Standard reduction potential for a range of reactions of bromine compounds in aqueous solution are provided by "Handbook of Chemistry and Physics". Reactions involving undissociated bromine, bromide ions, hypobromic acid, hypobromous ion and the bromate ion are of particular interest. The values of the standard reduction potential are listed in Table D.1.

Equilibrium constants (expressed in terms of activities) for each reaction have been derived from the standard potential using the relationship:

$$\log_{10} K^o = \frac{nFE^o}{2.303RT}$$

where F is the Faraday constant= 23.061 kcal volt^{-1} equivalent^{-1};
n is the number of moles of electrons taking part in the reaction
R is the gas constant = 1.987 cal deg^{-1} mole^{-1};
T is the absolute temperature, 298 K

Substituting the numerical values gives $\log_{10}K^o=16.9nE^o$.Values of $\log_{10}K^o$ at 298 K are shown in Table D.1

Table D.1 Reactions Considered

	Standard reduction potential, V	$Log_{10}K^0$	Reference
$Br_2(aq)+2e^-\leftrightarrow 2Br^-$	1.087	36.73	Handbook of Chemistry and Physics
$HBrO+H^++2e^-\leftrightarrow Br^-+H_2O$	1.33	44.95	Handbook of Chemistry and Physics
$BrO^-+H_2O+2e^- \leftrightarrow Br^-+2OH^-$	0.70	23.66	Handbook of Chemistry and Physics
$BrO_3^-+6H^++6e^-\leftrightarrow Br^-+3H_2O$	1.44	146.0	Handbook of Chemistry and Physics
$H_2O\leftrightarrow H^++OH^-$		-14	Handbook of Chemistry and Physics

The ratio of each species activity to the activity of the bromide ion may then be calculated. For the bromate ion, for example, the ratio is given by:

$$(BrO_3^-) = (Br^-)10^{(-146+6\,pH+6\,pe)}$$

where pH =$-\log_{10}(H^+)$
and pe=$-\log_{10}(e^-)$.

In aqueous solutions in equilibrium with the atmosphere, with maximum oxygen partial pressures of around 0.2 atm, the value of pH+pe is limited to a maximum of 20.6 under

the most oxidising conditions. Thus the bromate ion activity at equilibrium is $10^{-22.4}$ of the bromide ion activity.

The activities of the other species are similarly small compared to the bromide ion activity except in strongly basic reducing environments. Thus it may be concluded that the bromate ion activity is approximately at most $10^{-22.4}$ of the total activity of bromine compounds in solution.

At the dilute concentrations involved, the activity approaches the concentration in moles /l and so it may be concluded that the bromate ion concentration is approximately at most $10^{-22.4}$ of the total concentration of bromine compounds in solution.

The standard reduction potential and equilibrium constants derived apply at 25 C. The temperature of fluids in the lung are rather higher: however, it is not likely that the conclusion will be altered. The temperature dependence of the equilibrium constant is given by the Gibbs-Helmholtz relationship:

$$\frac{\partial \ln K}{\partial T} = \frac{\Delta H}{RT^2}$$

Assuming that the heat of reaction is approximately constant over the temperature range from 25 C to the lung surface temperature this may be integrated to give:

$$\log_{10} K = \log_{10} K_{298} + \frac{\Delta H}{2.303R}\left(\frac{1}{298} - \frac{1}{T}\right)$$

For the reaction $BrO_3^- + 6H^+ + 6e^- \leftrightarrow Br^- + 3H_2O$, the heat of reaction can be calculated from the enthalpies of formation as shown in Table D.2.

Table D.2 Enthalpy of Bromate Formation

	Heat of formation, kJ mole^{-1}	Stoichiometric factor	Product kJ (mole bromate)$^{-1}$
Br^-	-121	1	-121
H_2O	-286	3	-858
H^+	0	-6	0
e^-	0	-6	0
BrO_3^-	-67	-1	67
Heat of reaction, kJ/mole			-912

For solution at 40C, the calculated value of $\log_{10}K$=146-912000/(2.303.8.3143).(1/298-1/313)=138.

The limiting value of pH+pe similarly decreases from 20.6 to 19.4. At this temperature, the predicted maximum bromate ion concentration is still only $10^{-138+6x19.4} = 10^{-21.9}$ of the bromide concentration.

Appendix E – 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
perivascular	near or around the ?
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	asame 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 F – 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 epidemiologic 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 epidemiologic 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.