

Department for Environment, Food and Rural Affairs,
Scottish Executive, National Assembly of Wales,
Department of the Environment in Northern Ireland

Expert Panel on Air Quality Standards

Guidelines for Halogens and Hydrogen Halides in Ambient Air for Protecting Human Health against Acute Irritancy Effects

Previous reports by the Expert Panel on Air Quality Standards (available on <http://www.defra.gov.uk/environment/airquality/aqs/index.htm>)

1st report	Benzene	February 1994	ISBN 011 752859 5
2nd report	Ozone	May 1994	ISBN 011 752873 0
3rd report	1,3-Butadiene	December 1994	ISBN 011 753034 4
4th report	Carbon Monoxide	December 1994	ISBN 011 753035 2
5th report	Sulphur Dioxide	September 1995	ISBN 011 753135 9
6th report	Particles	November 1995	ISBN 011 753199 5
7th report	Nitrogen Dioxide	December 1996	ISBN 011 753352 1
8th report	Lead	May 1998	ISBN 011 753447 1
9th report	Polycyclic Aromatic Hydrocarbons	July 1999	ISBN 011 753503 6
10th report	Airborne Particles	April 2001	ISBN 011 753599 0
11th report	Second Report on 1,3- Butadiene	February 2002	ISBN 0 85521 010 9

United Kingdom air quality information received from the automatic monitoring sites and forecasts may be accessed via the following media:

Freephone Helpline 0800 556677

TELETEXT page 156

Internet <http://www.airquality.co.uk>

<http://www.defra.gov.uk/environment/airquality/>

The cover photograph is reproduced by kind permission of Professor Stephen Holgate

Contents

Contents	iii
Terms of Reference	vi
Membership of the Panel	vii
Chairman	vii
Members	vii
Observers	viii
Assessors	viii
Secretariat	ix
Preface	x
Acknowledgments	xi
Introduction	1
1.1. Background to the report	1
1.1.1 Development of the report	2
1.1.2 How the Environment Agencies will use the guideline values	2
1.2. General issues	4
1.2.1 Exposure to multiple pollutants	4
1.2.2 Susceptible groups	6
1.2.3 Choice of averaging times and units of concentration	7
1.2.4 Safety factors	9
1.3. Introduction to the halogens and hydrogen halides	10
References	12
Chlorine	15
2.1. Background	15
2.1.1 Basic chemical information	15
2.1.2 Sources	15
2.1.3 Ambient levels	15
2.2. Health effects	15
2.2.1 Animal studies	16
2.2.2 Acute and subacute effects in humans	16
2.2.3 Carcinogenicity and effects on reproductive outcome	18
2.3. Justification for the air quality guideline value	18
2.4. Recommendation	19
References	19

Bromine	21
3.1. Background	21
3.1.1 Basic chemical information	21
3.1.2 Sources	21
3.1.3 Ambient levels	21
3.2. Health effects	22
3.2.1 Animal studies	22
3.2.2 Acute and subacute effects in humans	22
3.2.3 Carcinogenicity	24
3.3. Justification for the air quality guideline value	24
3.4. Recommendation	25
References	25
Hydrogen fluoride	27
4.1. Background	27
4.1.1 Basic chemical information	27
4.1.2 Sources	27
4.1.3 Ambient levels	27
4.2. Health effects	29
4.2.1 Animal studies	29
4.2.2 Acute effects in humans	30
4.2.3 Subacute effects in humans	30
4.2.4 Occupational exposure	31
4.2.5 Industrial accidents	31
4.2.6 Carcinogenicity	31
4.2.7 Evaluations and recommendations by other organisations	32
4.3. Justification for the air quality guideline value	32
4.4. Recommendation	33
References	33
Hydrogen chloride	37
5.1. Background	37
5.1.1 Basic chemical information	37
5.1.2 Sources	37
5.1.3 Ambient levels	37
5.2. Health effects	38
5.2.1 Animal studies	38
5.2.2 Acute and subacute effects in humans	39
5.2.3 Carcinogenicity	40
5.3. Justification for the air quality guideline value	40
5.4. Recommendation	40
References	41

Hydrogen bromide	43
6.1. Background	43
6.1.1 Basic chemical information	43
6.1.2 Sources	43
6.1.3 Ambient levels	43
6.2. Health effects	43
6.2.1 Animal studies	44
6.2.2 Acute effects in humans	45
6.2.3 Subacute effects in humans	45
6.2.4 Carcinogenicity	46
6.3. Justification for the air quality guideline value	46
6.4. Recommendation	47
References	47
Hydrogen iodide	49
7.1. Background	49
7.1.1 Basic chemical information	49
7.1.2 Sources	49
7.1.3 Ambient levels	49
7.2. Health effects	50
7.2.1 Animal studies	50
7.2.2 Effects in humans	50
7.3. Justification for the air quality guideline	51
7.4. Recommendation	52
References	52
Future research	53
Abbreviations	55
Glossary	57
Appendix 1: Children as a vulnerable group	67
A1.1 Background	67
A1.2: Lung growth and physiology	67
A1.3: Lung defences	68
A1.4: Models of exposure	69
A1.5: Summary	69
References	69
Appendix 2: Irritant-induced asthma and RADS	71
A2.1: Summary	71
A2.2: Terminology and definition	71
A2.3: Pathology	73
A2.3: Risk Factors	73
A2.5: Prognosis	74
A2.6: Summary	74
References	75
Appendix 3: Respondents to <i>Guidelines for Halogens and Hydrogen Halides in Ambient Air for Protecting Human Health against Acute Irritancy Effects – Draft for comment</i>	77

Terms of Reference

The Expert Panel on Air Quality Standards was established in 1991. The terms of reference of the Panel are:

"To advise the Secretary of State for Environment, Food and Rural Affairs, Scottish Ministers, the National Assembly for Wales and Department of the Environment (Northern Ireland) as required, on non-occupational ambient air quality standards, with particular reference to the levels of airborne pollutants at which no or minimal effects on human health are likely to occur;

i. taking account of the best available evidence of the effects of air pollution on human health and of progressive development of the air quality monitoring network; but

ii. without reference to the practicality of abatement or mitigation measures, the economic costs and economic benefits of pollution control measures or other factors pertinent to the management rather than the assessment of risk;

Where appropriate, for example for pollutants where no threshold for adverse effects can be determined, the Panel may wish to recommend exposure-response relationships or other information Government might use to set policy objectives.

to identify gaps in the knowledge needed for standard setting and suggest potential priority areas for future research;

to advise on other aspects of air quality and air pollution referred to it;

for the purpose of informing the development of policy on the improvement of air quality and increasing public knowledge and understanding of air quality issues."

EPAQS does not give approval for products or equipment.

Membership of the Panel

Chairman

Professor Stephen Holgate BSc, MD, DSc, FRCP, FRCPath, FRCPE, FIBiol,
FmedSci, FRSA
University of Southampton

Members

Professor H Ross Anderson MD, MSc, FFPH
St George's Hospital Medical School

Dr Peter Baxter MD, MSc, FRCP, FFOM
University of Cambridge

Dr Paul Cullinan MD, MSc, FRCP, FFOM
Imperial College (National Heart and Lung Institute)

Professor Dick Derwent OBE, MA, PhD
rdscientific

Dr Jonathan Grigg BSc, MD, MRCP, FRCPCH
University of Leicester

Professor Roy Harrison OBE, BSc, PhD, DSc, FRSC, CChem, FRMetS, Hon
MFPH, Hon FFOM
University of Birmingham

Professor Frank J Kelly BSc, PhD
King's College London

Dr Geoffrey H Pigott BSc, PhD
AH Marks & Co. Ltd

Dr Alison Searl BSc, MSc, PhD
Institute of Occupational Medicine, Edinburgh

Mr John Stedman BA
NETCEN (part of AEA Technology plc)

Ex officio member – Chairman of the Committee on the Medical Effects of Air Pollutants

Professor J G Ayres BSc, MD, FRCP, FRCPE, FFOM
University of Aberdeen

Ex officio members – Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

Professor Peter Blain, PhD
Newcastle University

Professor David Shuker BSc, ARCS, PhD, DIC, CChem, FRSC
Open University

Lay member

Ms Ann Davison BA

Observers

Mrs E Ball BSc, MSc
Health and Safety Executive

Ms Joan Forteath BEng, MSc, Mphil (Observer until September 2004)
Scottish Environment Protection Agency

Mr Colin Gillespie (Observer from September 2004)
Scottish Environment Protection Agency

Dr Colin Powlesland BSc, MSc, PhD
Environment Agency

Assessors

Mr Ronnie Alexander
Welsh Assembly Government

Dr A Branding PhD (Assessor until October 2004)
Scottish Executive

Ms Joan Forteath BEng, MSc, Mphil (Assessor from October 2004)
Scottish Executive

Mr Ivan Gregg
Department of the Environment in Northern Ireland

Secretariat

Ms Ingrid Holmes BSc, MSc (Secretariat from September 2004 to May 2005)
Department for Environment, Food and Rural Affairs

Dr Sarah Honour BSc, MSc, PhD
Department for Environment, Food and Rural Affairs

Professor R L Maynard CBE, BSc, MB, BCh, MRCP, FRCPath, FFOM
Department of Health

Dr Martin Meadows BSc, PhD, CBiol, MIBiol (Secretariat to February 2005)
Department for Environment, Food and Rural Affairs

Dr Heather Walton BSc, Dphil (Secretariat to February 2005)
Department of Health

Dr Martin Williams BSc, PhD, FRSA
Department for Environment, Food and Rural Affairs

Mr Tim Williamson BSc, MSc, MIScienv (Secretariat from February 2005)
Department for Environment, Food and Rural Affairs

Preface

The Expert Panel on Air Quality (EPAQS) has reviewed its role in light of the Royal Commission on Environmental Pollution's 21st report *Setting Environmental Standards*¹ and the growing practice of separating risk assessment from risk management. EPAQS' role is to advise on the impact levels of air pollution have on human health. Specifically, EPAQS' terms of reference are to advise on 'the level of airborne pollutants at which no or minimal effects on human health are likely to occur'. The risk management process is undertaken elsewhere. In particular, the Environment Agency uses EPAQS guideline values for minimal or no observable effects in its regulation to ensure that 'no significant pollution is caused'.

¹ RCEP (1998). *Setting Environmental Standards*. Twenty-first Report of the Royal Commission on Environmental Pollution. The Stationery Office, London.

Acknowledgments

We thank the following individuals and organisations for their help:

- Professor David Purser for his presentation and paper on *Irritancy, irritants and acid gases: effects and toxic mechanisms*;
- Professor John Widdicombe for his presentation on irritancy;
- Professor Judith Petts for her presentation on the public perception of risk from environmental pollutants;
- Dr Peter Coleman and Dr Reuben Mascarenhas for preparation of the dossiers; and
- Professor Raymond Agius (SWORD Database)

Chapter 1

Introduction

1.1. Background to the report

1. Previous reports by the Expert Panel on Air Quality Standards (EPAQS) have made recommendations to Government on non-occupational ambient air quality standards, with particular reference to the levels of airborne pollutants at which no or minimal effects on human health are likely to occur.
2. This report differs from previous reports in that the guideline values it recommends are not intended for use in national air pollutant standard setting. Instead, this report forms part of the Panel's current work programme in which it is advising the Environment Agency on some of the priority substances that it is responsible for regulating. Unlike the pollutants for which EPAQS has set air quality standards, these warrant special consideration for their emissions from a small number of point industrial sources and the guideline values are intended to protect local populations around these sites.
3. Scientists are often faced with a situation of uncertainty and this has been the case with EPAQS' assessments of the halogens and hydrogen halides. In recommending these guidelines there has been uncertainty both because the available data did not always apply to the actual chemical concerned and because the data were not usually obtained from the most susceptible groups of people (see Section 1.2.2 for a discussion of susceptible groups). In such cases, the Panel has divided the no observed adverse effect level (NOAEL) by a safety factor determined by the level of uncertainty (Renwick and Lazarus, 1998). This is in line with the precautionary approach favoured now in decisions concerning safety.
4. The guideline values recommended represent a level at which no significant health effects would be expected to occur over the short-term, specifically guarding against the effects of acute irritancy. They include a margin of safety so that slight exceedance would be unlikely to result in serious health effects. It should be noted, however, that for hydrogen fluoride and hydrogen iodide health effects resulting from longer-term exposure cannot be ruled out. EPAQS is currently investigating this issue and shall be producing an addendum to this report addressing the protection of human health over the long-term

against exposure to hydrogen fluoride and hydrogen iodide. The short-term guideline values are intended for use in the risk assessment of emissions arising from normal operating conditions. Separate guidelines are in place to deal with large releases during chemical incidents. Further information on the control and assessment of major accidental releases can be found on the Health and Safety Executive website at <http://www.hse.gov.uk/hid/index.htm>.

1.1.1 Development of the report

5. In order to facilitate the development of guideline values for a large number of compounds, the Environment Agency provided EPAQS with a peer-reviewed dossier on each of the substances under consideration. The dossiers included:
 - sources of the substance;
 - a summary of monitoring methods and UK ambient concentrations;
 - a review of relevant animal toxicity data;
 - a review and preliminary evaluation of existing literature on human toxicology and health effects; and
 - where possible, the identification of no observed (adverse) effect levels.

These dossiers have been published as Environment Agency Research and Development Reports and are available on the Agency publications website (<http://publications.environment-agency.gov.uk>).

6. EPAQS used the dossiers to provide background information and as an aid to identifying the key studies on which to base their recommendations. When appropriate, members of the Panel went back to the original papers and supplemented these with additional research of their own. Air quality guideline values were reached through reviewing the available literature and the application of expert judgement.
7. For the selected halogens and hydrogen halides included in this report the number of reliable human studies that have been performed are few and so safety factors, in a range of two to ten, have been used to reflect both the uncertainty in extrapolating the data to the general population, which contains susceptible groups, and the confidence of the Panel in the scientific information available on which to base its judgements.

1.1.2 How the Environment Agencies will use the guideline values

8. The Integrated Pollution Prevention and Control Directive applies an integrated environmental approach to regulating industrial emissions from specified installations. This has been implemented in the UK through the Pollution Prevention and Control Regime.
9. When the Pollution Prevention and Control Regime is fully implemented, the Environment Agency will regulate approximately 4,000 of the potentially most complex and polluting industrial installations in England and Wales with many smaller installations

being regulated by local authorities. The situation is slightly different in Scotland where the regulator, the Scottish Environment Protection Agency, regulates all installations covered by the regime. The Northern Ireland Environment and Heritage Service is the environmental regulator for Northern Ireland.

10. The Pollution Prevention and Control Regime requires the regulator to ensure that ‘no significant pollution is caused’ and that conditions are included in the permit, subject to the application of the Best Available Techniques (BATs) that:
 - ensure a high level of protection for the environment as a whole;
 - have regard to the potential to transfer pollution from one environmental medium to another;
 - take account of an installation’s geographical location and local environmental conditions;
 - are aimed at minimising long distance and transboundary pollution;
 - ensure appropriate protection of the soil and groundwater.
11. To gain a permit, operators will have to show that their proposals represent the BAT to prevent and minimise pollution from their installation. In order to assess the environmental impact of an installation or identify the BAT from a range of options, the Environment Agency in conjunction with the Scottish Environment Protection Agency and the Environment and Heritage Service is developing an assessment methodology known as H1: Guidance on Environmental Assessment and Appraisal of BAT. Operators are not required to use the methodology when making their application for a permit but it does provide a structured assessment process which addresses the specific requirements of the Pollution Prevention and Control Regime. Operators using an alternative approach would need to ensure that an equivalent level of assessment is made.
12. The H1 methodology consists of the following basic steps:
 - Define the objective and scope of assessment.
 - Generate options of techniques to control pollution.
 - Assess the environmental impacts of each option.
 - Evaluate the costs to implement each option.
 - Identify the option which represents the best available technique.
13. Environmental criteria are used within H1 primarily to:
 - assess the significance of releases to different environmental media and to screen out insignificant effects;
 - assess the relative effects of releases within and between different environmental media.
14. However, there are relatively few established environmental criteria that are suitable for use within the assessment methodology. For example, EPAQS have published standards for nine of the major air pollutants and the World Health Organization has set guideline values for 14 organic and 15 inorganic pollutants, including some for which standards have also been set by EPAQS. Overall, recognised air quality standards

are available for only approximately 31 different substances. This is to be compared with the 129 agents that are reported as being released to the air from industrial installations on the Environment Agency's Pollution Inventory and on the Scottish Environment Protection Agency's Scottish Pollutant Release Inventory.

15. In order to fulfil its regulatory role, the Environment Agency has developed environmental criteria known as *environmental assessment levels* (EALs) for different environmental media (air, water and land) for use within the H1 framework. A hierarchical approach has been used to develop EALs. For air, existing standards and guidelines are used as EALs; however, as there are only a limited number of appropriate values, EALs for most substances have been derived from occupational exposure values by the application of a simple safety factor (Environment Agency, 2003). The air quality guidelines proposed in this report by EPAQS will replace these less robust values for use within the H1 methodology.

1.2. General issues

1.2.1 Exposure to multiple pollutants

16. Individual industrial processes may release a wide variety of pollutants, which can include a number of the halides considered in this report. The principle hydrogen halide released is hydrogen chloride, which arises mainly from the burning of fossil fuels, especially the combustion of coal or oil. Since fossil fuels also contain trace amounts of the other hydrogen halides (hydrogen bromide, hydrogen fluoride and hydrogen iodide) these will be released in smaller quantities at the same time. Table 1.1 shows the releases of halogens and hydrogen halides by different industrial sectors as reported by the Environment Agency's Pollution Inventory in 2002.

Table 1.1 Releases of halogens and hydrogen halides from industry sectors reported in the Environment Agency's Pollution Inventory for 2002. (Data are for processes regulated under Integrated Pollution Control or Pollution Prevention Control by the Environment Agency in England and Wales. Nd indicates no data.)

Industry	Bromine ¹ (tonnes)	Chlorine ¹ (tonnes)	Hydrogen bromide ¹ (tonnes)	Hydrogen chloride ² (tonnes)	Hydrogen fluoride ² (tonnes)	Hydrogen iodide ¹ (tonnes)
Fuel and power production and associated processes	Nd	Nd	693	31710	2236	152
Metal production and processing	Nd	1.8	<0.1	586	237	Nd
Mineral industries	Nd	Nd	9.9	408	158	Nd
The chemical industry	0.7	26	0.2	63	<0.1	Nd
Waste disposal and recycling	Nd	<0.1	<0.1	146	<0.1	Nd
Other industry	Nd	Nd	Nd	Nd	73	Nd
Total (tonnes)	0.7	27.8	704	32914	2704	152

¹Substance reported where release greater than one tonne per year or as required by the Environment Agency. Totals may underestimate actual release.

²Substance required to be reported by all operators.

17. In addition to hydrogen chloride from combustion processes, some installations will release one or more hydrogen halides from other processes or activities being undertaken on the site. For example, hydrogen fluoride is emitted from some aluminium smelters and ceramic processes and chlorine from a range of chemical processes, such as the manufacture of organic chemicals. Typically, however, releases are dominated by combustion-derived hydrogen chloride and process releases are generally small by comparison.
18. In this report, the effects of individual pollutants have been considered separately. However, the Panel recognises that ambient air that includes localities around an industrial plant contains a complex mixture of pollutants at differing concentrations. The effects of exposure to more than one pollutant may be additive (i.e., the sum of the individual pollutant effects), synergistic (i.e., greater than the sum of the individual pollutant effects) or antagonistic (i.e., less than the sum of the individual pollutant effects).
19. There is a paucity of information on the effects of complex mixtures of pollutants. Whether effects are additive, synergistic or antagonistic will depend on the pollutants involved, their likely mechanisms of effect and their concentrations.
20. The issue of the health effects of exposure to mixtures of air pollutants was considered by the Advisory Group on the Medical Effects of Air Pollutants in their Fourth Report in 1995 (MAAPE, 1995). They recommended caution when considering the effects of exposure to more than one pollutant and pointed out that the level of understanding of the mechanisms of possible interactive effects is even less well developed than the understanding of the mechanisms underlying the health effects of individual pollutants. For all the halogens and hydrogen halides, the prominent effect at low concentration is irritation. Thus it is likely that exposure to mixtures of these substances will be additive. The effects of mixtures of other pollutants with halogen and hydrogen halide gases is unknown and synergistic effects in some instances can't be ruled out.
21. This report deals with the direct effects of chemicals on health but the Panel recognises that there may also be interactions with biological components in the air. This is an area that requires further research.

1.2.2 Susceptible groups

22. Studies examining the impact of ambient air pollution have identified a wide range of sensitivities within the population. Certain individuals appear to be sensitive to pollution for genetic reasons, whereas others become vulnerable as a result of environmental or social factors. For example, socio-economic status has been shown to modify the effects of ambient air pollution associated with asthma hospitalisations (Lin *et al.*, 2003). These variations within the human population mean that individuals are likely to fall somewhere along a continuum of susceptibility. However, most safety factors are not based on strong scientific evidence nor are they necessarily accurate predictors of

outcomes. They merely attempt to allow for all perceived possibilities and compensate for a lack of knowledge (RCEP, 2003).

23. Age has been identified as a strong predictor of susceptibility to pollution. Young children and the elderly are considered to be more at risk from respiratory (breathing) and cardiopulmonary (heart and lung) disease associated with exposure to air pollution (Burnett *et al.*, 1997; Sunyer *et al.*, 2003). The specific issue of the greater susceptibility of children is dealt with in more detail in Appendix 1. A precautionary approach is widely adopted for very young children.
24. Subgroups of the population who acquire increased sensitivity to pollution include those with existing cardiovascular and respiratory disease.
25. It should be noted that susceptible groups are less frequently used either in chamber studies or in occupational assessments – further appropriate research into the health effects of air pollutants on such groups would be desirable.

1.2.3 Choice of averaging times and units of concentration

26. Chamber studies are conducted at concentrations that are held constant for their duration, often for several hours and sometimes with the subject undertaking exercise. Ambient exposures, on the other hand, are generally more variable, a fluctuation that is seldom reflected in average measurements. The adverse effects of halogens and their hydrogen halides are largely irritant and are thought to depend on peak concentrations. For these reasons it is preferable to measure exposures over short periods in order to capture any transient but significant peaks. However, for chemicals present at low levels, very short collection periods are not technically feasible as they may yield insufficient material for analysis. When recommending time periods for the guideline values the Panel has balanced these factors. It is considered that an averaging time of 1 hour is the lowest that is technically feasible for the guideline values proposed.

27. Concentrations of pollutants in air can be expressed in two ways: as the mass of pollutant per unit volume of air (expressed in this report as mg/m^3) or as the ratio of the volume of the pollutant to the volume of air in which it is contained (expressed in this report as parts per million or ppm). A more detailed explanation of these units is given in Box 1. In this report we have used the volume mixing ratio as the main unit of concentration. This is the appropriate unit to use if the toxicities of different gases, at different concentrations, are to be compared: the comparative toxic effects being dependent on the relative toxicological properties of the molecules and on the numbers present, but not on the masses of those molecules.

Box 1: Units used to express the concentration of gases in air

Concentrations of gases in air are expressed in two ways:

1. As the mass of gas in a specified volume of air, usually expressed as mg (one thousandth of a gram) or μg (one millionth of a gram) per cubic metre and generally written as mg/m^3 or $\mu\text{g/m}^3$.
2. As the ratio of the volume of the gas to the volume of air in which the gas is contained, usually expressed as a volume mixing ratio, that is parts per million (ppm) or parts per billion (ppb).

The mass concentration as expressed above will be dependent on the ambient temperature and pressure. The volume mixing ratio is independent of temperature and pressure, if ideal gas behaviour is assumed. The two systems of units are interchangeable.

Given that 1 mole of gas occupies 22.41 litres (l) at standard temperature and pressure (STP), and letting the gram molecular weight of the gas in question equal M,

$$1 \text{ mol} = M \text{ grams occupies } 22.41 \text{ l at STP}$$

Therefore, $1 \text{ mg occupies } \frac{22.41}{M} \div 1000 \text{ l} = \frac{22.41}{M} \text{ ml}$

As $1 \text{ ppm} = 1 \text{ ml/m}^3$

$$1 \text{ ppm} = \frac{M}{22.41} \text{ mg/m}^3$$

or $1 \text{ mg/m}^3 = \frac{22.41}{M} \text{ ppm}$

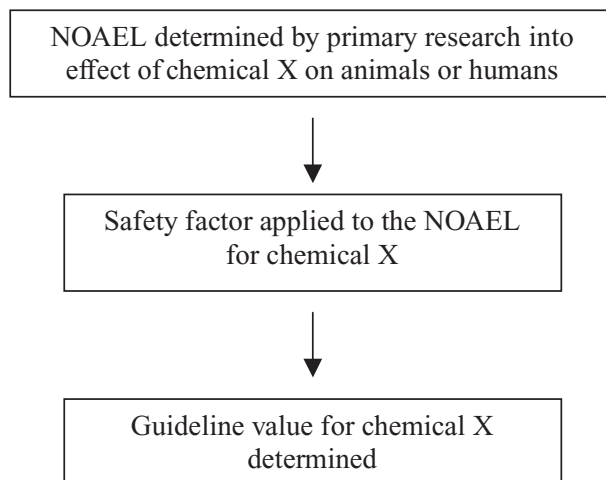
If ambient conditions of temperature and pressure need to be considered then the molar volume (22.41 l at STP) must be corrected:

$$\text{Molar volume at } T^\circ\text{C and } P \text{ millibars} = 22.41 \times \frac{273 + T}{273} \times \frac{1013}{P}$$

1.2.4 Safety factors

28. In its derivation of air quality guidelines, EPAQS has used the steps shown in Figure 1.1. It has taken account of the presence of susceptible groups in the general population by applying safety factors to the available human data. The values of the safety factors also incorporate the uncertainty of determining the no observed or lowest observed adverse effect levels (LOAEL) when the human data are sparse or inadequate. Justification of the safety factors adopted is given in respect of each individual compound in the specific sections. The basic rationale can be readily explained through the hydrogen halides. Hydrogen chloride proved to be the best starting point for the halide gases and a safety factor of 2 for this gas was applied by analogy with the method adopted by EPAQS in recommending the air quality standard for sulphur dioxide, another irritant acidic gas for which there is much more human data. Thus, a no observed adverse effect level (NOAEL) in subjects with mild asthma was considered to be 1 ppm for hydrogen chloride. The same starting value was assigned to hydrogen bromide because its irritant properties on the human lung were considered to be very similar to those of hydrogen chloride. Nevertheless, a higher safety factor of 5 reflected the uncertainty the Panel had because of the deficiency of human exposure data on hydrogen bromide itself. For hydrogen iodide a safety factor of 10 was used to reflect the uncertainty caused by the virtual absence of reliable human data on its irritant properties at low concentrations and because it has the potential to be a greater irritant at molar equivalent concentrations than hydrogen chloride is. The safety factors are summarised in Table 1.2.

Figure 1.1 Sequence of steps taken to arrive at a guideline value for a particular chemical pollutant.



29. In most instances, the information available on ambiguous, subjective reports of ‘irritation’ and odour detection was not regarded by the Panel to be sufficiently reliable or robust to be included. The exception was hydrogen fluoride in the one human exposure study in which symptoms of irritation of the upper and lower respiratory tract, as well as eye irritation, had been shown to be more reliable study endpoints for exposure to low concentrations of this gas (Lund *et al.*, 1997).

Table 1.2 Summary of safety factors used in arriving at the guideline value, averaged over a 1-hour time period, for each halogen and hydrogen halide.

Substance	NOAEL	Normal volunteers used ?	Volunteers with asthma used?	Safety factor	Guideline value (1-hour average) ¹
Chlorine	0.5 ppm	Y	Y	5	0.1 ppm (0.29 mg/m ³)
Bromine	0.05 ppm	Y	N	10	0.01ppm (0.07 mg/m ³)
Hydrogen fluoride	1 ppm	Y	N	5	0.2 ppm (0.16 mg/m ³)
Hydrogen chloride	1 ppm	Y	Y	2	0.5 ppm (0.75 mg/m ³)
Hydrogen bromide ²	1 ppm	Y	N	5	0.2 ppm (0.70 mg/m ³)
Hydrogen iodide ²	1 ppm	Y	N	10	0.1 ppm (0.52 mg/m ³)

¹See Box 1 for an explanation of the units of concentration.

²Hydrogen chloride was used as a starting point for determining the guideline value.

1.3. Introduction to the halogens and hydrogen halides

30. In this report EPAQS recommend air quality guideline values for six halogens and hydrogen halides: chlorine (Cl₂), bromine (Br₂), hydrogen chloride (HCl), hydrogen bromide (HBr), hydrogen fluoride (HF) and hydrogen iodide (HI). Some of these compounds are among the substances most frequently encountered by the Environment Agency in ambient air around industrial activities that do not currently have robust EALs. This group was therefore selected to be the first considered by EPAQS.
31. The halogens (fluorine, chlorine, bromine, and iodine) are a coherent series of elements with similar chemistry. Molecular weight increases from fluorine to iodine and chemical reactivity shows a downward trend with molecular weight. The lower atomic weight (and thus size) of fluorine and chlorine mean that these bind tightly within organic molecules and are difficult to displace, so chemical compounds of these halogens can be persistent. In contrast, bromine and iodine are more readily displaced and thus their compounds are generally less biopersistent. In terms of their reaction products with water, acid

strength increases from fluorine to iodine, but the oxidising strength of the hypo-halous acids also formed decreases, that is, hypochlorite is a stronger oxidising agent than hypobromite.

32. Because of the similar chemical properties of halogens and hydrogen halides, as well as the fact that a number of them have common sources, it is useful to consider them together. However, individual air quality guideline values have been derived on a substance-by-substance basis. For a number of compounds – in particular hydrogen iodide – where the literature on the health effects is sparse or non-existent, effects have been inferred from other similar substances being considered.
33. The halogens and hydrogen halides share the common property of irritancy to mucous membranes (the moist lining of airways). These irritant effects arise from the fact that these substances behave as strong acids in aqueous (water) media, i.e. they dissociate forming high concentrations of hydrogen ions that cause irritation. In the respiratory (breathing) tract the extent to which this impacts on symptoms largely depends upon their deposition in the nose or lung. Sensory irritant potency is particularly dependent upon the nature and specificity of interactions between the substance and irritant nerve receptors. The irritant potency depends upon a range of properties related to reactions at the site of deposition, physical properties such as aqueous (water) and lipid (fat) solubility and reactions with other tissue components that may compete with receptor stimulation (that is reactions that take place before the substance can cause irritation). Acid gases rarely exist in a pure gaseous state, but in a form that is partitioned between the gas and aqueous phases. They can also be adsorbed onto the surface of solid particles. These physical properties determine their bioavailability and thus the irritant outcomes of inhaling such gases. The studies used to inform current air quality guidelines have been based on exposure to substances in the gaseous phase. There is uncertainty surrounding their actual health effects. This needs to be taken into account when safety factors are chosen.
34. In 1998 the Health and Safety Commission's Advisory Committee on Toxic Substances (WATCH Panel) discussed the European Union criteria for classifying substances as respiratory tract sensory irritants (WATCH Panel, unpublished). It considered that ambiguous, subjective reports of 'irritation' that were not further qualified do not provide reliable evidence of the irritant potential of a chemical because the term 'irritation' can be used to describe a wide range of sensations including smell, unpleasant taste, 'tickling sensation' and dryness. Thus in reviewing its criteria for the European Union classification scheme for the supply of substances and preparations, the WATCH Panel considered that ambiguous, subjective reports of 'irritation' should be excluded, an approach that EPAQS has also adopted.
35. While acidity accounts for a high proportion of the irritancy of halides and hydrogen halides, the chemical nature of the reactive base may also contribute to stimulation of nerve receptors in the airways. This triggers subjective sensations such as cough, chest tightness and breathlessness and also reflex responses that can provoke bronchoconstriction,

increased mucus secretion and vascular engorgement, all of which may contribute to symptoms. In the case of more severe sensory irritancy involving the respiratory tract, subjective symptoms usually precede bronchoconstriction (constriction of the large air passages that lead to the lungs) and nasal obstruction.

36. There is limited information available concerning ambient concentrations of the halogens and hydrogen halides in the United Kingdom. The only reported ambient concentration data currently available from monitoring air quality are monthly mean concentrations for a small number of rural locations for hydrogen chloride and hydrogen fluoride. There are no short-term data – for example, at the 1-hour averaging period – for any of these substances and no reported data with which to assess population exposures.

References

Burnett, R.T., Dales, R.E., Brook, J.R., Raizenne, M.E., Krewski, D. (1997). Association between ambient carbon monoxide levels and hospitalizations for congestive heart failure in the elderly in 10 Canadian cities. *Epidemiology* **8**,162–167.

Environment Agency (2003). Integrated Pollution Prevention and Control. Environmental Assessment and Appraisal of BAT: Horizontal Guidance Note H1. Draft July 2003.

Lin, M., Chen, Y., Burnett, R.T., Villeneuve, P.J., Krewski, D. (2003). Effect of short-term exposure to gaseous pollution on asthma hospitalization in children: a bi-directional case-crossover analysis. *Journal of Epidemiology and Community Health* **57**, 50-55.

Lund, K., Ekstrand, K., Boe, J., Sosstrand, P., Kongerud, J. (1997). Exposure to hydrogen fluoride: an experimental study in humans of concentrations of fluoride in plasma, symptoms and lung function. *Occ. Environ. Med.* **54**, 32–37.

MAAPE (1995). Health Effects of Exposures to Mixtures of Air Pollutants. Fourth report of the Advisory group on the Medical Aspects of Air Pollution Episodes. HMSO, London.

RCEP (2003). *Chemicals in Products: Safeguarding the environment and human health*. Twenty-fourth Report of the Royal Commission on Environmental Pollution. The Stationery Office, London.

Renwick, A.G. and Lazarus, N.R. (1998). Human variability and noncancer risk assessment – an analysis of the default uncertainty factor. *Regulat. Toxicol. Pharmacol.* **27**, 3–20.

Sunyer, J., Atkinson, R., Ballester, F., Le Tertre, A., Ayres, J.G., Forastiere, F., Forsberg, B., Vonk, J.M., Bisanti, L., Anderson, R.H., Schwartz, J. and

Katsouyanni, K. (2003). Respiratory effects of sulphur dioxide: a hierarchical multicity analysis in the APHEA 2 study. *Occup. Environ. Med.* **60**, 2.

WATCH Panel. Discussion paper reference number WATCH/4/98/Rev.
Copies are available on request from Mrs E. Ball at
elanor.ball@hse.gsi.gov.uk.

Chapter 2

Chlorine

2.1. Background

2.1.1 Basic chemical information

37. Chlorine (Cl₂) is a greenish-yellow gas with a very pungent odour, which is readily detectable at low concentrations in the air. It is 2.47-times denser than air.

Conversion factors at 25°C:

$$1 \text{ ppm} = 2.90 \text{ mg/m}^3; 1 \text{ mg/m}^3 = 0.34 \text{ ppm}$$

2.1.2 Sources

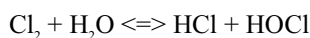
38. Releases of chlorine to air are not estimated by the National Atmospheric Emission Inventory and reporting is only required by the Environment Agency where the release is greater than one tonne per annum or as a specific permit condition. From the limited information available, the major source is the chemical industry, with a small amount arising from the metals industry.

2.1.3 Ambient levels

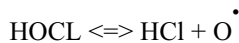
39. There are no reported air quality data for chlorine with which to assess population exposures.

2.2. Health effects

40. The mechanism of action of chlorine lies in two different free radical pathways. The first of these involves the action of the chlorine atom, which is itself a free radical; when released it reacts with other molecules to oxidise them. The second pathway is via the indirect generation of reactive oxygen species. On entering the respiratory (breathing) tract, chlorine reacts with water forming hydrochloric acid (HCl) and hypochlorous acid (HOCl).



Hypochlorous acid is a strong oxidising agent and on dissolution it releases hydrochloric acid and reactive oxygen species.



These react with the surrounding tissue components causing oxidative changes that lead to the generation of pro-inflammatory signals and the initiation of an inflammatory response in the airways. The hydrochloric acid then acts as a secondary irritant (Wolf *et al.*, 1995).

2.2.1 Animal studies

41. Chlorine is acutely toxic with LC_{50}^2 values of 700 ppm (2030 mg/m^3) in rats and 500 ppm (1450 mg/m^3) in mice for a 30-minute exposure (Zwart and Woutersen, 1988). A two-year inhalation exposure study of female and male mice and rats found chlorine-induced changes in the cells lining the nasal passages (hyperplasia) in all sex and species groups, including those exposed to the lowest concentration at 0.4 ppm (1.16 mg/m^3). This figure may be regarded as a lowest observed adverse effects level (LOAEL) for upper respiratory tract irritation, but it is not known whether this value is directly applicable to human subpopulations exposed for short periods.

2.2.2 Acute and subacute effects in humans

42. The most important consequence of exposure to chlorine gas relates to its strong irritant action when in contact with the moist mucous membranes (linings) of the respiratory tract and, to a lesser extent, the eyes and the skin. As it is only moderately soluble in water, following inhalation the gas is incompletely extracted in the nose and upper respiratory tract and so can exert a direct toxic effect on the lungs. At high concentrations – as may be encountered in accidental inhalation exposures in industry or when the gas was used in chemical warfare in World War I – a potentially lethal chemical-induced lung injury, toxic pneumonitis (inflammation of the lungs), can occur. As a bulk commercial chemical, chlorine is the commonest toxic gas for which emergency planning is required under major accident hazard regulations (Baxter *et al.*, 1989; COMAH, 1999). Between 1989 and 2003, 228 occupational inhalation accidents involving chlorine were reported to the SWORD database in the United Kingdom and of these 69 (16%) were estimated to have led to reactive airways dysfunction syndrome (RADS), a form of irritant-induced asthma (see Appendix 2). The exposures involved, however, are far higher than those encountered in ordinary ambient conditions.
43. Minimal and rapidly reversible changes in a range of lung function parameters were observed in a study of eight healthy volunteers who were exposed to 1 ppm (2.9 mg/m^3) of chlorine gas for up to eight hours (Rotman *et al.*, 1983). Symptoms of itchy eyes, runny nose and mild burning of the throat were also found. An 8-hour exposure to 0.5 ppm

² LC_{50} is that concentration lethal to 50% of those exposed of the stated time.

- (1.45 mg/m³) produced no changes in lung function and no significant symptoms of sensory irritation (Rotman *et al.*, 1983). However, one sensitive volunteer in this study did suffer an asthmatic attack from exposure to 1 ppm (2.9 mg/m³) chlorine and left the exposure chamber after four hours.
44. A study at the TNO Nutrition and Food Research Institute of the nasal and respiratory effects of chlorine was undertaken with eight male volunteers exposed to 0, 0.1, 0.3 and 0.5 ppm (0, 0.29, 0.87 and 1.45 mg/m³) for six hours per day on three consecutive days to each of four exposure conditions spaced 11 days apart. Measurements were made of lung function and nasal lavage (nose washings) parameters. The results did not reveal an inflammatory effect in the nose nor did they show a consistent effect on respiratory function at repeated exposure up to 0.5 ppm (1.45 mg/m³) (Emmen *et al.*, 1997).
 45. It is clearly established that individuals with pre-existing non-specific airway hyper-responsiveness, with and without clinical asthma, can be more adversely affected by inhaled irritant substances such as sulphur dioxide. To determine the responses to chlorine in this susceptible group, D'Alessandro *et al.* (1996) exposed ten healthy volunteers to low levels of chlorine gas and the effect on their lung function was measured. Five volunteers had, and five did not have, baseline airway hyper-responsiveness as defined by baseline methacholine challenge testing (that is exaggerated constriction of the airways in response to stimuli, tested by inhaling methacholine). After exposure to 1 ppm of chlorine for 60 minutes both groups experienced a temporary fall in lung function (as FEV1 - forced expiratory volume in 1 second), which was greater in those with methacholine hyper-responsiveness. However, after exposure to 0.4 ppm (1.16 mg/m³) of chlorine there was no significant fall in lung function in either group (D'Alessandro *et al.*, 1996).
 46. In a nasal provocation study by Shusterman *et al.* (1998) involving eight volunteers in each of two groups that were either normal or had seasonal allergic rhinitis (hay fever), those with rhinitis had a greater increase in nasal airway resistance than the non-rhinitic subjects. The concentration of chlorine gas was 0.5 ppm (1.45 mg/m³) and exposure lasted for 15 minutes. Individuals identified as having asthma were excluded. There were no clinically significant changes in peak expiratory flow (exhalation), whereas both nasal irritation and nasal congestion were reported more frequently in the subjects with rhinitis.
 47. There have been no published studies undertaken on the effects of low levels of chlorine on people with asthma, but anecdotally such exposures are widely considered to acutely aggravate their condition.
 48. Few epidemiological studies have been undertaken in industry that can be used to correlate low-level exposures to chlorine with chronic (irreversible) lung disease developing at low-level industrial exposures. Wide variations in exposure, potential confounding effects of previous exposures to chlorine and/or other chemicals and lack of information on

smoking habits make it difficult to correlate exposure with potential effect (NIOSH, 1976).

49. Other acute accidental exposures can occur at home or inside buildings during domestic cleaning with chlorine-releasing agents. The concentrations of chlorine in the air to which individuals are exposed are usually unknown. However, a recent study (Medina-Ramón *et al.*, 2005) showed that cleaners with respiratory symptoms were more likely than those without to have used bleach regularly with a dose response relationship. Airborne chlorine levels during cleaning activities for ten of the cleaners ranged from unrecordable to 0.4ppm although shorter-lived peaks to 1.3 ppm (3.77 mg/m³) were recorded. Chlorine-releasing agents are also commonly used as disinfectants for swimming pools, but clinically significant levels of chlorine are unlikely to be present in the atmosphere. Asthmatic responses because of swimming pools are more likely to be due to chloramines (chemical compounds of chlorine and nitrogen), in particular NCl₃, that are produced by chlorine reacting rapidly with body secretions and excretions (Thickett *et al.*, 2002).
50. The Health and Safety Commission (HSE, 2002a,b) has set occupational exposure limits of 1 ppm (2.9 mg/m³) (as a 15-minute time-weighted average) and 0.5 ppm (1.5 mg/m³) (as an 8-hour time-weighted average) based on the lung function data of Rotman *et al.*, (1983) (HSE, 1993; 2002a,b). This evidence was considered to be more objective than the reports of 'irritation' described elsewhere.

2.2.3 Carcinogenicity and effects on reproductive outcome

51. Published studies give no evidence that chlorine vapour is carcinogenic in mice or rats (Wolf *et al.*, 1995). IARC (The International Agency for Research on Cancer) concluded that there was no substantive evidence for carcinogenicity of chlorine in drinking water in either humans or animals (group 3 unclassifiable IARC 1991). There is insufficient evidence available to determine whether there is an effect of chlorine vapour on reproductive outcomes.

2.3. Justification for the air quality guideline value

52. Chlorine has an acute irritant effect on the airways and as a consequence the Panel recommends a short averaging exposure time, similar to the approach taken for sulphur dioxide. The Panel considered that for irritant or potential inflammatory effects on the upper and lower respiratory tract, a concentration of 0.5 ppm (1.45 mg/m³) over 6 to 8 hours was acceptable as a no observed adverse effect level (NOAEL) in fit volunteers and in subjects with a degree of pre-existing airway hyper-responsiveness. To take into account the more susceptible members of the general population, in particular those with asthma who may be particularly sensitive to exposure to chlorine gas, a safety factor of 5 was chosen, which allows for the irritant effects on the upper and lower respiratory tract. This factor should also be protective in subjects

with seasonal allergic rhinitis who may also be particularly sensitive to the adverse effects of chlorine gas on the lining of the nasal passages.

53. The Panel considered that there were no grounds for regarding chlorine as a human carcinogen.

2.4. Recommendation

54. **The Panel recommends that a concentration of chlorine gas or mass equivalent aerosol not exceeding 0.1 ppm (0.29 mg/m³) over a 1-hour averaging period should protect against irritant and inflammatory effects on the skin, eye and breathing airways. Long-term effects at these low concentrations are considered most unlikely.**

References

Baxter, P.J., Davies, P.C., Murray, V. (1989). Medical planning for toxic releases into the community: the example of chlorine gas. *Brit. J. Ind. Med.* **46**, 277–285.

COMAH (1999). *The Control of Major Accident Hazard Regulations*. Health & Safety Executive. Available from: <http://www.hse.gov.uk/comah/background/comah99.htm>.

D'Alessandro, A., Kuschner, W., Wong, H., Boushey, H.A., Blanc, P.D. (1996). Exaggerated responses to chlorine inhalation among persons with nonspecific airway hyperreactivity. *Chest* **109**, 331–337.

Emmen, H.H., Hoogendijk, E.M.G., Borm, P.J.A., Schins, R. (1997). *Nasal Inflammatory and Respiratory Parameters in Human Volunteers During and After Repeated Exposure to Chlorine*. TNO Report V97.517. TNO Food and Research Institute, Zeist, The Netherlands.

HSE (2002a). Occupational exposure limits. EH40/2002. HSE Books, Norwich.

HSE (2002b). Summary Criteria for Occupational Exposure Limits, EH64/D12. Hydrogen chloride. HSE Books, Norwich.

IARC (1991). Overall evaluations of carcinogenicity to humans: Chlorine in water. *IARC Monogr.* **52**.

Medina-Ramón, M., Zock, J.P., Kogevinas, M., Sunyer, J., Torralba, Y., Borrell, A., Burgos, F., Antó, J.M. (2005). Asthma, chronic bronchitis and exposure to irritant agents in occupational domestic cleaning: a nested case control study. *Occup. Environ. Med.*; **62**, 598-606.

NIOSH (1976). *Criteria for a Recommended Standard. Occupational Exposure to Chlorine*. US Dept. of Health Education and Welfare, Public Health Service, Washington DC USA.

Rotman, H.H., Fliegelman, M.J., Moore, T. (1983). Effects of low concentrations of chlorine on pulmonary function in humans. *J. Appl. Physiol.* **54**, 1120–1124.

Shusterman, D.J., Murphy, M.A., Balmes, J.R. (1998). Subjects with seasonal allergic rhinitis and nonrhinitic subjects react differentially to nasal provocation with chlorine gas. *J. Allergy Clin. Immunol.* **101**, 732–740.

Thickett, K.M., McCoach, J.S., Gerber, J.M., Sadra, S., Burge, P.S. (2002). Occupational asthma caused by chloramines in indoor swimming-pool air. *Eur. Resp. J.* **19**, 790–793.

Wolf, D.C., Morgan, K.T., Gross, E.A., Barrow, C., Moss, O.R., James, R.A., Popp, J.A. (1995). Two-year inhalation exposure of female and male B6C3F1 mice and F344 rats to chlorine gas induces lesions confined to the nose. *Fund. Appl. Toxicol.* **24**, 111–131.

Zwart, A. and Wouterson, R.A. (1988). Acute inhalation toxicity of chlorine in rats and mice: time-concentration-mortality relationships and effects on respiration. *J. Haz. Mat.* **19**, 195–208.

Chapter 3

Bromine

3.1. Background

3.1.1 Basic chemical information

55. Bromine (Br_2) is a reddish-brown liquid at room temperature. Bromine has a high vapour pressure (175 mmHg at 20°C) and has a pungent odour. Bromine is highly reactive and water soluble (3.5 g/100 ml), producing a mixture of hypobromous (HOBr) and hydrobromic (HBr) acids. Under some conditions a proportion of bromic acid (HBrO_3) can also be formed, but this reaction has little or no relevance for dissolution of bromine in the presence of organic matrices.

Conversion factors at 25°C and 101 kPa

$$1 \text{ ppm} = 6.6 \text{ mg/m}^3; 1 \text{ mg/m}^3 = 0.15 \text{ ppm}$$

3.1.2 Sources

56. Releases of bromine to air are not estimated by the National Atmospheric Emission Inventory and reporting is only required by the Environment Agency where the release is greater than one tonne per annum or as a specific permit condition. From the limited information available the largest point sources appear to be those at which bromine is used in chemical manufacturing. However, the total declared release was less than one tonne in 2002.

3.1.3 Ambient levels

57. No measurements of ambient bromine levels have been reported in the United Kingdom. Measurements are not made regularly around the one production plant in the United Kingdom.

3.2. Health effects

58. The Panel considered animal studies involving exposure to bromine vapour and human studies of acute exposures (including one study of an accidental industrial release in an urban area) and chronic occupational exposures.

3.2.1 Animal studies

59. Bromine is acutely toxic with an LC_{50}^3 (observed up to 30 days after the end of exposure) observed in male albino mice following 9-minute exposures to 750 ppm (4950 mg/m^3) and 100-minute exposures to 240 ppm (1584 mg/m^3) (Bitron and Aharonson, 1978). Post mortem examinations conducted on guinea pigs and rabbits after exposure to bromine vapour at 300 ppm (1980 mg/m^3) for three hours revealed evidence of pulmonary oedema (fluid in the lungs), with deposits on the surface of the upper airways and bleeding from the stomach lining (Perry *et al.*, 1994).
60. Rats, mice and rabbits inhaling 0.2 ppm (1.3 mg/m^3) of bromine for four months developed disturbances in the respiratory (breathing), nervous and endocrine (hormone) systems. However, no adverse effects were observed after four months at 0.02 ppm (0.13 mg/m^3) (NRC, 1981).

3.2.2 Acute and subacute effects in humans

61. Initial irritant symptoms of bromine vapour inhalation include: shortage of breath, coughing, choking and wheezing, with immediate or delayed bronchoconstriction (constriction of the large air passages that lead to the lungs), inflammation of the windpipe, 'laryngeal spasm' and swelling of the throat. With increased exposure extending deeper into the lung, abscesses in the larger airways and inflammation of the lungs may occur. Acute impairment to breathing may lead to severe hypoxaemia (shortage of circulating oxygen), metabolic acidosis, measles-like rash and subsequent death (IPCS, 1999).
62. Calabrese and Kenyon (1991) report that bromine has a mean odour threshold of about 0.05 ppm (0.33 mg/m^3): the geometric mean of a range of reported values. Ruth (1986) reported a wider range of odour threshold from 0.05-3.8 ppm (0.33-25 mg/m^3). Lachrymation (watering eyes) has been reported at exposure concentrations below 1 ppm (6.6 mg/m^3) (HSDB, 2003). Elkins (1959) reported that workers exposed to 1 ppm (6.6 mg/m^3) bromine found this level excessively irritant.
63. A report by Morabia *et al.* (1988) on an accidental release of bromine in an urban area has provided some useful information on human responses. The exposure assessed using chlorine-reactive detection tubes was in the range 0.2-0.5 ppm (1.32-3.30 mg/m^3), although the

³ LC_{50} is that concentration lethal to 50% of those exposed of the stated time.

- initial concentration in the bromine cloud following the release was probably much higher. As a result of the release 91 people (about 0.4% of the estimated exposed population) were seen at the local university hospital. Among the 59 whose complaints were recorded, the main symptoms were conjunctivitis (90%), upper respiratory tract irritation (68%), coughing (47%) and headache (46%). A follow-up after one month found that symptoms persisted for more than three days in 22% of those with eye irritation and 29% of those with upper airway irritation.
64. The delayed effects of severe exposure to bromine vapour following spillage caused by a traffic accident were studied by Carel *et al.* (1992). The exposures lasted from 45 to 240 minutes and a cloud of bromine was clearly visible. No concentrations were estimated. Six of the exposed people were studied and all experienced acute eye and skin irritation. Five were hospitalised for one to four days and four received intravenous corticosteroids for their complaint of shortness of breath. At follow-up six to eight weeks later, a wide range of symptoms was reported, but there were no abnormalities in clinical signs or from special investigations, which included chest X-ray and a range of blood tests. There was considerable delay in their returning to work, but the reasons for this included psychological factors resulting from the incident.
 65. Another accidental exposure, probably to both bromine and hydrogen bromide, occurred in two individuals using a hot tub in which a bromine-based disinfectant had been used (Burns and Linden, 1997). Both subjects were non-smokers and had no previously reported respiratory problems. It is not known what concentrations were present. Both had acute upper and lower respiratory tract and eye symptoms but there was little clinical or radiological evidence of lung abnormality. However, pulmonary (lung) function testing up to 10 months following the acute exposure revealed strongly positive responses to methacholine challenge, consistent with reactive airways dysfunction syndrome (RADS, see Appendix 2).
 66. Regular occupational exposure to bromine at concentrations ranging from 0.3 to 0.6 ppm (1.32 to 3.96 mg/m³) was associated with headache, loss of appetite and pains in the joints, abdomen and chest (Alexandrov, 1983). Alexandrov recommended that a concentration of 0.08 ppm (0.53 mg/m³) should not be exceeded in cases of prolonged exposure. Henderson and Haggard (1943) quote a maximum permitted level for prolonged exposure of 0.1-0.05 ppm (0.66-0.99 mg/m³) based on several earlier publications.
 67. The Health and Safety Commission of the Health and Safety Executive (HSE, 2002) has set an occupational exposure standard of 0.1 ppm (0.66 mg/m³) averaged over eight hours and a short-term exposure limit of 0.3 ppm (1.98 mg/m³) averaged over 15 minutes. The American Congress of Governmental Occupational Hygienists (ACGIH, 2001) set a threshold limit value (TLV) also at 0.1 ppm (0.66 mg/m³) but with a short-term limit at 0.2 ppm (1.3 mg/m³) averaged over 15 minutes.

68. The United Kingdom Committee on Toxicity (CoT) considered the dietary intake of bromide in 2003. The Committee reviewed an evaluation by the Joint Evaluation Committee for Food Additives (JECFA) and the Joint Meeting on Pesticide Residues (JMPR), both of which are Subcommittees of the World Health Organisation (WHO) and the Food and Agriculture Organisation (FAO) that established an acceptable daily intake (ADI) in the region of 0-1 mg/kg body weight. CoT considered it inappropriate to recommend a range of intake that included zero, as it is uncertain whether bromine is an essential trace element. CoT considered the upper bound of 1 mg/kg body weight/day to be unlikely to pose a risk to health. The estimated dietary intake is equivalent to about 0.06 mg/kg/day and it is unlikely that exposure by inhalation will significantly erode the margin between this value and the ADI.

3.2.3 Carcinogenicity

69. No long-term studies on the carcinogenicity of bromine are available. No epidemiological studies on human exposures to bromine are available.

3.3. Justification for the air quality guideline value

70. The Panel noted that the chemical reactions of bromine are similar to those of chlorine, but the effects in the lung are more severe. This probably reflects the lower reactivity of bromine and hypobromite, allowing penetration into the superficial tissues of the lung rather than reacting at the surface. As a result tissue damage will be increased. This damage will take more time to recover and may vary with the individual concerned. This is the probable reason why the adverse effects arising from exposure to low levels of bromine are difficult to define. Nevertheless, the primary effects result from the irritant effects of bromine vapour.
71. The information available on the irritant effects of bromine at low concentrations in humans is sparse and is of insufficient quality to define exposure levels and their effects with a high degree of confidence (IPCS, 1999). Bromine inhalation is also associated with subacute effects but these are likely to result from repeated irritation and they are found at comparable exposure levels to those associated with acute responses.
72. In the Panel's judgement, a concentration of 0.1 ppm (0.66 mg/m³) can be considered as a no observed adverse effect level (NOAEL) for irritant or potentially inflammatory effects on the lower respiratory tract and outer eye. To take into account the relatively sparse data on which this value is based and the severity of the irritant response reported, the Panel considered that in this case a safety factor of 10 should be applied to protect a greater number of susceptible individuals in the general population. The Panel accepted that at 0.01 ppm (0.07 mg/m³), irritant effects would be very unlikely, even in these individuals.

73. The Panel considered that there were no grounds for regarding bromine as a human carcinogen.

3.4. Recommendation

74. **The Panel recommends that a concentration of bromine gas or mass equivalent aerosol not exceeding 0.01 ppm (0.07 mg/m³) over a 1-hour averaging period should protect against irritant and inflammatory responses to the skin, eyes and breathing airways. Long-term effects at these low concentrations are considered most unlikely.**

References

- ACGIH, (2001). *Documentation of the TLVs, Bromine*. American Conference of Government Industrial Hygienists, Cincinnati, Ohio.
- Alexandrov, D.D. (1983). Bromine and compounds. In: *Encyclopaedia of Occupational Health and Safety*. Parmaggia, C. (ed) vol. 1, pp 326–329 (edn 3). ILO, Geneva, Switzerland.
- Bitron, M.D. and Aharonson, E.F. (1978). Delayed mortality of mice following inhalation of acute doses of CH₂O, SO₂Cl₂ and Br₂. *Am. Ind. Hyg. Assoc. J.* **32**, 129–138.
- Burns, M.J. and Linden, C.H. (1997). Another Hot Tub Hazard: Toxicity secondary to bromine exposure and hydrobromic acid exposure. *Chest* **111**, 816–819.
- Calabrese, E.J. and Kenyon, E.M. (1991). *Air Toxics and Risk Assessment*, pp 173–175. Chelsea, Lewis Publishers Inc.
- Carel, R.S. (1992). Delayed health sequelae of accidental exposure to bromine gas. *J. Toxicol. Environ. Health* **36**, 273–277.
- Elkins H.B. (1959). *Chemistry of Industrial Toxicology*, p. 89. John Wiley and Sons, New York.
- Henderson, Y. & Haggard, H.W. (1943). *Noxious Gases*, p. 133. Reinhold Publishing Co, New York, New York. Cited in ACGIH (2001).
- HSDB (Hazardous Substances Database) (2003). On-line database available at: <http://toxnet.nlm.nih.gov/>
- HSE (2002) Occupational exposure limits. EH40/2002. HSE Books, Norwich.
- IPCS (1999). Poison Information Monograph 080: Bromine. WHO, Geneva, Switzerland.

Expert Panel on Air Quality Standards

Morabia, A., Selleger C., Landry J.C., Conne P., Urban P., and Fabre J. (1988). Accidental bromine exposure in an urban population: An acute epidemiological assessment. *Int. J. Epidemiol.* **17**, 148–152.

NRC (1981). *Prudent Practices for Handling Hazardous Chemicals in Laboratories*. National Academy Press, Washington DC, USA. p. 115. Cited in the Hazardous Substances Database (2003).

Perry, W.G., Smith, F.A., and Kent, M.B. (1994). The halogens. In: *Patty's Industrial Hygiene and Toxicology* (edn 4). Volumes 2A–F: Toxicology. Clayton, G.D. & Clayton, F.E. (eds.) John Wiley & Sons Inc., New York, NY, USA.

Ruth, J.H. (1986). Odor Thresholds and Irritation Levels of Several Chemical Substances: A Review. *Am. Ind. Hyg. Ass. J.* **47**, A142-A151.

Chapter 4

Hydrogen fluoride

4.1. Background

4.1.1 Basic chemical information

75. Hydrogen fluoride (HF) is primarily a gas under environmental conditions. The gas is colourless with a pungent odour. It is highly toxic and irritating and dissolves in water to produce hydrofluoric acid.

Conversion factors at 25°C and 101 kPa:

$$1 \text{ ppm} = 0.82 \text{ mg/m}^3; 1 \text{ mg/m}^3 = 1.22 \text{ ppm}$$

4.1.2 Sources

76. Estimates of the release of hydrogen fluoride to air are reported by the National Atmospheric Emission Inventory and the Pollution Inventories of the Environment Agency and Scottish Environment Protection Agency. The largest sources of hydrogen fluoride in the atmosphere are coal-fired power stations (the largest emission sector in the United Kingdom) and aluminium smelters. Other smaller sources include phosphate fertiliser plants; glass, brick and tile works; plastics manufacture; copper and nickel production; and adhesive production. Some releases may also come from the chemical and oil industries.
77. In the United Kingdom emissions of hydrogen fluoride fell by 73% between 1970 and 2000 as a result of the decline in coal use and, since 1993, the installation of flue gas desulphurisation at Drax and Ratcliffe power stations.
78. Hydrogen fluoride is produced at three sites in the United Kingdom for organic chemistry uses, namely Runcorn, Avonmouth and Rotherham.

4.1.3 Ambient levels

79. Hydrogen fluoride can be measured using several methods many of which measure the fluoride present in the resulting sample but none of these are able to determine short-term exposures at likely environmental concentrations. There are no ongoing long-term measurements of hydrogen fluoride in United Kingdom ambient air. As such, levels of

exposure and the number of persons potentially exposed to hydrogen fluoride are not known.

80. A modelling study suggested that the natural background concentration of fluoride was 0.61×10^{-6} ppm (0.5×10^{-6} mg/m³). When anthropogenic emissions were included, the background concentration increased to 3.66×10^{-6} ppm (3×10^{-6} mg/m³) (Slooff *et al.*, 1988).
81. In heavily industrialised urban areas within Europe, background concentrations are in the range of 0.61×10^{-3} to 2.44×10^{-3} ppm (0.5×10^{-3} to 2.0×10^{-3} mg/m³) but in some cases are as high as 3.66×10^{-3} ppm (3×10^{-3} mg/m³) (WHO, 2000).
82. Only a very limited number of recent ambient measurements of hydrogen fluoride have been made in the United Kingdom and these have been in the vicinity of three industrial plants. Although many samples were below the limit of detection, measurable values were in the range 4.1×10^{-5} to 2.87×10^{-3} ppm (3.36×10^{-5} to 2.35×10^{-3} mg/m³) as approximate monthly averages. Values at one site in Wales with results reported up to 13.4×10^{-3} ppm (11×10^{-3} mg/m³) have been excluded because of uncertainty in the analysis. Brickworks are a known source of fluoride emissions and measurements made between 1984 and 1986 in the Marston Vale region of Bedfordshire revealed monthly mean concentrations of gaseous fluorides of 4.9×10^{-5} to 10.5×10^{-4} ppm (4×10^{-5} to 8.6×10^{-4} mg/m³), and daily mean fluoride concentrations of up to 2.7×10^{-3} ppm (2.2×10^{-3} mg/m³) (99.8%ile). Monthly mean concentrations were correlated with brick production over the same period (Clark *et al.*, 1990; 1991). If it is assumed that nationally, coal burning is the largest source of hydrogen fluoride and that all the reactive fluorine is emitted as hydrogen fluoride, it is possible to estimate hydrogen fluoride levels from those of SO₂, by using a method directly analogous to that indicated for hydrogen chloride in paragraphs 110-111. On this basis it might reasonably be expected that maximum 1-hour mean hydrogen fluoride concentration would reach about 3.0×10^{-3} ppm (2.46×10^{-3} mg/m³) at a rural site exposed to power station plumes.
83. Estimates of total oral fluoride intake may vary from 0.9-3.0 mg/day, depending on diet and whether the water is fluoridated. The World Health Organisation (WHO) guideline for drinking water is 1.5 mg/l; this is higher than that recommended for fluoridation of water supplies, which stands at 1 mg/l (WHO, 1984). Children appear more sensitive to fluoride intake than adults, as dental fluorosis is closely associated with fluoride intake during the period of tooth development (Fomon *et al.*, 2000).

4.2. Health effects

84. The Panel considered controlled animal and human studies involving acute and subacute exposure to hydrogen fluoride. In addition, data from occupational exposures and industrial accidents were reviewed.
85. Hydrogen fluoride is a highly irritating and corrosive gas with a pungent odour. Skin contact with liquid hydrogen fluoride can cause severe burns. It is a severe irritant to eyes, skin and nasal passages. When inhaled, the absorption of hydrogen fluoride will be virtually complete, due to a strong reaction with mucous membranes (moist body linings) at the site of deposition. On absorption, hydrogen fluoride gives rise to the fluoride ion that is taken up by bone and enamel in teeth (WHO, 1984) and is excreted mainly in the urine. Penetration into the lungs results in pulmonary haemorrhage and oedema (bleeding and build up of fluids in the lungs) and may result in death.
86. The critical effects of chronic exposure to low concentrations of hydrogen fluoride are due to the systemic effects of fluoride (fluorosis), which affects the skeleton. Classical symptoms are osteosclerosis, formation of exostose and ossification of ligaments.
87. Skeletal fluorosis is associated with a systemic uptake of hydrogen fluoride exceeding 5 mg/day in a relatively sensitive section of the general population (WHO, 2000), whereas dental fluorosis occurs at concentrations in drinking water above 1.5-2.0 mg/l (WHO, 1984).

4.2.1 Animal studies

88. Large variations exist in the reported concentrations of hydrogen fluoride causing similar effects among different animal species. Some of this variation may be due to strain and species differences, but the diversity in the results is more likely to be explained by changes in sampling and analytical methodology.
89. For 60-minute inhaled exposures, only mild and occasional signs of eye, nasal or respiratory (breathing) irritation were observed in the dog at 157 ppm (131 mg/m³) and in the rat at 103 and 126 ppm (86 and 105 mg/m³) (Rosenholtz *et al.*, 1963). Gross and microscopic examination revealed concentration-dependent lesions in the kidney, liver, nasal passage, bone marrow and skin.
90. The lowest 60-minute LC₀⁴ values ranged from 263 ppm (219 mg/m³) for the mouse to 1087 ppm (904 mg/m³) for the rat (Wohlslagel *et al.*, 1976).

⁴ LC₀ is the highest concentration resulting in no deaths.

91. Sixty-minute LC₅₀⁵ values ranged from 342 ppm (284 mg/m³) for the mouse (Wohlschlager *et al.*, 1976) to 2300 ppm (1900 mg/m³) for the rat (Haskell Laboratory, 1990). The lowest LC₅₀ for the rat was 996 ppm (803 mg/m³) (Vernot *et al.*, 1997). Pathological examination of rats and mice that died during or after exposure revealed pulmonary oedema (build up of fluid in the lungs). For the rhesus monkey, statistical analysis has led to an LC₅₀ value of 1774 ppm (1476 mg/m³) (MacEwen and Vernot, 1970).
92. One subacute study using rats reported a no observable adverse effect level (NOAEL) of 1 ppm (0.72 mg/m³) (Placke and Griffin, 1991). In other subacute studies, using a variety of species, lung and kidney damage was found at 18.5 ppm (15.4 mg/m³) and 33 ppm (27 mg/m³).

4.2.2 Acute effects in humans

93. The acute effects of hydrogen fluoride have been assessed in 20 healthy, non-smoking male volunteers who were exposed for 1 hour to three concentration ranges known to occur among workers in the aluminium industry: 0.2 to 0.7 ppm (0.17 to 0.58 mg/m³) (*n* = 9); 0.85 to 2.9 ppm (0.71 to 2.4 mg/m³) (*n* = 7); and 3.0 to 6.3 ppm (2.5 to 5.2 mg/m³) (*n* = 7) (Lund *et al.*, 1997). Volunteers rested during the first 45 minutes of exposure and exercised during the last 15 minutes on a stationary bicycle. The two lower ranges resulted in either no or low sensory and lower airway irritation (chest tightness, soreness, coughing, expectoration and wheezing). In the highest exposure group, three subjects reported upper respiratory irritation (itching or soreness of the nose or throat) of greater than three on a scale of 0 (no symptoms) to 5 (the most severe symptoms), and one subject reported a lower airway irritation score of greater than three.
94. Hydrogen fluoride has also been shown to induce an immediate nasal inflammatory and antioxidant response in healthy human volunteers (Lund *et al.*, 2002). Following a 1-hour exposure to hydrogen fluoride at a concentration range 4.0 to 4.8 ppm (3.3-3.9 mg/m³), seven out of ten individuals reported upper airway symptoms. These airways symptoms correlated significantly with changes in indicators of inflammatory response in nasal lavage (washings) fluid, including a statistically significant increase in the number of nasal neutrophils. Like all irritant gases, accidental inhalation exposure to high levels of hydrogen fluoride has the potential to initiate reactive airways dysfunction syndrome (RADS), a form of irritant-induced asthma (see Appendix 2).

4.2.3 Subacute effects in humans

95. Largent (1960, 1961) exposed five male volunteers to variable concentrations of hydrogen fluoride (0.9-8.1 ppm or 0.75-6.70 mg/m³) for six hours per day over a period of 15 to 50 days. Effects in two

⁵ LC₅₀ is that concentration lethal to 50% of those exposed of the stated time

individuals exposed to up to 7.9 and 8.1 ppm (6.6 and 6.7 mg/m³) over a 25- and 50-day period, respectively, were no more severe than in other volunteers exposed to lower concentrations. One individual who tolerated 1.42 ppm (1.18 mg/m³) for 15 days without noticeable effects was, at a later date, exposed to 3.39 ppm (2.82 mg/m³) and experienced redness of the face by day 10 and some flaking of the skin by day 11. At 2 ppm (1.7 mg/m³) subjects experienced slight irritation to the eyes, nose and facial skin and noted a sour taste during the exposure. Any signs of discomfort disappeared after cessation of exposure and systemic effects were not observed (USEPA, 2000).

4.2.4 Occupational exposure

96. Chronic industrial exposure to hydrogen fluoride has been reported to lead to skeletal fluorosis, but airborne concentrations are often estimated or are unknown and exposures are usually to both hydrogen fluoride and fluoride dusts (NIOSH, 1976; ATSDR, 1993). Reports of asthmatic symptoms in pot room workers engaged in the production of aluminum have suggested that respiratory irritants in the working atmosphere (hydrogen fluoride, sulphur dioxide and fluoride particles) may cause asthma or chronic obstructive pulmonary disease (Lund *et al.*, 1997). Despite numerous studies the relation between the irritant agents and the symptoms remains unresolved.

4.2.5 Industrial accidents

97. Approximately 3,000 people were evacuated from a community in Texas, USA when around 24100 kg of caustic hydrogen fluoride and 3000 kg of isobutene were released from a petrochemical plant (Wing *et al.*, 1991). Samples taken down-wind one and two hours after the release contained 10 ppm (8.3 mg/m³) and minimal traces of hydrogen fluoride, respectively. The most frequently reported symptoms in people presenting at emergency rooms were eye irritation, burning throat and soreness, headache, shortness of breath, chest pain, cough and nausea. The USEPA (1993) cited a separate study by Trevino (1991) in which an industrial accident in Mexico resulted in seven workers being exposed to approximately 10000 ppm (8300 mg/m³) of hydrogen fluoride for several minutes. Periodic examinations for up to 11 years after exposure revealed no long-term or delayed effects.
98. Several instances of exposure to hydrogen fluoride have resulted in death but no data have been located on human deaths following inhalation-only exposure.

4.2.6 Carcinogenicity

99. Several studies indicated an increased incidence of respiratory cancers among workers in industries with exposure to hydrogen fluoride and fluoride dusts. However, the confounding effects of exposure to other chemicals, the lack of information on smoking status of these individuals and the absence of data on exposure concentrations make the studies of questionable relevance (ASTDR, 1993). No experimental or epidemiological studies with hydrogen fluoride are available. IARC

(The International Agency for Research on Cancer) concluded that there was no substantive evidence for carcinogenicity of fluoride in drinking water in either humans or animals (group 3 unclassifiable IARC 1987). This view was supported by a report from the UK Medical Research Council (MRC, 2002). IARC (1992) has evaluated the carcinogenicity of mists of strong inorganic acids. However hydrogen fluoride was not included in this evaluation and the overall evaluation is not relevant for the concentrations considered here.

100. Studies of other health consequences of chronic exposure to hydrogen fluoride in humans, including developmental or reproductive effects or genotoxicity, have not been identified, as far as the Panel is aware.

4.2.7 Evaluations and recommendations by other organisations

101. The Health and Safety Commission (HSE 2002) has set an occupational exposure limit of 3 ppm (2.5 mg/m^3) as a 15-minute short-term exposure limit based on human volunteer data from the study of Largent and Columbus (1960). In addition, an 8-hour time-weighted average limit of 1.8 ppm (1.5 mg/m^3), which would not be expected to cause fluorosis in workers exposed day after day, was set based on evidence by Dinman *et al.* (1976). This is in accordance with the European Commission's indicative occupational exposure limit values (IOELVs) listed in the First Consolidated IOELV Directive (2000/39/EC).

4.3. Justification for the air quality guideline value

102. The Panel considered the effects arising from exposure to low levels of hydrogen fluoride on the eyes, skin and respiratory tract owing to its well-known irritant properties. As noted, hydrogen fluoride is a highly irritating and corrosive gas and has a pungent odour that is detectable at about 0.04 ppm (0.03 mg/m^3) (European Union Risk Assessment Report, 2001). It is a severe irritant to eyes, skin and nasal passages.
103. The Panel considered that a concentration of 1 ppm (0.82 mg/m^3) should be regarded as a NOAEL for irritant effects on the face, eye and respiratory airways. This is based on the human healthy volunteer studies of Largent (1960, 1961), which indicate that hydrogen fluoride concentrations of 2 ppm (1.7 mg/m^3) were slightly irritating, and Lund *et al.* (1997), which reported respiratory irritation at concentrations of 3.0-6.3 ppm ($2.5\text{-}5.2 \text{ mg/m}^3$). To take into account the more susceptible individuals in the general population, the Panel considered the application of a safety factor of 5 would be adequate for exposure in the ambient air. Therefore the Panel concluded that 0.2 ppm (0.16 mg/m^3) would be an appropriate guideline value for hydrogen fluoride, allowing for its irritant effects on the skin, eyes and respiratory mucosa (moist lining of the breathing airways). A longer-term guideline value to protect against the chronic effects of hydrogen fluoride exposure will be recommended in an addendum to this report.

104. The Panel considered that there were no grounds for regarding hydrogen fluoride as a human carcinogen, especially at the very low levels considered.

4.4. Recommendation

105. **The Panel recommends that a concentration of hydrogen fluoride gas or mass equivalent aerosol not exceeding 0.2 ppm (0.16 mg/m³) over a 1-hour averaging period should protect against irritant and inflammatory effects on the eyes, skin and breathing airways.**

References

ATSDR (1993). *Toxicological Profile for Fluorides, Hydrogen Fluoride, and Fluorine (F)*. TOP-91/17, Agency for Toxic Substances and Disease Registry, Public Health Service, Washington DC, USA.

Clarke, E.R., Robins, P.C., Irwin, J.G., Barratt, R.S. (1990). Air quality monitoring for fluorides: I. Establishment and quality assurance. *Intern. J. Anal. Chem.* **39**, 223-237.

Clarke, E.R., Robins, P.C., Irwin, J.G., Barratt, R.S. (1991). Air quality monitoring for fluorides: II. Spatial and temporal distributions around a brickworks. *Intern. J. Anal. Chem.* **39**, 223-237.

Dinman, B., Elbow, D., Bonney, M.J. (1976). A 15-year retrospective study of fluoride excretion and bone radiopacity among aluminium smelter workers – Pt 4. *J. Occup. Med.* **18**, 21–25.

European Union Risk Assessment Report, Hydrogen Fluoride, Cas-No: 7664-39-3, 2001.

Fomon, S.J., Ekstrand, J., Ziegler, E.E. (2000). Fluoride intake and prevalence of dental fluorosis: trends in fluoride intake with special attention to infants. *J. Public Health Dent.* **60**, 131–139.

Haskell Laboratory (1990). *Acute Inhalation Toxicity of Hydrogen Fluoride in Rats* (final report, with attachments and cover letter dated 082390). EPA/OTS; Doc#FYI-OTS-0890-0607.

HSE (2002). Summary Criteria for Occupational Exposure Limits, EH64/D31. Fluorine, hydrogen fluoride and inorganic fluorides. HSE Books, Norwich.

IARC (1987). International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Supplement No. 7. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. IARC, WHO, Lyon, France.

Expert Panel on Air Quality Standards

IARC (1992). International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 54. Occupational Exposures to Mists and Vapours from Strong Inorganic Acids; and Other Industrial Chemicals. IARC, WHO, Lyon, France.

Largent, E.J. & Columbus, A. (1960). The metabolism of fluorides in man. *Am. Med. Assoc. Arch. Ind. Health* **21**, 318–323.

Largent, E.J. (1961). *Fluorosis: The Health Aspects of Fluorine Compounds*, pp. 34–39 & 43–48. Ohio State University Press, Columbus, OH, USA.

Lund, K., Ekstrand, K., Boe, J., Sosstrand, P., Kongerud, J. (1997). Exposure to hydrogen fluoride: An experimental study in humans of concentrations of fluoride in plasma, symptoms and lung function. *Occup. Environ. Med.* **54**, 32–37.

Lund, K., Refsnes, M., Ramis, I., Dunster, C., Boe, J., Schwarze, P.E., Skovlund, E., Kelly, F.J. and Kongerud, J. (2002). Human exposure to hydrogen fluoride induces acute neutrophilic, eicosanoid and antioxidant changes in nasal lavage fluid. *Inhalation Toxicity* **14**, 119–132.

MacEwen, J.D. & Vernet, E.H. (1970) *Toxic Hazards Research Unit Annual Technical Report: 1970*. AMRL-TR-70-77, AD 714694, Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH, USA.

MRC (2002). Medical Research Council working group report: Water fluoridation and health. Medical Research Council, September 2002.

NIOSH (1976). *Criteria for a Recommended Standard Occupational Exposure to Hydrogen Fluoride*. NIOSH Publication 76-143, US Department of Health, Education and Welfare.

Placke, M.E. & Griffin, S. (1991). *Subchronic Inhalation Exposure Study of Hydrogen Fluoride in Rats*. Battelle Memorial Institute, Columbus, OH, USA; Docket No. OPPTS 42187. Submitted by Battelle Washington Environmental Program, Arlington, VA, USA.

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

Slooff, W., Eerens, H.C., Janus, J.A. and Ros, J.P.M., (1988). *Basis Document Fluoriden*. RIVM, Bilthoven, Netherlands.

Trevino, M.A. (1991). *Hydrofluoric Acid Exposures: Long-term Effects*. Draft report cited in USEPA (1993).

USEPA (1993). *Hydrogen Fluoride Study: Final Report*. Report to Congress, Section 112(n) (6), Clean Air Act as amended. EPA 550-R-93-001, USEPA, Washington DC, USA.

USEPA (2000). Office of Pollution Prevention and Toxics: Hydrogen fluoride proposed acute exposure guideline levels (AEGLs). Public Draft.

Vernot, E.H., MacEwen, J.D., Haun, C.C., Kinkead, E.R. (1997). Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. *Toxicol. Appl. Pharmacol.* **42**, 417–423.

WHO (1984). International Programme on Chemical Safety. Environmental health criteria 36. Fluorine and Fluorides. World Health Organisation, Geneva, Switzerland.

WHO (2000). *Air Quality Guidelines for Europe* (edn 2). World Health Organisation, Geneva, Switzerland.

Wing, J.S., Sanderson, L.M., Brender, J.D., Perrotta, D.M., Beauchamp R.A. (1991). Acute health effects in a community after a release of hydrofluoric acid. *Arch. Environ. Health.* **46**, 155–160.

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

Chapter 5

Hydrogen chloride

5.1. Background

5.1.1 Basic chemical information

106. Hydrogen chloride (HCl) is a water-soluble, colourless to light-yellow, corrosive gas. It is 1.27-times denser than air. Anhydrous hydrogen chloride produces aqueous hydrochloric acid when dissolved in water.

Conversion factors at 25°C:

$$1 \text{ ppm} = 1.49 \text{ mg/m}^3; 1 \text{ mg/m}^3 = 0.67 \text{ ppm}$$

5.1.2 Sources

107. Estimates of the release of hydrogen chloride to air are reported by the National Atmospheric Emission Inventory and the Pollution Inventories of the Environment Agency and Scottish Environment Protection Agency. The main source of hydrogen chloride in the atmosphere is its release from combustion-related activities, particularly the large coal-burning power stations, with a minor source from the displacement reactions of acidic gases with sea salt particles. The ratio by mass of hydrogen chloride to sulphur dioxide in UK power station emissions is currently 0.088.
108. In the United Kingdom emissions of hydrogen chloride fell by 75% between 1970 and 2000 as a result of the decline in coal use and also the installation of flue gas desulphurisation at Drax and Ratcliffe power stations since 1993.

5.1.3 Ambient levels

109. Hydrogen chloride is monitored at only 12 rural locations in the United Kingdom as part of the Defra nitric acid network. In 2002 annual average concentrations ranged from 0.08×10^{-3} to 0.27×10^{-3} ppm (0.12×10^{-3} to 0.41×10^{-3} mg/m³).
110. There is an absence of continuous and short-term observations of outdoor hydrogen chloride. However, SO₂ is expected to be a good surrogate for hydrogen chloride because they share common emission

sources and they are both reactive and acidic gases. On this basis, exposures to hydrogen chloride are expected to occur downwind of the large coal-burning power stations. As with SO₂, the pattern of hydrogen chloride air pollution is expected to be characterised by short-term peak concentrations typically lasting a few minutes to no more than a few hours at some point downwind of a power station where the plume reaches ground level. These episodes tend to occur as daytime turbulence breaks up night-time temperature inversions in a process called fumigation.

111. At the Ladybower Reservoir site in Derbyshire, which is exposed to plumes from a few distant high-level power station stacks, maximum 15-minute mean SO₂ concentrations have reached 0.19 ppm (0.5 mg/m³, measured in 2001) and are about 20% higher than the maximum hourly mean concentrations. On this basis, maximum 15-minute mean hydrogen chloride concentrations could be reasonably expected to reach about 0.027-0.040 ppm (0.04-0.066 mg/m³), although there are no monitoring data to confirm this expectation (see www.airquality.co.uk).

5.2. Health effects

112. The Panel considered animal studies involving exposure to hydrogen chloride and human studies of acute exposures that included occupational and one laboratory controlled exposure study, as well as chronic exposures focusing on carcinogenicity.

5.2.1 Animal studies

113. Hydrogen chloride is acutely toxic with LC₅₀⁶ values of around 4700 ppm (7003 mg/m³) in rats and 2650 ppm (3948 mg/m³) in mice for a 30-minute exposure (Darmer *et al.*, 1974). Exposure of rats to 1300 ppm (1940 mg/m³) for 30 minutes caused severe ulcerative changes to the nasal cavity compatible with hydrogen chloride's property as a strong acid. There were no effects on the lungs to nose breathers, although mouth-breathing animals developed equivalent damage to the upper respiratory (breathing) tract (Stavert *et al.*, 1991). In rats, chronic dosing studies at 10 ppm (14.9 mg/m³) show that rhinitis (inflammation of the nose lining) and epithelial hyperplasia or squamous metaplasia (changes in the nature or number of cells) are common (Sellakumar *et al.*, 1985). This may be regarded as a lowest observed effects level (LOEL), but it is not known whether this value is directly applicable to human subpopulations (Kamrin, 1992). No other animal studies have been published that provide useful evidence on the health effects of ambient exposures to hydrogen chloride in humans.
114. Concerns have been raised in the past that co-exposure to hydrogen chloride and formaldehyde (HCHO) may enhance the known carcinogenicity of formaldehyde, possibly by the formation of bis(chloromethyl)ether (BCME), a human and animal carcinogen

⁶ LC₅₀ is that concentration lethal to 50% of those exposed of the stated time.

(Sellakumar *et al.*, 1985). However, after careful review of the literature, at ambient concentrations this reaction was considered not to occur to any significant degree and so the Panel did not consider that hydrogen chloride would develop carcinogenic potential via this mechanism.

5.2.2 Acute and subacute effects in humans

115. Hydrogen chloride is a sensory and respiratory irritant. Being highly soluble in water, following inhalation the gas is readily deposited in the nose and upper respiratory tract. At raised concentrations and at high breathing rates, it may penetrate deeper into the lower respiratory tract. At high concentrations, as encountered in accidental exposures in industry, hydrogen chloride causes painful irritation of the eyes, nose, mouth and throat, and acute chemical injury to the lungs may cause severe difficulty in breathing and death. Fortunately, such exposures are uncommon, but a form of irritant-induced asthma – reactive airways dysfunction syndrome (RADS) – has been reported following such inhalation accidents (see Appendix 2). Between 1989 and 2003, 130 inhalation accidents involving hydrogen chloride have been reported to the Surveillance of Work-Related & Occupational Respiratory Disease (SWORD) database in the UK and of these 26 (20%) were reported as having led to asthma or RADS. However, the exposures involved are far higher than those encountered in ambient conditions.
116. For occupational exposure, the Health and Safety Commission has set a short-term exposure limit (measured as an average over 15 minutes) of 5 ppm for gas (8 mg/m³ for aerosol) and a long-term exposure limit (measured as an average over 8 hours) of 1 ppm for gas (2 mg/m³ for aerosol) (HSE, 2002a,b). The information on toxicity is only available for the gas and, therefore, the concentrations used for aerosolised hydrogen chloride are made equivalent in terms of airborne mass concentrations.
117. The information available on the sensory effects of hydrogen chloride at low concentrations in humans is sparse and, in the Panel's view, is of insufficient quality to define exposure levels and their effects with much confidence. The exception is the one inhalation study by Stevens *et al.* (1992) in which ten young volunteers with mild asthma were exposed to concentrations of 0.8 or 1.8 ppm (1.19 or 2.68 mg/m³) and the respiratory effects of inhaling the gas while exercising for 15-minute periods were measured. No adverse respiratory symptoms and no decrement in lung function tests were found. In addition, the blinded testing included a 15-minute period of exposure to air. At these levels The volunteers were not able to detect any difference between air and hydrogen chloride, with symptom scores for unusual taste or smell being the same during the air and gas exposures.

5.2.3 Carcinogenicity

118. IARC (1992) concluded that there was no substantive evidence for carcinogenicity of hydrogen chloride in either humans or animals (group 3 unclassifiable). This evaluation included assessment of the effect of mineral acid mists in battery plants and steel mills, where acid mists have been suspected of causing an increase in respiratory cancer, although most such exposures involve mixtures of acids. Exposure to aerosols of hydrogen chloride is known to lead to dental discolouration and erosion (IPCS 1992). There are no studies on potential effects of hydrogen chloride on human reproduction.

5.3. Justification for the air quality guideline value

119. As its starting point the Panel took the need to consider the irritant effects arising from exposure to low levels of hydrogen chloride. In both anhydrous and aerosol forms, hydrogen chloride is a strong irritant that affects the conjunctivae (eye) and respiratory mucosa (moist lining of the breathing airways). Because of its high solubility in water, the major irritant effects of acute exposure are usually limited to the upper respiratory tract.
120. The Panel considered that a concentration of 1 ppm should be regarded as a no observed adverse effect level (NOAEL) for irritant or potentially inflammatory effects on the lower respiratory tract and outer eye, while noting that this view was based on the only available study of a small group of selected volunteers with mild asthma (Stevens *et al.*, 1992). In this study there were two exposure values where there was an absence of effect and the Panel chose the lower of the two as a more conservative option, particularly as the number of participants was small. To take into account the more susceptible individuals in the general population, the Panel considered that applying a safety factor of 2 would be adequate for exposure in the ambient air. This would be consistent with the approach adopted by the Panel in recommending the air quality standard for sulphur dioxide (EPAQS, 1995). The Panel therefore concluded that 0.5 ppm (0.75 mg/m³) would be an appropriate guidance value for hydrogen chloride, which allowed for its irritant effects on the respiratory mucosa.
121. The Panel considered that there were no grounds for regarding hydrogen chloride as a human carcinogen.

5.4. Recommendation

122. **The Panel recommends that a concentration of hydrogen chloride gas or mass equivalent aerosol not exceeding 0.5 ppm (0.75 mg/m³) over a 1-hour averaging period should protect against irritant and inflammatory effects on the eyes, skin and breathing airways. Long-term effects at these low concentrations are considered unlikely.**

References

- Darmar, K.L., Kinkead, E.R., Dipasquale, L.C. (1974). Acute toxicity in rats and mice exposed to hydrogen chloride gas and aerosols. *Am. Ind. Hyg. Assoc. J.* **35**, 623–631.
- EPAQS (1995). Expert Panel on Air Quality Standards: *Sulphur Dioxide*. HMSO, London.
- HSE (2002a). Occupational exposure limits. EH40/2002. HSE Books, Norwich.
- HSE (2002b). EH64/D36. Summary criteria for occupational exposure limits. EH64/D36 Hydrogen chloride. HSE Books, Norwich.
- IARC (1992). International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 54. Occupational Exposures to Mists and Vapours from Strong Inorganic Acids; and Other Industrial Chemicals. IARC, WHO, Lyon, France.
- IPCS (1982). International Programme on Chemical Safety. IPCS Environmental Health Criteria Monographs. *Environmental Health Criteria 21. Chlorine and Hydrogen Chloride*. WHO, Geneva, Switzerland.
- Kamrin, M.A. (1992). Workshop on the Health Effects of HCl in Ambient Air *Regulat. Toxicol. Pharmacol.* **15**, 73–82.
- Sellakumar, A.R., Snyder, C.A., Solomon, J.J., Albert, R.E. (1985). Carcinogenicity of formaldehyde and hydrogen chloride in rats. *Toxicol. Appl. Pharmacol.* **81**, 401–406.
- Stavert, D.M., Archuleta, D.C., Behr, M.J., Lehnert, B.E. (1991). Relative acute toxicities of hydrogen fluoride, hydrogen chloride and hydrogen bromide in nose- and pseudo-mouth-breathing rats. *Toxicol. Appl. Pharmacol.* **81**, 401–406.
- Stevens, B., Koenig, J.Q., Rebolledo, V., Hanley, Q.S., Covert, D.S. (1992). Respiratory effects from the inhalation of hydrogen chloride in young adult asthmatics. *J. Occup. Med.* **34**, 923–929.

Chapter 6

Hydrogen bromide

6.1. Background

6.1.1 Basic chemical information

123. Hydrogen bromide (HBr) is a colourless, nonflammable, corrosive gas with a sharp, unpleasant, pungent odour. It is 3.5-times denser than air. Anhydrous hydrogen bromide produces aqueous hydrobromic acid when dissolved in water.

Conversion factors at 25°C and 101 kPa:

$$1 \text{ ppm} = 3.5 \text{ mg/m}^3; 1 \text{ mg/m}^3 = 0.29 \text{ ppm}$$

6.1.2 Sources

124. Releases of hydrogen bromide to air are not estimated by the National Atmospheric Emission Inventory and reporting is only required by the Environment Agency where the release is greater than one tonne per annum or as a specific permit condition. The Environment Agency's Pollution Inventory indicates that approximately 700 tonnes of hydrogen bromide were released to atmosphere in 2002, predominantly from the large coal-burning power stations. Other minor sources include the mineral industries, waste combustion, metals recycling and the displacement reactions of acidic gases with sea salt particles.

6.1.3 Ambient levels

125. Ambient levels of hydrogen bromide are not monitored routinely at any site in the United Kingdom. However, quarterly mean concentrations of particle-associated bromide have been made at three rural sites in the Defra Rural Trace Elements Network. In 2002 quarterly concentrations of particle associated bromide ranged from 2.7×10^{-6} to $11 \times 10^{-6} \text{ mg/m}^3$.

6.2. Health effects

126. The Panel considered animal studies involving exposure to hydrogen bromide and human studies of acute exposures that included both

occupational and one laboratory controlled exposure study as well as chronic exposures.

6.2.1 Animal studies

127. One acute animal study of inhaled hydrogen bromide at a high dose has been published. Stavert *et al.* (1991) exposed groups of male Fischer 344 rats under light anaesthesia to filtered air or 1300 ppm (4550 mg/m³) of hydrogen bromide vapour for 30 minutes. The study compared the effects of hydrogen bromide exposures to equal concentrations (ppm) of hydrogen chloride and hydrogen fluoride. Each treatment had a nose-breathing group and a group intubated to simulate mouth breathing. Twenty-four hours after the exposure, all surviving rats were killed and body and lung lobe weights were measured. Histological sections from the nasal passages, trachea (windpipe) and lung were examined under the microscope.
128. In all the nose-breathing groups, mean body weight was statistically reduced compared to the controls. The reduction seen in the hydrogen bromide-treated group was less than that seen in the groups treated with hydrogen chloride or hydrogen fluoride. In hydrogen bromide-treated rats mean absolute lung weights were similar to controls. Nose breathers exhibited severe damage to the surface tissue in the nose, in some cases extending to the underlying bone. Blood clots were seen in the nasal passages and in the upper airways, but these did not extend into the deeper lung. Fluid and fibrin in the nasal passages often accompanied these lesions. The effects were not observed in the lower regions of the respiratory (breathing) tract. Approximately 8% of nose-breathers died within 24 hours after exposure.
129. In the intubated rats (pseudo-mouth-breathers) exposed to hydrogen bromide, 20% died within 24 hours of exposure. Mean body weight was slightly reduced compared to the controls but the difference was not statistically different. Mean lung weights also were not statistically different compared to controls. Mouth breathers had variable degrees of superficial tissue damage to the upper airways accompanied by fluid in the trachea. The damage did not extend into the deep lung, and it was considered to be less severe than that observed with hydrogen chloride.
130. No subchronic animal studies on hydrogen bromide were found. However, in a 90-day toxicity study rats were fed diets containing from 75–19200 ppm sodium bromide. At the highest dose animals were poorly groomed and showed reduced weight gain: the effect was more prominent in male rats. In all groups, bromide level in the plasma rose to a plateau after 3 weeks. In female rats thyroid weight was increased from 1200 ppm: in males the effect was confined to the group dosed at 19200 ppm, but prostate weight was decreased from 4800 ppm. Microscopic examination of tissues confirmed an effect on the endocrine system. No effects were seen at or below 300 ppm in diet. (van Logten *et al.*, 1974)

6.2.2 Acute effects in humans

131. The only laboratory investigation conducted in humans is an unpublished volunteer study conducted in 1955 and cited by ACGIH (2001), which reported that inhalation of 2 ppm (7 mg/m³) hydrogen bromide vapour for 'several minutes' did not result in eye, nose or throat irritation, although an odour was detected by the volunteers. Inhalation at 3 ppm (10.5 mg/m³) for several minutes resulted in nasal and throat irritation in one out of six volunteers, with nose irritation being observed in three out of six, six out of six and six out of six volunteers at 4, 5 and 6 ppm (14, 17.5 and 21 mg/m³), respectively. The one out of six incidence of throat irritation was unchanged up to 6 ppm (20 mg/m³). No eye irritation was observed up to hydrogen bromide concentrations of 6 ppm (21 mg/m³). The imprecision of this study is a concern, especially the duration of exposure.
132. Garlanda and Basilico, (1993) reported that (presumably accidental) inhalation of approximately 35 ppm (118 mg/m³) hydrogen bromide for a short period was associated with irritation of the throat, with 'more severe exposures' resulting in pulmonary oedema (fluid accumulation in the lung), which was at times accompanied by 'laryngeal spasm'. A few minutes exposure to a hydrogen bromide release estimated to be 1400-2100 ppm (4710-7100 mg/m³) was reported to be lethal.
133. The Health and Safety Commission has set an occupational exposure limit of 3 ppm (10.5 mg/m³) (as a 15-minute time-weighted average) based on unpublished human volunteer data summarised by the ACGIH in their supporting documentation for the threshold limit value (HSE 2002a,b).
134. An accidental exposure, probably to both bromine and hydrogen bromide, occurred in two individuals using a hot tub in which a bromine based disinfectant had been used (Burns and Linden, 1997). Both subjects were non-smokers and had no previously reported respiratory problems. It is not known what concentrations of hydrogen bromide were present. Both subjects had acute upper and lower respiratory and eye symptoms but there was little clinical or radiological evidence of lung abnormality. However, pulmonary (lung) function testing up to 10 months subsequently revealed strongly positive responses to methacholine challenge, consistent with reactive airways dysfunction syndrome (RADS, see Appendix 2).

6.2.3 Subacute effects in humans

135. Alexandrov (1983) reported that chronic occupational exposure (concentration and duration not reported) to hydrogen bromide was associated with inflammation of the upper airways lining, indigestion, reduced red blood cell counts and possible changes to reflexes and sense of smell. Bromide salts have found therapeutic use as anti-convulsants, analgesics and sedatives. Excessive doses (not achievable by inhalation) cause headache, drowsiness and lethargy and, occasionally, skin lesions and psychotic behaviour.

136. The United Kingdom Committee on Toxicity (CoT) considered the dietary intake of bromide in 2003. The Committee reviewed an evaluation by the Joint Evaluation Committee for Food Additives (JECFA) and the Joint Meeting on Pesticide Residues (JMPR), both of which are Subcommittees of the World Health Organisation (WHO) and the Food and Agriculture Organisation (FAO) that established an acceptable daily intake (ADI) in the region of 0-1 mg/kg body weight. CoT considered it inappropriate to recommend a range of intake that included zero, as it is uncertain whether bromine is an essential trace element. The Committee considered the upper bound of 1 mg/kg body weight/day to be unlikely to pose a risk to health. The estimated average dietary intake is equivalent to about 0.06 mg/kg/day and it is unlikely that exposure by inhalation will significantly erode the margin between this value and the ADI.

6.2.4 Carcinogenicity

137. No studies on the carcinogenicity of hydrogen bromide were found. Limited studies with bromides administered orally gave no evidence for carcinogenicity. IARC (1992) has evaluated the carcinogenicity of mists of strong inorganic acids. However hydrogen bromide was not included in this evaluation and the overall evaluation is not relevant for the concentrations considered here.

6.3. Justification for the air quality guideline value

138. The adverse effects of potential concern arising from exposure to low levels of hydrogen bromide are those on the respiratory tract and the eyes, due to its well known irritant and acidic properties.
139. In both anhydrous and aerosol forms, hydrogen bromide is a strong irritant, affecting the conjunctivae (eye) and respiratory mucosa (moist linings of the breathing airways). Because of its high solubility in water, the major irritant effects of acute exposure are usually limited to the upper passages of the respiratory tract.
140. The information available on the sensory effects of hydrogen bromide at low concentrations in humans is sparse and, in the Panel's view, is of insufficient quality to allow a confident definition of exposure levels associated with specific effects. Evidence from animal studies indicates that effects are similar in character, but less severe than those seen after exposure to a similar concentration of hydrogen chloride. This similarity in both chemistry and biological effects allows direct comparison of effect and no effect levels to be used to increase confidence in the value derived.
141. By analogy with hydrogen chloride, with which hydrogen bromide has many similarities, the Panel considered that a concentration of 2 ppm (7 mg/m³) should be regarded as a no observed adverse effect level (NOAEL) for irritant effects on the upper respiratory tract and outer eye. It was noted that this view was based on the only available study of

a small group of volunteers. Nevertheless this concentration is in good accord with the similar effects seen with hydrogen chloride, which increases confidence in the value. To reflect the uncertainty in the derivation of the NOAEL and to take into account the presence of potentially susceptible individuals in the general population, the Panel considered that applying a safety factor of 10 to the 2 ppm (3.5 mg/m³) value would be adequate for exposure in the ambient air. The Panel therefore concluded that 0.2 ppm (0.7 mg/m³) would be an appropriate guidance value for hydrogen bromide that allowed for its irritant effects on the respiratory mucosa.

142. The Panel considered that there were no grounds for regarding hydrogen bromide as a human carcinogen.

6.4. Recommendation

143. **The Panel recommends that a concentration of hydrogen bromide gas or mass equivalent aerosol not exceeding 0.2 ppm (0.7 mg/m³) over a 1-hour averaging period should protect against irritant and inflammatory effects on the skin, eyes and breathing airways. Long-term effects at these low concentrations are considered most unlikely.**

References

Alexandrov, D.D. (1983). Bromine and Compounds. In: *Encyclopaedia of Occupational Health and Safety*, 3rd Ed. Vol. 1, p. 326-329. C. Parmaggianni, Ed. International Labour Office, Geneva, Switzerland. Cited in ACGIH (2001).

ACGIH, (2001). *Documentation of the TLVs, Hydrogen Bromide*. American Conference of Government Industrial Hygienists, Cincinnati, Ohio.

Burns, M.J. and Linden, C.H. (1997). Another hot tub hazard: Reactive airway disease secondary to bromine exposure and hydrobromic acid exposure. *Chest* 111(3): 816-818.

Garlanda, T. and Basilico, S. (1993). *Occupational Exposure Limits - Criteria Document for Hydrogen Bromide*. Office for Official Publications of the European Communities, 2985 Luxembourg, Grand Duchy of Luxembourg, vi, 16.

HSE, (2002a). Occupational exposure limits. EH40/2002. HSE Books, Norwich.

HSE, (2002b). Summary Criteria for Occupational Exposure Limits, EH64/D35: Hydrogen bromide. HSE Books, Norwich.

IARC, (1992). International Agency for Research on Cancer: Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 54, Occupational

Expert Panel on Air Quality Standards

Exposures to Mists and Vapours from Strong Inorganic Acids; and Other Industrial Chemicals, pp. 189–211. IARC, Lyon, France.

Stavert, D.M., Archuleta, D.C., Behr, M.J. and Lehnert, B.E. (1991). Relative acute toxicities of hydrogen fluoride, hydrogen chloride and hydrogen bromide in nose- and pseudo-mouth-breathing rats. *Toxicol. Appl. Pharmacol.* **81**, 401–406.

van Logten, M., Wolthuis, M., Rauws, A.G., Kroes, R., den Tonkelaar, E.M., Berkvens, H. and van Esch, G.J. (1974). Semichronic toxicity study of sodium bromide in rats. *Toxicology* **2**, 257-267.

Chapter 7

Hydrogen iodide

7.1. Background

7.1.1 Basic chemical information

144. Hydrogen iodide (HI) is a water-soluble, colourless pungent gas. It is 4.4-times denser than air. Anhydrous hydrogen iodide produces aqueous hydroiodic acid when dissolved in water, which is a strong acid that is corrosive and reacts violently with bases.

Conversion factors at 25°C and 101 kPa:

$$1 \text{ ppm} = 5.231 \text{ mg/m}^3; 1 \text{ mg/m}^3 = 0.1912 \text{ ppm}$$

7.1.2 Sources

145. Releases of hydrogen iodide to air are not estimated by the National Atmospheric Emission Inventory and reporting is only required by the Environment Agency where the release is more than one tonne per annum or as a specific permit condition. The main source of hydrogen iodide in the United Kingdom is coal-fired power stations. Although the releases are not quantified, a small amount of hydrogen iodide is also likely to be released from chemical processes, domestic coal burning, clinical waste incineration and from disinfectants. Historically, iodine was also released from burning seaweed to produce fertiliser. Hydrogen iodide may also form in the atmosphere through the reaction of sea salt with acids such as nitric acid.

7.1.3 Ambient levels

146. No atmospheric measurements of hydrogen iodide in the United Kingdom have been identified. Concentrations of particle-bound iodide measured at Chilton (Oxfordshire), Styrupp (Nottinghamshire) and Warymires (Cumbria) between 1996 and 2001 range from 0.8×10^{-6} - 2.0×10^{-6} mg/m³.
147. The average global total iodine/iodide concentration has been reported by the United States Agency for Toxic Substances and Disease Registry (ATSDR, 2004) to range between 1×10^{-5} - 2×10^{-5} mg/m³ with

concentrations of between 2×10^{-6} - 1.4×10^{-5} mg/m³ being measured over land and higher levels found over the oceans.

148. On the basis of differences in their emission rates, mass concentrations of hydrogen iodide in the United Kingdom might be expected to be less than 2% of those of hydrogen chloride. Hydrogen iodide released to the atmosphere is likely to be rapidly deposited because of its high solubility in water.

7.2. Health effects

149. The Panel was unable to find any animal or human studies that specifically investigated the toxicology of hydrogen iodide. There is an extensive literature on the effects of iodine and iodide salts, largely in relation to dietary intake.

7.2.1 Animal studies

150. There is no information about the effects of acute exposure to hydrogen iodide in animals. No animal studies have been published that provide useful evidence on the health effects of ambient exposures in humans.

7.2.2 Effects in humans

151. Hydrogen iodide is a sensory and respiratory (breathing) irritant. Being highly soluble in water, the gas, following inhalation, is readily deposited in the nose and upper respiratory tract. At raised concentrations and at high breathing rates it may penetrate deeper into the lower respiratory tract and the lungs. A report in the Hazardous Substances Database indicates that exposure to about 35 ppm caused irritation of the throat after short exposure (Braker *et al.*, 1980). More severe exposures have been reported to lead to pulmonary and laryngeal oedema (build up of fluid in the lungs and walls of the voice box).
152. The irritant effect of hydrogen halides arises from the fact that they behave as strong acids in aqueous media, i.e. they dissociate forming high concentrations of hydrogen ions. Although hydroiodic acid is the thermodynamically strongest acid – i.e. the most highly dissociated when dissolved in water – hydroiodic acid, hydrobromic acid and hydrochloric acid all behave as very strong acids, and for equal molar concentrations they are expected to behave very similarly in their capacity to release hydrogen ions and cause irritation to the respiratory system.
153. Accidental exposures to high concentrations of hydrogen chloride in the workplace can lead to a form of irritant-induced asthma, reactive airways dysfunction syndrome (RADS, see Appendix 2). It seems plausible that high levels of exposure to hydrogen iodide would have similar effects. However, the exposures to hydrogen chloride involved in the development of RADS are thought to be far higher than ambient exposures to hydrogen halides.

154. Limited experience from volunteer experiments suggests that exposures to 3 ppm (10.50 mg/m³) of hydrogen bromide are associated with irritation of the nose and throat in some individuals, with a no effects level of 2 ppm (7.00 mg/m³) (see hydrogen bromide assessment). The no effects level in experiments with hydrogen chloride appears to be about 1 ppm (5.23 mg/m³) (see hydrogen chloride assessment). The Health and Safety Executive cite lowest observed effects levels (LOELs) for irritation arising from exposure of animals to hydrogen bromide or hydrogen chloride as 5 and 10 ppm (17.50 mg/m³ and 14.90 mg/m³), respectively, although the experimental data are sparse (HSE, 2002).
155. In the absence of specific information about hydrogen iodide, a committee of the United States Environmental Protection Agency (USEPA, 2003) has recommended an acute exposure guideline level for hydrogen iodide that is the same as that for hydrogen bromide. A guideline of 1 ppm (5.23 mg/m³) is recommended for averaging times of between 10 minutes and 8 hours to prevent nose irritation in humans.
156. In addition to short-term irritant effects, long-term exposure to hydrogen iodide may be associated with systemic effects. The Panel is not aware of any studies in humans or animals on the long-term consequences of hydrogen iodide inhalation. The International Agency for Research on Cancer (IARC) has evaluated the carcinogenicity of mists of strong inorganic acids (IARC, 1992). However, hydrogen iodide was not included in this evaluation and the overall evaluation is not relevant for the concentrations considered here.
157. It should be noted that the effects of inhaled iodine or iodide on iodine metabolism overall are unknown, but there is no reason to assume that this will not be absorbed and will thus probably contribute to the general body burden. Iodine is an essential element used in the synthesis of thyroid hormones. An excess intake of iodine, however, may adversely affect thyroid function. The potential effects of long-term exposure to hydrogen iodide will be discussed in an addendum to this report.

7.3. Justification for the air quality guideline

158. There are two adverse effects of potential concern: (i) the effects of iodine on the respiratory tract and the eyes due to its irritant acidic properties; and (ii) the longer term adsorption of iodine from the inhalation of hydrogen iodide.
159. In the absence of specific information about the effects of hydrogen iodide on humans, the Panel has recommended a short, 1-hour, guideline value based on its similar physico-chemical properties to the other hydrogen halides. A longer-term guideline value to protect against the chronic effects of iodine exposure will be recommended in an addendum to this report.

160. The information available on the irritant effects of hydrogen chloride or hydrogen bromide at low concentrations in humans is also sparse. Although, some data exist, as described in the relevant chapters of this report, there are insufficient data on which to base a firm opinion on the irritant effects of low exposure to these gases in the general population.
161. Based on comparison with the other hydrogen halides, the Panel considered that a concentration of 1 ppm (5.23 mg/m³) should be regarded as a no observable adverse effect level (NOAEL) for irritant or potentially inflammatory effects on the lower respiratory tract and outer eye. To reflect the uncertainty in the derivation of the NOAEL and to take into account the presence of potentially susceptible individuals in the general population, the panel considered the application of a safety factor of 10 would be adequate for exposure in the ambient air. Therefore the Panel concluded that 0.1 ppm averaged over 1 hour would be an appropriate guideline value for hydrogen iodide that allowed for its irritant effects on the outer eye and lower respiratory tract
162. The Panel considered that by analogy with other hydrogen halides there were no grounds for regarding hydrogen iodide as a human carcinogen.

7.4. Recommendation

163. **The Panel recommends that a concentration of hydrogen iodide gas or mass equivalent aerosol not exceeding 0.1 ppm (0.52 mg/m³) over a 1-hour averaging period should protect against irritant and inflammatory effects on the skin, eye and breathing airways.**

References

- ATSDR, (2004). United States Agency for Toxic Substances and Disease Registry. *Toxicological Profile for Iodine*. Available at: <http://www.atsdr.cdc.gov/toxprofiles/tp158.html>.
- Braker, W. and Mossman, A. (1988). *Matheson Gas Data Book* (edn 6). Available from the Hazardous Substances Database online database. Available at www.toxnet.nlm.nih.gov.
- HSE, (2002). Health and Safety Executive. Summary Criteria for Occupational Exposure Limits, EH64/D35: Hydrogen bromide. HSE Books, Norwich.
- IARC, (1992). International Agency for Research on Cancer: Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 54, Occupational Exposures to Mists and Vapours from Strong Inorganic Acids; and Other Industrial Chemicals, pp. 189–211. IARC, Lyon, France.
- USEPA, (2003). National Advisory Committee for Acute Exposure Guidelines Levels for Hazardous Substances. 31st Meeting (10-12/12/03). Available from www.epa.gov.

Chapter 8

Future research

164. Uncertainty surrounds the application of appropriate safety factors to data on halogens and hydrogen halides, especially for potentially susceptible groups such as the young, especially the very young, and the old. Further data are required in this area.
165. Currently no human chamber experiments have been reported with hydrogen bromide or hydrogen iodide: this is another area for which further appropriate research is recommended.
166. EPAQS has noted the complete absence of any short-term measurements of the halogens and hydrogen halides dealt with in this report, in UK urban areas. It recommends that a monitoring programme be established in urban areas, preferably in the vicinity of the large industrial plants that synthesize and utilize these compounds and downwind of large coal-fired power plants that emit them directly. This monitoring should usefully focus on short-term averaging periods (hourly periods) and should cover those compounds with large national emissions, such as hydrogen chloride, and with high toxicity, for example, chlorine. In view of the large tonnages of chlorine that are handled by industry and its apparent toxicity, continuous monitoring of short-term concentrations is recommended in the immediate vicinity of chlorine production and utilization plants.

Abbreviations

For an explanation of many of these terms see the Glossary.

ADI	Acceptable daily intake
BAT	Best available technique
CoT	The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
EAL	Environmental Assessment Level
EPAQS	Expert Panel on Air Quality Standards
FEV1	Forced expiratory volume in 1 second
HSC	Health and Safety Commission
H1	Horizontal guidance note
HSE	Health and Safety Executive
IARC	International Agency for Research on Cancer
IIA	Irritant-induced asthma
IOELV	Indicative occupational exposure limit value
IPC	Integrated pollution control
IPPC	Integrated pollution prevention and control
l	Litre
LC₅₀	Lethal concentration to 50%
LOAEL	Lowest observed adverse effects level
mg	Milligram (one thousandth of a gram)
mg/m³	Milligrams per cubic meter of air
ml	Millilitre (one thousandth of a litre)
NOAEL	No observed adverse effect level
OEL	Occupational exposure limit
PPC	Pollution prevention and control
ppm	Parts per million
RADS	Reactive airways dysfunction syndrome
STP	Standard temperature and pressure
SWORD	Surveillance of Work-Related & Occupational Respiratory Disease
USEPA	United States Environmental Protection Agency
WHO	World Health Organisation

Glossary

Acute toxicity/effects	Adverse effects occurring within a short time of administration of a single dose of a chemical, or immediately following short or continuous exposure, or multiple doses over 24 hours or less.
Allergic rhinitis	Medical term for hay fever. A common allergic reaction that causes inflammation of the nose. Symptoms typically include sneezing, congestion, a runny nose, and an itchy nose.
Alveoli	Tiny sac-like air spaces in the lung where carbon dioxide and oxygen are exchanged.
Antioxidant	A substance that inhibits oxidation, and can guard the body from the damaging effects of free radicals.
Asthma	A disease in which the lung's airways become inflamed and prone to become narrowed in response to provoking stimuli, including allergens and irritating chemicals.
Best available technique (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.
Bronchi	The large air passages that lead from the trachea (windpipe) to the lungs.

Broncho-constriction	Constriction of the bronchial airways in the lungs, causing shortness of breath, tightness in the chest, coughing, and wheezing.
Carcinogen	An agent capable of inducing cancer.
Cardiopulmonary	Relating to the heart and lungs.
Cardiovascular	Relating to the heart and blood vessels.
Chemical pneumonitis	An inflammation of the lungs (pneumonitis) or breathing difficulty caused by inhalation of noxious chemicals.
Chronic toxicity/effects	Adverse effects occurring as a result of multiple exposures occurring over an extended period of time, or a significant fraction of the animal's or the individual's lifetime (usually more than 50%).
Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (CoT)	An independent scientific committee that provides advice to the Food Standards Agency, the Department of Health and other Government Departments and Agencies on matters concerning the toxicity of chemicals.
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).
Conjunctivitis	Inflammation or infection of the membrane lining the eyelids (conjunctiva).
Corticosteroids	Anti-inflammatory drugs created from or based on a naturally occurring hormone (cortisone) produced by the cortex of the adrenal glands.
Dental fluorosis	A condition that results from excessive fluoride exposure that often causes the teeth to become discolored and the enamel of the teeth to look spotted, pitted, or stained.
Dose-response relationship	The relationship between a quantified exposure (dose), and the proportion of subjects demonstrating specific, biological changes (response).
Dyspepsia	Digestive upset, which can include nausea, vomiting, and heartburn.

Environmental assessment level (EAL)	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.
Epithelium	The tissue that covers the external surface of the body and lines hollow structures.
Exostosis	An overgrowth of bone which results in a bony projection or spur.
Fibrin	A protein essential for the clotting of blood.
Forced expiratory volume in 1 second (FEV1)	The volume of air that can be expired during the first second of a forced expiration, i.e. during blowing out as hard as possible.
Forced vital capacity (FVC)	The volume of air expired in a forced expiration following maximum inspiration.
Free radical	A molecule containing an unpaired electron, typically highly unstable and reactive. Free radicals can damage the molecular machinery of biological systems, leading to cross-linking and mutation.
Health and Safety Commission (HSC)	The Health and Safety Commission's remit is to protect everyone in Great Britain against risks to health or safety arising out of work activities; to conduct and sponsor research; promote training; provide an information and advisory service; and submit proposals for new or revised regulations and approved codes of practice.
Health and Safety Executive (HSE)	Britain's Health and Safety Commission (HSC) and the Health and Safety Executive (HSE) are responsible for the regulation of almost all the risks to health and safety arising from work activity in Britain.

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.
Hyperplasia	An increase in the number of cells in a tissue or organ, not due to tumour formation.
Hyper-responsiveness	Exaggerated response to a variety of stimuli.
Hypohalous	Compound in which a hydroxyl group (OH) is combined with a halogen atom.
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 them 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.

Lacrymation

The production of excess tears; crying.

Laryngeal

Having to do with the larynx (voice box).

LC₅₀

LC₅₀ is that concentration lethal to 50% of those exposed for the stated time.

Metabolic acidosis

A condition in which the blood is too acidic.

Methacholine challenge

A type of bronchial challenge or inhalational challenge used as a test for airway reactivity or atopic asthma; aerosolised methacholine is applied to the airways and the patient is assessed for responsiveness or hyper-responsiveness.

Mucous membranes	The moist membrane lining all body passages that communicate with the air, such as the nasal sinuses and respiratory and alimentary tracts, and having cells and associated glands that secrete mucus. Also called <i>mucosa</i> .
Mucosa	See mucous membranes.
Nasal	Of the nose.
Nasal lavage	Washing from the nose by repeated injections with a solution.
Neural	Having to do with nerves or the nervous system.
Neutrophil	A type of white blood cell that is active in immune responses and inflammatory reactions.
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. (Sometimes referred to as no observed adverse effect concentration (NOAEC)).
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.
Oedema	Excessive accumulation of fluid in the body tissues When fluid accumulates in the lungs, this is known as a pulmonary oedema.
Ossification	Process by which bone is formed.
Osteosclerosis	Abnormal hardening or increased density of bone.
Pharmacokinetic	Referring to the absorption, distribution, metabolism and excretion of a drug.
Plasma	The liquid part of the blood in which the red blood cells, the white blood cells, and platelets are suspended.
Pneumonitis	An inflammation of the lungs.

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.
ppm	Parts per million.
Pulmonary	Relating to the lung.
Pulmonary oedema	Build up of fluid in the lungs which causes breathlessness.
Respiratory airway resistance	The resistance of the airways to airflow through them. Measured in some animal experiments and occasionally in man.
Respiratory tract	The organs that are involved in breathing. These include the nose, throat, larynx, trachea, bronchi, and lungs. Also known as the respiratory system.
Respiratory mucosa	The moist membrane lining the organs involved in breathing including the nose, throat, larynx, trachea, bronchi, and lungs.
Rhinitis	Inflammation of the lining of the nose.
Safety factor	A number (equal or greater than 1) used to divide NOAEL or LOAEL values derived from measurements in animals or small groups of humans, in order to estimate a NOAEL or LOAEL value for the whole human population; also called uncertainty factor. Safety factors are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to humans, (3) the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure to lifetime 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.

SHEILD	Midland Thoracic Society's Surveillance Scheme for Occupational Asthma for the West Midlands.
Skeletal fluorosis	An excessive accumulation of fluoride in bone associated with increased bone density and outgrowths.
Squamous cell metaplasia	A change in the nature of tissue into squamous epithelium; may be an early sign of malignant change.
Squamous cell	An epithelial cell that is flat like a plate and forms a single layer of epithelial tissue (tissue that covers the external surface of the body and lines hollow structures).
Subacute toxicity/effects	See subchronic toxicity/effects.
Subchronic toxicity/effects	Between acute and chronic toxicity, also called subacute toxicity. Adverse effects occurring as a result of repeated daily dosing of a chemical, or exposure to the chemical, for part of an organism's lifespan (usually not exceeding 10%). With experimental animals, the period of exposure may range from a few days to 6 months.
Surfactant	A substance formed in the lungs that helps keep the small air sacs, or alveoli, from collapsing and sticking together.
Surveillance of Work-Related & Occupational Respiratory Disease (SWORD)	Scheme that aims to determine the scale and patterns of work-related respiratory disease in the UK and to identify the agents thought to be responsible along with information on industry and occupation. It has been running since 1988 and is funded by the Health and Safety Executive, with the support of the British Thoracic Society and the Society of Occupational Medicine. Approximately 450 respiratory physicians throughout the UK participate in reporting occupational respiratory disease. Twenty of these are core reporters who report every month; the remainder are sample reporters who are sampled at random and report for one month only each year.
Susceptible group	A group of people who, as a result of genetic predisposition, age, illness or unusual exposure, are more affected by toxic substances than other people (See Section 1.2.2 and Appendix 1 for more detail).

Systemic effect	Concerning or affecting the body as a whole.
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.
Time-weighted average	The average concentration of a chemical to which it is permissible to expose a person to over a given time period.
Tracheobronchitis	Common respiratory infection characterised by inflammation of the trachea (windpipe) and the bronchi (tubes that carry air from the trachea to the lungs).
Upper respiratory tract	Includes the nose, sinuses, pharynx (throat), and larynx (voice box). The lower respiratory tract includes the trachea (windpipe), bronchial tubes (two branches from the windpipe), bronchioles (smaller bronchial tubes), and alveoli (tiny sacs in the lungs where the exchange of oxygen and carbon dioxide occurs).
Uric acid	Product of protein metabolism (breakdown).
WATCH Panel	Health and Safety Commission's Advisory Committee on Toxic Substances.

Appendix 1: Children as a vulnerable group

A1.1: Background

167. In 1997, the environmental ministers of the G8 signed a declaration that national policies should take into account the specific exposure pathways and dose-response characteristics of children when conducting risk assessment and setting protective standards. When considering the effect of breathing halide gases, EPAQS considered the factors that could increase the vulnerability of children to these agents.

A1.2: Lung growth and physiology

168. From birth to 8 years of age, the lung grows by developing new breathing units (i.e., new alveoli and capillaries). Thereafter, lung growth is maintained through expansion of these structures (Dietert *et al.*, 2000). At birth, the surface area of the lung is 3 m², which increases in proportion to the rest of the body to 75 m² in adulthood (Clewell *et al.*, 2002). Since changes in lung surface area closely match overall body growth (e.g., weight), exposure of the lower airway to inhaled gases per breath is approximately the same in children and adults. However, the metabolic rate of children is significantly higher than in adults. In order to match oxygen consumption with carbon dioxide production, children must breathe more frequently than adults. This, in turn, results in an increased exposure per minute of the lower airways of children to inhaled gases (de Zwart *et al.*, 2004). Thus the volume of inhaled air indexed to body weight (a marker of lung surface area) is 400 ml/minute/kg for newborns (Figure 1) and 150 ml/minute/kg for adults (Etzel & Balk, 2003).
169. Over the longer-term, inhaled toxins that deviate the normal pattern of lung growth may impair lung function in adulthood. For example, Gauderman recently reported that children exposed to a combination of high levels of nitrogen dioxide, acid vapour and particulate matter over an eight year period showed deficits in growth in their forced expiratory volume in one second (FEV1) (Gauderman *et al.*, 2004). Although it is not clear whether these changes are permanent or reversible, these data suggest that long-term exposure to pollutants from fossil fuels may affect lung growth.

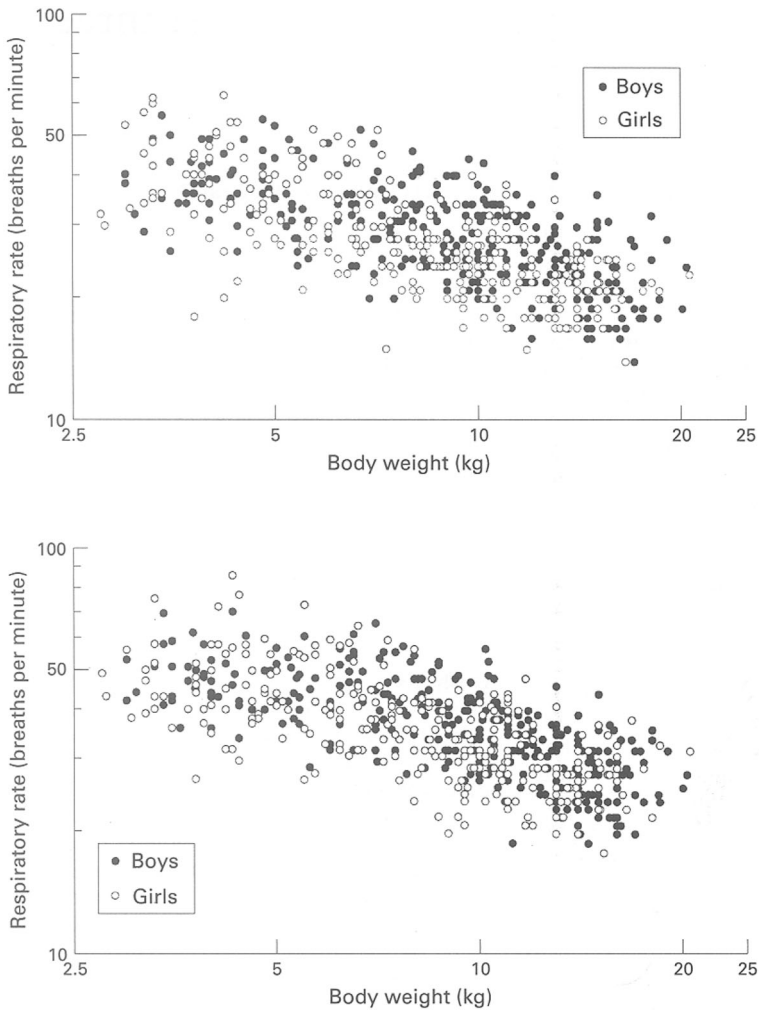


Figure 1. Relationship between respiratory rate and body weight. (Source: Gagliardi & Rusconi, 1997).

A1.3: Lung defences

170. Many respiratory pollutants are powerful oxidants and their impact relates in part to the ability of the lung to nullify the oxidant challenge (Kelly, 2003). The mature lung has a range of antioxidant defences, which together perform this task. Prior to birth, pulmonary (lung) antioxidant defences, like the surfactant system, are immature. This developmental pattern is highlighted in babies born prematurely and who require supplemental oxygen – resulting in oxidative lung injury (Schock *et al.*, 2001). It is unclear whether the lung antioxidant defences in children are better, worse or the same as adults.

A1.4: Models of exposure

171. Models have been developed that compare the effects of irritant gases in adults and children (Sarangapani *et al.*, 2003). Table 1 shows the effect of age on the modelled exposure of lower respiratory tract cells for ozone (an irritant and oxidising gas). There is little difference in exposure between males and females, but for the same inhaled concentration, infants and children have increased exposure compared with adults.

Table 1. Effect of age and gender on extraction of ozone by lower airway cells, indexed to a 25-year-old. (Adapted from Sarangapani *et al.*, 2003).

Age (years)	Extraction of ozone per unit surface area of airway	
	Male	Female
1	4.5	6.6
5	1.9	2.8
10	1.8	2.4
15	1.4	1.6
25	1.0	1.0

A1.5: Summary

172. There are factors that could increase the vulnerability of children's lungs to irritant gases. However, it remains uncertain whether children are a vulnerable group when considering the effects of halide gases. We have therefore taken a precautionary approach, and have explicitly considered children as a “potentially” vulnerable group. A correction factor has therefore been applied to take this uncertainty into account.

References

- Clewell, H.J., Teeguarden, J., McDonald, T., Sarangapani, R., Lawrence, G., Covington, T. (2002). Review and evaluation of the potential impact of age- and gender-specific pharmacokinetic differences on tissue dosimetry. *Crit. Rev. Toxicol.* **32**, 329–389.
- Dietert, R.R., Etzel, R.A., Chen, D., Halonen, M., Holladay, S.D., Jarabek, A.M. (2000). Workshop to identify critical windows of exposure for children's health: immune and respiratory systems work group summary. *Environ. Health Perspect.* **108**, Suppl. 3, 483–490.
- Etzel, R.A. & Balk, S.J. (eds) (2003). Developmental toxicity: special considerations based on age and developmental stage. In: *Pediatric Environmental Health*. pp 9–23. American Academy of Pediatrics, Elk Grove Village, IL, USA.

Expert Panel on Air Quality Standards

Gagliardi, L., Rusconi, F. (1997). Respiratory rate and body mass in the first three years of life. The working party on respiratory rate. *Arch. Dis. Child*; 76, 151-4.

Gauderman, W.J. *et al.* (2004) The effect of air pollution on lung development from 10 to 18 years of age. *N. Engl. J. Med.* **351**,1057–1067.

Kelly, F.J. (2003). Oxidative stress: its role in air pollution and adverse health effects. *Occup Environ Med.* **60** (8), 612-6.

Sarangapani, R., Gentry, P.R., Covington, T.R., Teeguarden, J.G., Clewell, H.J. (2003). Evaluation of the potential impact of age- and gender-specific lung morphology and ventilation rate on the dosimetry of vapors. *Inhal. Toxicol.* **15**, 987–1016.

Schock, B.C. *et al.* (2001). Oxidative stress in lavage fluid of preterm infants at risk of chronic lung disease. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **281**, 1386–1391.

de Zwart, L.L., Haenen, H.E., Versantvoort, C.H., Wolterink, G., van Engelen, J.G., Sips, A.J. (2004). Role of biokinetics in risk assessment of drugs and chemicals in children. *Regul. Toxicol. Pharmacol.* **39**, 282–309.

Appendix 2: Irritant-induced asthma and RADS

Note that this appendix, which was originally published on the internet at <http://www.defra.gov.uk/environment/airquality/aqs/pdf/rads.pdf>, was commissioned to inform EPAQS about the general issues associated with irritancy. It is not specific to halogens and hydrogen halides.

A2.1: Summary

173. A single high exposure of a person to an irritant chemical by inhalation, typically as an accidental incident involving a gas or vapour, can mean they run the risk of developing a type of asthma called reactive airways dysfunction syndrome or RADS. These people have irritable bronchial tubes and this hypersensitive state may last for some years. In many cases (although not all) it is much more resistant to treatment than conventional asthma but is a relatively rare condition; fewer than one in a thousand of all cases of asthma starting in adulthood are RADS. The condition has not been reported in children.
174. More recently, it has been suggested that lower levels of exposure to irritant substances repeatedly over time may also lead to the development of asthma. As it is possible that the biological processes involved in these people are similar to those seen in RADS, the general term irritant induced asthma (IIA) has been applied to this condition, a term which now includes RADS itself. Little is known of the outcome for IIA in general, but it is unlikely that it differs substantially from that in conventional asthma. Although outdoor air contains substances which, at high dose, have been known to cause RADS, levels of exposure to the population breathing outside air on a day-to-day basis are very much lower than those which would result in RADS. Consequently, although in theory persistent exposure to low levels of substances which at high dose can cause RADS could themselves lead to the development of asthma, it is most unlikely that this occurs in the population at large.

A2.2: Terminology and definition

175. The term, reactive airways dysfunction syndrome (RADS) was first coined by Brooks in 1985 (Brooks *et al.*, 1985) when he produced fairly

strict criteria for an asthmatic-like state occurring within 24 hours of an acute, very high dose exposure and the presence of bronchial hyper-responsiveness to methacholine. In 1995 a consensus statement on asthma in the workplace (Chan-Yeung, 1995) suggested that these strict criteria should be relaxed slightly and a more comprehensive term introduced, namely irritant induced asthma (IIA). The criteria for IIA were laid down as:

- absence of previous respiratory complaints;
- onset of asthma symptoms within 24 hours of a single exposure to a high concentration of respiratory irritant gas;
- persistence of asthma symptoms for at least 3 months after exposure;
- symptoms associated with increased bronchial responsiveness and/or the presence of airflow obstruction with reversibility to bronchodilator in the absence of previous lung disease.

176. This definition would cover all forms of IIA, including classical RADS and low-dose exposure to irritants over time. This issue of a changing definition was highlighted in a recent review of the area (Tarlo, 2003), where it was recognised that some authors included multiple acute exposures as causing IIA, some allowed up to a week after exposure for the onset of symptoms to occur, and some allowed lesser degrees of exposure – so called low-dose RADS or “not so sudden IIA” in their definition of IIA (Brooks *et al.*, 1998). The possibility of exposures such as those which are recognised to lead to RADS/IIA could cause a stepwise worsening of patients with pre-existing respiratory disease is plausible but does not fall under these definitions. However, in the context of considering the health effect of the specific ambient exposures considered here, this should be regarded as possible although difficult to prove.
177. This raises the issue of non-peak irritant exposures to gases, fumes and some dusts as a cause of airways disease but, while the causal pathways may be real, the evidence is based on isolated reports or small series. However, this concept fits with reports of asthma developing in cleaners and workers chronically exposed to solvents (Medina-Ramon *et al.*, 2003; Rosenman *et al.*, 2003) and is consistent with the finding that 18% of cases of occupational asthma reported to the SHIELD Scheme in the West Midlands were due to irritants (Gannon & Burge, 1993). More recently a European survey (Kogevinas *et al.*, 1999) also showed similar associations in workers exposed to irritants. In the occupational setting, small but above normal exposures have been reported to result in accelerated fall in forced expiratory volume in one second (FEV1) and enhanced bronchial responsiveness (Gautrin *et al.*, 1999).
178. If accepted, this variation in the diagnostic criteria for IIA will lead to differences in assessment of its prevalence. Estimates depending upon the diagnostic criteria used, range from 2-3% (Brooks *et al.*, 1985; Tarlo & Broder, 1989) up to 18% (Ross & MacDonald, 1996).
179. From the point of view of environmental exposures, the possibility that longer-term exposures to chemicals might lead to asthma is therefore of

great relevance when deciding about air quality standards. However, there are no usable data to aid our deliberations in this regard.

180. The SWORD database has had 301 cases of halide exposure resulting in respiratory disease reported to them, with an estimate of the likely total UK number being 477 between 1989 and 2003. Using the estimated UK figures, 338 were due to chlorine, 130 to hydrogen chloride (either as gas or acid) and 9 to bromine. Most were recorded simply as inhalation accidents (with presumably no medium- to long-term sequelae) but 69 (20%) of those exposed to chlorine were reported to have developed asthma (whether irritant or sensitised) as did 26 (20%) of those exposed to hydrogen chloride. The commonest occupational group exposed was chemical, gas and petroleum operators (10% for chlorine, 8.5% for hydrogen chloride). This implies that a substantial minority of those exposed to either of these agents in an acute high dose develop an asthma type syndrome as a result, but these exposures are generally assumed to be far higher than any ambient exposures other than those encountered as spills/leaks.

A2.3: Pathology

181. There is very little difference if any between the histological appearances of IIA/RADS and conventional occupational asthma. There is some suggestion that in RADS there is less airway eosinophilic infiltration and more fibrosis (Brooks *et al.*, 1985) but data are very limited.
182. It is possible that specific exposures may lead to reproducible patterns of IIA, such as exposures to chlorine (Chan-Yeung *et al.*, 1994; Gautrin *et al.*, 1994). In one such worker (Lemiere *et al.*, 1997) who underwent bronchial biopsies on four occasions, initial epithelial desquamation with fibrinous exudate was followed by proliferation of basal cells and regeneration of the epithelium leading to collagen deposition in the submucosa with basement membrane thickening (Boulet *et al.*, 1997) which might explain the attenuated airflow limitation reversibility seen in RADS. These steps were confirmed in animal models (Demnati *et al.*, 1998) but, interestingly, inflammatory cells do not seem to play an essential role. However, this proposed model is not consistently supported in larger studies (Glindmeyer *et al.*, 1997).
183. The association of what appears to be IIA in rescue workers involved in the destruction of the World Trade Centre (Prezant *et al.*, 2002) suggests that this condition merely represents the final common pathway of a number of patterns of insults resulting in persistent airway irritative symptoms but with no specific underlying pathology.

A2.4: Risk Factors

184. Specific risk factors may contribute to the development of IIA. The most important causal factor is the dose of the agent as the nearer

individuals are to a spill, the greater is the risk of developing RADS (Jajosky *et al.*, 1999; Renisch *et al.*, 2001). Current cigarette smoking and atopy also appear to be risk factors although less strongly than has been identified for conventional occupational asthma.

A2.5: Prognosis

185. In classical RADS, the tendency is for improvement to occur over time, although in many individuals symptoms continue for years. There is much less evidence about what happens with IIA more broadly although the implication is that this is a much more permanent state of affairs. However, as yet, there are no longitudinal studies in these particular groups.
186. In one follow up study (Malo *et al.*, 1994), normalisation of FEV1 and PC₂₀⁷ to methacholine in approximately 25% of subjects after two and a half years was seen, the time course of recovery being similar to occupational asthma with a latency period, the maximum improvement occurring in the first two years.
187. Treatment is based on conventional asthma therapy but the response is often poor raising the issue of whether this should be regarded as more of a chronic obstructive pulmonary disease (COPD)/bronchitic picture rather than asthma. There is very limited information on treatment of the condition, the role of oral steroids being debatable although apparently conferring some protection in a mouse model (Das *et al.*, 1993).

A2.6: Summary

188. In summary, IIA is probably commoner than has been thought; is associated with acute high exposures to irritant substances (not just gases); and has a variable prognosis, with some people being disabled for some years after exposure. In general terms, the response to anti-asthma therapy is disappointing.
189. Longer-term exposure to lower levels of irritants may also lead to the development not only of asthma but a COPD/bronchitis picture in exposed workforces (Balmes, 2002). The inference of this observation is that environmental exposures, at an appropriate level, might also be contributing to the development of airways disease in the community. However, the data on dosing is very limited and at this stage it would probably be unwise to infer that ambient (i.e. low-level) exposures to gases or fumes which at high level are known to cause RADS, might contribute to the burden of airways disease.

⁷ Provocation concentration 20: the dose of a test compound which causes a 20% fall in FEV1.

References

- Balmes, J. (2002). Occupational airways disease from chronic low-level exposures to irritants. *Clinics in Chest Medicine* **23**, 727-35.
- Boulet, L.P., Laviolette, M., Turcotte, H., Cartier, A., Dugas, M., Malo, J.L., Boutet, M. (1997). Bronchial subepithelial fibrosis correlates with airway responsiveness to methacholine. *Chest*; **112**, 45-52.
- Brooks, S.M., Weiss, M.A., Bernstein, I.L. (1985). Reactive airways dysfunction syndrome (RADS): persistent asthma syndrome after high level irritant exposures. *Chest*. **88**, 376-84.
- Brooks, S.M., Hammad, Y., Richards, I. (1998). The spectrum of irritant-induced asthma: sudden and not-so sudden and the role of allergy. *Chest* **113**, 42-9.
- Chan-Yeung, M., Lam, S., Kennedy, S., Frew, A.J. (1994). Persistent asthma after repeated exposure to high concentrations of gases in pulp mills. *Am J Respir Crit Care Med*. **149**,1676-80.
- Chan-Yeung, M. (1995). ACCP Consensus Statement on Assessment of Asthma in the Workplace. *Chest*. **108**, 1084-113.
- Das, R., Blanc, P.D. (1993). Chlorine gas exposure and the lung: a review. *Toxicol. Indust. Health*. **9**, 439-55.
- Demnati, R., Fraser, R., Ghezzi, H., Martin, J.G., Plaa, G., Malo, J.L. (1998). Time-course of functional and pathological changes after a single high acute inhalation of chlorine in rats. *Eur. Respir. J.* **11**, 922-8.
- Gannon, P.F., Burge, P.S. (1993). The SHIELD scheme in the West Midlands Region, United Kingdom. *Br. J. Ind. Med.* **50**, 791-6.
- Gautrin, D., Boulet, L.P., Boutet, M., Dugas, M., Bherer, L. *et al.* (1994). Is reactive airways dysfunction syndrome a variant of occupational asthma? *J. Allergy Clin. Immunol.* **93**, 12-22.
- Gautrin, D., Leroyer, C., Infante-Rivard, C., Ghezzi, H., Dufour, J.G., Girard, D., Malo, J.L. (1999). Longitudinal assessment of airway caliber and responsiveness in workers exposed to chlorine. *Am. J. Respir. Crit. Care Med.* **160**, 1232-7.
- Glindmeyer, H., Lefante, J., Freyder, L., Jones, R., Freidman, M., Weill, H. (1997). Relative rate of new onset asthma among workers exposed to irritant chemicals. *Am. J. Respir. Crit. Care Med.* **155**, A258.
- Jajosky, R.A., Harrison, R., Flattery, J. *et al.* (1999). Surveillance of work-related asthma in selected U.S. States - California, Massachusetts, Michigan, and New Jersey, 1993-1995. *MMWR Surveill. Summ.* **48(3)**, 1-20.

Expert Panel on Air Quality Standards

Kogevinas, M., Anto, J.M., Sunyer, J., Tobias, A., Kromhout, H., Burney, P. (1999). Occupational asthma in Europe and other industrialised areas: a population-based study. European Community Respiratory Health Survey Study Group. *Lancet*. **353**, 1750-4.

Lemière, C., Malo, J.L., Boutet, M. (1997). Reactive airways dysfunction syndrome due to chlorine: sequential bronchial biopsies and functional assessment. *Eur. Respir. J.* **10**, 241-4.

Malo, J.L., Cartier, A., Boulet, L.P., L'Archevêque, J., Saint-Denis, F., Bhérier, L., Courteau, J.P. (1994). Bronchial hyperresponsiveness can improve while spirometry plateaus two to three years after repeated exposure to chlorine causing respiratory symptoms. *Am. J. Respir. Crit. Care Med.* **150**, 1142-5.

Medina-Ramon, M., Zock, J.P., Kogevinas, M. *et al.* (2003). Asthma symptoms in women employed in domestic cleaning: a community based study. *Thorax* **58**, 950-4.

Prezant, D.J., Weiden, M., Banauch, G.I., McGuinness, G., Rom, W.N. *et al.* (2002). Cough and bronchial responsiveness in firefighters at the World Trade Center site. *N. Engl. J. Med.* **347**, 806-15.

Renisch, F., Harrison, R.J., Cussler, S. *et al.* (2001). Physician reports of work-related asthma, 1993-1996. *Am. J. Ind. Med.* **39**, 72-83.

Rosenman, K.D., Reilly, M.J., Schill, D.P. *et al.* (2003). Cleaning products and work-related asthma. *J. Occup. Environ. Med.* **45**, 556-63.

Ross, D.J., McDonald, J.C. (1996). Asthma following inhalation accidents reported to the SWORD project. *Ann. Occup. Hyg.* **40**, 645-50.

Tarlo, S.M., Broder, I. (1989). Irritant-induced occupational asthma. *Chest*. **96**, 297-300.

Tarlo, S.M. (2003). Workplace irritant exposures: do they produce true occupational asthma? *Ann. Allergy Asthma Immunol.* **90(suppl)**, 19-23.

Appendix 3: Respondents to Guidelines for Halogens and Hydrogen Halides in Ambient Air for Protecting Human Health against Acute Irritancy Effects – Draft for comment

Comments were gratefully received from the following organisations and individuals on the draft of this report, which was published in April 2005.

British Coatings Federation Ltd.

Institute of Occupational Medicine

Dr A.K. Mallett

Mr A.M. Moses

The Chartered Institution of Water and Environmental Management (CIWEM)

Dr R. Barrett, Open University

Scottish Environment Protection Agency (SEPA)

Joint Environmental Programme (JEP)

Natural Environment Research Council (NERC)