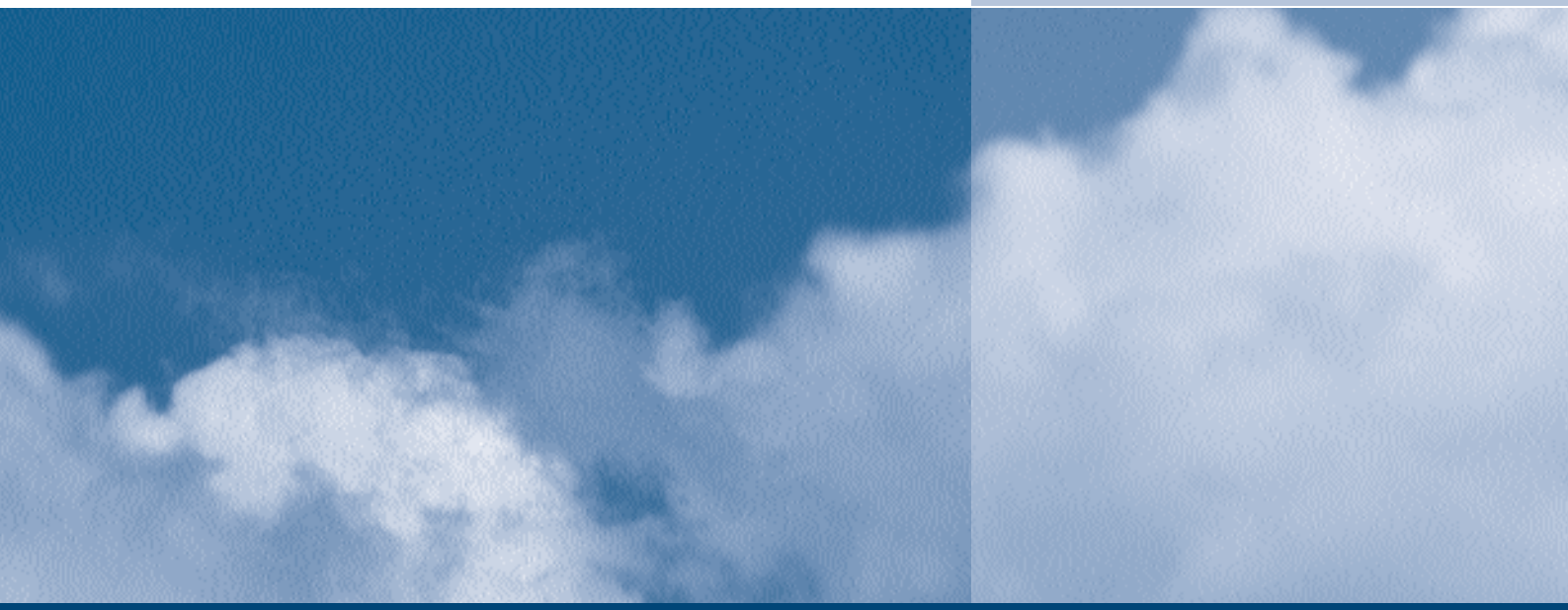

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A Review of the Toxicity and Environmental Behaviour of Hydrogen Fluoride in Air

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Professor Mike Depledge Head of Science

EXECUTIVE SUMMARY

Hydrogen fluoride is a colourless, extremely reactive water-soluble gas that dissolves to form hydrofluoric acid. It is a widely used industrial chemical. The major UK source of hydrogen fluoride is coal combustion. Other processes such as aluminium smelting and the glass and brick industries are also sources of emissions. Some releases may also occur from the chemical and oil industries. In 1995 there were three locations in the UK at which hydrogen fluoride was synthesised. However, releases from these works were very low. There has been a considerable decrease in UK annual emissions over the past 20 years as a result of the reduction in solid fuel use and the installation of flue gas desulphurisation at some power stations. It has been estimated that volcanic activity is a major global source of hydrogen fluoride.

Hydrogen fluoride does not react with hydroxyl radicals, nor does it degrade by UV light in the atmosphere. However, the removal of hydrogen fluoride from the atmosphere is likely to be rapid as a result of its high reactivity and water solubility leading to high dry and wet deposition velocities. Estimated half-lives of 14 and 12 hours for dry and wet deposition, respectively, have been calculated.

There are no ongoing long-term measurements of hydrogen fluoride in UK ambient air. A number of short term studies have been carried out around industrial sites, but these are generally of short duration and designed to determine boundary fence concentrations rather than population exposure.

Fluoride concentrations in vegetation are monitored around some industrial plants, aluminium smelters and chemical works. A survey of tree health was recently carried out around one of the largest aluminium smelters in the UK. The conclusions of the study were equivocal as to whether the poor health of some trees near to, but outside the plant boundary was a result of the poor nurturing quality of the colliery spoil in which they were grown, or air pollution.

Several sampling methods exist for hydrogen fluoride, many of which measure the fluoride present in the resulting sample. Open path monitoring methods appear to be available which may have sufficient sensitivity and response time to detect short-term fluctuations in concentration. However these methods have generally not been demonstrated in routine use and are generally regarded as research methods suitable for short-term campaigns rather than continuous measurement networks. However if cost was not a significant barrier then it is likely that these methods could be so used.

Extensive toxicological reviews for hydrogen fluoride, including the inhalation route, have been published by the American Conference of Governmental Industrial Hygienists (ACGIH), the United States Environmental Protection Agency (USEPA), the United States Department of Health and Human Services, the Agency for Toxic Substances and Disease Registry (ATSDR), the European Chemicals Bureau (ECB) and the World Health Organization International Programme on Chemical Safety (IPCS). This document is largely based on these reviews. Particular mention is made of those studies that have been used to derive the inhalation limits.

Although it is the form of fluoride during exposure that may influence the amount of fluoride that finally reaches the systemic circulation, studies have determined that this is

not dependent on the fluoride species to which one is exposed. Therefore, where there are data gaps for systemic effects for hydrogen fluoride these are addressed by using experimental results of other inorganic fluorides, even if administered by a route other than inhalation. Where appropriate in this document, comment has been made to this effect although the studies are not described in detail as extensive reviews are available as mentioned above.

Hydrogen fluoride is a colourless, highly irritating and corrosive gas. It is extremely soluble in water and reacts with water to produce heat and forms hydrofluoric acid. Skin contact with liquid hydrogen fluoride can cause severe burns. The acute inhalation toxicity of hydrogen fluoride has been studied in several laboratory animal species and its irritant properties have been studied with human volunteers. It is a severe irritant to the eyes, skin, and nasal passages. Exposure to high concentrations may result in hydrogen fluoride penetration into the lungs, resulting in oedema and haemorrhage. There are large variations in reported concentrations causing the same effect among animal studies. This is due to difficulties in measurement techniques encountered by some of the investigators, thus limiting the value of their quantitative data. In addition, experimental details and descriptions of effects are inadequate in some of the studies.

There are numerous sub-lethal and lethal acute inhalation studies on six mammalian species. Sixty-minute LC_{50} values ranged from 342 ppm (284 mg/m^3; mouse) to 2300 ppm (1000 mg/m^3; rat) with mild symptoms (eye, nasal or respiratory irritation) seen at concentrations of between 103 ppm (86 mg/m^3; rat) and 157 ppm (131 mg/m^3; dog). The main animal experiment from which a no observed adverse effect level (NOAEL) could be derived was a 90-day rat study in which no changes in blood parameters were observed at a dose of 1 ppm (0.72 mg/m^3).

In acute human volunteer studies, bronchial inflammation was observed after one-hour exposure to concentrations of 1.8 to 7.8 ppm (1.5 to 6.4 mg/m^3) while a further study reported lower and upper respiratory irritation at concentrations of 3.0 to 6.3 ppm (2.5 to 5.2 mg/m^3). In a sub-chronic experiment, exposure to 2 ppm (1.7 mg/m^3) for 6 hours/day for 15-50 days was only slightly irritating.

Exposure to multiple airway irritants and incomplete exposure data prevented definitive conclusions being drawn from occupational studies.

Contents

1. Introduction

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

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

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

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

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

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

Hydrogen fluoride (HF) (CAS number 7664-39-3) is a gas or vapour under environmental conditions. It has a melting point of -83ºC and a boiling point of 19.5ºC. It is a colourless gas with a pungent odour. It is non-flammable, but is highly toxic and irritating, dissolving in water to produce a strongly acidic solution that gives rise to fluoride salts. It is in this aqueous form that it is usually encountered (hydrofluoric acid) containing up to 70% hydrogen fluoride. Hydrofluoric acid dissolves glass and attacks many metals (releasing flammable hydrogen in the process), minerals and organic substances. As a result of its aggressive properties solutions of hydrogen fluoride are kept in plastic containers.

The data for the inhalation toxicity of hydrogen fluoride has been summarised within this document. Although the form of fluoride during exposure may influence the amount of fluoride that finally reaches the systemic circulation, studies have determined that the form circulating in the body following exposure is not dependent on the fluoride species to which one is exposed. Therefore, where there are data gaps for systemic effects for HF, these may be addressed by using experimental results of other inorganic fluorides, even if administered by a route other than inhalation. Where appropriate in this document, comment has been made to this effect although the studies are not described in detail as extensive reviews carried out for the European Commission (ECB 2003) and by the World Health Organisation have addressed the systemic toxicity of the fluoride ion.

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

1.1 Anthropogenic Sources of Hydrogen Fluoride

Hydrogen fluoride is released when fluorine-containing minerals are heated to high temperatures. The largest sources are coal-fired power stations, the largest emission sector in the UK, and aluminium smelters. Concentrations of fluoride in coal have been found to range between 4 to 30 g/kg.

Other smaller sources include phosphate fertiliser plants, glass, brick and tile works, plastics manufacture, copper and nickel production, and adhesive production. The actual production of hydrogen fluoride itself is estimated to account for less than 2% of all industrial releases of the substance.

The production of hydrogen fluoride for chemical industry purposes involves the mineral fluorspar (CaF_2) being treated with concentrated sulphuric acid under temperatures around 200 to 300ºC. The hydrogen fluoride formed evaporates and is condensed and purified by distillation. On the basis of the quantity produced, hydrogen fluoride is the most important fluoride manufactured. About 74,000 tonnes were produced in 1993 in the UK at three sites; ICI (Runcorn), Rhône-Poulenc (Avonmouth) and Laporte Fluorides (Rotherham). Most hydrogen fluoride was subsequently used at these sites for the production of fluorinated organic chemicals. About 300,000 tonnes of HF are produced per year in the EU, with 875,000 tonnes being the annual worldwide production in 1990.

Hydrogen fluoride is used mainly in the production of synthetic cryolite (Na_3AlF_6) and aluminium fluoride (AlF_3). Its other major use was in the production of chlorofluorocarbons, but with the Montreal Protocol restrictions this market has been severely limited. Hydrogen fluoride has a specialised use in the nuclear industry in the synthesis of uranium tetrafluoride (UF_4) and uranium hexafluoride (UF_6) for isotope separation. Other uses include etching semiconductor devices, manufacture of dental prostheses, cleaning and etching glass, ceramics manufacture, electroplating, cleaning brick and aluminium, removing rust and tanning leather, as well as in petrochemical manufacturing processes.

Hydrogen fluoride may also be formed when organic fluorine compounds (e.g. CFCs, halons, fluoropolymers etc used as aerosol propellants, refrigerants, flame-retardant chemicals, plastics or rubbers) are exposed to fires.

The UK's national atmospheric emissions inventory provides estimates of the emissions of hydrogen fluoride from 1970 to 2002. Hydrogen fluoride is primarily released to air from combustion of fuels that contain trace amounts of fluorine. This results in the emissions of hydrogen fluoride being dominated by the combustion of solid fuel. Table 1 and Figure 1 summarise the UK emissions of hydrogen fluoride. Emissions have fallen by 62.9% between 1970 and 2002. The increase in hydrogen fluoride emission between 1999 and 2002 is caused by an increase in the quantity of coal consumed for electricity generation. The main source of these emissions is coal combustion so the fall is a result of the decline in coal use and also the installation of flue gas desulphurisation at Drax and Ratcliffe power stations since 1993. The other sources of hydrogen fluoride which are significant on a national scale are its emission from other high temperature processes such as aluminium smelting and brick works (Dore 2003). The uncertainty of the national total emission is estimated as ±20%. This large uncertainty arises from the emission being dominated by a limited number of major sources that are relatively poorly characterised (Passant 2002).

Within England and Wales, the major industries are regulated by the Environment Agency. In other parts of the UK similar regulatory controls are in place. Although hydrogen fluoride is not on the list of compounds against which the Environment Agency requires companies to report estimates of their annual emissions to its Pollution Inventory, a limited amount of site-specific information is available. This indicates that in 2002 approximately 2.79 kilo tonnes of hydrogen fluoride were released. The largest reported sources are shown in Table 1.2.

Table 1.1 - UK Emissions of Hydrogen Fluoride by United Nations Economic Commission for Europe Source Category (kilotonnes)

BY UN/ECE CATEGORY		1970	1980	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2002 % emissions
Combustion in Energy Production	Public Power	6.1	7.1	6.6	6.5	6.1	5.1	4.6	3.5	2.9	2.0	2.1	1.8	1.8	2.3	3.6	66.4%
	Other Combustion & Transformation processes.	2.8	1.1	1.0	0.9	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.7	0.6	10.9%
Combustion in Commercial/ Institutional/ Residential Use	Residential Plant	1.8	0.8	0.4	0.4	0.4	0.4	0.4	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	3.0%
	Commercial /Public Sector /Agricultural Combustion.	0.4	0.2	0.1	0.1	0.1	0.1	0.1	0.0	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.3%
Combustion in Industry	Iron & Steel Combustion	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3%
	Other Industrial Combustion	2.8	1.4	1.2	1.1	1.1	1.0	1.1	1.1	1.0	1.0	0.9	0.8	0.7	0.7	0.6	11.6%
Production Processes		0.6	1.9	1.4	1.5	1.2	1.2	1.2	1.2	1.2	1.2	1.2	0.5	0.4	0.5	0.4	7.5%
TOTAL		14.5	12.6	10.7	10.6	9.8	8.6	8.0	6.9	6.1	5.3	5.2	4.1	3.9	4.5	5.4	100.0%

Table 1.2 – The Point Source Releases of Hydrogen Fluoride reported to the Environment Agency and SEPA

Operator	Site	Process	HF Emission 2002 Tonnes	SO_2 Emission 2002 Tonnes	SO_2/HF
Scottish Power PLC	Longannet Power Station, Kincardine-on-Forth, Fife	Coal fired power station	282	67100	238
RWE Innogy PLC	Tilbury Power Station, Tilbury, Essex	Coal fired power station	244	17100	70
EDF Energy (West Burton Power) Ltd	West Burton Power Station, Retford, Nottinghamshire	Coal fired power station	238	68461	288
Powergen UK PLC	Kingsnorth Power Station, Rochester, Kent	Coal and oil fired power station	228	32900	144
RWE Innogy PLc	Aberthaw Power Station, Barry, South Glamorgan	Coal fired power station	210	31100	148
AEP Energy Services UK Generation Ltd	Ferrybridge C Power Station, Knottingley, West Yorkshire	Coal fired power station	199	48144	242
AEP Energy Services UK Generation Ltd	Fiddlers Ferry Power Station, Widnes Warrington, Cheshire	Coal fired power station	191	28200	148
EDF Energy (Cottam Power) Ltd	Cottam Power Station, Retford, Nottinghamshire	Coal fired power station	189	70500	373
AES Drax Power Ltd	Drax Power Station, Selby, North Yorkshire	Coal fired power station	165	34800	211
Rugeley Power Ltd	Rugeley Power Stations, Rugeley, Staffordshire	Coal fired power station	161	34358	213
Alcan Primary Metal Europe	Lynemouth Smelter, Ashington, Northumberland	Aluminium smelter	140	2580	18
Powergen UK PLC	Ironbridge Power Station, Telford, Shropshire	Coal fired power station	124	31600	255

Operator	Site	Process	HF Emission 2002 Tonnes	SO_2 Emission 2002 Tonnes	SO_2/HF
Shanks Waste Services Ltd	Green Lane, Stewartby, Beds.	Waste management	97	0	0
Anglesey Aluminium Metal Ltd	Penrhos Works, Holyhead, Gwynedd	Aluminium smelter	90	1256	14
PPG Industries (UK) Ltd	Fiber Glass Division, Wigan, Lancashire	Glass fibre works	80.451	0	0
Powergen UK PLC	Ratcliffe-on-Soar Power Station, Nottingham, Nottinghamshire	Coal fired power station	78.655	15924	202
TXU Europe Power Ltd	High Marnham Power Station, Newark, Nottinghamshire	Coal fired power station	74	33290	450
Anglesey Aluminium Metal Ltd	Penrhos Works, Holyhead, Gwynedd	Aluminium smelter	73.1	0	0
Scottish Power PLC	Cockenzie Power Station, East Lothian	Coal fired power station	72.8	19700	271
Alcan Primary Metal Europe	Lynemouth Power Station, Ashington, Northumberland	Coal fired power station	72.5	28400	392
Powergen UK Plc	Drakelow B Power Station, Burton-on-Trent, Staffordshire	Coal fired power station	58	22529	388431
Hanson Building Products Ltd	Stewartby Works, Bedford, Bedfordshire	Brick works	38	-	-
Hanson Building Products Ltd	Saxon Works, Peterborough, Cambridgeshire	Brick works	19	-	-
Alcan Aluminium UK Limited	Lochaber Smelter, Fort William, Inverness-shire	Aluminium smelter	15.5	-	-
Hanson Building Products Ltd	Kings Dyke Works, Peterborough, Cambridgeshire	Brick works	15	-	-
Corus Uk Ltd	Teesside Works, Redcar, Cleveland	Steel works	6.5	-	-

Operator	Site	Process	HF Emission 2002 Tonnes	SO_2 Emission 2002 Tonnes	SO_2/HF
Owens Corning Fiberglas (Gb) Ltd	Bryn Lane, Wrexham Industrial Estate, Wrexham, Clwyd	Glass fibre works	4.73	-	-
Aes Fifoots Point Ltd	Fifoots Power Station, Newport, Gwent	Coal fired power station	2.04	-	-
British Sugar Plc	Cantley Sugar Factory, Norwich, Norfolk	Sugar works	1.87	-	-
Rockwool Ltd	Bridgend, Mid Glamorgan	Mineral fibre production	0.38	-	-
Alenoy Ltd	Bowling Iron Works, Bradford, West Yorkshire	Aluminium recycling	0.321	-	-
Castle Cement Ltd	Ketton Works, Stamford, Lincolnshire	Cement works	0.227	-	-
BA Tubes Ltd	Redditch, Worcestershire	Aluminium foundry	0.1448	-	-
Ervin Amasteel	Tipton, West Midlands	Abrasives manufacturer	0.14	-	-
International Flavours and Fragrances Iff (GB) Ltd	Haverhill, Suffolk	Combustion for Process heat	0.049		0
Asahi Glass Fluoropolymers UK Ltd	Thornton-Cleveleys, Lancashire	Fluorinated polymer production	0.028		0
Flight Refuelling Ltd	Wimborne, Dorset	Inorganic chemical process	0.012		0
Contract Heat And Power Ltd	Newport, Isle of Wight	RDF fuelled energy plant	0.01088		0
Johnson Matthey PLC	Enfield, Middlesex	Non ferrous	0.0085		0

Operator	Site	Process	HF Emission 2002 Tonnes	SO_2 Emission 2002 Tonnes	SO_2/HF
		metals			
White Rose Environmental Ltd	Ipswich, Suffolk	Clinical waste incinerators	0.0059		0
Pirelli Cables Ltd	Optical Fibre Manufacturing Unit, Eastleigh, Hampshire	Glass fibre manufacturing	0.0057		0
S Grundon (Services) Ltd	Lakeside Road, Slough, Berkshire	Municipal waste incinerator	0.00405		0
Medical Energy (Worcestershire) Ltd	Alexandra Hospital, Redditch, Worcestershire	Clinical waste incinerator	0.00333		0
Inergy Automotive Systems UK Ltd	Telford, Shropshire	Chemical industry	0.000879		0
Macdermid PLC	Albion Works, Birmingham, West Midlands	Chemical industry	0.00032		0
Atotech UK Ltd	West Bromwich, West Midlands	Chemical industry	0.0002	-	-

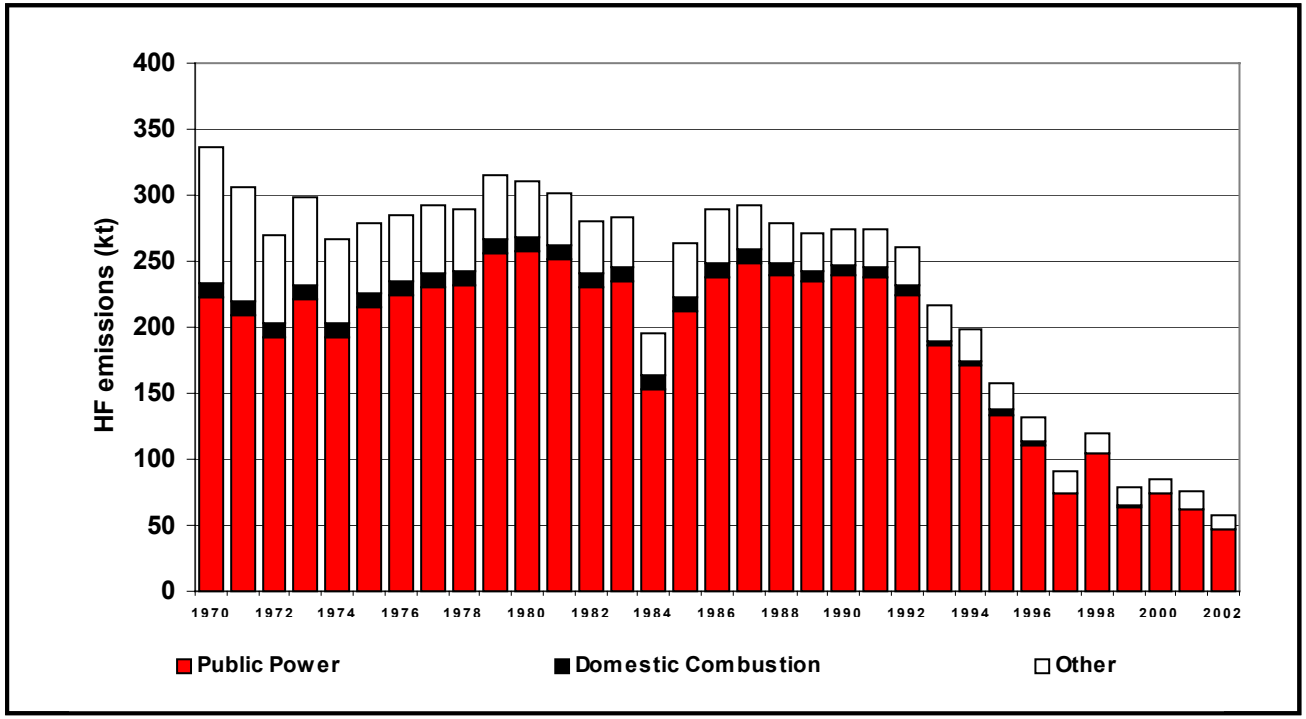

Figure 1.1 - Temporal Trends in Hydrogen Fluoride Emissions

1.2 Natural Sources of Hydrogen Fluoride

The biggest natural source of hydrogen fluoride and other fluoride emissions to the air is volcanic eruptions. The contribution of this source to the Earth's atmosphere is estimated to be in between 1 to 7 million tonnes per year, of which approximately 10% may be introduced directly into the stratosphere. Separately it has been calculated that approximately 20,000 tonnes of fluoride may be released into the atmosphere from marine aerosols every year. The other natural source of fluoride in the air is dust from soils, created through the weathering of rocks, which is then carried up into the atmosphere by winds. Even so, hydrogen fluoride is too reactive to persist for very long in the environment and is rapidly converted to other fluorides.

1.3 Atmospheric Chemistry of Hydrogen Fluoride

Fluorides in the atmosphere may be in gaseous or particulate form. The gaseous fluorides include hydrogen fluoride, carbon tetrafluoride (CF_4), hexafluoroethane (C_2F_6), fluorosilicic acid, sulphur hexafluoride and silicon tetrafluoride. Other lower concentration species include chlorofluorocarbons (CFCs) and hydrochlorofluorocarbons (HCFCs).

Particulate fluorides include cryolite, chiolite ($Na_5Al_3F_{14}$), calcium fluoride, aluminium fluoride, sodium hexafluorosilicate, lead fluoride (PbF_2), calcium phosphate fluoride (fluorapatite) and sodium fluoride.

Hydrogen fluoride does not react rapidly with hydroxyl radicals in the atmosphere (DeMore *et al* 1997) and fluoride released as gaseous and particulate matter is deposited in the general vicinity of an emission source, although some particles may react with other atmospheric constituents. The distribution and deposition of airborne fluorides are dependent upon emission strength, meteorological conditions, particulate size and chemical reactivity. Globally, hydrogen fluoride and inorganic fluoride particulates (sodium and calcium fluoride) account for approximately 75% and 25%, respectively, of inorganic fluorides present in the atmosphere.

Fluorine and the silicon fluorides are hydrolysed in the atmosphere to form hydrogen fluoride, as is uranium hexafluoride, which is used in the separation of uranium isotopes and the purification of nuclear waste. HF may combine with water vapour to produce an aerosol or fog of aqueous hydrofluoric acid, and this may be a significant source of hydrogen fluoride in the troposphere. It is assumed that all irreversibly soluble gases such as hydrogen fluoride are washed out during rain showers. The washout process is of particular importance for the removal of soluble fractions, such as hydrogen fluoride, at short distances from the source. The washout process is more important for the removal of fluorides distant from the source when the plume is situated at least partially in the clouds.

The scavenging ratio, the ratio between measured concentrations in rainwater and the atmosphere, has been calculated to be 0.15×10^6. For large-scale dispersion of fluorides, the annual average wet deposition rate was 1.4% per hour for fluoride aerosol and 5.9% per hour for gaseous fluorides. These values give an atmospheric residence time of 12 hours for gaseous fluoride and 50 hours for particulates.

A number of dispersion models have been formulated to predict the formation and behaviour of the fog formed from a release of hydrogen fluoride to the atmosphere. Initially, the hydrogen fluoride will cool significantly due to depolymerisation. The fog will therefore stay near ground level, since it is denser than ambient air. As the fog mixes with more air, it will begin to warm up and it may rise, depending on the ambient air temperature and the relative humidity (Lines 1995).

However, once released into the environment, hydrogen fluoride is unlikely to remain in its original form for very long. In air, water and soil it is transformed into a variety of other fluorine compounds. Hydrogen fluoride released into the atmosphere is washed onto the earth's surface in rain and is neutralised to form inorganic fluoride salts. Airborne gaseous and particulate fluorides tend to accumulate within the surface layer of soils but may be displaced throughout the root zone, even in calcareous soils.

The cycling of fluoride through the biogeosphere is summarised in Figure 2.

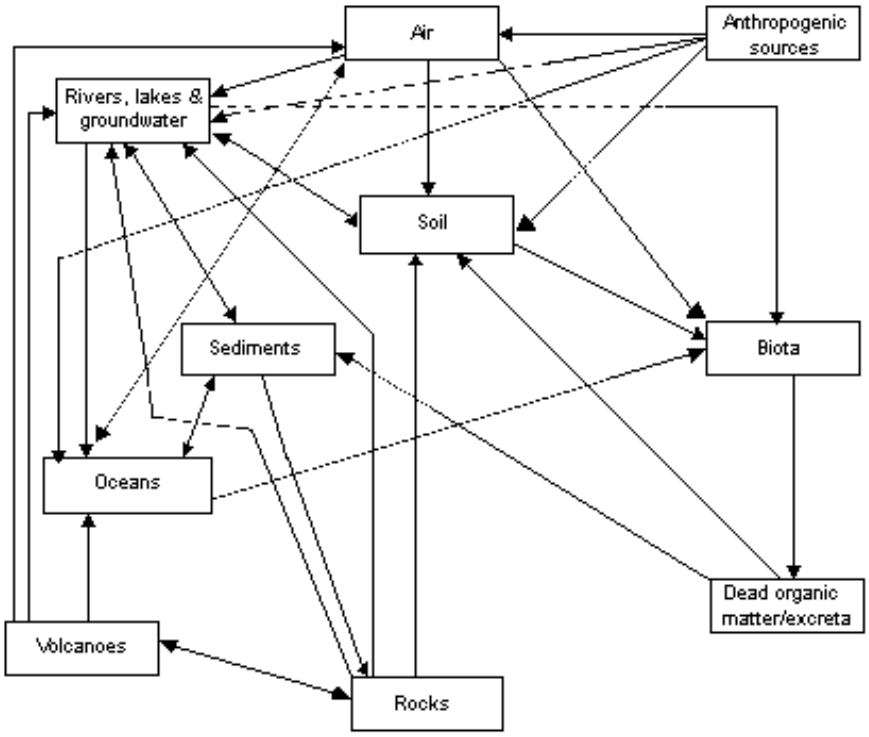

Figure 1.2 - Cycling of fluoride through the biogeosphere

1.4 Methods of Measurement

1.4.1 Bubbler methods

A method using midget impingers has been used for hydrogen fluoride determination. The air is passed through a pre–filter to exclude particulate fluorides and then the impingers at a flow rate of 2.5 l/min. The impingers contain 10ml of a 0.1 M NaOH

solution. It is recommended that an air volume of 10–200 l be sampled. No detection limit is quoted (Environment Agency 2000).

1.4.2 Denuder methods

Rupprecht and Pasternick market a denuder system for hydrogen fluoride measurement. The air is sampled at 15 l/min through two denuder tubes that are coated with sodium carbonate in glycerol. Following exposure for between 1 and 24 hours, the denuders are extracted with a small volume of deionised water. The hydrogen fluoride is measured by ion chromatography. The gas can be passed through a PTFE filter following the denuder to collect fluoride associated with particles. The detection limit can be as low as 5 ng/m^3 for a daily sample.

Lodge (1989) describes a denuder system which consists of a sodium bicarbonate coated 1220 mm by 7mm glass tube to collect gaseous fluorides followed by a filter to collect particulate fluoride. The fluoride collected on the coating is removed with water or buffer and analysed for fluoride by ion selective electrode. Ion selective electrode analysis appears less susceptible to organic acid interference than ion chromatography. For a 12-hour sample at 14 l/min, the method range is about 100 µg F/m^3, but this can be modified by altering the sample volume. Precision is quoted to be better than ±10%.

1.4.3 Impregnated filter methods

A method for ambient air sampling adopting the occupational methods MDHS 35 and NIOSH 84-100 was described by Clayton and Davis (1987). A cellulose ester pre-filter was used to exclude particulate associated fluoride. This was followed by a filter paper treated with a sodium hydroxide–glycerol solution. A flow rate of 2 l/min is suggested. The filter papers are acid extracted and the fluoride content of the eluent measured using ion selective electrodes. A detection limit of around 10 µg/m^3 for an air sample volume of 200 l was reported. The precision was quoted as being better than 10% for air sample volumes of >120 l in the concentration range 0.05-10 mg HF/m^3.

Katz (1977) describes a method using a tape sampler to give a number of short-term samples. Two tapes are used, the air passing first through an acid treated filter to remove particle associated fluoride. Gaseous fluorides are collected on the second filter paper treated with alkali. Sampling is carried out for 1 hour per position on the filter tape. Care must be taken to keep the two tapes separate during handling. The sample positions are cut from the tape and analysed either by ion selective electrode or by colorimetric analysis.

Ion chromatography being a more recent method may well be suitable if organic acids can be shown to be absent. A detection limit of around 0.1 µg/m^3 is claimed with a precision of ±10%.

Andersen (2003) describes a method using a treated filter held inside a Stevenson screen as a passive sampler of fluoride.

1.4.4 Diffusion tube

Diffusion tubes are marketed for the measurement of hydrogen fluoride. They are passive samplers. An unreactive tube is used to provide a known diffusion path length. An adsorbant at one end reacts with the hydrogen fluoride to adsorb it. Hence a concentration gradient is set up along the tube and by determining the amount of fluoride recovered from the adsorbant, an estimate of the hydrogen fluoride concentration can be made. Diffusion tubes are generally useful for indicative concentration estimates however for hydrogen fluoride they appear to be subject to greater uncertainty than is normal even for a diffusion tube. This may be due to the ion chromatography problems discussed earlier or improperly characterised diffusion characteristics or adsorbent behaviour.

1.4.5 Passive Treated Filter Paper

Around one of the aluminium smelters in the UK measurements are taken using a filter paper pre-treated with sodium carbonate and then exposed in a Stevenson screen. Hydrogen fluoride diffuses into the Stephenson screen and reacts with the filter paper. The fluoride content of the filter paper is then measured by ion selective electrode or ion chromatography and the amount referred back to an air concentration.

1.4.6 DIAL

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

1.4.7 DOAS

Differential Optical Absorption Spectroscopy uses a light emitter to project a beam of light with wavelengths between visible and ultra violet. The light beam passes through a known distance to a receiver. The monitoring path is usually between 300 and 800 metres. As the beam of light passes through the air, the different molecules absorb different wavelengths dependant on their spectra. The light is then returned through a fibre optic cable to a spectrometer. The spectrometer measures the intensity of the different wavelengths compared this to the original beam and then calculates the air concentrations of the particular gases. A detection limit of HF 1 $\mu g/m^3$ has been quoted.

1.4.8 DLSIOS

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

1.5 UK Measurements

1.5.1 Crmylyn Burrows

A measurement programme has been undertaken by the Environment Agency at a number of sites to the east of Swansea to establish the impact of a number of industrial sites on some vulnerable ecosystems. Reported concentrations are between 0.1 and 11 ug/m^3 as approximately monthly averages. However, this measurement series has been beset by analytical uncertainty. A large increase in measured concentrations is reported between the December and January samples. This appears to have been caused by a change in the type of column in the ion chromatograph used for these samples. It is known that fluoride analysis is susceptible to interference from organic acids such as acetic and lactic acid that can co-elute with the fluoride ion. A UKAS accredited laboratory carried out the analysis.

Table 1.3 - Hydrogen Fluoride Concentrations (μg/m^3) in the Swansea area measured using Diffusion Tubes and Ion Chromatography

Site	Grid Reference	Aug to mid Sept 2002	Mid Sept to mid Oct 2002	Mid Oct to early Dec 2002	Late Nov/ early Dec 2002 to late Jan early Feb 2003	Late Jan/early Feb to March 2003	28 Feb to 10 Apr 2003
Pipeline	SS 70511 93610	1.48	0.94	< 0.10	11	5.7	4.6
Picnic Table	SS 69580 93493	0.99	0.13	0.20	7.4	2.3	5.9
Tree, Jersey Marine	SS 70795 93928	1.66	< 0.11	0.29	6.9	5.3	5.0
HLC, Crymlyn	SS 69462 93273	2.34	0.32	1.66	4.3	10	6.1
Merthyr Mawr	SS 86842 77484	1.95	1.00	0.68	11	4.3	5.7
Silver Birch	SS 70084 93540	1.15	0.67	< 0.10	7.3	5.3	4.3
Tir John	SS 69460 93797	1.06	0.11	0.29	4.8	3.5	6.3
Sheep Enclosure	SS 78346 82762	1.85	0.90	0.15	16	3.4	8.1

1.5.2 Ashington

Samples have been taken over an extended period around the aluminium smelter at Lynemouth in Northumberland (Miller 2003). The results for 1999 to 2002 are shown in Figure 3 below (Andersen 2003). The method used was using a passive treated filter paper as described above. Samples are taken monthly. Concentrations ranged between 0.05 and 1.17 μg F/m^3. The average concentration at all the sites was 0.17 μg F/m^3. There was no clear seasonal dependency.

A recent report on tree health around the Ashington aluminium smelter noted that while certain trees within the smelter site showed poor health it was also the case that trees at some distance form the works showed similar symptoms. The trees were growing on colliery spoil tips with limited topsoil, hence it is possible that the poor tree health was indicative of poor growing conditions rather than atmospheric pollution.

1.5.3 Penicuik

Following intermittent complaints concerning effects of emissions from a glass process on glazing SEPA organised three campaigns of sampling around a works in Penicuik. An active treated filter method was used in which air was drawn over a pre-filter then a filter treated with sodium carbonate. Samples were taken over 4-day periods at a flow rate of around 2 l/min. The fluoride recovered from the first filter was assigned to water soluble aerosol fluoride and that from the second filter to volatile fluoride. The water-soluble aerosol fluoride samples were analysed by ion chromatography and the volatile fluoride samples by ion selective electrode.

During the winter 1999 campaign, four sampling sites were used. One of which was an urban background site. The volatile fluoride was detectable in 6 out of 19 samples. The detection limit was between 0.4 and 0.6 μg HF/m^3. The measured concentrations were 0.4, 0.6, 0.6, 0.7, 0.9, 1.2, 2.0, 2.8, 3.5 μg HF/m^3. The water soluble aerosol fluoride was detectable in none of the 16 samples. The detection limit was between 0.3 and 0.6 μg HF/m^3 (Drummond 2001).

In the spring 2000 campaign, the same four sampling sites were used. The volatile fluoride was detectable in 9 out of 16 samples. The detection limit was between 0.3 and 0.7 μg HF/m^3. The measured concentrations were 2.1, 3.2, 0.35, 2.6, 1.1, 0.5 μg F/m^3. The water soluble aerosol fluoride was detectable in 3 out of 19 samples. The detection limit was between 0.3 and 0.7 μg HF/m^3. The measured concentrations were 2.0, 1.6, 1.7 μg F/m^3.

In the summer 2002 campaign five sampling sites were used, one of which was an urban background site. Many results were below the detection limit. For volatile fluoride this was around 0.4 μg HF/m^3 and 0.02 μg HF/m^3 for water-soluble aerosol. Volatile fluoride was detected in one of 20 samples at 0.88 μg HF/m^3. Water soluble aerosol fluoride was detected in 3 of 20 samples at concentrations of 0.12, 0.16 and 0.78 μg HF/m^3. The latter result occurring at the same time as the elevated volatile fluoride result. The same site as in the earlier study experienced the highest concentration but it was considerably lower than before.

During these studies the authors note that during sampling periods in which it rained there appeared to be conversion of volatile fluoride to aerosol fluoride. This may be a sampling artefact in humid conditions or a result of washout of gaseous fluoride and reaction with particles (Drummond 2003).

1.5.4 Armadale

In response to complaints about air pollution in Armadale SEPA carried out a monitoring exercise over an 8-week period for volatile fluorides around a brick works. A similar approach as at Penicuik was used except samples were taken over a week period. Only 5 out of 30 samples were above the detection limit. Detected levels ranged between 0.31 and 0.49 μg HF/m^3 (Drummond 2000).

1.5.5 UK Hydrogen Fluoride Production Sites

Measurements are quoted in the review of hydrogen fluoride under the EU Existing Substances Directive (ECB 2002) around UK production sites for hydrogen fluoride. At one of the three UK hydrogen fluoride production sites annual average concentrations of between 0.06 and 0.23 μg/m^3 are quoted for the years 1991 to 1994. The relation of the sampling locations to the discharge points is not described.

At a similar site, daily mean concentrations in 1984 were between 0.03 and 1.71 μg/m^3 at 1000m from the plant and between 0.01 and 1.01 μg/m^3 at 500m from the site. In 1988 concentrations ranged between 2.31 and 5.36 μg/m^3 and were between 1.12 and 3.14 μg/m^3 in 1995.

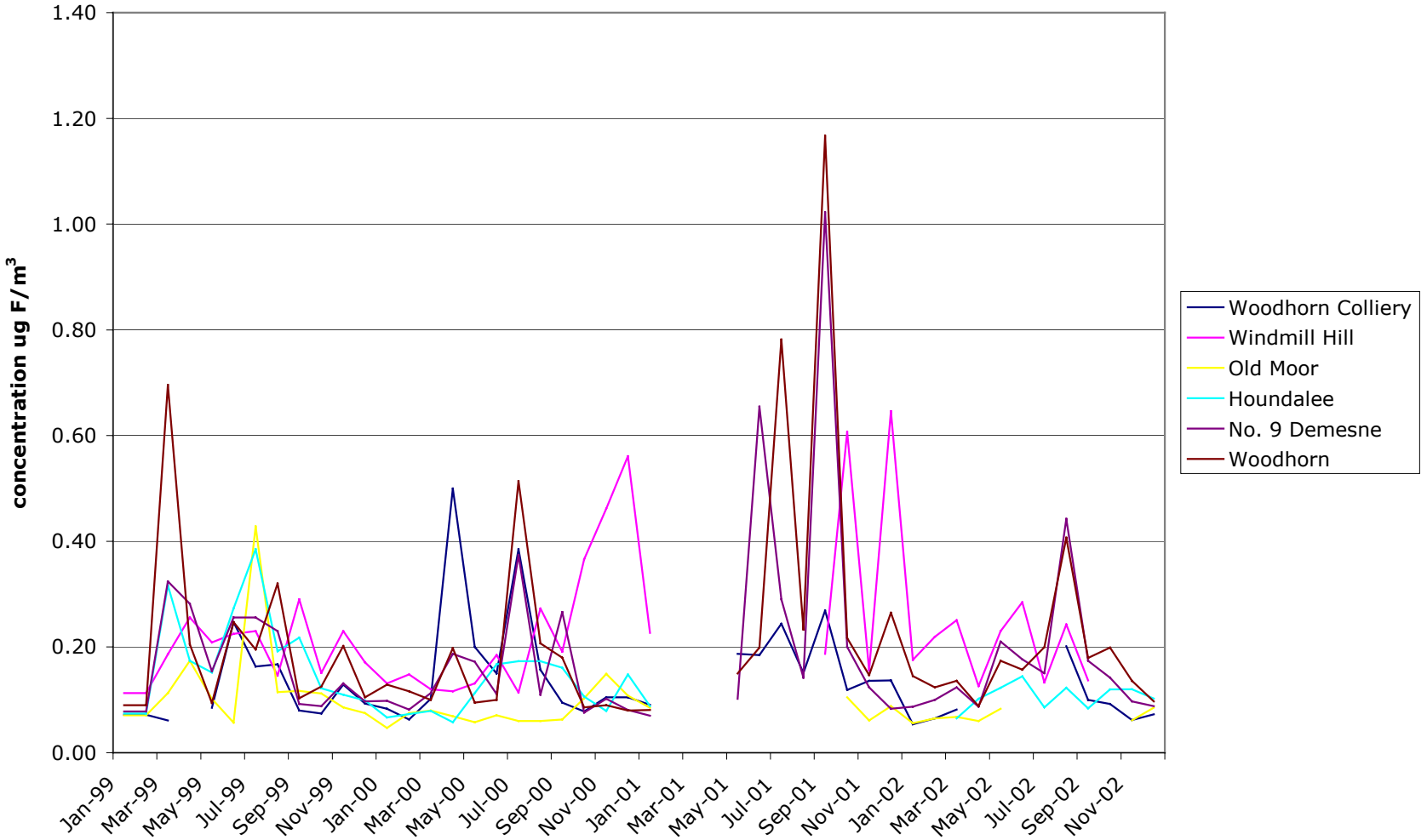

Figure 1.3 - Measurements of Gaseous Fluoride Concentration (µg F/m^3) around the Aluminium Smelter at Lynemouth Northumberland 1999-2002.

1.6 Other Ambient Air Measurements of Hydrogen Fluoride

Measurements of total fluoride in Canada around certain industrial works are reported in the HF risk assessment, but as the works concerned emit both hydrogen fluoride and particle-associated fluoride, these do not provide relevant information for human health assessment.

The review of hydrogen fluoride under the EU Existing Substances Directive (European Chemicals Bureau 2002) quotes measurements of fluoride ions in air in Greater Cologne, Germany, in 1980, between 0.3 and 1.0 $\mu g/m^3$. They also quote a maximum fluoride content in air of 1.89 $\mu g/m^3$ at an unspecified US location. Neither the averaging time nor sampling method is described for either source.

Measurements are quoted in the same document from around a site producing hydrogen fluoride in the Netherlands, with a yearly emission of 50kg fluoride leading to measured fluoride concentrations ranging between 0.1 and 1 $\mu g/m^3$. Mean concentrations are quoted for this site, though the type of mean is not specified of 0.3-0.4 $\mu g/m^3$. Other measurements are reported for a German hydrogen fluoride production facility giving annual average fluoride concentrations of 0.3 $\mu g/m^3$ with a 98^{th} percentile of 2.4 $\mu g/m^3$. The short-term period to which the percentile refers is not quoted.

The EU Existing Substance Directive risk assessment for hydrogen fluoride calculates predicted local atmospheric concentrations of hydrogen fluoride around the hydrogen fluoride production and usage plants in the EU. The predictions were carried out according to the Technical Guidance Document. This uses worse case emission assumptions and meteorology from the Netherlands to predict concentrations at 100m from the plant. These are shown in Table 1.4. It is noticeable that the assumed emissions from the production plant are generally much lower than the emissions from individual point sources shown in Table 1.2 above.

Table 1.4 - Calculated local atmospheric hydrogen fluoride concentrations around production and usage plants in the EU (European Chemicals Bureau 2002)

Site No	Production Plant tonnes/year	End use plant tonnes/year	Total emission amount tonnes/year	Calculated Annual average air concentration $\mu g/m^3$	Year
1	0.065	0.055	0.120	0.091	1994
2	1.360	-	1.360	1.03	1994
	0.376	-	0.376	0.29	1995
	0.359	-	0.359	0.27	1996
	-	0.347	0.347	0.26	1997
		0.078	0.078	0.06	1998
3	3.100	-	3.100	2.36	1994
	2.100	-	2.100	1.6	1995
	1.300	-	1.300	1.0	1996
	1.200	-	1.200	0.91	1997
	1.260	-	1.260	0.95	1998
4	0.114	0.200	0.314	0.24	1995
	0.0866	0.120	0.207	0.16	1997
5	0.177	-	0.177	0.13	1994
	0.159	-	0.159	0.12	1995
6	<0.031	-	0.031	0.024	1994
7	0.0175	-	0.0175	0.013	1994
8	0.150	0.250	0.400	0.30	1994
	-	-	0.0492	0.037	1997
9	0	0	0	0	1997
10	2.020	-	2.020	1.54	1994
	0.0392	-	0.0392	0.03	1998
11	0.0004	0.030	0.0304	0.023	1994
12	0.030	-	0.030	0.023	1994
					1996
13	0.050	0.289	0.339	0.26	?
	0.044	1.000	1.044	0.79	1997
14	0.172	0.172	0.344	0.26	
	-	-	0.147	0.11	
15	-	0.040	0.040	0.030	1994
16	-	4.200	4.200	3.2	1998
17	-	0.0209	0.0209	0.016	1994
		0.0155	0.0155	0.012	1995
18	-	0.005	0.005	0.038	1994
19	-	0.013	0.013	0.0099	1994

2. Animal TOXICITY DATA

2.1 Introduction to animal studies

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

In general, inhalation studies have limited applicability to humans where mouth breathing dominates. Therefore, human studies are likely to provide most relevant information on the nature and extent of toxicity. However, consideration of the animal studies may be important in the identification of hazard and the type of lesion to be anticipated and where there are insufficient appropriate human studies.

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

While there is much information on absorption and systemic toxicity following gastrointestinal absorption in both humans and other animals. There are no reports on the absorption of fluoride ion from the lung following inhalation. However, acute high-dose studies and more importantly, a lower dose 91-day study (Placke and Griffin, 1991), report systemic toxic effects suggesting significant absorption following exposure by inhalation. There are, however, little data on mutagenicity, carcinogenicity and reproductive and development toxicity following exposure by inhalation. These data gaps have been filled with reports of toxicity following oral administration. Although it is unclear whether fluoride would behave in this way following inhalation exposure, the systemic effects following inhalation are similar to those observed with oral administration.

2.2 Summary

The acute toxicity of hydrogen fluoride has been extensively investigated in laboratory animals. USEPA (2000) cited that for 60-minute exposures, only mild and occasional

signs of eye, nasal or respiratory irritation were observed in the dog at 157 ppm (130 mg/m^3) and in the rat at 103 and 126 ppm (86 and 105 mg/m^3)(Rosenholtz *et al*, 1963). Sixty-minute LC_{50} values ranged from 342 ppm (284 mg/m^3) for the mouse (Wohlslagel *et al*, 1976) to 2,300 ppm (1900 mg/m^3) for the rat (Haskell Laboratory, 1990). The lowest LC_{50} for the rat was 966 ppm (803 mg/m^3) (Vernot *et al*, 1977).

There are great variations in the results reported in the animal studies as may be seen in the summary table of key animal studies below (from USEPA 2000). Some of this may be due to strain and species differences, but the diversity in the results is more likely to be explained by variation in sampling and analytical methodology.

Table 2.1 – Summary table of Key Animal Studies

Species	Concentration (ppm)	Exposure time	Effect	Reference
Rat	4970	5 minutes	LC_{50}	Rosenholtz *et al* (1963)
Rat	2689	15 minute	LC_{50}	Rosenholtz *et al* (1963)
Rat	2042	30 minutes	LC_{50}	Rosenholtz *et al* (1963)
Rat	2300	1 hour	LC_{50}	Haskell Laboratory (1990)
Rat	1395	1 hour	LC_{50}	Wohlslagel *et al* (1976)
Rat	1307	1 hour	LC_{50}	Rosenholtz *et al* (1963)
Rat	966	1 hour	LC_{50}	Vernot *et al* (1977)
Rat	2432	5 minutes	Respiratory distress; severe eye and nasal irritation; weakness, sluggishness for 2 days	Rosenholtz *et al* (1963)
Rat	1438	5 minutes	Severe eye and nasal irritation	Rosenholtz *et al* (1963)
Rat	749	5 minutes	Moderate eye an nasal irritation	Rosenholtz *et al* (1963)
Rat	1410	15 minutes	Respiratory distress; severe eye and nasal irritation; weakness, sluggishness for two days	Rosenholtz *et al* (1963)
Rat	590	15 minutes	Moderate eye an nasal irritation	Rosenholtz *et al* (1963)
Rat	376	15 minutes	Mild eye and nasal irritation	Rosenholtz *et al* (1963)
Rat	307	15 minutes	Slight eye and nasal irritation	Rosenholtz *et al* (1963)

Species	Concentration (ppm)	Exposure time	Effect	Reference
Rat	1377	30 minutes	Increase in activity; respiratory distress; severe eye and nasal irritation;	Rosenholtz *et al* (1963)
Rat	1300	30 minutes	Nasal lesions, necrosis and inflammation	Kusewitt *et al* (1989)
Rat	1000	30 minutes	Nasal fibrinonecrotic rhinitis + fibrin thrombi in the submucosa and haemorrhage	Stavert *et al* (1991)
Rat	489	1 hour	Respiratory distress; severe eye and nasal irritation; weakness, sluggishness for two days	Rosenholtz *et al* (1963)
Rat	291	1 hour	Moderate eye an nasal irritation	Rosenholtz *et al* (1963)
Rat	126	1 hour	Mild eye and nasal irritation	Rosenholtz *et al* (1963)
Rat	103	1 hour	Occasional signs of eye and nasal irritation during exposure	Rosenholtz *et al* (1963)
Rat	0.1-10	91 day	Not significant decrease in numbers of lymphocytes and serum albumin/ globulin	Placke and Griffin, (1991)
Mouse	6247	5 minutes	LC_{50}	McEwen and Vernot (1971); Higgins *et al* (1971)
Mouse	501	1 hour	LC_{50}	MacEwen and Vernot (1970)
Mouse	456	1 hour	LC_{50}	Vernot *et al* (1977)
Mouse	342	1 hour	LC_{50}	Wohlslagel *et al* (1976)
Mouse	263	1 hour	No deaths	Wohlslagel *et al* (1976)

2.3 Acute Toxicity

2.3.1 Rats

Groups of 10 young male Wistar rats were exposed to various measured concentrations (concentration range not stated) of hydrogen fluoride for 5, 15, 30, or 60 minutes (Rosenholtz *et al*, 1963). Surviving rats were weighed daily and observed for 14 days after exposure at which time LC_{50} values were calculated; 4970, 2689, 2042 and 1307 ppm (4130, 2237, 1698, 1087 mg/m^3) for exposure periods of 5, 15, 30 and 60 minutes, respectively. During the exposures, there were signs of irritation of the conjunctiva and nasal passages, indicated by reddened conjunctivae, pawing at the nose, marked lacrimation, nasal secretion, and sneezing. In addition to some delayed deaths, respiratory distress, body weight loss (10-15% during days 3-7 post exposure), and general weakness for several days were also observed in some animals. Pathologic examinations were performed on groups of rats exposed in the lethal range for 15 or 30 minutes (Rosenholtz *et al*, 1963). Gross and microscopic examination revealed concentration-dependent lesions in the kidney, liver, nasal passage, bone marrow, and skin. These lesions included nasal passage necrosis with associated acute inflammation, selective renal tubular necrosis, hepatocellular intracytoplasmic globules, dermal collagen changes with acute inflammation, and possible myeloid hyperplasia of the bone marrow. Many of the lesions showed signs of reversibility by 48 hours to 7 days after exposure.

Further investigations by Rosenholtz *et al* (1963) involved the exposure of groups of 10 young Wistar male rats to various concentrations of hydrogen fluoride below the LC_{50} values for 5, 15, 30, or 60 minutes (Rosenholtz *et al*, 1963). These concentrations were 2,432, 1,438 and 749 ppm (2023, 1196 and 623 mg/m^3) for 5 minutes (approximately 50, 25, and 12.5% of the 5-minute LC_{50}); 1410, 590, 376, and 307 ppm (1170, 995, 518, 313 and 255 mg/m^3) for 15 minutes (approximately 50, 25, 12.5, and 6% of the 15-minute LC_{50}); 1377 ppm (1145 mg/m^3) for 30 minutes (68% of the 30-minute LC_{50}); and 489, 291, 126, and 103 ppm (407, 242, 105, 86 mg/m^3) for 60 minutes (approximately 50, 25, 12.5, and 6% of the 60-minute LC_{50}). Rats were observed for up to 45 days post exposure. Clinical signs of toxicity included an increase in activity (at 68% of the LC_{50}), and conjunctival and nasal irritation, with a lessening of symptoms at lower doses. There were no significant body or organ weight changes. No lesions were present in the nasal passages, lungs, kidney, liver, or bone marrow.

Kusewitt *et al* (1989) exposed Fischer-344 rats to concentrations of 100-1000 ppm (83 - 830 mg/m^3) for 30 minutes and sacrificed them 8 and 24 hours later. There was no mortality arising directly from hydrogen fluoride exposure and the lesions, necrosis and inflammation observed were restricted to the nasal region. Histopathologic examinations and gravimetric measurements revealed no damage to the lungs.

Stavert *et al* (1991) exposed groups of eight male Fischer-344 anaesthetised rats to filtered air or 1300 ppm (1100 mg/m^3) of hydrogen fluoride gas for 30 minutes. Ventilatory rates were measured during the exposure and body weights and respiratory tract histology were investigated 24 hours later. Rats exposed to hydrogen fluoride experienced an immediate and persistent drop in ventilatory rate of 27%. A 10% reduction in body weight compared to non-exposed rats occurred by 24 hours post exposure. No changes in lung weights were observed. Changes in the nasal passages

were limited to the anterior passages, with moderate to severe fibrinonecrotic rhinitis accompanied by large fibrin thrombi in the submucosa and haemorrhage. Lesions did not extend into the trachea. No mortality was observed.

Groups of 10 adult Wistar rats were exposed to concentrations of hydrogen fluoride ranging from 12440 to 25690 ppm (10350 to 21370 mg/m^3) for five minutes in order to calculate the 5 minute LC_{50} (MacEwen and Vernot, 1971; DiPasquale and Davis, 1971; Higgins *et al*, 1972). Hydrogen fluoride produced pulmonary oedema of varying degrees of severity in most of the exposed rats. Pulmonary haemorrhage was a common finding in rats that died during or shortly after exposure to concentrations above the LC_{50}. In exposures below the LC_{50}, delayed deaths occurred about 24 hours after exposure; occasionally deaths occurred three to four days later. LC_{10} and LC_{100} values were also reported.

Groups of eight male Wistar rats were exposed to concentrations of 480-2650 ppm (400 - 2200 mg/m^3) for 60 minutes (MacEwen and Vernot, 1970). No deaths occurred at 480 ppm (400 mg/m^3). The 1 hour LC_{50}, calculated by probit analysis, was 1276 ppm (1061 mg/m^3) (confidence limits 1036-1566 ppm (862 - 1302 mg/m^3)). Massive lung haemorrhage and oedema were present in animals that died. Signs of toxicity during exposures included respiratory distress, paresis, salivation, lacrimation, and nasal discharge. In a similar study, groups of male Sprague-Dawley rats were exposed to various concentrations for 1 hour (Vernot *et al*, 1977). The 1 hour LC_{50} was 966 ppm (803 mg/m^3) with 95% confidence limits of 785-1190 ppm (653- 990 mg/m^3). No further details were given.

In another study, exposure of rats to 148 mg fluoride/m^3 (190 ppm hydrogen fluoride) for 6 hours resulted in 100% mortality within 3 hours post exposure (Morris and Smith, 1982). Discharge of fluid from the external nares was observed prior to death, but no pulmonary lesions were present.

Groups of 10 male Sprague-Dawley-derived rats were exposed to concentrations of 1087, 1108, 1405, 1565, or 1765 ppm (904, 921, 1169, 1302 or 1468 mg/m^3) for 60 minutes (Wohlslagel *et al*, 1976). Animals were observed for toxic signs and mortality at 14 days post exposure. Some animals that died following exposure or were sacrificed after the 14-day observation period were examined histologically. The 60-minute LC_{50} was 1395 ppm (1160 mg/m^3). Signs during the exposures included eye and mucous membrane irritation, respiratory distress, corneal opacity, and erythema of the exposed skin. Pathological examinations of rats that died during or after exposure revealed pulmonary congestion, intra-alveolar oedema, and some cases of thymic haemorrhage.

2.3.2 Non-human Primates

Groups of four male and female rhesus monkeys were exposed to concentrations of 690, 1035, 1575, 1600, 1750, or 2000 ppm (574, 867, 1310, 1330, 1460 or 1660 mg/m^3) for 1 hour (MacEwen and Vernot, 1970). No deaths occurred at 690, 1575, or 1600 ppm (574, 1310 or 1460 mg/m^3); one death occurred in the group exposed to 1035 ppm (867 mg/m^3) and three deaths occurred in each of the groups exposed to 1750 and 2000 ppm (1460 and 1660 mg/m^3). Using probit analysis, the authors calculated an LC_{50} of 1774 ppm (1476 mg/m^3) (95% confidence limits 1495-2105 ppm (1243 and 1751 mg/m^3)).

Signs of toxicity during exposures included respiratory distress, paresis, salivation, lacrimation, nasal discharge, gagging, sneezing, and vomiting. Skin burns were observed post-exposure; these healed after several days.

2.3.3 Mice

During an investigation of the 5-minute LC_{50}, groups of 15 adult ICR mice were exposed to concentrations of hydrogen fluoride ranging from 2430 to 11,010 ppm (2021 to 9458 mg/m^3) (Higgins *et al*, 1972). The post-exposure observation period was 7 days. Exposure to hydrogen fluoride produced pulmonary oedema of varying degrees of severity in most of the exposed mice. Pulmonary haemorrhage was a common finding in mice that died during or shortly after exposure to concentrations above the LC_{50} of 6247 ppm (5196 mg/m^3). In exposures below the LC_{50}, delayed deaths occurred about 24 hours after exposure, with a few deaths occurring three to four days later.

Groups of five male ICR mice were exposed to concentrations of 500, 550, or 600 ppm (420, 460 or 500 mg/m^3) for 1 hour (MacEwen and Vernot, 1970). Deaths occurred at all exposures; the LC_{50}, calculated by probit analysis, was 501 ppm (417 mg/m^3) (confidence limits 355-705 ppm (295- 586 mg/m^3)). In a similar study, male CF-1 mice were exposed to various concentrations for 1 hour (Vernot *et al*, 1977). The LC_{50}, calculated by probit analysis, was 456 ppm (379 mg/m^3) (confidence limits 426-489 ppm (354 - 407 mg/m^3)).

2.3.4 Dogs

Groups of two mongrel dogs were exposed to hydrogen fluoride at concentrations of 666 or 460 ppm (554 or 383 mg/m^3) for 15 minutes or at concentrations of 243 or 157 ppm (202 or 131 mg/m^3) for 60 minutes and observed for 14 days post exposure (Rosenholtz *et al*, 1963). During the exposure to 666 and 243 ppm (554 or 383 mg/m^3), the dogs showed signs of discomfort including blinking, sneezing, and coughing. After removal from the exposure chambers, the dogs rubbed their noses and bodies on the grass. The cough persisted for one to two days and reappeared during the next ten days only during periods of exercise. No skin lesions were noted and there were no changes in haematological parameters. Signs and effects were less severe at the exposure concentrations of 460 ppm (383 mg/m^3) for 15 minutes and 157 ppm (131 mg/m^3) for 60 minutes. Eye irritation was mild following exposure. Sneezing, rubbing of bodies on the ground, and a dry cough lasting two days were also observed following withdrawal. No gross lesions were noted and no microscopic examinations were performed.

2.3.5 Guinea pigs and Rabbits

Groups of 10 young male Hartley guinea pigs were exposed to various measured concentrations of hydrogen fluoride for 15 minutes (Rosenholtz *et al*, 1963). A 15-minute LC_{50} of 4327 ppm (3599 mg/m^3) was calculated following a 14-day observation period. Signs of irritation of the conjunctiva and nasal passages lasting 7 days post exposure were observed. These included reddened conjunctivae, pawing at the nose,

marked lacrimation, nasal secretion, and sneezing. For animals surviving a week or more, respiratory distress, a body weight loss of 25% during the first week, and general weakness were observed.

Machle *et al* (1934) exposed guinea pigs and rabbits to concentrations ranging from 30 to 9760 ppm (25 to 8120 mg/m^3) for exposure times of 5 minutes to 41 hours. The authors reported that a concentration of 1220 ppm (1014 mg/m^3) for 30 minutes did not produce death, but concentrations of >1220 to 1830 ppm (>1014 to 1522 mg/m^3) for as little as 5 minutes produced death in a significant number of animals.

2.4 Subchronic Studies

Groups of ten male and ten female rats were exposed to concentrations of 0, 0.1, 1.0 or 10 ppm (actual concentrations 0, 0.098, 0.72 and 7.52 mg/m^3) hydrogen fluoride for 91 days (Placke and Griffin, 1991). Animals were observed for clinical signs, weighed, and subjected to haematology and clinical chemistry examinations; tissues were examined microscopically. No deaths occurred in the groups exposed to 0.1 or 1.0ppm (actual concentrations 0.72 and 7.52 mg/m^3). Although blood changes including decreased numbers of lymphocytes and serum albumin/globulin were noted in the mid-dose males, these changes were not statistically or biologically significant. No histopathological changes were found. From this study it is possible to derive a NOAEL for blood changes of 1 ppm (0.72 mg/m^3).

Two groups of rats were exposed to 33 ppm (27 mg/m^3) (30 animals) or 8.6 ppm (7.2 mg/m^3) (15 animals) 6 hours/day for a period of 5 weeks (166 hours) (Stokinger, 1949). Mortality was total in the 33 ppm (27 mg/m^3) concentration group. There was no mortality at the 8.6 ppm (7.2 mg/m^3) concentration. During exposure to the higher concentration, subcutaneous haemorrhages developed around the eyes and feet. Pathologic examinations at the end of the exposure period revealed moderate haemorrhage, oedema, and capillary congestion in the lungs of twenty of thirty animals and renal-cortical degeneration and necrosis in 27 of thirty animals at the higher exposure concentration. In a complementary study, mice were exposed to 33 ppm, (27 mg/m^3) 6 hours/day, for a period of 5 weeks (166 hours) (Stokinger, 1949). All 18 mice died during the exposure to 33 ppm, whereas all mice survived the exposure period at the 8.6 ppm. A similar study in guinea pigs observed no mortality at either exposure regime. No pathologic examinations were undertaken in this study (Stokinger, 1949). Rabbits were exposed to either 33 or 8.6 ppm (27 or 8.6 mg/m^3) of hydrogen fluoride, 6 hours/day for a period of 5 weeks (166 hours) (Stokinger, 1949). No deaths occurred at either exposure regime. Slight pulmonary haemorrhage was observed in four of ten rabbits at the higher exposure regime.

In a range-finding study, groups of five male and five female Fischer 344 rats were exposed to measured concentrations of 0, 1, 10, 25, 65 or 100 ppm (0, 0.83, 8.3, 21, 54 and 83 mg/m^3) for 6 hours/day, 5 days/week, for 2 weeks; survivors were sacrificed 2 days later (Placke *et al*, 1990). Exposures to 25 ppm (21 mg/m^3) and above resulted in deaths of all females, with deaths beginning on the eighth, third, and second day of exposure at the 25, 65, and 100 ppm (21, 54 and 83 mg/m^3) concentrations, respectively. Exposures to 65 and 100 ppm (54 and 83 mg/m^3) resulted in deaths of all males, with deaths beginning on the third and second day at the 65 and 100 ppm

concentrations, respectively. No deaths occurred during the first day of exposure at any concentration, and no deaths occurred at the lower concentrations.

A group of 20 Wistar rats was exposed to a concentration of 0.0016 mg/m^3 (0.002 ppm) for 5 hours/day for 3 months (Humiczewska *et al*, 1989). Compared to a group of control rats, there were emphysemal changes in the lung involving enlarged alveoli and alveolar ducts and a narrowed interalveolar septum. Necrotic and hyperplastic areas were also noted. In the risk assessment report for hydrogen fluoride, the European Chemicals Bureau indicate that these changes were not clearly documented and, therefore, difficult to interpret these effects observed at low exposure concentrations (ECB 2002).

Groups of 10 female ICR-derived mice were exposed to concentrations of 263, 278, 324, 381, or 458 ppm (219, 231, 269, 317 or 381 mg/m^3) for 60 minutes (Wohlslagel *et al*, 1976). Animals were observed for toxic signs and mortality during a 14-day post-exposure period. Some animals that died following exposure or were sacrificed after the 14-day observation period were examined histologically. The 60-minute LC_{50} was 342 ppm (284 mg/m^3). Signs of toxicity during the exposures included eye and mucous membrane irritation, respiratory distress, corneal opacity, and erythema of exposed skin. Pathological examinations of mice that died during or after exposure revealed pulmonary congestion and haemorrhage.

Two rhesus monkeys were exposed to a concentration of 18.5 ppm (15.4 mg/m^3), 6-7 hours/day for 50 days for a total of 309 exposure hours (Machle and Kitzmiller, 1935). Except for an occasional cough during the first week of exposure, the animals appeared normal and the concentration was considered tolerable and respirable. One monkey was sacrificed eight months post exposure. The only prominent lesions were degenerative and inflammatory changes in the kidney. This is an old study and may not reflect the best study conditions now carried out, otherwise it may suggest that primates are less susceptible to the irritant effects of hydrogen fluoride.

Two groups of dogs were exposed to 33 (27 mg/m^3) (4 dogs) or 8.6 ppm (7.2 mg/m^3) (5 dogs), 6 hours/day for a period of 5 weeks (166 hours) (Stokinger, 1949). No deaths occurred in either group. Pathologic examinations at the end of the exposure period revealed degenerative testicular changes (4/4 animals), moderate haemorrhage and oedema of the lungs (3/4 animals), and ulceration of the scrotum (4/4 animals) at the 33 ppm (27 mg/m^3) exposure concentration. At the lower exposure concentration, localised haemorrhagic areas in the lungs in one of the five animals were observed. Clinical chemistry and haematology observations were unremarkable except for an increase in fibrinogen level at the higher exposure concentration.

Machle and Kitzmiller (1935) exposed three guinea pigs to a concentration of 18.5 ppm (15.4 mg/m^3), 6-7 hours/day, for 50 days for a total of 309 exposure hours. After an initial weight gain, two guinea pigs lost weight and died during the exposures, one after 160 hours of exposure and the other after approximately 250 hours of exposure. Pathological examinations of the two animals revealed the following lesions in one or both: pulmonary haemorrhage, inflammation and hyperplasia of the bronchial epithelium, congested and fatty liver with fibrotic changes, and renal tubular necrosis. The surviving animal was sacrificed nine months after the conclusion of the exposure.

In this animal, the lungs showed haemorrhages, alveolar exudates, and alveolar wall thickening. The liver showed degeneration and necrosis.

Machle and Kitzmiller (1935) exposed four rabbits to a concentration of 18.5 ppm (15.4 mg/m^3), 6-7 hours/day for 50 days for a total of 309 exposure hours. The animals gained weight throughout the exposure although at a slower rate than a group of control rabbits. Pathological examinations at 7-8 months post exposure revealed the following lesions: leucocytic infiltration of the alveolar walls of the lungs, fatty changes in the liver, and degeneration, necrosis, and fibrosis of the kidneys. Two rabbits had acute lobular pneumonia. During metabolism studies, rabbits were exposed to concentrations ranging from 1.05 mg/L (1283 ppm) for one hour to 0.0152 mg/L (18.5 ppm) for 13 days (Machle and Scott 1935). Sacrifice occurred 9-15 months later; no early deaths were reported.

2.5 Developmental/Reproductive Toxicity

No studies addressing developmental or reproductive effects following acute inhalation exposure to hydrogen fluoride were located. However, because effects on development and reproduction would be systemic, due to circulating fluoride, it was considered that the effects of oral administration of fluoride might be relevant.

There are several studies on the effects of orally administered fluoride on testicular function, the key series of experiments being conducted by Chinoy and Sequeira (1989). Similarly, there is a key oral fertility study by Collins *et al* (2001). These studies have been reviewed as part of the EU risk assessment report. Although they involved oral administration, an equivalent inhalation dose could be estimated. Overall, it is considered that the reproductive/developmental toxicity of hydrogen fluoride cannot be fully assessed as a number of the studies, reviewed by ATSDR (1993) and ECB (2002) produced conflicting results. However, studies do indicate that there are no effects on animal reproduction and development when fluoride is administered at 400 ppm in the drinking water.

Oral administration of sodium fluoride at 70 mg/kg for five days (Li *et al*, 1987) or 75 ppm in drinking water for 21 weeks (Dunipace *et al*, 1989) had no effect on spermatogenesis of B6C3F1 mice. However, intraperitoneal injection of 8 mg/kg for five consecutive days (Pati and Buhnya, 1987) and administration of 500 or 1000 ppm for up to three months (DHHS, 1991) resulted in abnormal spermatozoa in mice. The impact of acute inhalation exposures cannot be assessed from these findings.

Sodium fluoride was administered in the drinking water at concentrations of 0, 10, 25, 100, 175, or 250 mg/L throughout gestation (Collins *et al*, 1995). At the highest dose level, maternal toxicity (reduced growth) and an increase in the number of foetuses with skeletal variations but not the number of litters were observed. No signs of retarded foetal development were observed and the compound was not considered to have developmental toxicity.

Administration of sodium fluoride in the drinking water (0, 50, 150, or 300 ppm) to pregnant rats during gestation days 6 through 15 or to pregnant rabbits at 0, 100, 200, or 400 ppm from gestation days 6 through 19, did not significantly affect the frequency of

post implantation loss, mean foetal weight/litter, or external, visceral or skeletal malformations in either the rat or rabbit. Thus the NOAEL for developmental toxicity was >300 ppm (~27 mg/kg/day) for the rat and >400 ppm (~29 mg/kg/day) for the rabbit (Heindel *et al*, 1996).

2.6 Genotoxicity

There are few data concerning the genotoxicity of hydrogen fluoride from inhalation exposures. Voroshilin *et al* (1975) found hyperploidy in bone marrow cells of rats exposed to 1.0 mg/m^3 (1.22 ppm) for 6 hours/day, 6 days/week for one month. The significance of this hyperploidy is not known. The same authors found no effects in C57B1 mice under the same conditions.

The dataset for the genotoxicity of hydrogen fluoride is sparse and therefore it is necessary to use studies on sodium and potassium fluoride to fill the gaps in the database. Other genotoxicity studies conducted with sodium fluoride or potassium fluoride have been reviewed in the EU risk assessment document on hydrogen fluoride (ECB 2002) including an *in vivo* micronucleus test with sodium fluoride in mouse bone marrow that was reported to be negative. Negative results were found for *Salmonella typhimurium* with and without metabolic activation and positive results were found in the mouse lymphoma (with and without activation), sister chromatid exchange (with and without activation), and chromosome aberration tests (without activation) (NTP, 1990). However, the positive results were obtained, in general, at high doses at which fluoride acts as a general "protein poison" (ATSDR, 1993). The weight of evidence suggests that hydrogen fluoride is not genotoxic.

2.7 Carcinogenicity

No carcinogenicity studies using acute or longer-term inhalation exposures were located. Inhaled hydrogen fluoride would exert its systemic effects as fluoride ion; therefore, oral studies of fluoride administration may be relevant. A chronic oral carcinogenicity study in which sodium fluoride was administered to male and female rats and mice in the drinking water resulted in equivocal evidence of bone cancer in male rats, but not in female rats or mice of either gender (NTP, 1990). The cancer was a rare bone osteosarcoma. Another chronic study (Maurer *et al*, 1990) found no evidence of cancers in male or female rats.

3 Human Studies

3.1 Summary

Human volunteer studies indicate concentrations of 2 ppm (1.7 mg/m^3) for 6 hours/day were only slightly irritating (Largent, 1960; 1961). Male subjects (3-4 of 14) reported upper and lower respiratory irritation of >3 on a scale of 0 to 5 at a concentration of 3.0 to 6.3 ppm (2.5 to 5.2 mg/m^3) (Lund *et al*, 1997). The exposures were obtained by diluting hydrogen fluoride supplied with a certified accuracy of 3% then diluted. While the materials of the gas supply lines to the ventilation duct and the exposure chamber are described in the paper the material of the duct is not mentioned. While it is possible that at high humidity levels losses to the walls may have been significant the study allowed for this. The actual concentrations to which the subjects were exposed were sampled continuously in the inhalation chamber and analysed by ion-selective electrode. None of the subjects had obvious symptoms reflecting bronchial constriction. No human lethality studies following inhalation-only exposures were located. The key studies are summarised in the table below and further detail may be found in the text.

Table 3.1 – Key Human Studies

Concentration (ppm)	**Exposure time**	**Effects**	**Reference**
0.2-0.7	1 hour	No to low sensory and lower airway irritation; no change in FEV1; decrease in FVC	Lund *et al* (1997)
0.85-2.9	1 hour	No to low sensory and lower airway irritation; no change in FVC; FEV1	Lund *et al* (1997)
3.0-6.3	1 hour	No eye irritation, upper (3/14 subjects) and lower (1/14 subjects) airway irritation, No change in FVC, FeV1	Lund *et al* (1997)
1.83-7.8	1 hour	No change in spirometry parameters, increase in fraction of lymphocytes and neutrophils in bronchoalveolar lavage fluid	Lund *et al* (1997)
1.42	6 hours/day, 15 days	No noticeable effects	Largent (1960, 1961)
2.59-4.74 (avg.) 0.9-8.1 (range)	6 hours/day, 10-50 days	Slight irritation of the skin, nose and eyes; sour taste in the mouth	Largent (1960, 1961)
4.6 (avg) 3.5-7.1 (range)	7 hours	Irritant effect followed by accommodation	Collings *et al* (1951)
32	3 minutes	"Tolerated" with discomfort; mild irritation of eyes and nose	Machle *et al* (1934)
61	approx. 1 minute	Eye and nasal irritation	Machle *et al* (1934)

3.2 Mechanism of Toxicity

The available studies indicate that hydrogen fluoride is a severe irritant to the skin, eyes, and respiratory tract, particularly the anterior nasal passages where, depending on species and concentration, it appears to be effectively scrubbed from the inhaled air. Effective deposition in the anterior nasal passages may be attributed to the high solubility and reactivity of hydrogen fluoride. Penetration into the lungs results in pulmonary haemorrhage and oedema and may result in death. Although renal and hepatic changes have been observed in animal studies, serious systemic effects are unlikely to occur from an acute exposure.

3.3 Absorption, Distribution, Metabolism and Excretion

3.3.1 Absorption

In humans, the dominating route of fluoride absorption is via the gastrointestinal tract. Fluoride ions are released from readily soluble fluoride compounds, such as sodium fluoride, hydrogen fluoride and fluorosilicic acid and almost completely absorbed. Fluoride compounds with low solubility, on the other hand, including calcium fluoride, magnesium fluoride and aluminium fluoride, are poorly absorbed The absorptive process occurs by passive diffusion, and fluoride is absorbed principally from both the stomach and the intestine (ECB 2002, WHO 2003). The mechanism and the rate of gastric absorption of fluoride are related to gastric acidity. Fluoride is mainly absorbed in the form of hydrogen fluoride (when ionic fluoride enters the acidic environment of the stomach lumen, it is largely converted into hydrogen fluoride). Most of the fluoride that is not absorbed from the stomach will be rapidly absorbed from the small intestine.

3.3.2 Distribution

Fluoride is rapidly distributed by the systemic circulation to the intracellular and extracellular water of all tissues and organs; however, the ion normally accumulates only in calcified tissues, such as bone and teeth (WHO 2002). The rates of delivery are generally determined by the blood flow to the tissues in question. Consequently, steady-state fluoride concentrations are achieved more rapidly between plasma and well-perfused tissues, such as the heart, lungs and liver, than between plasma and less well perfused tissues, such as resting skeletal muscle, skin and adipose tissue (WHO 2002). Human studies have shown that the placenta is not in any sense a barrier to the passage of fluoride to the foetus. There is a direct relationship between the serum fluoride concentration of the mother and that of the foetuses; the cord serum concentration is 75% that of the maternal fluoride concentration. From the foetal blood, fluoride is readily taken up by the calcifying fettle bones and teeth (WHO 2002).

3.3.3 Excretion

The major route for the removal of fluoride from the body is by the kidneys. The renal clearance of fluoride in the adult typically ranges from 30 to 50 ml/min. The percentage of the filtered fluoride reabsorbed from the renal tubules can range from about 10 to

90%. The degree of reabsorption depends largely on the pH of the tubular fluid, urinary flow and renal function. Most fluoride is excreted via urine with faeces and sweat playing only a minor role. Urinary fluoride clearance increases with urine pH due to a decrease in the concentration of HF.

3.4 Acute Toxicity

Although several instances of exposure to hydrogen fluoride have resulted in death, no data were located regarding human deaths following inhalation-only exposure to hydrogen fluoride. However, several studies indicated that humans have died from accidental exposure via a combination of inhalation and dermal exposure to hydrofluoric acid (Kleinfeld, 1965; Tepperman, 1980; Braun *et al*, 1984; Mayer and Gross, 1985; Chan *et al*, 1987; Chela *et al*, 1989; ATSDR, 1993). Deaths were attributed to pulmonary oedema and cardiac arrhythmias, the latter a result of acidosis from pronounced hypocalcemia and hypomagnesemia following dermal fluoride uptake. No doses or exposure levels could be determined.

Lund *et al* (1995) exposed 15 healthy male volunteers to concentrations of 1.5-6.4 mg/m^3 (1.83-7.8 ppm) for one hour in order to study sensory irritation and pulmonary parameters. Hydrogen fluoride induced a bronchial inflammatory reaction as indicated by an increase in the fraction of lymphocytes and neutrophils in the bronchoalveolar lavage fluid. There was no change in spirometry measurements.

A further study by Lund *et al* (1997) involved the exposure of 20 healthy, non-smoking male volunteers to concentrations of 0.244 to 6.34 ppm (0.2 to 5.2 mg/m^3) of hydrogen fluoride for 1 hour. This range of concentrations was chosen, as these levels were known to occur among "potroom" workers in the aluminium industry. Two of the subjects had hay fever; one subject also had an increased total IgE immunoglobulin level. Three ranges of exposure concentrations were used: 0.2-0.7 ppm (0.17 - 0.58 mg/m^3) (n = 9); 0.85-2.9 ppm (0.71- 2.4 mg/m^3) (n = 7); and 3.0-6.3 ppm (2.5 – 5.2 mg/m^3) (n = 7). Upper and lower airway and eye irritation were subjectively scored on the basis of 0 (no symptoms) to 5 (the most severe symptoms). In addition, the forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) were measured before, during (every 15 minutes) and at the end of the exposures and at 4 and 24 hours post exposure. Subjects rested during the first 45 minutes of exposure; during the last 15 minutes the subjects exercised on a stationary bicycle.

Five subjects reported minor upper and lower respiratory symptoms (mild coughing or expectoration and itching of the nose) before entering the chamber. Symptoms increased after the one hour exposure, but none of the subjects in the lower two exposure groups reported symptom scores of >3. FVC was significantly decreased after exposure in the lowest exposure group. The lack of significant changes in the higher exposure groups makes it unlikely that the change in FVC in the lowest group was a result of chemical exposure. In the highest exposure group, no eye irritation was reported but 3 subjects reported upper airway irritation (itching or soreness of the nose or throat) scores of >3 and one subject reported a lower airway irritation score of >3. Specific symptoms and actual scores were not reported. The authors noted that lower airway symptoms were not reported to a significant degree in relation to exposure to

hydrogen fluoride and none of the subjects had obvious signs reflecting bronchial constriction (USEPA 2000).

Lund *et al* (2002) examined the effect on the nasal response (as measured by changes in neutrophilic, eicosanoid and antioxidant changes in nasal lavage fluid) in humans, subsequent to short-term exposure to hydrogen fluoride at a concentration range of 3.3-3.9 mg/m^3. Ten healthy volunteers were involved in the study that lasted for 1 hour. Nasal lavage was performed before, immediately after and 1.5 hours after the end of the exposure. Control lavages were performed at the same time periods in controls that were not exposed to hydrogen fluoride. At the end of the exposure period, seven out of ten individuals reported upper airway symptoms. There was a significant increase in the number of neutrophils and total cells while there was a decrease in cell viability. The changes in neutrophil numbers correlated significantly with the reported airway symptoms. Eicosanoids were increase and of the antioxidants measured the concentration of uric acid increased after exposure. The authors concluded that exposure to HF resulted in an immediate nasal inflammatory and antioxidant response in healthy human volunteers.

3.5 Subchronic Toxicity

Largent (1960, 1961) exposed five male volunteers (ages 17-46) to variable concentrations of hydrogen fluoride for 6 hours/day over a period of 15 to 50 days. Average concentrations over the exposure period ranged from 1.42 to 4.74 ppm (average, 3.2 ppm (2.7 mg/m^3); total range, 0.9 to 8.1 ppm (0.75 to 6.7 mg/m^3)). Effects in two subjects, who were exposed to concentrations up to 7.9 and 8.1 ppm (6.6 and 6.7 mg/m^3) over a 25- and 50-day period, respectively, were no more severe than in the other subjects exposed to lower concentrations. Although it was stated that one subject tolerated 1.42 ppm (1.18 mg/m^3) for 15 days (6 hours/day) without noticeable effects, exposure of the same subject to 3.39 ppm (2.82 mg/m^3) for 10 days at a later time resulted in redness of the face and, by day 11, some flaking of the skin. The subjects experienced very slight irritation of the eyes, nose, and skin at 2 ppm (1.7 mg/m^3) and noted a sour taste during the exposures. It is not clear whether the subject exposed to 1.42 ppm for 15 days also experienced these effects. Application of a coating of face cream prior to exposure was found to prevent any discomfort or redness of the skin. Any signs of discomfort disappeared after cessation of exposure and systemic effects were not observed (USEPA 2000).

Chan-Yeung *et al* (1983a) studied the health effects in 2066 workers in an aluminium smelter in British Columbia, Canada. The cohort comprised high and medium exposed pot-room workers as well as low exposed controls and an external control group consisting of 372 railway repair workers. For each group inhalation exposure to particulate and gaseous fluoride and urinary fluoride excretion were determined. No overt signs of skeletal fluorosis were observed in workers exposed up to 0.48 mg F^- /m^3 (0.2 mg /m^3 of gaseous F^- and 0.28 mg/m^3 of particulate associated fluoride).

In a parallel study in the same aluminium smelter, Chan-Yeung *et al* (1983b) reported on the association between working in pot-rooms and respiratory performance. The following respiratory parameters were studied: Forced expiratory volume in 1 second (FEV_1), Forced vital capacity (FVC), maximum mid-expiratory flow rate (FEF_{25-50}),

chest X-ray and chest symptoms. The observations were corrected for smoking habits, age and duration of employment. The cohorts consisted of a high exposed group (>50% of the working time in the pot-rooms, n=495) a medium exposed group (<50% of the time spent working tin the pot-rooms, n=302) and a control group (office and casting personnel, n=713).

The air was analysed for particulate matter, fluoride (total fluoride made up of 2 measurements, gaseous and particulate), carbon monoxide, sulphur dioxide and benzo(a)pyrene. The high exposure workers exhibited a statistically significant decrease in FEV_1 and FEF_{25-50} along with chest symptoms coughing and wheezing. No changes in FVC were observed. The medium group did not deviate statistically from the control group. However, as the pot-room workers were exposed to several airway irritants at the time, a definite conclusion about the cause of the changes in the high exposure group cannot be drawn.

3.6 Occupational Exposure

Derryberry *et al* (1963) investigated chronic exposure to fluoride in the workplace. Chronic exposures in industrial situations have led to skeletal fluorosis in exposed workers. Concentrations of airborne hydrogen fluoride in these studies are often estimated or unknown and exposures are usually to both hydrogen fluoride and fluoride dusts (NIOSH, 1976; ATSDR, 1993). However, studies with long-term exposure levels can be used to determine no-effect concentrations. Derryberry *et al* (1963) reported that there were no statistically significant differences in several respiratory parameters between a control group and a group of 57 workers engaged in the manufacture of phosphate fertiliser. Exposure concentrations to dust and hydrogen fluoride gas combined ranged from 0.50-8.32 mg fluoride/m^3 (0.64-10.7 ppm F) with an average for the group of 2.81 mg fluoride/m^3 (3.6 ppm hydrogen fluoride) over a 14-year period.

Collings *et al* (1951) subjected two volunteers to an atmosphere containing hydrogen fluoride and silicon tetrafluoride during an 8-hour work shift; the subjects left the area for 15 minutes every two hours and during a lunch break. The average concentration of fluoride during the exposure was 3.3 mg/m^3 (4 ppm). The authors reported, "both subjects experienced the anticipated irritant effect of the gases and the remarkably rapid acclimation which is so well known." However, no further details on irritant effects were reported.

Machle and Evans (1940) studied a group of workers exposed to hydrogen fluoride and, to a lesser extent, calcium fluoride dust during the manufacture of hydrofluoric acid. Over a five-year period, the workers were exposed intermittently, in the vicinity of equipment or while repairs were made, to concentrations of 0.011 to 0.021 mg/L of F (14 to 27 ppm hydrogen fluoride). Medical examinations revealed no clinical or roentgenological evidence of damage (USEPA 2000).

In a monitoring study, Kono *et al* (1987) measured air and urinary concentrations of fluoride of 82 unexposed subjects and 142 workers engaged in the manufacture of hydrofluoric acid in Japan. The air concentration for unexposed workers was 0 ppm whereas the air concentrations in different areas of the manufacturing sites ranged from

0.3 ppm (16 workers) to 5.0 ppm (10 workers) (0.25 to 4.2 mg/m^3). Irritant or health problems of the workers were not identified (USEPA 2000).

Waldbott and Lee (1978) reported a case of chronic poisoning of a worker exposed to hydrogen fluoride at an alkylation unit of an oil company. The worker was exposed, over the course of a 10-year period, to variable and unknown concentrations of hydrogen fluoride daily during an 8-hour shift. About 10 to 15 times a year, he experienced "acute episodes". Acute symptoms consisted of intense eye irritation, lacrimation, blurred vision, marked dyspnoea, nausea, epigastric pain, vomiting, and sudden weakness.

The worker had repeated minor hydrogen fluoride "burns" on the skin. Estimates of exposure concentrations given by the worker and his co-workers (for example, a concentration of >25 ppm during acid tank gauging) were considered to be of limited value (USEPA 2000). During the ten-year period the previously healthy worker suffered increasingly worsening back and leg pains, loss of memory, osteoarthritis, restrictive and obstructive lung disease, and haematuria.

3.7 Industrial Accidents

Approximately 3000 people were evacuated from a community in Texas, USA, following the release of 53,000 pounds of caustic hydrogen fluoride and 6,600 pounds of isobutene from a petrochemical plant (Wing *et al*, 1991). The nearest residential community was 0.25 miles from the plant. Within 20 minutes of the release, people within 0.5 miles of the plant were evacuated and eventually a 5 square mile area was evacuated. Samples taken downwind (distance not stated) one hour after the release contained 10 ppm (8.3 mg/m^3) while samples obtained after 2 hours contained "minimal traces" of hydrogen fluoride. The most frequently reported symptoms stated by persons presented at emergency rooms at two area hospitals were eye irritation, throat burning, headache, shortness of breath, throat soreness, chest pain, cough, and nausea.

Himes (1989) reported an incident in which a cloud of gases was released from an oil refinery. The major constituent of the cloud was hydrogen fluoride, which based on computer simulations was calculated to have potentially reached an airborne concentration of 20 ppm (17 mg/m^3). A total of 36 people including emergency personnel responding to the incident were treated at area hospitals for acute chemical exposure. There were no fatalities. No measurements were taken and no further details of the incident were given.

In the third incident, 13 workers at an oil refinery were exposed to a maximum concentration of 150-200 ppm (125 - 170 mg/m^3) of hydrofluoric acid mist for approximately 2 minutes (Lee *et al*, 1993). Prompt treatment with nebulised calcium gluconate was given. The workers were medically evaluated within an hour of exposure at which time the only symptoms were minor upper respiratory tract irritation.

U.S. EPA (1993) cited a study by Trevino (1991) in which an industrial accident in Mexico resulted in exposure of seven workers to approximately 10,000 ppm (8300 mg/m^3) hydrogen fluoride for several minutes. Periodic examinations for up to 11 years

after exposure revealed no long-term or delayed effects. No measurement methods and no further details of the study were provided.

3.8 Developmental/Reproductive Toxicity

No studies were located regarding reproductive or developmental effects in humans after inhalation exposure to hydrogen fluoride. Fluoride is rapidly absorbed following oral ingestion, crosses the placental in limited amounts, and is found in placental and foetal tissue (ATSDR, 1993). Studies on the incidence of reproductive or developmental effects in areas using fluoridated water have found no correlation between fluoridation levels and birth defects (ATSDR, 1993).

3.9 Genotoxicity

No data specifically concerning the genotoxicity of hydrogen fluoride in humans were identified in the available literature.

3.10 Carcinogenicity

Several studies indicated an increase in respiratory cancers among workers engaged in industries where they could be exposed to hydrogen fluoride or fluoride dusts. However, the confounding factors of exposure to other chemicals and smoking status of the workers, along with the lack of clear exposure concentrations, make the studies of questionable relevance (ATSDR, 1993).

4. Evaluations and recommendations by other Organisations

4.1 US Environmental Protection Agency

The USEPA Office of Pollution Prevention and Toxics proposed Acute Exposure Guideline Levels (AEGLs) for hydrogen fluoride in 2000. There are three types of guidelines: AEGL-1, AEGL-2 and AEGL-3. The definitions of these provided in the public draft document for hydrogen fluoride are:

AEGL-1 is the airborne concentration (expressed as ppm or mg/m^3) of a substance at or above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain sub-clinical non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance at or above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance at or above which it is predicted that the general population, including susceptible individuals, could experience life threatening health effects or death.

For the purposes of this evaluation it is considered that AEGL-1 is the most appropriate guideline to consider. Further details for the derivation of AEGL-2 and AEGL-3 are available in the USEPA (2000) reference. It was considered that the human data available were suitable for the derivation of AEGL-1.

The results of studies by Largent (1960, 1961), in which human volunteers were exposed to hydrogen fluoride for an extended period of time and reported only mildly irritant effects, are close to, but below the definition of the AEGL-1 (notable discomfort at or above the AEGL-1, but only odour, taste, slight or mild sensory irritation below the AEGL-1). In this study, concentrations of 2 ppm (1.7 mg/m^3) for 6 hours/day were reported as only slightly irritating.

When data are lacking for desired exposure times, scaling across time may be based on the relationship between acute toxicity (concentration) and exposure duration (USEPA 2000). Using 5-, 15-, 30-, and 60-minute LC_{50} values of Rosenholtz *et al* (1963), Alexeeff *et al* (1993) showed that the association between concentration and exposure duration for hydrogen fluoride can be described as $C^2 \times t = k$ (where C = concentration, t = time, and k is a constant). The least-squares linear curve fit of the graph, log time vs log LC_{50} resulted in the equation, $y = 7.69 - 1.89 x$. The slope of the line, 1.89, rounded to 2, is the value of the exponent n. ten Berge *et al* (1986) using the data of Machle *et al* (1934) found the same relationship between concentration and time, i.e., $C^2 \times t = k$.

The basis for the AEGL-1 is the 2 ppm concentration and exposure time of 6 hours. This concentration-time relationship for an acute exposure can be considered

conservative as the exposure was tolerated repeatedly for up to 50 days without increased irritancy. In addition, industrial exposures of ~4 ppm have been experienced without effects. An uncertainty factor of 3 was applied to protect sensitive individuals and the resulting value was scaled to the 30-minute and 1-, 4-, and 8-hour time periods using the relationship described above, $C^2 \times t = k$. The resulting AEGL-1 values are listed in the table below. The 10-minute AEGL-1 was set equal to 2 ppm (1.7 mg/m^3), because irritant properties would not change greatly between the 10-minute and 30-minute time frames.

Table 4.1 - AEGL-1 Values for Hydrogen Fluoride

Time	AEGL-1 Value
10 minutes	2 ppm (1.6 mg/m^3)
30 minutes	2 ppm (1.6 mg/m^3)
1 hour	2 ppm (1.6 mg/m^3)
4 hours	1 ppm (0.8 mg/m^3)
8 hours	1 ppm (0.8 mg/m^3)

The study of Lund *et al* (1997) provides data similar to that of Largent (1960, 1961) and reinforces the 1-hour AEGL-1 of 2 ppm. In this study, no to low sensory irritation was reported at concentrations 2.9 ppm (2.4 mg/m^3) for an exposure duration of 1 hour.

Alexeeff *et al* (1993) used a "benchmark dose" approach to estimate an exposure level that would protect the public from any irritation during a routine emission of hydrogen fluoride. Their approach employed a log-probit extrapolation of concentration-response data to the 95% lower confidence limit on the toxic concentration producing a "benchmark dose" of 1% response called a practical threshold. Species-specific and chemical-specific adjustment factors were applied to develop exposure levels applicable to the general public. The 1-hour value calculated in this manner was 0.7 ppm. Alexeeff *et al* (1993) also calculated a 1-hour value of 2 ppm, which they defined as the concentration that would protect against severe irritation from a once-in-a-lifetime release.

The ATSDR have also derived an acute duration inhalation Minimal Risk Level (MRL) of 0.03 ppm (0.024 mg/m^3) based on a NOAEL of 98 ppm for nasal irritation in rats (Rosenholz *et al*., 1963), adjusted for 24 hour exposure and an uncertainty factor of 30. An intermediate MRL has also been derived of 0.02 ppm (0.016 mg/m^3) based on a lowest observed adverse effect level of 2.98 ppm for slight nasal irritation (6 hours/day for 15-50 days), adjusted for intermittent exposure and an uncertainty factor of 30 (US EPA, 2001). The MRL is an estimate of human exposure to a hazardous substance likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure.

4.2 US ACGIH

ACGIH have set a Threshold Limit Value as a ceiling limit of 3 ppm for hydrogen fluoride (2.6 mg/m^3) based on the results of controlled inhalation studies in human volunteers. It was considered that this limit would minimise the toxicity and irritation from exposure to hydrogen fluoride and also the potential for occurrence of dental fluorosis or osteofluorosis associated with occupational exposure to hydrogen fluoride.

4.3 UK Health and Safety Executive

The HSE have set an occupational exposure limit of 3 ppm (2.5 mg/m^3) as a 15 minute short term and 1.8 ppm (1.5 mg/m^3) as an 8-hr exposure level. This is in accordance with the European Commission's Indicative Occupational Exposure Limit Values (IOELVs) listed in the 1st Consolidated IOELV Directive (2000/39/EC).

4.4 World Health Organization

The WHO concluded that the available information did not permit the derivation of an air quality guideline value for fluoride(s). The WHO also note that except for occupational exposure, exposure to fluoride by inhalation is negligible.

The WHO noted that fluoride levels in ambient air should be less than 1μg/m3 to prevent effects on livestock and plants. They stated that such levels would also be sufficiently low to protect human health. It is noted that the EU Risk Assessment Report concludes that the NOEC of atmospheric fluoride for livestock and plants is less than 1μg/m^3 fluoride (WHO 2000).

4.5 Other Standards and Guidelines

Other published occupational health standards or guidelines are listed in the table below.

Table 4.2 – Standards and Guidelines for Hydrogen Fluoride

Agency/Organization	Exposure Concentration
OSHA PEL-TWA (OSHA, 1990)	3 ppm (as fluoride)
OSHA PEL-STEL (OSHA, 1990)	6 ppm (as fluoride)
NIOSH REL-TWA (NIOSH, 1976)	3 ppm (as fluoride)
NIOSH STEL (NIOSH, 1976)	6 ppm (as fluoride)
NIOSH IDLH (NIOSH, 1976)	30 ppm (as fluoride)
ERPG-1 (AIHA, 1996)	2 ppm
ERPG-2 (AIHA, 1996)	20 ppm
ERPG-3 (AIHA, 1996)	50 ppm
OEHHA (2002) – chronic toxicity REL	40 ppb as HF and as fluoride
OEHHA (1999) – acute toxicity REL	0.3 ppm

HSE – 15 minute STEL	3 ppm (as fluoride)
HSE – 8-hour OEL	1.8 ppm

OSHA PEL-TWA (Permissible Exposure Limits – Time Weighted Average) is for no more than 8 hours/day, 40 hours/week.
OSHA PEL-STEL (Permissible Exposure Limits – Short Term Exposure Level) is for no more than 15 minutes/day, 40 hours/week.
NIOSH REL-TWA (Reference Exposure Level – Time Weighted Average) is for no more than 8 hours/day, 40 hours/week.
NIOSH STEL (Short Term Effect Level) is for no more than 15 minutes/day, 40 hours/week.
NIOSH IDLH (Immediately Dangerous to Life or Health) is for no more than 30 minutes.
(Basis: animals tolerated 30 ppm for 41 hours without a fatality [Machle *et al*, 1934]).

OEHHA - acute Inhalation Reference Exposure Level is for one hour

5. Conclusions

Inhaled gaseous HF is virtually completely absorbed in the upper airways. Fluoride circulates in the body as F^- and in association with proteins and lipids and its distribution and elimination do not depend on its place of entry into the body. Fluoride can be found in all tissues in the body and sequestration takes place in bone tissue in which about half of the absorbed fluoride is deposited. Excretion is mainly via the urine. In humans, half-lives are in the range of 8-20 years for fluoride in plasma and bone deposits, respectively.

Human volunteer studies indicate concentrations of 2 ppm (1.7 mg/m^3) for 6 hours/day were only slightly irritating although there is data to suggest that at lower doses than this, inflammatory and antioxidant responses occur. The available animal data set for HF also permits the derivation of a NOAEL for repeated subchronic inhalatory exposure. No suitable studies are available to derive a NOAEL for HF for other routes of exposure. In the Placke and Griffin 91 day subchronic study in rats, a NOAEL of 1 ppm (actual concentration 0.72 mg/m^3) was identified.

It is noteworthy that the fluoride intake by adults has been estimated in several studies. Human intake of fluoride may also include iatrogenic sources such as toothpaste. Taken as a whole, the estimates of total daily intake of fluoride in adults is as follows: food and drinking water 5640 µg F^-/day; toothpaste 300 µg F^-/day and air 50 µg F^-/day (ECB 2002). As can be seen by the above intakes, the HF contribution to the total daily fluoride intake is almost two orders of magnitude lower than that for drinking water and food combined.

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List of Figures

List of Tables

Appendix A – Key References

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

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Appendix B – Literature Search Strategy

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

The initial search included the following literature sources;

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

The later searches looked at the following;

Search with search term 'Hydrogen AND fluoride and limited to reviews
Search with search term 'Hydrogen AND fluoride and limited to reviews and 01/01/1995 – 30/04/2003
Search of PubMed with search term 'Hydrogen AND fluoride and limited to reviews with search terms Hydrogen and Fluoride and toxicity

Appendix C - Medical Glossary

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

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

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

pulmonary	relating to the lung
renal	relating to the kidneys
rhinitis	inflammation of the mucous membrane of the nose
rhinorrhea	a persistent watery mucous discharge from the nose, as in the common cold
septal	partition between the left and right halves of the chest
serous membrane	a smooth transparent membrane, consisting of mesothelium and underlying elastic fibrous connective tissue lining certain large cavities of the body
squamous cell	an epithelial cell that is flat like a plate and forms a single layer of epithelial tissue
squamous metaplasia	a change in the nature of tissue into *squamous epithelium; may be an early sign of malignant change
submucosa	the layer of loose connective tissue underlying a mucous membrane
synctial	made up of a mass of *protoplasm containing several nuclei, e.g, muscle fibres are *synctia*
tachypneoa	rapid breathing
thrombosis	a condition in which the blood changes from a liquid to a solid state and produces a blood clot
protoplasm	the material of which living cells are made, which includes the cytoplasm and nucleus
trigeminal nerve	the fifth and largest cranial nerve; controls the muscles involved in chewing and relaying information about temperature, pain and touch from the whole frond half of the head
turbinate bone	any of the three thin scroll-like bones that form the sides of the nasal cavity (also known as nasal concha)

Appendix D – Glossary of Terms and Acronyms

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

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

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

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

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

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

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

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

Carcinogen: An agent capable of inducing cancer.

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

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

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

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

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

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

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

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

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

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

Horizontal Guidance Note (H1): The name of the guidance note issued by the Environment Agency which describes how operators should assess the environmental impact of processes and appraise the Best Available Techniques when applying for a permit under the Pollution Prevention and Control (PPC) regime. The term 'Horizontal' refers to the fact that the guidance can be applied across all the sectors covered by PPC.
Indicative Occupational Exposure Limit Values (IOELVs): European Community limit values, which are health based and are set under the EU Chemical Agents Directive

(98/24/EC) (earlier Directives referred to the as ILVs). They indicate levels of exposure to hazardous substances considered to provide protection from ill health caused by work. IOELVs are similar to the British OELs system under COSHH.

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

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

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

Maximum Exposure Limit (MEL): Maximum Exposure Limits (MELs) are one of the two types of Occupational Exposure Limits (OELs) the UK Health and Safety Commission (HSC) sets. A MEL is proposed for substances, which may cause the most

serious health effects, such as cancer and occupational asthma. These are substances for which no threshold level of exposure for the key health effect can be determined or for which exposure thresholds may be identified but at a concentration that is not yet routinely achievable in the workplace. The Control of Substances Hazardous to Health (COSHH) regulations 1999 require that exposure should be reduced as far below the MEL as reasonably practicable. See also Occupational Exposure Standard (OES).

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

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

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

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

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

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

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

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

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

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

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

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

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