Institute for Health and Consumer Protection

European Chemicals Bureau

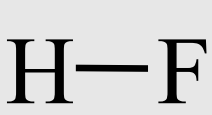
Existing Substances

European Union Risk Assessment Report

CAS No.: 7664-39-3

EINECS No.: 231-634-8

hydrogen fluoride



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European Union Risk Assessment Report

HYDROGEN FLUORIDE

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RISK ASSESSMENT

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RISK ASSESSMENT

Final report, October 2001

The Netherlands

Rapporteur for the risk evaluation of Hydrogen Fluoride is the Ministry of Housing, Spatial Planning and the Environment (VROM) in consultation with the Ministry of Social Affairs and Employment (SZW) and the Ministry of Public Health, Welfare and Sport (VWS). Responsible for the risk evaluation and subsequently for the contents of this report, is the rapporteur.

The scientific work on this report has been prepared by the Netherlands Organisation for Applied Scientific Research (TNO) and the National Institute of Public Health and the Environment (RIVM), by order of the rapporteur.

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Date of Last Literature Search :	**1998**
Review of report by MS Technical Experts finalised:	**December 1999**
Final report:	**October 2001**

Foreword

We are pleased to present this Risk Assessment Report which is the result of in-depth work carried out by experts in one Member State, working in co-operation with their counterparts in the other Member States, the Commission Services, Industry and public interest groups.

The Risk Assessment was carried out in accordance with Council Regulation (EEC) 793/93[1] on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.

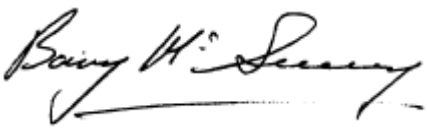
There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.

The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94[2], which is supported by a technical guidance document[3]. Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a Meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) which gives its opinion to the European Commission on the quality of the risk assessment.

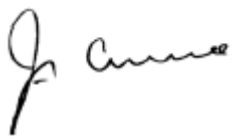
If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.

The Risk Assessment Report is also presented to the Organisation for Economic Co-operation and Development as a contribution to the Chapter 19, Agenda 21 goals for evaluating chemicals, agreed at the United Nations Conference on Environment and Development, held in Rio de Janeiro in 1992.

This Risk Assessment improves our knowledge about the risks to human health and the environment from exposure to chemicals. We hope you will agree that the results of this in-depth study and intensive co-operation will make a worthwhile contribution to the Community objective of reducing the overall risks from exposure to chemicals.



Barry Mc Sweeney
Director-General
Joint Research Centre



J. Currie
Director-General
Environment, Nuclear Safety and Civil Protection

[1] O.J. No L 084 , 05/04/199 p.0001 – 0075

[2] O.J. No L 161, 29/06/1994 p. 0003 – 0011

[3] Technical Guidance Document, Part I – V, ISBN 92-827-801 [1234]

0 OVERALL RESULTS OF THE RISK ASSESSMENT

CAS-No. 7664-39-3
EINECS-No. 231-634-8
IUPAC-name hydrogen fluoride

Environment

( ) There is need for further information and/or testing
( ) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied
(X) There is a need for limiting the risks: risk reduction measures which are already being applied shall be taken into account

Conclusion iii) is reached because:

- for a number of HF producing and HF using sites the local environmental risk characterisation points to risks for either 1) the aquatic compartment, or 2) the atmospheric compartment or 3) livestock and wildlife exposed via air.

Man indirectly exposed via the environment

( ) There is need for further information and/or testing
( ) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied
(X) There is a need for limiting the risks: risk reduction measures which are already being applied shall be taken into account

Conclusion iii) is reached because:

- for one HF using site the local environmental risk characterisation indicates a significant risk for humans indirectly inhalatory exposed via the environment

Consumers

( ) There is need for further information and/or testing
( ) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied
(X) There is a need for limiting the risks: risk reduction measures which are already being applied shall be taken into account

Conclusion iii) is reached because of concerns for skin irritation and/or corrosivity, depending on concentration, as a consequence of single exposure to the hydrogen fluoride liquid arising from the use of HF containing rust cleaning and stone and wood cleaning agents.

Workers

( ) There is need for further information and/or testing
( ) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied
(X) There is a need for limiting the risks: risk reduction measures which are already being applied shall be taken into account

Conclusion iii) is reached because:

- the general warnings on (1) the formation of H_2 by reaction of HF solutions of less than 65% with metals, and (2) on the violent behaviour upon dilution of concentrated HF with water, should be included in all MSDSs.
- concerns for skin and respiratory tract irritation and/or corrosivity, depending on concentration, as a consequence of repeated exposure to gaseous hydrogen fluoride at production and use as an intermediate in the chemical industry and use of aqueous HF-solutions.
- concerns for general systemic toxicity as a consequence of repeated inhalatory exposure arising from the use of aqueous HF-solutions.
- concerns for skin irritation and/or corrosivity, depending on concentration, as a consequence of single exposure to the hydrogen fluoride liquid arising from the use of aqueous HF-solutions.
- concerns for respiratory tract irritation and/or corrosivity, depending on concentration, as a consequence of single exposure to gaseous hydrogen fluoride at production and use as an intermediate in the chemical industry and at the use of aqueous HF-solutions.

Table 0.A Overview of conclusions with respect to occupational risk characterisation

End-point	conclusions valid for the occupational scenario's			
	scenario 1		scenario 2	
	MOS	conclusion	MOS	conclusion
acute toxicity - dermal - inhalation (LC_{50}, 1 hr, 280-1900 mg/m^3)	 na >112	 ii ii	 na >47	 ii ii
irritation, single exposure, liquid HF - dermal	 na	 ii	 na	 iii
irritation, single exposure, gaseous HF - dermal - inhalation - eyes	 na na na	 ii iii ii	 na na na	 ii iii ii
irritation, repeated exposure, liquid HF - dermal	 na	 ii	 na	 ii
irritation, repeated exposure, gaseous HF - dermal (LOAEL 1.16 mg/m^3, human study) - inhalation (LOAEL 1.16 mg/m^3, human study) - eyes (LOAEL 1.16 mg/m^3, human study)	 0.5 0.5 0.5	 iii iii iii	 0.2 0.2 0.2	 iii iii iii
sensitisation	na	ii	na	ii
repeated dose toxicity, systemic effects - dermal (NOAEL 0.48 mg/m^3, epi-study workers) - inhalation (NOAEL 0.48 mg/m^3, epi-study workers)	 not relevant 1	 ii ii	 24 0.2	 ii iii
Mutagenicity	na	ii	na	ii
Carcinogenicity	na	ii	na	ii
reproductive toxicity, developmental effects	na	ii	na	ii
reproductive toxicity, fertility effects - dermal (10 mg/kg b.w./d, oral 2-gen study with NaF) - inhalation (10 mg/kg b.w./d, oral 2-gen study with NaF)	 not relevant 50	 ii ii	 15 10	 ii ii
Flammability	na	ii	na	ii
explosive properties	na	ii	na	ii
oxidising properties	na	iii[a]	na	iii[a]

na = Not applicable

[a]Formation of H_2 by reaction of HF-solutions of less than 65% with metals, and violent behaviour upon dilution of concentrated HF with water

CONTENTS

TABLES

1 GENERAL SUBSTANCE INFORMATION

Identification of the substance

CAS-No.:	7664-39-3
EINECS-No.:	231-634-8
IUPAC name:	hydrogen fluoride
Synonyms:	hydrofluoric acid anhydrous hydrofluoric acid
Molecular formula:	HF
Structural formula:	H - F
Molecular weight:	20.01

Purity/impurities, additives

Purity:	>99.9% (w/w)
Impurity:	<1% water
Additives:	none

Physico-chemical properties

Physical state:	liquid/gas
Melting point:	- 83^{o}C
Boiling point:	19.5^{o}C at 1013 hPa
Relative density:	1.016 g/cm^3 at 0^{o}C (liquid) 0.901 g/cm^3 at 22^{o}C (liquid)
Vapour pressure:	1033 hPa at 20^{o}C
Water solubility:	miscible in all proportions
Partition coefficient n-octanol/water (log-value):	- 1.4
Granulometry:	not applicable
Flammability:	non-flammable [4]
Explosive properties:	non-explosive [1]
Oxidising properties:	not oxidising in the sense of reaction with oxygen[1]
Conversion factors:	1 mg/m^3 = 1.22 ppm (101 kPa, 25^{o}C) 1 ppm = 0.82 mg/m^3 (101 kPa, 25^{o}C)
Odour threshold:	30 µg/m^3

These data are based on references as mentioned in the HEDSET and Van Gemert and Nettenbreijer (1977).

Remark 1

Hydrofluoric acid with concentrations of less than about 65% reacts with metals (e.g. iron from steel drums or from reactors) under the formation of H_2. Mixtures of H_2 in air can be explosive.

[4] See remark 1

Remark 2

High heat of dilution may cause violent behaviour upon dilution of concentrated HF with water.

Remark 3

There are no R- and S-sentences appropriate for the properties as mentioned in remark 1 and 2. Therefore it is recommended to include these remarks in the Material Safety Data Sheets.

Classification

Classification according to Annex I
Symbol T+, C
R-phrases: 26/27/28 - 35
S-phrases: 7/9 - 26 - 36/37/39 - 45

Proposal of the rapporteur: agreement with Annex I (see above), with the addition of R54 (Toxic to plants). It must be noted that HF is very toxic to plants and is a possible candidate for R54 (toxic to plants). Since no criteria have been established yet this R-phrase cannot be assigned yet.

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

The production of HF is located at different sites in the European Union (see **Table 2.1**).

Table 2.1 Production sites of HF in the EU (CTEF 1995)

Company	Location
ICI Chemicals & Polymers Limited	Runcorn (Cheshire), United Kingdom
Laporte Fluorides	Rotherham, United Kingdom
Bayer AG	Leverkusen, Germany
Rhone-Poulenc Chimie	Salindres, France
Rhodia LTD	Avonmouth, United Kingdom
Ausimont	Porto Marghera, Italy
Derivados del Fluor S.A.	Onton/Bilbao, Spain
Elf Atochem	Pierre Benite, France
Solvay Fluor und Derivate GmbH	Bad Wimpfen, Germany
Allied Signal Europe bv	Weert, the Netherlands
Fluorchemie Dohna*	Dohna, Germany
Fluorchemie Stulln*	Stulln, Germany
SICNG	Thessaloniki, Greece
Soderec*	Pierre Latte, France
Riedel-de Haën AG	Seelze, Germany

*Company which did not provide a Hedset (production <1000 t/a?)

Table 2.2 HF production plant size distribution for 1994 (source: fax CEFIC 11-12-1995)

Tons	Number of reporting companies	Production size
30,000-35,000	1	30,000 - 35,000
25,000-30,000	2	50,000 - 60,000
20,000-25,000	3	60,000 - 75,000
15,000-20,000	0	-
10,000-15,000	1	10,000 - 15,000
5,000-10,000	3	15,000 - 30,000
Less than 5,000	6	unknown - 30,000
Total	16	>165,000 - 245,000

The maximum total production of HF in the European Union for 1994 is 245,000 tonnes (see **Table 2.2**). There are no import or export data available. The raw material for the production of HF is the mineral fluorspar (30-60% CaF_2), which is treated with acids to the so-called acid spar quality (about 97% CaF_2). HF is produced by the conversion of dried acid spar with concentrated

sulphuric acid at elevated temperatures. The volatile HF formed is condensed and purified by distillation (VDI 1987).

2.2 USE PATTERN

Table 2.3 shows the industrial and use categories of HF. Anhydrous HF and hydrofluoric acid is used for the production of organofluor compounds and inorganic fluorides, as well as a catalyst of alkylation reactions in the petrochemical industry. It is also used for etching of glass and pickling of stainless steel. The two main types of use categories for HF can be characterised as use in closed systems and non dispersive use. Paragraphs 4.1.1.0 and 4.1.1.1 contain more detailed information on the usages of HF.

The quantitative estimate currently available for the industrial and use category distribution of HF is 60% for the synthesis of organofluor compounds, 30% as intermediate in chemical synthesis of inorganic fluorides, 4% as pickling agent of metal surfaces, 3% for etching of glass surfaces, and 2% as catalyst in alkylation reactions in the petrochemical industry (CTEF 1995).

Data of one factory showed a different pattern for the industrial and use category distribution: 10% as pickling agent for metal surfaces, 10% for etching glass surfaces, 10% as catalyst in petrochemical industry, and 70% of the produced quantity as intermediate in chemical synthesis. In Sweden more than 99% of the imported HF is used for pickling of steel (Kemi 1995).

Table 2.3 Industrial and use categories of HF

Industrial category	EC No.	Use category	EC No.
Chemical industry: basic chemicals	2		
Chemical industry: used in synthesis	3	Intermediates	33
Mineral oil and fuel industry	9	Process regulators (catalysts)	43
Metal extraction, refining and processing	8	Others: descaling and pickling of steel	55
Others: mining industry	15	Other: special metal extraction	55
Others: electrotechnical industry	15	electroplating agents	17
Others: Glass industry	15	Others: frosting, etching and polishing	55

Major users of HF as an intermediate for the production of organofluor compounds and inorganic fluorides are shown in **Table 2.4**.

Table 2.4 Users of HF in organofluor compound and inorganic fluorides production (CTEF 1995)

Company	Location
Dupont	Dordrecht, the Netherlands
Ausimont	Porto Marghera/Spinetta Marengo, Italy
Elf Atochem	Pierre Benite, France
Hoechst (owned by Solvay now)	Frankfurt, Germany
ICI	Runcorn, United Kingdom
Solvay	Tavaux, France

3 ENVIRONMENT

3.1 EXPOSURE ASSESSMENT

3.1.1 General

HF may enter the environment from both natural (volcanoes, weathering of minerals and marine aerosols) and anthropogenic sources. The latter includes production of HF itself, but HF is also formed as a by-product during other industrial processes (phosphate fertiliser, aluminium and steel production, ceramic industry etc.). The contribution of HF emissions from the HF industry is limited compared to those from other industrial sources (see paragraph 3.3.1).

Once released in the environment HF is unlikely to remain in its original form for very long. In air, water and soil HF is transformed to a variety of other F-compounds. This transformation of HF in the environment will be discussed in more detail in the subsequent paragraphs. An extensive overview of the fate of fluorides is given in the RIVM Criteria Document on Fluorides (Slooff *et al*. 1988).

3.1.2 Aquatic compartment

3.1.2.1 Release and fate

HF (F) enters the aquatic environment via industrial waste water, atmospheric deposition or runoff from fertilisers and F-containing sludge.

Freshwater

In fresh water at pH above 5, the free ion is the main fluoride species. At lower pH, the proportion of fluoride ion decreases, while HF_2^- and non-dissociated HF increase. In the presence of phosphate insoluble fluorapatite is formed, a large part of which is transferred to the bottom sediments (Sloof *et al*. 1988).

Seawater

In seawater fluoride belongs to the macrocomponents; the total fluoride content is divided in 51% F^-, 47% MgF^+, 2% CaF^+, and traces of HF and HF_2^- (Sloof *et al*. 1988).

3.1.2.2 Ambient and natural background concentrations

The concentration of fluoride in natural waters depends on the geological, physical and chemical characteristics at the location. In surface waters that are not influenced by F-containing rock formations, the natural F-concentration is between 0.01 and 0.3 mg/l (Sloof *et al*. 1988).

In surface waters influenced by F-containing rock formations the natural F-concentration is considerably higher. Water of small rivers in the highlands of Germany (e.g. Black Forest) contain up to 4.7 mg/l (Geochemischer Atlas 1985). High fluoride levels (>20 mg/l) are also reported in natural waters from other European countries (WHO 1970).

Mean F-concentrations in the Netherlands are 0.2 mg/l (Rhine-IJssel) and 0.2 to 1.7 mg/l in the river Meuse with seasonal variations. In waters in the Dutch province Zeeland, concentrations vary between 1.0 and 9.5 mg/l (Slooff *et al*. 1988).

In seawater, F-concentrations are higher than in freshwater with an average of 1.4 mg/l (Slooff *et al*. 1988).

3.1.2.3 Accumulation

Bioaccumulation

Freshwater

In aquatic organisms fluoride accumulates primarily in the exoskeleton of crustacea and in the bones of fish. No F accumulation was reported in edible tissues. In fish, BCF-values of 53-58 (d.w.) and <2 (w.w.) were found (Slooff *et al*. 1988). In crustacea BCF-values based on whole body fluoride content are found to be < 1 (based on dry weight). The highest reported BCF-values for mollusca and aquatic macrophyta were 3.2 and 7.5 (w.w.), respectively (Chaisemartin).

Seawater

In an experimental marine ecosystem with fish, crustaceans and plants, F was found to accumulate in all species. The highest value, 149, was found in fish. BCF-values for crustacea range from 27 to 62 (Hemens and Warwick 1972). Fluoride concentrations up to 30 mg F/kg were found in consumption fish (Slooff *et al*. 1988).

3.1.3 Terrestrial compartment

3.1.3.1 Release and fate

Besides naturally occurring fluoride, fluoride may enter the terrestrial environment via atmospheric deposition, fluoride containing sludge or phosphate fertilisers.

The dry deposition for the whole Netherlands is calculated to be 30 and 1 mg/m^2 per year for gaseous and aerosol fluoride, respectively. Corrected for the whole area, this is 1300 tonnes per year. The wet deposition in the Netherlands is calculated to be 13 and 4 mg/m^2 for gaseous and aerosol fluoride, respectively. The total wet deposition ranges from 700 to 1100 tonnes per year (Slooff *et al*. 1988).

In soils (pH<6) fluor is predominantly found in bound form in fluoride containing minerals as fluorspar, cryolite and apatite, and clay minerals. Therefore fluoride is immobile in soils, but leaching to the B horizon is possible in soils with a low clay content. A direct consequence of the strong complex forming properties of fluoride is that with increasing F concentrations in pore water or groundwater, the Al and Fe concentrations also increase. In addition, a positive correlation was found between the concentration of fluoride and that of organic carbon in the soil solution, which may indicate that fluoride also forms complexes with carbon.

At a pH above 6, the fluoride ion is the dominant species.

3.1.3.2 Ambient and natural background concentrations

The mean fluoride content of mineral soils is 200-300 mg/kg, whereas that of organic soils is usually lower (97). In the Netherlands fluoride concentrations in clay soils range from 80 to

700 mg/kg (d.w.). In soils with higher pH values a higher amount of soluble F-complexes is found. In the USA average soil fluoride concentrations are 340 mg/kg in the east and 410 mg/kg in the west. The F-concentration increases with the soil depth; at a depth of 0-8 cm 190 mg/kg and at a depth of 8-25 cm averages of 292 mg/kg are found (Slooff *et al*. 1988).

Fluoride content in groundwater depends on many factors such as geological, chemical and physical characteristics of the water-supplying area, the consistency of the soil, the temperature, the pH, the depth of the well etc. Groundwater concentrations range within wide limits, from <1 to 25 mg or more per litre in India, Kenya and South Africa (97). Mean F-concentrations in Dutch groundwater are <0.01-1.5 mg/l (pH > 6) and < 0.01-0.58 mg/l (pH <6) (Stuyfzand 1991). In Germany concentrations of 0.07-0.13 mg/l are measured in the riverbank groundwater of the Rhine (Slooff *et al*. 1988). In the USA fluoride levels in groundwater range from 0.02 to 1.5 mg/l.

3.1.3.3 Accumulation

Bioaccumulation

Earthworms collected from F-polluted sites reflected F contamination very well. At the highest polluted sites the F content in worms reached values of up to 135 mg/kg (without gut), whereas worms from unpolluted sites showed contents of 6-14 mg/kg. The F content in the whole worm from unpolluted sites was found to be much higher and reached values up to 150 mg/kg. This was due to the fluoride content of soil contained in the gut (Breimer *et al*. 1989).

Woodlice (*Oniscus asellus, Porcellio scaber*) from different sites in the vicinity of a F-producing plant showed F-contents ranging from 90 to 1800 mg/kg (d.w.) in *O. asellus* and from 240 to 1360 mg/kg (d.w.) in *P. scaber*. F levels in animals collected from control site were 35 and 180 mg/kg, respectively (Janssen *et al*. 1989).

The most important F exposure route for plants is uptake from the atmosphere. Atmospheric accumulation is described in 3.1.3.3. Fluoride uptake by plants from soil may also occur, but the (bio)availability of fluoride in soil is usually low. The application of fluoride containing sludge or phosphate fertilisers may lead to considerable increase of F-concentrations in plants, dependent on soil characteristics and pH (Slooff *et al*. 1988).

3.1.4 Atmosphere

3.1.4.1 Release and fate

Fluorides are emitted to the atmosphere as gaseous compounds (75%) or as solids in the form of aerosols (25%). In the Netherlands the atmospheric F-concentrations originate for approximately 70% from outside the country.

Gaseous fluorides in the atmosphere are predominantly HF (and SiF_4). HF is removed relatively rapidly from the atmosphere by both wet and dry deposition. Gaseous fluoride is eliminated from the atmosphere by both dry and wet deposition with a half-life of ca. 14 hours and ca. 12 hours for dry and wet deposition, respectively. Fluoride aerosol is eliminated slowly predominantly (65%) by wet deposition with a half-life of 50 hours. For dry deposition of fluoride aerosol a half life of 12 days is reported (Slooff *et al*. 1988).

3.1.4.2 Ambient and natural background concentrations

The natural occurring background concentration of fluoride is calculated to be 0.0005 μg/m^3. Taking into account the anthropogenic emissions the world-wide background concentration is estimated to be 0.003 μg/m^3 (Slooff *et al*. 1988).

Air concentrations measured in the Netherlands for 1982-1983 range from 0.03-0.1 μg/m^3 with the highest concentrations in the south-west. Mean concentration for the whole country is 0.07 μg/m^3 (Slooff *et al*. 1988).

For the area of Greater Cologne (671 km^2) in Germany measurements of fluorides (as F^-) in the air showed values between 0.3 and 1.0 μg/m^3 (data from 1980; Luftreinhaltplan Rheinschiene Sud 1982-1986). In urban air samples in the USA a maximum F-content of 1.89 μg/m^3 is found, in rural samples the F-levels are lower.

Background F-levels in rainwater in the USA are usually between 2-20 μg/l with a mean of 8.1 μg/l (Barnard and Nordstrom 1982). Rainwater F-levels in India are 6.5, 16.0, 6.1, 3.3, and 21.3-40.0 μg/l in marine, unpolluted coastal, inland, deep inland and industrial samples, respectively (Mahdevan *et al*. 1986). In the Netherlands an average F-concentration in rainwater of 0.027 mg/l is measured (Stuyfzand 1991).

3.1.4.3 Accumulation

Bioaccumulation

The most important exposure route of F for plants is uptake from the atmosphere.

Grass species have in comparison to other plant species a relatively high uptake rate. The equilibrium between the concentration in the atmosphere and in the grass is generally reached within 24 hours. In a period without rainfall the half-life of fluoride in grass is ca. 4 days in the summer and ca. 12 days in the winter (Slooff *et al*. 1988).

Consumption of fluoride containing plants may lead to elevated fluoride levels in both humans and animals. Fluoride concentrations in grass range from 1-10 mg/kg (dry weight) in areas with low fluoride emissions to 10-150 mg/kg (dry weight) in areas with high fluoride emissions. Fluoride concentrations in consumer crops range from 0.1-1.8 mg/kg. In other consumer products (tea, beer, wine, meat, eggs and milkproducts) fluoride concentrations of 0.05 (milk) to 6 mg/kg (wine) were measured (Slooff *et al*. 1988). Near an aluminium factory in the USA, the fluoride content in the foliage of cherry and peach trees raised from 13 mg/kg to 65 and 76 mg/kg, respectively. The highest values, 196 and 186 mg/kg, respectively, were found 2 years after the factory began operating (Slooff *et al*. 1988).

3.1.5 Non compartment specific exposure relevant to the food chain

Aquatic environment

In the RIVM Criteria Document on Fluorides (Slooff *et al*. 1988) it was concluded that the limited data available indicate that accumulation through food chains (biomagnification) is of little significance in the aquatic environment.

Terrestrial environment

Fluorides accumulate in the skeletal tissues of terrestrial animals, both vertebrates and invertebrates, depending on their feeding habit. Data on a variety of invertebrates, collected from F-polluted sites, indicate that the lowest fluoride levels are found in cambial region feeders and herbivores, followed by omnivores, and were highest in predators, scavengers and pollinators. The relatively high levels in the latter three indicate possible biomagnification. For example accumulation factors (= level in organisms in polluted zone: level in organisms in control zone) of 1.5, 25, 21, and 54 were found for casebearer *Coleophora laricella*, predatory spiders (arachnida), the honeybee *Apis mellifera* and bumblebees (*Bombus sp.*), respectively. Vertebrates store most of the fluoride retained in the body bones and, to a lesser content in the teeth.

This was demonstrated in herbivorous field voles *Microtus agrestis* and wood mice *Apodemus sylvaticus* and insectivorous common shrews *Sorex araneus* collected near an aluminium reduction plant. In moles *Talpa europaea* higher fluoride levels were found in consistency with fluoride levels in earthworms, their main food source. Higher fluoride levels were also found in foxes, ungulates and birds collected from polluted areas. Field voles and wood mice with gross changes in their teeth showed bone fluoride levels of 2500 to 15000 mg/kg (d.w.), which levels were 15- to 90-fold those in animals from unpolluted areas. Bone fluoride levels increased with age and were, as in invertebrates, dependent on feeding habit, with the lowest levels in herbivores and somewhat higher levels in omnivores and carnivores (Janssen *et al*. 1989).

From the above-mentioned examples for the terrestrial environment it can be concluded that in vertebrates and invertebrates a similar food-dependent relationship was found for fluoride accumulation: the lowest levels in herbivores and (somewhat) higher levels in predators. The relatively high fluoride concentrations in predators indicate a moderate degree of biomagnification for fluoride in the terrestrial environment (Slooff *et al*. 1988).

3.1.6 Emissions

3.1.6.1 General

The emission data and other relevant information of HF producing and using (inorganic and organofluor compounds) plants are listed in **Tables 3.1** and **3.2** (Note: the plant numbers in this table do not correspond with the production and use companies in **Tables 2.1** and **2.2**). These data are the building blocks for the exposure assessment. The emission data represent about 85% of the total emissions in the EU from HF producers and users (CTEF 1995).

Fluorides are also emitted by other industries than the HF-producing and -using industries. The emissions of these industry categories for The Netherlands in 1992 are given in **Table 3.3**. The distribution of all fluoride emissions to water and air over the different branches of industry in The Netherlands is given in **Table 3.4**.

Table 3.1 Aquatic emissions from HF industry and major users of HF in the EU

No.	Production plant Emission amount per year (kg/year)	End use plant Emission amount per year (kg/year)	Measured Estimated[1]	Concentration in effluent[1] (mgF⁻/l)	Effluent flow[1] (m^3/hr)	Low flow receiving water[1] (m^3/s)	Mean flow receiving water[1] (m^3/s)	Reference available[22]	Year
1.	6500	-	M	10.2	73	1170	2000	Yes[a,c]	1995
	-	5500	M	39.8	16	1170	2000	Yes[a,c]	1995
2.	384,000[2]	-	M	2374	25	na	na	Yes[a,b,c]	1994
	29,900[14]	-	M	165	20	na	5.3		1995
	36,600	-	M	184	0-40	na	5.3		1996
	-	58,900	M	407	0-40	na	5.3		1997
		18,670	M	170	0-40	na	5.3		1998
3.	181,000	-	E	20	450	0.072	0.13	Yes[a]	1994
	132,000[15]	-	E	20	450	0.072	0.13		1995
	6,000	-	E	27[16]	150	na[17]	na[17]		1996
	6,500	-	E	29[16]	150	na[17]	na[17]		1997
	6,700	-	E	30[16]	150	na[17]	na[17]		1998
4.	4000	4000	E	5	100[3]	3.5[4]	4.6[4]	No[d]	1994[5]
5.	31,700	-	M	10.4	350	8[4]	30[4]	Yes[b]	1994
	53,100	-	M	15.3	400	8[4]	30[4]		1995
6.	246,000	-	M	1250	27	- [7]	- [7]	Yes[a,b]	1994
	136,500[21]	-	M[6]	100	185	- [7]	- [7]		1995
	428,681	-	M	245	200	-	-		1996
	328,440	-	M	178	210	-	-		1997
7.	5000	15,000	na[8]	na[8]	300[8]	18	55	No	1994
8.	10,000	50,000	M	34.1	201	40	50	Yes[a]	1994
	62,200 [18]		M	31	279[19]	40	50		1997
9.	9902	9902	M	12	94	110	152	Yes	1997
10.	1281	-	M	1.5	200	3.5	5.5	Yes[a]	1994
	800	-	M/E	0.6	200	3.5	5.5		1995
11.	48,330	-	M[9]	200	32	320	1000	Yes[a]	1994
	-	21,600	M[10]	200	14	320	1000	Yes[a]	1994
12.	-	0[22]	E	na	na	na	na	Yes	1999
13.	16,000	-	M	22[20]	83	- [11]	- [11]	Yes[a,b]	1994
	-	65,000	M	22[20]	340	- [11]	- [11]	Yes[a,b]	1994
14.	122	122	M	15.3	0.95	1	1.8	Yes	1997

Table 3.1 continued overleaf

Table 3.1 continued

No.	Production plant Emission amount per year (kg/year)	End use plant Emission amount per year (kg/year)	Measured Estimated[1]	Concentration in effluent[1] (mgF^-/l)	Effluent flow[1] (m^3/hr)	Low flow receiving water[1] (m^3/s)	Mean flow receiving water[1] (m^3/s)	Reference available[22]	Year
14.	122	122	M	15.3	0.95	1	1.8	Yes	1997
a	-	900	na	na	na	na	na	No	1994
b	-	13,100	E	110[12]	14	300	na	No	1994
c	-	11,030 10,850	M E	0.22 0.28	4000 4000	na na	na na	Yes[a,b]	1994 1995
d	-	53,000	na	na	na	na	na	No	1994
e	-	173	M	14	1.5	na	0.3	No	1994
Total	918,741	260,303							1994
	455,160	260,123							1995[13]

- = Not applicable
na = Not available or not submitted
[1]Data is only applicable to production plants, except for end use plants (a-e) or mentioned otherwise
[2]To effluent plants (precipitation plant under construction)
[3]Total effluent flow for production and use is 200 m^3/hr
[4]Canal system with outflow to a tidal estuary (lagoon)
[5]Same for 1995
[6]Monitoring data in receiving environment: 200 mg/l. STP influent and effluent concentrations are respectively 2500 mg/l and 100 mg/l
[7]The dilution factor according to industrial information is 200 (=(effluent/day)/(river-flow/day)). Estuarial discharge
[8]No industrial monitoring for only the HF production site, all waste waters are treated in a common sewage treatment plant with an effluent flow of 7200 m^3/d
[9]According to industrial information the F^--concentration in receiving water is $1.52.10^{-3}$ mg/l (calculated with dilution factor)
[10]According to industrial information the F^--concentration in receiving water is $0.7.10^{-3}$ mg/l (calculated with dilution factor)
[11]Ocean
[12]Production effluent
[13]When there is no data for 1995 available, the amount of 1994 has been used
[14]Precipitation plant in operation
[15]21,000 kg/yr emission after treatment in the central waste water treatment plant
[16]This concentration is due basically to the fertiliser activity of the factory (83% of the total amount of F^- emissions)
[17]Outflow canal to the sea
[18]Total value for production and end use plants
[19]Based on a total waste water flow of 2,006,430 m^3/year and 300 production days/year
[20]22 mg/l is the value at the emission point before reaching the ocean. 4.24 mg/l is measured just on the ocean surface at the falling point and mixing zone of the effluent to the ocean
[21]A later submitted emission is 444,795 kg/year for 1995
[22]References are known at the rapporteur
[a]Reference available for monitoring/analysis techniques
[b]Reference available for the emissions controlled by local law or other authorities
[c]Internal industrial report available for the emission values (not required by authorities)
[d]Monitoring and measurement methods discribed without an acknowledgement or a reference
[23]No aquatic discharge. All waste removed from this site for treatment and disposal elsewhere

Table 3.2 Atmospheric gaseous F emissions (mainly HF) from HF industry and major users of HF in the EU

No.	Production plant: Emission amount per year (kg/year)	End use plant: Emission amount per year (kg/year)	Measured Estimated[1]	Hight source (i.e. chimney)[1] (m)	Detection limit (mg/m³)	Reference available[16]	Year
1.	65	-	M	25	na	Yes[a,b]	1994
	-	55	M	25	na	Yes[a,b]	1994
2.	1360	-	M	15[2]	0.01	Yes[a,c]	1994
	376	-	M	15[2]	0.01		1995
	359	-	M	15	0.01		1996
	-	347	M	15	0.01		1997
		78	M	15	0.01		1998
3.	3100	-	E [3]	28	na	Yes[c]	1994
	2100	-	E [3]	28	na		1995
	1300	-	M/E	28	na		1996
	1200	-	M/E	28	na		1997
	1260	-	M/E	28	n/a		1998
4.	114[11][12]	200[11]	M	37	na	Yes[a]	1995
	86.6	<120	M	37	na		1997
5.	177	-	M	21/25/30[5]	0.2	No	1994
	159	-	M	21/25/30[5]	0.2		1995
6.	<31	-	M	27	0.001	Yes[b]	1994
	<31	-	M[6]	27	0.001		1995
7.	17.5	-	E	na	3	No	1994
8.	150	250	M	23	0.03	Yes[a]	1994
	60[13]		M	23	0.03		1997
9.	0[4]	0[4]	M	35	-	Yes	1997
10.	2020[7]	-	M/E[7]	22	1	Yes[c]	1994[8]
	39.2	-	M	-	-	Yes[c]	1998
11.	0.4	30	M[9]	25	$0.5.10^{-3}$	Yes[a]	1994
12.	30	-	na	na	na	No	1994
13.	50	289	M	20	na	Yes[a,b]	1994
	44	1000	M	20	na		1996
14.	172	172	M	39	mg/m³:±5%	Yes	?
	147[14][15]		M	39			1997

Table 3.2 continued overleaf

Table 3.2 continued

No.	Production plant: Emission amount per year (kg/year)	End use plant: Emission amount per year (kg/year)	Measured Estimated(1)	Hight source (i.e. chimney)(1) (m)	Detection limit (mg/m^3)	Reference available(16)	Year
a.	-	40	na	na	na	No	1994
b.	-	4200(17)	na	na	na	Yes[c]	1998
c.	- -	20.9 15.5	M M	70 70	0.1 0.1	Yes[a,b]	1994 1995
d.	-	5	na	na	na	No	1994
e.	-	13	M	35	na	No	1994
Total	7137	903					1994
	6119	898					1995 (10)

- = Not applicable.
na = Not available or not submitted.
(1)Data is only applicable to production plants, except for end use plants (a-e) or mentioned otherwise
(2)On average
(3)Monitoring data in receiving environment: 50 mg/m^3 (production) 20 mg/m^3 (use)
(4)Gas-washer installation
(5)Three chimneys
(6)Monitoring data in the receiving environment: <0.001 mg/m^3
(7)HF emitted via the central chimney is measured at a level of about 20 kg/year
Diffuse emissions of 2000 kg HF/year resulting from loading/unloading activities, tank valves, pumps etc. are calculated by TNO using emission factors. According to industrial information the emission factors used by TNO are very high, mainly as a result of different valve emissions and emission duration. The actual diffuse emissions are not known at the moment
(8)Same for 1995
(9)Monitoring data in the receiving environment: < $0.5.10^{-3}$ mg/m^3
(10)When there is no data for 1995 available, the amount of 1994 has been used
(11)Emissions expressed as F^-
(12)The also submitted upper bound of the emission amount at production is 2900 kg/year
(13)Equal to 6.83 g/h. Total value for production and end use plants
(14)Total value for production and end use plants
(15)Based on emission of 20.4 g/h (=0.49 kg/day) and 300 production days per year
(16)References are known at the rapporteur
[a]Reference available for monitoring/analysis techniques
[b]Reference available for the emissions controlled by local law or other authorities
[c]Internal industrial report available for the emission values
(17)Total atmospheric HF emission from plant amounts to 4200 kg/a in 1998. According to industry, however, this HF release is due to formation of HF during production of organofluor compounds (by-product). HF release due to handling of HF itself during the processes is assumed to be 0. At the plant an emission of 959 t/a of various organofluor compounds is reported

Table 3.3 Fluoride emissions in The Netherlands in 1992 in kg/year (VROM 1992)

No	Industry	Water	Air
1	Fertilizer compounds	19,100,000	19,100
2	Other raw chemicals		101,000
3	Ceramics, glass and building materials		758,000
4	Basemetals	2,470,000	319,000
5	Electrotechnical		10,200
6	Storage and trans-shipping, metal products, building trades, coal using power plants, public utilities		30,800
7	Other (fabrication of coach-works, trailers, semi-trailers, aeroplanes, bicycles and accessories, contractor companies)		89,600
	Total	21,570,000	1,327,700

For water the total EU emission is about 1,390 tonnes for 1994 (1180 tonnes from **Table 3.1** a. is about 85%, thus 100% is 1,390 tonnes) for the HF-industry, whereas only in The Netherlands more than 21,000 tonnes have been emitted to water in 1992 by other F emitting industries (**Table 3.3**). In The Netherlands the fertiliser industry (87%) is responsible for the largest F emission to water (**Table 3.4**). For 1992 the water emissions as a result of phosphate ore processing (fertiliser compounds) amounted 19,100 tonnes in The Netherlands (**Tables 3.3** and **3.4**). About 80% of the fluoride emissions from phosphate industries are in the form of insoluble fluorapatite. For the basemetal industry it is assumed that all the fluoride emissions are soluble. The situation in The Netherlands can be extrapolated to a European situation, with a factor of 0.2 for the soluble fluoride fraction of the phosphate industry and with a factor of 10 (extrapolation from region to EU, TGD) for effluent discharged in surface water for both the phosphate and basemetal industry.

The calculated European load of soluble fluorides to surface water is $19{,}100 \cdot 0.2 \cdot 10 = 38{,}200$ t/a for the phosphate industry and $2{,}470 \cdot 1 \cdot 10 = 24{,}700$ t/a for the basemetal industry. With these calculated loads, the total European load is about 63,000 t/a. Hence, it can be concluded that the European fluoride emission from the HF industry only amounts to about 2% of the total industrial fluoride emission to surface water.

The difference between the HF industry and the other industry categories is even larger for the emissions to air (**Tables 3.3** and **3.4**). In The Netherlands the ceramic industry is responsible for the largest F emissions to air (**Table 3.4**; 57%). More than 1,300 t/a are emitted in The Netherlands by other fluoride emitting industries than the HF industry, which is estimated to be 13,000 t/a for the EU. It can be concluded that the atmospheric emission of the HF industry (>9 t/a, **Table 3.2**) accounts for less than 0.1% of the total European emission.

Overall, it can be concluded that F-emissions from HF industry and HF users are far below those from other fluoride emitting industries.

Table 3.4 Distribution (in %) of F-emissions in The Netherlands in 1992 (VROM 1992)

No.	Branche of industry	Water	Air
1	Petrochemical	0.3	0.2
2	Chemical	7.9	9.3
3	Fertilizer compounds	87.3	1.4
4	Dyes and dye-compounds	0.3	0.3
5	Remaining chemical raw materials		7.6
6	Building materials, ceramics and glass		56.6
7	Basemetals	11.3	23.9
8	Electrotechnical	0.1	0.8
9	Other public utilities		0.2
10	Other services	0.1	2.3
11	Other industrial branches		6.7

3.1.6.2 Emission reduction during production and use

Several technical emission reduction steps can be taken to minimise the F-emissions to water and air during production and processing (CTEF 1995; VDI 1987).

Water

Waste water treatments at HF production or use plants can involve neutralisation and precipitation of F^-, before it is released in the aquatic environment. Effluent concentrations less than 10 mg/l cannot be easily reached, because of high influent concentrations, the water solubility of CaF_2, the kinetics of the reaction and colloidal problems.

Air

According to information from the industry (CTEF 1995), anhydrous HF or hydrofluoric acid is produced in completely closed and strictly controlled systems. Off gas from the system passes through gas scrubbing facilities before it is released into the atmosphere. In the working area of HF producing sites minor fugitive gaseous emissions are detected in the air (usually < 0.1 mg/m^3).

Anhydrous HF or hydrofluoric acid is used as a catalyst in completely closed and strictly controlled systems in the petrochemical industry. The off gases are scrubbed with water.

In the glass industry glassware is submerged in baths containing about 5% HF aqueous solution. Silica in glass reacts with HF which produces SiF_4. According to industrial information SiF_4 in the off gas undergoes wet scrubbing to form H_2SiF_6 by reaction with added HF. Finally H_2SiF_6 is condensed and the off gas passes through gas scrubbing facilities.

In the production of stainless steel, steel sheets are submerged in a bath containing HF and HNO_3 in aqueous solution. HF removes the oxidised impurities from the surface. After the bath has reached a minimum of activity it is neutralised and lime is added to precipitate F^--ions as CaF_2. The total precipitate, containing for instance ironhydroxide and CaF_2, is landfilled.

3.1.6.3 Predicted Environmental Concentrations

General

As stated before, not only the HF industry, but also other industrial and natural sources contribute to the regional and the continental fluoride emissions. At these regional and continental levels the fluoride emissions from the HF industry are limited compared to other sources. They cannot be considered to contribute significantly to the fluoride concentrations in the aquatic, terrestrial or atmospheric compartment. For this reason the exposure assessment will be focused on the local level close to HF producing and end use plants.

The exposure assessment is based both on calculations according to the EU-Technical Guidance Document (1996) and on actual measured concentrations near HF emitting plants. For the aquatic and atmospheric compartment the available emission data and effluent concentrations from the HF industry and major end users (see **Tables 3.1** and **3.2**) are used as a starting point for calculating the PEC values in the various environmental compartments.

Aquatic compartment

Calculated local concentrations (F^-)

For all HF production and use plants in the EU site-specific effluent concentrations or emission data are used for calculating the aquatic PEC values. For some sites the PECs are calculated both with a mean value and a low value for the receiving water flow (**Table 3.5**). For the HF plant numbers a and d it is assumed that they discharge their final effluent to the surface water without neutralisation, precipitation or filtration. Only for these two plants the receiving water concentration is calculated with the emission amount and a default effluent flow of 2000 m^3/day, because local effluent concentrations were not submitted. Local surface water concentration for the HF plants number 3, 13, a, c and d are calculated with a default dilution factor of 10, because no receiving water flows or dilution factors were submitted. For all other plants receiving water concentrations are calculated with actual measured effluent concentrations and dilution factors. The dilution factor is calculated with the submitted effluent discharge rate of the STP and the flow rate of the river (**Table 3.5**) according to the following equation:

$$D = \frac{EFFLUENTlocal_{STP} + FLOW}{EFFLUENTlocal_{STP}}$$

D:	dilution factor	
$EFFLUENTlocal_{STP}$:	effluent discharge rate of local STP	(m^3/d)
FLOW:	flow rate of the receiving river	(m^3/d)

The daily releases to water are the input for the calculations of the PECs, only if no site specific effluent concentrations are available. In this case the concentration of fluoride in the effluent of an STP is calculated with the equation:

$$C_{effluent}STP(kg/m^3) = \frac{emissionrate(kg/d)}{volumewastewater(m^3/d)}$$

Subsequently, from the effluent concentration in the STP the local concentration in the receiving water surface water during the emission episode can be calculated with the equation:

$$PEClocal_{water} = \frac{C_{effluent}STP}{(1 + Kp_{susp} + C_{susp}) \cdot D}$$

$PEClocal_{water}$: local predicted environmental concentration in water during emission episode (kg/m^3)
Kp_{susp}: solids-water partition coefficient of suspended matter (m^3/kg)
C_{susp}: concentration of suspended matter in river water (0.015 kg_{dwt}/m^3)
D: dilution factor (default = 10)

For the final PEC calculations it is assumed that the solids water partition coefficient of suspended matter (Kp_{susp}) for the fluoride ion (F^-) in water is very low. All data for calculating the receiving water concentrations are presented in **Table 3.5**. It should be noted that the calculated surface water concentrations are actually contributions to the receiving water.

The range of calculated local PEC values is $7.9 \cdot 10^{-4}$ - 237 mg/l for 1994, $8.8 \cdot 10^{-5}$ - 9.8 mg/l for 1995 and $2.24 \cdot 10^{-3}$ - 2.9 mg/l for 1996/1997 (**Table 3.5**). For 1997 and 1998 a rather limited number of PEC-values are available (see also risk characterisation).

Measured data

For a HF producing site a value of 200 mgF^-/l is submitted for the waters of the adjacent estuary. For other sites the reported concentration of the effluent receiving river is $1.52 \cdot 10^{-3}$ mgF^-/l for a production plant and $0.7 \cdot 10^{-3}$ mg for an end use plant. At a distance of 100-150 meters from a HF production and end use plant the measured concentration in the receiving ocean is not higher than 1.4 mgF^-/l, this is about the environmental background concentration according to the industry.

Sediment

In paragraph 3.1.1.1 it is mentioned that fluoride can be transformed to insoluble fluorapatite in the presence of phosphates in surface water. Fluorapatite, but also other insoluble fluoride complexes, precipitate to sediment. There are no data available on fluoride levels in sediment

Table 3.5 Calculated local water concentrations (F^-) and corresponding data for each HF plant

No.	Production and end use Emission amount		Effluent flow	Concentration in effluent	Low flow receiving water	Mean flow receiving water	Dilution factor (low)	Dilution factor (mean)	Concentration receiving water (low flow)	Concentration receiving water (mean flow)	Year	Note
	(kg/year)	(kg/day)	(m^3/day)	(mg F^-/l)	(m^3/s)	(m^3/s)			(mg F^-/l)	(mg F^-/l)		
1	-	-	1752	10.2	1170	2000	57700	98630	$1.77.10^{-4}$	$1.03.10^{-4}$	1995	(a)
	-	-	384	39.8	1170	2000	263250	450000	$1.51.10^{-4}$	$8.84.10^{-5}$	1995	(b)
2	-	-	600	2374	na(1)	na(1)	-	10	-	237.4	1994	(a)(c)
			480	165	na	5.3	-	955	-	0.17	1995	(a)
			480	184	na	5.3		955	-	0.19	1996	(a)
			480	407	na	5.3		955	-	0.43	1997	(b)
			480	170	na	5.3		955		0.18	1998	(b)
3	-	-	10800	20	0.072	0.13	1.58	2.04	12.7	9.80	1994 (2)	(a)
			3600	27	na	na	-	10	-	2.7	1996	(a(c)
			3600	29	na	na	-	10	-	2.9	1997	(a)(c)
			3600	30	na	na	-	10	-	3	1998	(a)(c)
4	-	-	2400	5	3.5(3)	4.6(3)	127(3)	166.6(3)	0.039(3)	0.030(3)	1994(2)	(a)(b)
5	-	-	8400	10.4	8	30	83	310	-	0.034	1994	(a)
			9600	15.3	8	30	73	271	-	0.056	1995	(a)
6	-	-	648	1250	- (5)	- (5)	- (5)	200(5)	-	6.25(5)	1994	(a)
			4440	100	- (5)	- (5)	- (5)	200(5)	-	0.50(5)	1995	(a)
			4794	245	- (5)	- (5)	- (5)	200(5)	-	1.23(5)	1996	(a)
			5048	178	- (5)	- (5)	- (5)	200(5)	-	0.89(5)	1997	(a)
7	20000(6)	66.67	7200(7)	9.26	18	55	217	661	0.043	0.014	1994	(a)(b) (c)(d)
8	-	-	4824	34.1	40	50	717	897	0.048	0.038	1994	(a)(b)
			6688	31	40	50	518	647	0.060	0.048	1997	(a)(b)
9	-	-	2256	12	110	152	4214	5822	$2.85.10^{-3}$	$2.06.10^{-3}$	1997	(a)(b)
10	-	-	4800	1.5	3.5	5.5	64	100	0.023	0.015	1994	(a)
			4800	0.6	3.5	5.5	64	100	0.009	0.006	1995	(a)

Table 3.5 continued overleaf

Table 3.5 continued

No.	Production and end use Emission amount		Effluent flow	Concentration in effluent	Low flow receiving water	Mean flow receiving water	Dilution factor (low)	Dilution factor (mean)	Concentration receiving water (low flow)	Concentration receiving water (mean flow)	Year	Note
	(kg/year)	(kg/day)	(m^3/day)	(mg F^-/l)	(m^3/s)	(m^3/s)			(mg F^-/l)	(mg F^-/l)		
11	-	-	768	200	320	1000	36000	112500	$5.56.10^{-3}$	$1.78.10^{-3}$ (8)	1994	(a)
	-	-	343	200	320	1000	80610	251900	$2.48.10^{-3}$	$7.94.10^{-4}$ (8)	1994	(b)
12	-	0	-	-	-	-	-	-	-	0	1998	(b)
13	-	-	1992	22	- (9)	- (9)	- (9)	- (9)	-	0.42(9)(10)	1994	(a)
	-	-	8160	22	- (9)	- (9)	- (9)	- (9)	-	0.42(9)(10)	1994	(b)
14	-	-	22.8	15.3	1	1.8	3790	6822	$4.04.10^{-3}$	$2.24.10^{-3}$	1997	(a)(b)
a	900	3.00	2000	1.50	na	na	-	10	-	0.15	1994	(b)(c)(d)
b	-	-	328.8	110	300	na	78830	-	$1.40.10^{-3}$	-	1994	(b)
c	-	-	96000	0.22	na	na	-	10	-	0.022	1994	(b)(c)
			96000	0.28	na	na	-	10		0.028	1995	(b) (c)
d	53,000	177	2000	88.3	na	na	-	10	-	8.83	1994	(b)(c) d)
e	-	-	36	14	na	0.3	-	721	-	0.0194	1995	(b)

- = Not applicable
na = Not available or not submitted
(a)Data for production plants
(b)Data for end use plants
(c)Concentration receiving water is calculated with default dilution factor of 10, no receiving water flow or dilution factor is available
(d)Concentration receiving water is calculated with the emission amount, no effluent concentration available. The final effluent is emitted to the surface water without neutralisation, precipitation or filtration
(e)Emission data is not available. The concentration of the receiving water is calculated with a estimated production volume of 5,000-10,000 t/a according a generic scenario
(1)Only the river name is available. The default dilution factor is used for calculating the receiving water concentration
(2)Same for 1995
(3)Canal system. Emission into canal system with close outflow to a tidal estuary
(4)Canal system to sea lagoon, no receiving water flow or dilution factor available for canal system. Concentration receiving water (sea) can not be calculated. With a default dilution factor of 10 for rivers, the calculated receiving water concentration is 1.04 and 1.53 mg F^-/l
(5)Estuarial discharge. The dilution factor according to industrial information is 200
(6)Total amount for production (5000) and end use plant (15,000), because all waste waters are treated in a common sewage treatment plant
(7)Effluent water not only from HF production site, all effluent water is treated in a common sewage treatment plant. The HF production site is not monitored seperately.
(8)According to industrial information the concentration in the river is $1.52.10^{-3}$ mg/l for the production plant and $0.7.10^{-3}$ mg F^-/l for the end use plant. According to later received information the concentration at the emission end point is 2.77 mg/l for the production plant and 1.33 mg F^-/l for the end use plant
(9)Ocean, no dilution factor available. Concentration receiving water can not be calculated. 4.24 mg/l is measured just on the ocean surface at the faling point and mixing zone of the effluent to the ocean. With a default dilution factor of 10, the calculated receiving water concentration is 0.42 mg F^-/l
(10)At a distance of 100-150 meters from point source the measured concentration is not higher than 1.4 mgF-/l, this is about the environmental background concentration according to the industry

Atmospheric compartment

Calculated local concentrations

For every HF producing and end use plant the annual average local atmospheric PEC value at a distance of 100 meters is calculated with EUSES (OPS model) from the daily amounts released to air (TGD, 1996).

Atmospheric emission values during production and end use are added, when they are available for one plant (**Table 3.6**). The total daily emission of each plant has been used as an input for the OPS-model. All calculated annual local atmospheric HF concentrations at a distance of 100 meters of each plant are listed in **Table 3.6**.

The range of calculated local PEC values is 0.01 – 2.36 $\mu g/m^3$ for 1994. When available, calculated values for 1995, 1996, 1997 are slightly lower (**Table 3.6**), except for plant No. 13. For 1998 only a limited number of atmospheric PECs could be calculated (see also risk characterisation)

To bring the above mentioned data into a broader perspective: for the major coarse ceramic industries in The Netherlands local concentrations of 6.1 - 16.0 $\mu g/m^3$ were calculated based on HF emissions of 8-21 t/a (Huizinga *et al*. 1995).

Acidification

After atmospheric deposition, HF may lead to acidification of the receiving soil or surface water. The contribution of locally emitted HF to acidification can be determined by comparison of all acidifying components in air. The most important acidifying components are ammonia, sulphur dioxide, nitrogen oxides and their reaction products. The total deposition flux of acidifying compounds in the Netherlands is estimated to be 4200 mol H^+/ha.y (RIVM, personal comm.) The critical deposition fluxes for forest and surface water are 1400 and 400 mol/ha.y, respectively.

The maximum HF concentration in air calculated with a site-specific emission amount for production plant b would be 3.2 $\mu g/m^3$ (=$3.2 \cdot 10^{-9}$ kg/m^3).

The deposition velocity of HF is 2 cm/s = 1728 m/d. Corresponding deposition fluxes are:

plant : $3.2 \cdot 10^{-9}$ $kg/m^3 \cdot 1728$ m/d = $5.53 \cdot 10^{-6}$ kg/m^2

in moles/ha/y:

(1 $kg/m^3 \cdot d$ = (1/20) mol/ (0.0001ha.1/86400 y) = $4.32 \cdot 10^7$ mol/ha.y)

plant b: $5.53.10^{-6}$ $kg/m^2 \cdot 4.32 \cdot 10^7$ = 238 mol/ha.y

It can be concluded that for plant b the deposition flux is lower than the critical fluxes for forest and surface water. Compared to the total deposition flux of acidifying compounds in the Netherlands (4200 mol/ha.y) the relative contribution of plant No. 3 is 6%.

Table 3.6 Calculated local atmospheric HF concentrations for each production and end use plant

No.	Production plant: Emission amount kg/year	End use plant: Emission amount kg/year	Total Emission amount kg/year	Annual average air concentration[1] (100 m) µg/m3	Year
1	65	55	120	0.091	1994
2	1360	-	1360	1.03	1994
	376	-	376	0.29	1995
	359	-	359	0.27	1996
	-	347	347	0.26	1997
		78	78	0.06	1998
3	3100	-	3100	2.36	1994
	2100	-	2100	1.60	1995
	1300	-	1300	1.0	1996
	1200	-	1200	0.91	1997
	1260	-	1260	0.95	1998
4	114[2]	200[2]	314	0.24	1995
	86.6	120	207	0.16	1997
5	177	-	177	0.13	1994
	159	-	159	0.12	1995
6	<31	-	31	0.024	1994[3]
7	17.5	-	17.5	0.013	1994
8	150	250	400	0.30	1994
	-	-	49.2[7]	0.037	1997
9	0[6]	0[6]	0	0	1997
10	2020	-	2020	1.54	1994[3]
	39.2	-	39.2	0.03	1998
11	0.4	30	30.4	0.023	1994
12	30	-	30	0.023	1994
13	50	289	339	0.26	1994
	44	1000	1044	0.79	1996
14	172	172	344	0.26	?
	-	-	147[8]	0.11	1997
a	-	40	40	0.030	1994
b	-	4,200	4,200	3.2	1998
c	-	20.9	20.9	0.016	1994
		15.5	15.5	0.012	1995
d	-	5	5	0.0038	1994
e	-	13	13	0.0099	1994

- = Not applicable
Na = Not available
[1]Calculated with EUSES according the Technical Guidance Document (1996)
[2]Emissions expressed as F^-. An atmospheric emission of of 2900 kg/year should be regarded as an upper bound value
[3]Same for 1995
[4]The HF company uses 330 production days and a total emission amount of 1.21 kg/day
[6]Gas-washer installation
[7]Calculated with a submitted emission of 6.83 g/h and 300 production days per year
[8]Calculated with a submitted emission of 20.4 g/h and 300 production days per year

Measured data (CTEF 1995)

Concentrations of 2-4 mg/m^3 are regularly measured in a chimney from a HF plant in The Netherlands, with a yearly emission of 50 kg fluorides. At a distance of 500 metres from this site, the measured atmospheric fluoride concentration varies between 0.1 and 1 μg/m^3 (mean 0.3-0.4 μg/m^3). In Germany, around a HF production facility, the mean value (three year average) measured within 1 km of this site was 0.2 μg/m^3, with a value of 1.3 μg/m^3 as 98 percentile (1993). Near another HF plant in Germany a mean (yearly) fluoride concentration of 0.3 μg/m^3 was measured, with a 98 percentile of 2.4 μg/m^3. Fluoride emissions are routinely measured around a HF production site in the UK. Annual averages at several farms within a distance of 0.5 to 4 km of this site vary between 0.06 and 0.23 μg/m^3 (1991-1994). At the boundaries of another HF site in the UK ambient air concentration of fluorides are measured of 2.31-5.36 μg/m^3 for 1988 and 1.12-3.14 μg/m^3 for 1995 (industry report). For the same site are in 1984 daily fluoride concentration measured of 0.03-1.71 μg/m^3 (mean=0.58 μg/m^3) and of 0.01-1.01 μg/m^3 (mean=0.24 μg/m^3), respectively measured at a distance of 1000 meters and 500 metres of the production plant. European data for another HF end-use site of various chemical synthesis show general F-concentrations (measured over 6 months) below the (large) detection limit of 0.01 μg/m^3, with peak levels of 0.05-0.06 μg/m^3 at a distance of 700 meters downwind. The total gaseous emissions of this site amounted to 14 g HF/day. For two other plants the concentrations in air were measured below the detection limit of 1 μg/m^3 and 0.5 μg/m^3.

Very recently (2001) additional monitoring data have become available for plant no. 13. Atmoshpheric concentrations amounted to 1.0 and 0.7 μg/m^3 for the years 1999 and 2000, respectively.

When these measured data are compared with the calculated data (range 0.01 - 3.2 μg/m^3), they are found to be in the same order of magnitude.

There are also local fluoride concentrations known of other industrial activities than the HF industry. F-levels measured downwind an Al-plant that emitted 34 kg F/hour were found to be about 0.66 μg/m^3 (Slooff *et al*. 1988). Other HF concentrations in air around emission sources in Canada are usually less and are summarised in **Table 3.7**.

Table 3.7 Measured HF concentrations in air around emission sources in Canada (CEPA 1993)

Type of installation	Concentration measured (μg/m^3)	Remark
Aluminium production	0.1 - 0.71 0.79 - 0.85 0.43	up to 8 km 1.6 km from site 4 km from site
Steel production	0.17 - 0.24	close to the site
Phosphate fertilisers	0.4 - 0.59	less than 5 km
Phosphorous production	0.14 - 0.15	close to the site
Brick production	0.73	less than 1 km

Soil

Model calculations

The concentration F^- in waste water from HF production or use can be reduced by adding lime to form CaF_2. Solid CaF_2 from these industrial waste water cleaning operations are generally not used for the amendment of soil, but are landfilled or recycled for re-use. Percolation of CaF_2 (insoluble) from these landfills to groundwater is assumed to be low under normal conditions.

One European HF producer (non-EU) stated that their CaF_2 from the neutralisation process is discharged directly to waste water. The total quantity of discharged F^- at this plant was 300 tonnes in 1996. Measures are planned to reduce this discharge at this plant. From 1998/1999 the CaF_2-waste will be landfilled.

For the HF industry only the atmospheric deposition is used for calculating the concentrations in soil and the contribution of STP sludge applied on agricultural soils is not taken into account. A soil concentration is calculated for the plant with the highest emission to air (use plant b, 11.5 kg/d) with EUSES. The maximum calculated fluoride concentration in soil would be about 0.5 µg/kg for this plant. In addition an EUSES calculation is carried out with a higher deposition velocity (1.4 cm/s) (Slooff *et al*. 1988), which results in a soil concentration of about 1.5 mg/kg for the same plant. From this it is clear that the soil concentrations for all other plants will be lower than either 0.5 µg/kg or 1.5 mg/kg.

Measured data

In the neighbourhood of an HF emitting factory (2.8 kg/day as HF) accumulation of F was restricted to the upper 40-50 cm in calcareous soils (CTEF 1995). In the most heavily polluted area around the factory the mean content of HCl-extractable F-compounds decreased from 446 mg/kg at a depth of 0-20 cm, 194 mg/kg at a depth of 20-40 cm, 102 mg/kg at a depth of 40-60 cm, to 58 mg/kg at depths below 60 cm. In groundwater around the factory a concentration of 0.5 mg F/l was measured.

In the USA F-concentrations in the range of 265 to 1840 mg/kg were found in the top 0.5 inch of soil near a P-extraction facility (Slooff *et al*. 1988).

Vegetation

Monitoring of fluoride levels in vegetation samples is performed routinely (12-year program) around a German HF producing and using (chemical synthesis) plant at a distance of about 1 km. The mean F-levels comprise between 20 and 50 mg/kg d.w. with peak values up to 150-200 mg/kg (Solvay unpublished data). Peak levels could be linked to particular operations at the plant (e.g. chimney cleaning) or to small incidents.

Fluoride concentrations in grass from uncontaminated areas ranges from 1-10 mg/kg d.w. (see paragraph 3.1.3.3).

Another vegetation fluoride monitoring programme is running around site b (HF end use plant). Fluoride levels in grass are being measured both at a distance of 150-500 m from the emission source and at 1500-2000 m. Data are available for the period 1988-1998. Annual average grass

fluoride levels in that period range from 10 to 90 µg/g dwt at 150-500 m and 10 to 25 µg/g d.w.t at 1500-2000m.

3.2 EFFECTS ASSESSMENT

3.2.1 Aquatic compartment

All reported tests with aquatic organisms were performed with NaF. Because HF occurs in the aquatic compartment mainly as fluoride ion, the NaF tests can be used for the evaluation of HF effects in aquatic organisms. All reported test results were corrected for the fluoride ion.

It has to be noted that there is a clear relation between toxicity and water hardness. Tests performed in soft water (< 50 mg $CaCO_3$/l) showed a higher toxicity than those performed in hard water (> 50 mg $CaCO_3$/l), due to the precipitation of fluoride as CaF_2.

Ecotoxicity data for sediment are not available.

3.2.1.1 Toxicity to fish

The short-term toxicity studies with fluoride for freshwater fish are summarised in **Table 3.8**.

Table 3.8 Short-term toxicity data of fluoride for freshwater fish

No.	Species	Duration (h)	LC_{50} (mg/l)	Method	Hardness (mg $CaC0_3$/l)	References
1	Leuciscus idus melanotus	48	299	other	25	(Juhnke and Ludemann 1978)
2	Oncorhynchus mykiss	96	51	other	17	(Janssen *et al*. 1989)
3	Oncorhynchus mykiss	96	108	other	22	(Camargo and Tarazona 1991)
4	Salmo trutta	96	165	other	21	(Camargo and Tarazona 1991)
5	Gasterosteus aculeatus	96	340	other	78	(Janssen *et al*. 1989)

The short-term LC_{50}-values for fish range from 51 to 340 mg/l. All tests were carried out in soft water. The LC_{50}-values of test no. 1, 3, and 5 are based on nominal concentrations, the values of test no. 2 and 4 on actual concentrations. In the Integrated Criteria Document Fluoride (Slooff *et al*. 1988) more short-term fish data were reported, ranging from 128 to 460 mg/l.

The RIVM document (Slooff *et al*. 1988) also contained short-term toxicity data for marine fish. However, as all reported values were above the solubility of NaF in seawater (100 mg/l) they were not considered suitable for the evaluation of the risk of fluoride in the aquatic environment.

In addition to the base set information for fish, also a long-term NOEC-value is available. In a 21-days test with *Oncorhynchus mykiss* a LC_5 value of 4 mg/l was reported (actual concentration) (Slooff *et al*. 1988). This value is considered to be equivalent to the NOEC for mortality. The test was conducted in very soft (12 mg $CaCO_3$/l) natural water with daily renewal of the test water.

Long-term toxicity data for marine fish are not available.

The NOEC-value of 4 mg/l may be taken into consideration with the test results of other taxonomic groups for the derivation of PNEC for the aquatic environment. It should be borne in mind, however, that this test was carried out in very soft water.

3.2.1.2 Toxicity to aquatic invertebrates (e.g. Daphnia)

The short-term toxicity studies with fluoride for freshwater aquatic invertebrates are summarised in **Table 3.9**.

Table 3.9 Short-term toxicity data of fluoride for freshwater invertebrates

No.	Species	Duration (h)	EC_{50} (mg/l)	Method	Hardness (mg CaCO3/l)	References
1	Benthic macroinvert.	96	26-48	other	12-19	(Camargo and Tarazona 1990)
2	Daphnia magna	48	97	other	250	(Janssen *et al*. 1989)
3	Daphnia magna	48	153	other	173	(LeBlanc 1984)
4	Daphnia magna	24	352	DIN 38411 L 11	250	(Kühn *et al*. 1988)
5	Daphnia sp.	48	270	Bringman & Kühn, 1959	204	(Bringman and Kühn 1959)

The EC_{50}-values for daphnids range from 97 to 352 mg/l and are based on nominal concentrations. Benthic insect larvae were found to be more sensitive with EC50-values ranging from 26 to 48 mg/l (actual concentrations), but these tests were carried out in soft water. In the RIVM Criteria Document on Fluorides (Slooff *et al*. 1988) more short-term invertebrate data were reported, ranging from 109 to 340 mg/l.

The short-term toxicity studies with fluoride for marine invertebrates are summarised in **Table 3.10**.

Table 3.10 Short-term toxicity of fluoride to marine invertebrates

No.	Species	Duration (h)	EC_{50} (mg/l)	Method	Salinity (‰)	References
1	Mysidopsis bahia	96	10.5	other	unknown	(LeBlanc 1984)
2	Perna perna (1.5-2.5 cm)	120	39	other	20	(Hemens and Warwick 1972)
3	Perna perna (4.5-7 cm)	120	20	other	20	(Hemens and Warwick 1972)

The EC_{50}-values for marine invertebrates range from 10.5 to 39 mg/l. The EC_{50}-values for *Perna perna* were derived from the reported effect concentrations using the Spearmann-Karber environmental scenario (Hamilton *et al* 1977). In the RIVM Criteria Document on Fluorides (Slooff *et al*. 1988) more short-term marine invertebrate data were reported, ranging from 30 to 500 mg/l.

In addition to the base set information, also long-term toxicity studies for freshwater invertebrates are available. These tests are summarised in **Table 3.11**.

Table 3.11 Long-term toxicity of fluoride to freshwater invertebrates

No.	Species	Duration (d)	NOEC (mg/l)	Method	Hardness (mg CaCO3/l)	References
1	Daphnia magna	21	3.7	other	250	(Janssen *et al*. 1989)
2	Daphnia magna	21	14.1	Kühn, 1988	250	(Kühn *et al*. 1988)

In both long-term tests with daphnids the NOEC is based on effects on reproduction. Test concentrations were only analysed in the second test. The arithmetic mean of both test gives a value of 8.9 mg/l. In the RIVM document (Slooff *et al*. 1988) more long-term invertebrate data were reported, ranging from 10 to 48 mg/l.

Long-term toxicity studies for marine invertebrates are not available.

The calculated NOEC-value of 8.9 mg/l will be taken into consideration with the results of other taxonomic groups for the derivation of the PNEC for the aquatic environment.

3.2.1.3 Toxicity to algae

The short-term toxicity studies with fluoride for freshwater algae are summarised in **Table 3.12**.

Table 3.12 EC_{50}-values of fluoride for freshwater algae

No.	Species	Duration (h)	EC_{50}, biomass (mg/l)	Method	Hardness (mg CaCO3/l)	References
1	Scenedesmus sp.	96	43	Other	unknown	(Slooff *et al*. 1988)
2	Selenastrum capricornutum	96	122	Other	unknown	(LeBlanc 1984)

The EC_{50}-values for freshwater algae range from 43 to 122 mg/l (nominal concentrations). Data on test conditions are not available.

For marine algae only one 96 hour EC_{50}-value is available, i.e. 81 mg/l for *Skeletonema costatum*. Further data on test conditions are lacking (LeBlanc 1984). In addition to the base set information, also NOEC-values for freshwater algae are available.

These tests are summarised in **Table 3.13**.

Table 3.13 NOEC-values of fluoride for freshwater algae

No.	Species	Duration (d)	NOEC (mg/l) biomass	Method	Hardness (mgCaCO3/l)	Reference
1	Ankistrodesmus braunii	7	50	other	unknown	(Janssen *et al*. 1989)
2	Cyclotella meneghiniana	7	50	other	unknown	(Janssen *et al*. 1989)
3	Oscillatoria limnetica	7	50	other	unknown	(Janssen *et al*. 1989)
4	Scenedesmus quadricauda	7	50	other	unknown	(Janssen *et al*. 1989)
5	Stephanodiscus minutus	7	50	other	unknown	(Janssen *et al*. 1989)
6	Synechococcus leopoldiensis	7	50	other	unknown	(Janssen *et al*. 1989)
7	Scenedesmus quadricauda	8	249	Bringmann & Kühn, 1977	28.7	(Bringmann and Kühn 1977)

The NOEC-values for freshwater algae range from 50 to 249 mg/l. The values reported in tests 1 to 6 are based on actual concentrations. Hardness information is lacking.

The toxicity studies for marine algae are summarised in **Table 3.14**.

The exposure time in the tests mentioned in **Table 3.14** was 2 to 3 weeks. In general, after such a (relatively) long exposure period algae are not in the exponential growth-phase any more, but have already reached the lag-phase. Furthermore, it is expected that the bioavailability of the test substance would probably have been low at that time. For these reasons the results of these marine tests will only be used as supportive information.

Table 3.14 Toxicity of fluoride to marine algae

No	Species	Duration (d)	NOEC, biomass (mg/l)	Method	Salinity (‰)	References
1	Amphidinium carteri	14-21	50-100	Other	15-26	(Janssen *et al*. 1989)
2	Chaetoceros gracilis	14-21	200	Other	15-26	(Janssen *et al*. 1989)
3	Dunaliella tertiolecta	14-21	200	Other	15-26	(Janssen *et al*. 1989)
4	Pavlova lutheri	14-21	50	Other	15-26	(Janssen *et al*. 1989)

The lowest EC_{50}-value of 43 mg/l derived for *Scenedesmus sp.* will be taken into consideration with the test results of other taxonomic groups for the derivation of the PNEC for the aquatic environment.

3.2.1.4 Toxicity to micro-organisms

The toxicity studies with fluoride for micro-organisms are summarised in **Table 3.15**. The table contains data for both bacteria and protozoa.

The long-term NOEC-values for micro-organisms range from 7.1 to 510 mg/l. Only the test with activated sludge was performed according to international accepted guidelines. In this test the given EC_{10}-value for respiration inhibition is considered to be an equivalent for a NOEC.

Endpoints for viability measured in the tests with *Escherichia coli* and *Microregma heterostoma* are inhibition of acid formation from glucose and inhibition of feed uptake, respectively.

The NOEC-values for protozoa (tests No. 2, 3, 5 and 6) are only used as supportive information for the derivation of the PNEC. The same is true for *E.coli* bacteria.

Table 3.15 Toxicity of fluoride to micro-organisms

No.	Species	Duration (h)	NOEC (mg/l)	Method	Hardness (mg CaCO3/l)	References
1	Activated sludge	3	510	OECD 209	unknown	(Bayer AG 1987)
2	Chilomonas paramaecium	48	83	Bringmann & Kühn, 1981	42.3	(Bringmann and Kühn 1981)
3	Entosiphon sulcatum	72	101	Bringmann & Kühn, 1981	35.3	(Bringmann and Kühn 1981)
4	Escherichia coli	48	180	Bringmann & Kühn, 1959	unknown	(Bringmann and Kühn 1959)
5	Uronema parduczi	20	7.1	Bringmann & Kühn, 1981	35.3	(Bringmann and Kühn 1981)
6	Microregma heterostoma	28	226	Bringmann & Kühn, 1981	204	(Bringmann and Kühn 1981)
7	Pseudomonas putida	16	231	Bringmann & Kühn, 1977	42.5	(Bringmann and Kühn 1977)

3.2.1.5 PNEC for the aquatic compartment

Freshwater

The PNEC for the freshwater compartment is extrapolated from the calculated mean NOEC-value for *Daphnia magna* (8.9 mg/l) using an extrapolation factor of 10. This factor is chosen because long term NOEC-values for more than three trophic levels are available. The extrapolation leads to a PNEC for the freshwater environment of 0.9 mg/l ($PNEC_{aqua}$). (A short term EC_{50} of 43 mg/l for *Scenedesmus sp.* was found to be the lowest value for the algae group. The corresponding NOEC-value will probably be a factor 3 lower, i.e. about 14 mg/l, which is still higher than the NOEC for *D.magna*. On top of that, there is also no information on hardness conditions in this test). The set of aquatic ecotoxicity data consists of test results based on both actual and nominal concentrations. The assumption is made that this PNEC already includes a background fluoride level.

One should further realise that the PNEC of 0.9 mg/l is based on daphnid tests carried out under hard water conditions. Given the clear relation between toxicity and water hardness, this PNEC may underestimate soft water conditions. There are no long-term daphnid tests in soft water, but there is one very soft water test (12 mg/l $CaCO_3$) with *Oncorhynchus mykiss*. Using this fish test and applying an assessment factor of 10 would result in a PNEC of 0.4 mg/l for soft water conditions.

Another important issue in this context is that natural background fluoride levels may vary substantially within the EU. Under natural conditions elevated natural background F levels can be encountered in certain regions (see paragraph 3.1.1.2). This means that the above-mentioned PNEC is therefore not directly applicable to those regions with high natural F-levels. An option

would be that in case of high natural background levels, this background concentration is added to the PNEC when carrying out the risk characterisation .

The statistical extrapolation method of Aldenberg and Slob (Appendix V of TGD), in which all available NOEC-values in the HEDSET for both soft and hard water were taken into account, gives a PNEC for the aquatic compartment of 3.3 mg/l.

In the RIVM Criteria Document on Fluorides (Slooff *et al*. 1988) PNEC-values of 1, 1.5 and 3.2 mg/l were derived for soft, hard and soft+hard water, respectively. This was done according to the Van Straalen & Denneman method. It should also be noted that a larger set of data was used. In the light of the high hardness of Dutch surface waters, the value of 1.5 mg/l is currently considered as the limit value for fluoride (dissolved) in the Netherlands (VROM 1994).

Micro-organisms

From the available data on micro-organisms the results of the activated sludge test (510 mg/l) and the *P. putida* test (231 mg/l) can theoretically be used for deriving a PNEC for micro-organisms. The former results in a PNEC of 51 mg/l (AF of 10), the Pseudomonas test would lead to a PNEC of 231 mg/l (AF of 1).

The lowest value is taken as the PNEC:

$PNEC_{microorganisms}$ = 51 mg/l

3.2.2 Terrestrial compartment

The original HEDSET contained no toxicity data for terrestrial organisms. However, an on-line literature search in Biosis revealed some data, which are presented below. All test results are based on the fluoride ion.

3.2.2.1 Toxicity to soil organisms

The long-term toxicity studies with fluoride for terrestrial organisms are summarised in **Table 3.16**.

Table 3.16 Long-term toxicity of fluoride to soil organisms

No.	Species	Duration (d)	NOEC (mg/kg)	Method	Reference
1	Porcellio scaber	126	800	other	(Beyer *et al*. 1987)
2	Eisenia fetida	154	1200[a]	OECD 207	(Vogel and Ottow 1992)

[a]NOEC for growth, maturity, fertility and hatchability of cocoons

The NOEC-values in **Table 3.16** are based on tests with sodium fluoride. The earthworm test was also carried out with potassium fluoride, resulting in a NOEC of 750 mg/kg.

A reduced yield of maize was reported in NaF-treated mineral soil at F concentrations above 200 mg/kg (Slooff *et al*. 1988). The authors stated, however, that this effect may have been due to a secondary effect of aluminium (see also paragraph 3.1.2.1).

3.2.2.2 Toxicity to micro-organisms

The toxicity studies with fluoride for soil microbial processes are summarised in **Table 3.17**.

Table 3.17 Toxicity data of fluoride to soil microbial processes

No.	Microbial process	Duration (d)	NOEC (mg/kg)	Method	Reference
1	Dehydrogenase inhibit.	24	3000	Klein *et al*. 1971	(Rogers and Li 1985)
2	NH4-mineralization	63	340	other	(Van Wensem and Adema 1991)
3	NO3-mineralization	63	106	other	(Van Wensem and Adema 1991)
4	P-mineralization	63	1060	other	(Van Wensem and Adema 1991)

The NOEC-values for soil microbial processes range from 106 to 3000 mg/kg. The dehydrogenase assay was carried out with sodium fluoride. Tests No. 2, 3 and 4 were performed with potassium fluoride in a micro-ecosystem containing poplar litter (30% o.m) and the isopod *Porcellio scaber* Latr. Nitrification was found to be the most sensitive in the micro-ecosystem test. No effects were found on the functioning of the isopods during the experiment (highest test concentration: 3200 mg/kg). This result differs from the result of the isopod test (**Table 3.16**) in which a NOEC of 800 mg/kg was found. The difference may be due to several factors (e.g. other background F concentrations, NaF treatment versus KF treatment).

3.2.2.3 PNEC for the terrestrial compartment

From the **Tables 3.16** and **3.17** the lowest available NOEC, i.e. 106 mg/kg for nitrification, was selected for deriving the PNEC for the terrestrial compartment. Applying an assessment factor of 10 gives a PNEC of 11 mg/kg. The factor 10 was chosen because long-term data are available for three trophic levels.

The background F concentrations in the above-mentioned test systems were very low. So, theoretically, the PNEC of 11 mg/kg is a concentration that must be added to the natural background concentration in soil. However, the PNEC is negligible (less than 10%) compared to the average natural background F concentrations in soil (see paragraph 3.1.2.2).

The current target value in the Netherlands for total fluorides in a standard soil (10% o.m. + 25% clay) is 500 mg/kg (d.w.) (VROM 1994). A target value of 175 mg/kg was suggested for soil with very little or no clay (e.g. sandy soils and peat soils, which together make about 50% of the Dutch land area). In Switzerland, the recommended guideline for the total fluoride content of soil is 400 mg/kg (d.w.).

3.2.3 Atmosphere

3.2.3.1 Toxicity to plants

The most important exposure route of HF for plants is uptake from the atmosphere.

Many experiments are available in which all kinds of plants (bean, barley, corn, garden flowers, strawberries, pine, shrubs, grass, rice etc.) are exposed to HF in fumigation experiments. Gaseous fluoride enters the leaves through the stomatal pores and causes foliar injury (chlorosis, necrosis), decreased sugar and chlorophyll content, respiration rate and ATPase activity.

Reduced yield and smaller fruits are also observed. Sensitive species are tulip, gladiolus, fruit crops, conifers and grasses, which are affected at concentrations ranging from 0.4 to 1.0 μg/m^3 after exposure for several days.

On the basis of a large number of fumigation experiments with plants (ornamental crops, fruit crops and conifers) exposed to HF, a relationship was derived between the no-effect-concentration and exposure time (Slooff *et al*. 1988). In the RIVM report NOEC values were calculated with this formula for several exposure times.

In Germany (VDI 1989) NOEC-values have been calculated for highly sensitive, sensitive and slightly sensitive plant species. The Dutch Health Council (Gezondheidsraad 1990) also gave NOEC-values for all plant species and different exposure periods.

A compilation of the NOEC-values is given in **Table 3.18**.

Table 3.18 NOEC-values for HF (in mg/m^3) for plants

Plant species	Exposure 1 day	Exposure 1 month	Exposure 7 months	Reference
All plant species	0.76	0.34	0.27 3 month exp.	(Slooff *et al*. 1988)
Highly sensitive species	1.0	0.3	0.2	(VDI 1989)
Sensitive species	2.0	0.6	0.4	(VDI 1989)
Slightly sensitive species	7.5	2.5	1.2	(VDI 1989)
All plant species	2.8	0.8	0.4	(Gezondheids-raad)

The lowest NOEC-value for 7-month exposure of highly sensitive plant species will be taken into consideration for the derivation of the PNEC for the atmospheric compartment.

3.2.3.2 Toxicity to invertebrates

Exposure of *Drosophila melanogaster* to gaseous HF at 6.3 mg/m^3 was lethal to all animals within 3 days (Slooff *et al*. 1988). Exposure to lower levels (1.5 and 3.3 mg/m^3) for 3 or 6 weeks adversely affected egg production, hatchability and male fertility.

3.2.3.3 PNEC for the atmosphere

The NOEC-value mentioned in 3.2.3.1 is derived from a large set of toxicity data for different sensitive and highly sensitive plant species. Because of the size and diversity of the data set and the character of the experimental set-up (ecosystem-like; 7 months exposure) the application of an extrapolation factor is considered not to be necessary. As no other trophic levels than plants are taken into account and as there are at this moment no TGD guidelines for deriving a PNEC atmosphere, the term $PNEC_{plant\text{-}air}$ is preferred.

$PNEC_{plant\text{-}air} = 0.2$ μg/m^3

It should be borne in mind that the atmospheric NOECs are based on results of fumigation experiments in which plants were exposed to HF, the most phytotoxic F compound. This is a worst case situation, because under field conditions fluoride may also be present in the form of other, less phytotoxic compounds. For the current risk assessment report, however, this HF-

based PNEC is directly relevant as local gaseous emissions from producers or users are mainly HF (see **Table 3.2**).

3.2.4 Non compartment specific effects relevant to the food chain

Invertebrates

Three invertebrate species were chronically exposed to fluoride via two different routes. Exposure via fluoride treated leaves adversely affected egg production and survival in flour beetles (*Tribolium confusum*), reproduction in fruit flies (*Drosophila melanogaster*) and food consumption, growth and development in cabbage looper (*Trichoplusia ni*), respectively. Dietary fluoride exposure via HF fumigated leaves resulted in much less pronounced adverse effects in the same species.

Two generations of Mexican bean beetle (*Epilachna varivestis*) that were cultured on HF fumigated plants, showed an adversely affected growth, development and reproduction. The leaves contained 1000 mg F/kg. After transferring the animals to non-fumigated plants the effects were found to be reversible. Irreversibility of the reproductive effects occurred when five consecutive generations were exposed. The 72-hour LD_{50} values for three species of leaf eating insects ranged from 46 to 118 mg F/kg body weight.

Exposure of the honeybee *Apis mellifera* and the silkworm *Bombix mori* to several soluble inorganic fluoride compounds resulted in oral LD_{50}-values of 50 to 400 mg/kg body weight. With less soluble compounds (CaF_2 and MgF_2) the LD_{50}-values were found to be above 540 mg/kg body weight (Slooff *et al*. 1988).

Livestock

Absorbed fluoride can induce various types of effects in livestock:

- impairment of the rumen flora and reduced enzyme activity in the gastro-intestinal tract. As result, digestion and consequently food utilisation are inhibited.
- the enamel being formed during the period of tooth development is of inferior quality, resulting in an increased rate of wear, sub-optimal mastication and impaired (pre-)digestion.
- enhanced bone dissolution and delayed bone formation. The tissues formed are deficient in calcium and phosphorus. Symptoms include stiffness, lameness and reluctance to stand.
- All these effects eventually lead to a loss of body weight and diminished meat and milk production.

Cattle were shown to be the most sensitive of domestic animals to dietary fluoride, particularly young animals. In the RIVM report (Slooff *et al*. 1988) NOEC values for cattle have been derived in relation to the F content of the total diet (**Table 3.19**).

Table 3.19 NOEC values (in mg F/kg dry weight) for cattle with respect to the fluoride content of feed (total diet)

Criterion	mg F/kg of feed (dry weight)
Annual average	30
2-Monthly average	45
Maximum	55

Atmospheric NOECs for livestock (and plants) of 0.8 μg and 0.3 μg/m^3 (daily averages) were calculated for the grazing season and winter season, respectively (Slooff *et al*. 1988, 177: see Appendix 3). These NOEC values have been derived from the relationship between F content of animal feed and (the absence of) effects on the one hand, and from the relationship between F contents of feed (grass) and atmospheric F concentrations on the other. Both values are based on a maximum acceptable F level in feed of 55 mg/kg dry weight. No allowance has been made for a possible increase in F intake from drinking water, because the ingestion of F from feed contributes by far the largest amount to the total F intake of animals. The Dutch Health Council (Gezondheidsraad 1990) suggested the above-mentioned atmospheric NOECs may underestimate the effects of fluoride in cattle. In the Netherlands a limit concentration of 2 mg fluoride per liter has been set for drinking water for ruminants and poultry (Stoop *et al*. 1994).

Wild-life

In white-tailed deer (*Odocoileus virginianus*) mottling of the enamel of the incisors, distinct large areas of enamel hypoplasia and periosteal hyperosteosis of the metacarpal bones was observed at dietary fluoride concentrations of 25 mg/kg (24 months).

In feeding studies with different species of birds, the observed effects included thicker egg shells, depressed weight gain and increased mortality rate. For *Sturnus vulgaris*, intubated with fluoride doses up to 160 mg/kg body weight for 16 days, a NOEC of 10 mg/kg body weight was derived for mortality; the LD_{50} was calculated to be 17 mg/kg body weight.

In an area near an aluminium plant fluorosis was seen in black-tailed deer *Odocoileus hemionus columbianus* due to high fluoride levels in their forage (10-146 mg/kg in grasses and 44-333 mg/kg in browse species).

In areas with fluorosis in mule deer, elk and bison, fluoride levels of vegetation and water were up to 430 mg/kg and 24 mg/l, respectively (Janssen *et al*. 1989).

Foxes fed a diet containing 98 to 136 mg F/kg showed reduced milk production which caused mortality of kits (Janssen *et al*. 1989).

The RIVM report (Slooff *et al*. 1988) concluded that wild herbivores are or may be more susceptible to fluoride toxicity than domestic live stock, on a dietary F content basis. This greater susceptibility is probably due to the larger variation in F intake by wild animals, in conjunction with the influence of other stress-inducing factors in the environment. This conclusion was supported by the Dutch Health Council (1990).

Thus the atmospheric NOECs derived for livestock may provide an insufficient guarantee for the protection of wild fauna.

3.3 RISK CHARACTERISATION

3.3.1 General

In paragraph 3.1.5.3 it was stated that not only the HF industry, but also other industrial and natural sources contribute to regional and continental fluoride emissions. At these regional and continental levels the fluoride emissions from HF industry are small compared to other sources. They cannot be considered to contribute significantly to the fluoride concentrations in the aquatic, terrestrial or atmospheric compartment at a larger scale. For this reason the environmental exposure assessment was restricted to local levels close to HF producing and end-use plants. As a consequence, also the risk characterisation is only performed for the local situation. Additional information on the whole range of other F release sources in the European Union (e.g. NaF industry) is needed for an in-depth risk evaluation of fluorides.

3.3.2 Aquatic compartment

The local PEC-values and the corresponding PEC/PNEC ratios for water are summarised in **Table 3.20**. The PNEC for aquatic organisms is 0.9 mg/l (see paragraph 3.2.1.5). For the risk characterisation the ambient background F concentration in water has been added to the PEC-values of **Table 3.5** as they only represent the contribution to the receiving water. For this ambient F background concentration a value of 0.2 mg/l is chosen (see paragraph 3.1.1.2). Strictly speaking this value is known to be too low for those plants (No. 3, 5, 6 and 13) releasing their effluent streams into a marine environment (background of 1.4 mg/l; paragraph 3.1.1.2).

Table 3.20 shows that based on the most recent information of each plant for two plants (No. 3 and d) the local aquatic PEC/PNEC values were larger than 1 **(conclusion iii)**. In case of plant 3 it should be borne in mind that according to industry 83% of the fluoride emissions originate from the fertiliser production activity of this plant. In addition, the risk assessment is still based on a default dilution factor of 10 for emission into sea. This factor is used as no site-specific alternative for this default value has been submitted to the rapporteur. For plant d industry has indicated that monitoring data will become available. Since these data were not submitted within the agreed deadline, **conclusion iii**) is applicable.

For the remaining plants the PECs in water do not exceed the PNEC **(conclusion ii)**.

The above-described risk characterisation is based on the 'hard water' PNEC of 0.9 mg/l as probably the greatest part of the receiving waters for plants 1-12/a-e is characterised by hard water conditions. However, there may be some waters with soft water conditions. If the PNEC of 0.4 mg/l for soft water would have been used in this risk characterisation the relative outcome (either PEC/PNEC >1 or PEC/PNEC <1) would have been the same (PEC/PNEC ratios in **Table 3.20** should be multiplied by a factor 2.25). An exception must be made for the plants number 6 and 13 for which a PEC/PNEC of larger than 1 would be reached with the soft water PNEC of 0.4 mg/l. However, it is known that the plants number 6 and 13 discharge their effluent into a marine environment (in any case no 'soft water').

Table 3.20 Local PEC-values and PEC/PNEC-ratios for the aquatic compartment

Plant No.	PEC (mg F^-/l)	PEC/PNEC	Year
1	0.2[L] 0.2[L]	0.2 0.2	1995[a] 1995 [b]
2	237 0.4 0.4 0.6 0.4	263 0.4 0.4 0.7 0.4	1994[a] 1995[a] 1996[a] 1997[b] 1998[b]
3	13[L] 2.9 3.1 3.2	14 3.2 3.4 3.6	1994[a](1) 1996 1997 1998
4	0.2[L]	0.2	1994[a](1)
5	~~1.2~~ 0.2 ~~1.7~~ 0.2	~~1~~ 0.2 ~~2~~ 0.2	1994[a] 1995 [a]
6	6.5 0.7 1.4 1.1	7 1 1 1	1994[a] 1995[a] 1996 1997
7	0.2[L]	0.2	1994[a]
8	0.2[L] 0.26[L]	0.2 0.3	1994[a] 1997[a]
9	0.2	0.2	1997[a]
10	0.2[L] 0.2[L]	0.2 0.2	1994[a] 1995[a]
11	0.2[L] 0.2[L]	0.2	1994[a] 1994[b]
12	0.2	0.2	1994[a]
13	0.6 0.6	0.7 0.7	1994[a] 1995[b]
14	0.2	0.2	1997
a	0.3	0.3	1994[b]
b	0.2[L]	0.2	1994[b]
c	0.2 0.2	0.2	1994[b] 1994[b]
d	9	10	1994[b]
e	0.2	0.2	1995[b]

[L]Low river flow value
(1)Same for 1995
[a]Production plant
[b]Use plant

If the risk characterisation would have been based on the $PNEC_{aquatic}$ of 3.3 mg/l according to the Aldenberg and Slob method, there are still a number of plants for which the PEC exceeds the PNEC (No. 2, 3, 6, and d in 1994, and no. 3 in 1995).

Sediment

As there are no measured data for fluoride levels in sediment and no ecotoxicity data for the sediment compartment, no quantitative risk characterisation is carried out for the sediment compartment. The bioavailability of fluorides in sediment is expected to be low.

3.3.3 Atmosphere

The local PEC-values and the corresponding PEC/PNEC ratios for air are summarised in **Table 3.21**. The PNEC for *plant*-air is 0.2 μg/m^3 (see paragraph 3.2.3.3). For the risk characterisation the ambient background F concentration in air has been added to the PEC-values of **Table 3.6**. For this ambient F background concentration a value of 0.07 μg/m^3 is chosen (see paragraph 3.1.1.2).

From **Table 3.21** it can be concluded that based on the most recent emission data for each plant for two HF producing plants (no.3 and 13) and one HF using plant (No. b) the calculated PEC in atmosphere exceeds the PNEC.

In case of plant 13 additional monitoring data for the years 1999 and 2000 have not removed the concern for this plant **(conclusion iii)**. The PEC for plant No. 3 is based on the most recent (1998) emission data **(conclusion iii)**. **Conclusion (iii)** is also drawn for site No. b (end use plant). The potential risk for this plant (PEC/PNEC of 17) is supported by the fact that during the 1988-1998 monitoring programme fluoride levels in grass in the vicinity of this plant were found to exceed the maximal acceptable level of 55 μg/g dw. On the other hand it should be stated that according to industry most of their HF emissions originate as a by-product during the production of organofluor compounds. In addition, industry has indicated that important reduction measures have been taken in 1998 which are expected to reduce releases substantially. For the remaining plants the PECs in air do not exceed the PNEC **(conclusion ii)**.

In addition to the PEC values in **Table 3.21** that are calculated with the OPS model, 1994-1995 monitoring data are available for seven EU plants (see paragraph 3.1.5.3). For four of these plants the PEC/PNEC ratios indicate a significant risk of HF for the local atmospheric compartment **(conclusion iii)**. Those ratios ranged from 1.2 to 12.0. The risk characterisation based on the monitoring data seems to support the one on the OPS-calculations for the years 1994-1995. At present it is not clear, however, whether the same plants are involved.

Table 3.21 Local PEC-values and PEC/PNEC ratios for the atmosphere

Plant No.	PEC (µg/m3)	PEC/PNEC	Year
1	0.16	0.8	1994
2	1.1 0.36 0.34 0.33 0.13	6 1.8 1.7 1.7 0.7	1994 1995 1996 1997 1998
3	2.43 1.67 1.1 0.98 1.02	12 8 5.5 5 5	1994 1995 1996 1997 1998
4	0.31 0.22	2 1	1995 1997
5	0.2 0.19	1 1	1994 1995
6	0.09	0.5	1994(1)
7	0.08	0.4	1994
8	0.37 0.1	2 0.5	1994 1997
9	0.07	0	1997
10	1.61 0.10	8 0.5	1994(1) 1998
11	0.09	0.5	1994
12	0.09	0.5	1994
13	0.33 0.86	2 4	1994 1996
14	0.18	0.9	1997
a	0.1	0.5	1994
b	12.3 3.3	62 17	1994 1998
c	0.09 0.08	0.5 0.4	1994 1995
d	0.07	0.4	1994
e	0.08	0.4	1994

(1)Same for 1995

3.3.4 Terrestrial compartment

Maximal local PEC values for the terrestrial compartment were calculated from deposition of HF (see paragraph 3.1.5.3). Levels were found to be negligible compared to background concentrations **(conclusion ii).** Measured data are only available for one HF emitting plant. Soil concentrations in the vicinity of this plant were in the range of natural and ambient background concentrations (see paragraph 3.1.2.2).

3.3.5 Non compartment specific effects relevant to the food chain

For a number of plants the fluoride surface water concentrations (see **Table 3.20**) exceed the Dutch drinking water limit concentration of 2 mg/l for ruminants and poultry (see paragraph 3.2.4). Local air concentrations (see paragraph 3.3.3) around a number of plants exceed the atmospheric NOECs for livestock of 0.8 μg and 0.3 $\mu g/m^3$ for the grazing season and winter season, respectively **(conclusion iii)**. It is emphasised that wild-life is probably more susceptible to fluorides than livestock.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure Assessment

4.1.1.1 General discussion

At room temperature hydrogen fluoride is a liquid/gas (b.p. 19.5°C) and therefore inhalation and dermal contact are the predominant routes of exposure for the human population. Oral exposure to fluoride occurs, indirectly via the environment, via drinking water and food.

An overview of the uses of HF (industrial and uses categories) is given in **Table 2.2**.

More specified uses of HF are (see also 4.1.1.1):

- as pickling agents (metal)
- as intermediates (raw material)
- as metal surface treatment agents
- as etching agents for glass

The main part of the population which is likely to be exposed to HF are workers involved in production and industrial manufacture such as workers in ceramic industry and aluminium and steel production.

The producers are not aware of any direct consumer use of HF (CTEF 1995). In Sweden HF has been found in 76 products 3 of which are available to consumers. Total registered volume for 69 products amounted in 1993 to 2235-2297 tonnes (Kemi 1995).

4.1.1.2 Occupational exposure

Hydrogen Fluoride (HF) is or may be produced or used in the following chemical industries (CTEF 1995; EPA 1993):

- basic chemicals: production of HF;
- basic chemicals: starting chemical or catalyst in the production of a variety of products such as:
  * inorganic fluorides for pharmaceuticals and personal care products, nuclear fuel processing (e.g. UF_6), wood preservatives, flotation agents, aluminium production
  * organofluoro compounds for fabric and fiber treating, surface-active agents, fluoropolymers
  * electronic grade inert fluorinated liquids and fluorinated gases for etching
  * refrigerants
  * pesticides
- oil refineries and fuel processing: HF is used as a catalyst in the production of gasoline

Occupational exposure is possible in industries where anhydrous HF is used (see 4.1.1.0) and in industries where hydrofluoric acid solution is used (see also section 2.1).

Approximately 65% of produced HF is used by the producers (e.g. for the synthesis of organofluoro compounds or inorganic fluorides) (CTEF 1995).

Solutions of HF (hydrofluoric acid) may further be used in the following industries (EPA 1993; CTEF 1995):

- metal industry: stainless steel pickling
- glass industry: glass etching, polishing agents, quartz purification
- electrotechnical industry: production of electronic components (etching)
- mining and ore industry: special metals extraction (e.g. Nb, Ta)

Further use is mentioned in corrosion inhibitors (Derivados del Fluor SA 1994; HEDSET 1994), and cleaning/washing agents, disinfectants, and polishing agents (Riedel de Haën 1994; Kemi 1995). This includes cleaning agents for facades of buildings, high pressure cleaning agents for trucks, cleaning agents for tanks and aircraft surfaces (EPA 1993; Luijk *et al*. 1989). Mentioned use of HF in rust removers (including consumer products) may be discontinued (CTEF 1995; Luijk *et al*. 1989). HF is also used in preparations used in dentistry to etch teeth before filling with composites (KEMI 1997).

Results from the Swedish product register are reported in Annex 1 (Kemi 1995).

The use of HF, HF solutions and products containing HF may include:

- transfer of liquids by means of a transfer line and pumping;
- manual transfer of liquids;
- manual use of cleaning/washing agents and disinfectants and etching preparations.

In the following applications, exposure to HF is possible, though in some cases to only very small amounts.

Fire-fighting

Exposure may occur due to the use of modern fire fighting foams containing organic fluorine compounds and due to the decomposition of fluorine compounds in the materials present in the fire (Jankovic *et al*. 1991).

Brazing and welding

During brazing and welding some HF may be formed by decomposition of fluorine compounds in welding rods or fluxes (Thorne and Hewitt 1988; Hodge and Smith 1970).

Pyrolysis of fluoropolymers

During the pyrolysis of fluoropolymers small amounts of HF may be formed. These activities are usually done under controlled conditions (Echt *et al*. 1993).

Production of fertiliser

In the production of fertilisers HF is formed during the reaction of the mineral with sulfuric acid (Hodge and Smith 1970; (Hery *et al*. 1990).
Routes of exposure to HF in all the mentioned situations are by inhalation and in a minority of situations also by skin contact.

Relevant populations potentially exposed are workers in the above mentioned industries, specifically those workers that may have more or less direct contact with the substance, being:

- workers involved in the production and transferal of HF;
- workers producing and drumming products containing HF (e.g. pickling agents, polishing agents, cleaning/washing agents);
- maintenance and (specialised) cleaning workers in production facilities of HF and of products containing HF;
- workers using products containing HF in the above mentioned industries;
- workers exposed to decomposition products of materials containing fluorine

The exposure is assessed using the available information on substance, processes and work tasks. More detailed information on these parameters may lead to a more accurate exposure assessment.

In this part of the assessment, external (potential) exposure is assessed using relevant models and other available methods in accordance with the Technical Guidance Documents and agreements made at official Meetings of Competent Authorities. Internal dose depends on external exposure and the percentage of the substance that is absorbed (either through the skin or through the respiratory system).

The exposure is assessed without taking account of the possible influence of personal protective equipment (PPE). If the assessment as based on potential exposure indicates that risks are to be expected, the use of personal protective equipment may be one of the methods to decrease actual risks, although other methods (technical and organisational) are to be preferred. This is in fact obligatory following harmonised European legislation.

Knowledge of effectivity of PPE in practical situations is very limited. Furthermore, the effectivity is largely dependent on site-specific aspects of management, procedures and training of workers. A reasonably effective use of proper PPE for skin exposure may reduce the external exposure with 85%. For respiratory protection the efficiency depends largely on the type of protection used. Without specific information, a tentative reduction efficiency of 90% may be assumed, equivalent to the assigned protection factors for supplied-air respirators with a half mask in negative pressure mode (NIOSH, 1987). Better protection devices will lead to higher protection. Imperfect use of the respiratory protection will lower the practical protection factor compared to the assigned factor. These estimations of reduction are not generally applicable "reasonable worst case" estimations, but indicative values based on very limited data. They will not be used directly in the exposure and risk assessment. Furthermore, the reduction of external exposure does not necessarily reflect the reduction of absorbed dose. It has to be noted, that the use of PPE can result in a relatively increased absorption through the skin (effect of occlusion), even if the skin exposure is decreased. This effect is very substance-specific. Therefore, in risk assessment it is not possible to use default factors for reduction of exposure as a result of the use of PPE.

In some specific situations the model estimates with normal assumptions for input parameters in the assessed exposure scenarios are expected not to lead to a reasonable assessment of exposure. For situations with high risk of direct acute effects, such as manual handling of corrosive substances and hot materials, or possible inhalation exposure of substances with severe acute effects on the respiratory tract, the total level of containment given by all exposure control measures is assumed to be higher than for similar scenarios with other substances. For estimating a single day exposure an extra protection is assumed, reducing exposure with 90%. The extra

protection can be reached by a combination of technical and organisational control measures and personal protective equipment. If the extra protection is reached (mainly) by using personal protective equipment, this is an unwanted situation that should be changed by further technical and organisational control measures.

Repeated exposure to corrosive concentrations will not normally occur. Some exposure to non-corrosive exposure may however still occur, *e.g.* to highly diluted concentrations after decontamination of surfaces. The estimate of repeated dermal exposure depends on the knowledge of the concentration that probably does not cause corrosive effects. If such a concentration can be estimated, this concentration will be used in estimating repeated dermal exposure. Otherwise the estimate for single day exposure will be used.

The following data (if available) are used for occupational exposure assessment:

- physico-chemical data of HF and products containing the substance: physical appearance, vapour pressure at room temperature, percentage of HF in products;
- data regarding methods of use and use pattern of the substance and products potentially containing HF and exposure control pattern in the relevant industries (from the HEDSET or other sources);
- exposure data for HF from the HEDSET and other sources (literature, exposure databases);
- results from exposure models if applicable (EASE model); in the exposure models the above mentioned types of data are used.

For the occupational exposure assessment the exposure situations can be clustered into three scenarios based on the type of use of HF. In the first scenario use of mostly anhydrous HF in almost completely closed systems is considered. The second scenario considers use of hydrofluoric acid solutions. The third scenario indicates possible exposure levels in situations where HF is not used, but is produced as a result of heating fluor containing components.

Occupational scenario 1	Production and use as an intermediate or catalyst (chemical industry).
Occupational scenario 2	Electronics manufacturing and other use of aqueous HF (use of hydrofluoric acid solutions).
Occupational scenario 3	Exposure not resulting from the use of HF (indirect exposure).

Occupational scenario 1: Chemical industry

This scenario includes the production of HF and its use as an intermediate (e.g. for fluorocarbons) or catalyst (e.g. production of alkylates for gasolines). HF is mainly used as anhydrous HF in this scenario, although some hydrofluoric acid solutions are used in the production of inorganic fluorides.

It has been known for many years that HF is (very) toxic and has a high vapour pressure (boiling point ≈ 19°C). Therefore production, transferal and subsequent use as a catalyst or intermediate occur in closed systems. Transferal may involve flexible hosing, pumping and cylinders that may lead to some leakage of HF. Some processes in which HF is used also require pumping. However, equipment and working methods are generally chosen to minimise possible losses of HF (EPA 1993). For certain activities, such as checking the level of HF catalyst and sampling for analytical purposes, valves may have to be opened manually and some HF will evaporate. These activities

are usually performed applying strict protective measures to keep exposure levels to a minimum. High exposures may occasionally be encountered by maintenance workers (Brown 1985).

A small number of exposure data regarding this type of use has been provided by the producers or was found in a literature search (see Annex 2). Exposure data gathered previous to 1970 are considered to be out-dated. In the abstract of a Health Hazard Evaluation Report (HHE) by NIOSH, short term workplace concentrations well below the NIOSH Short Term Exposure Limit (STEL) of 2.5 mg/m^3 are reported (Markel and Slovin 1982). The abstract of another HHE by NIOSH reports one sample approaching the same value (Gunther and Thoburn 1982). In an alkylation unit, plant operators and maintenance workers were exposed to < 0.005 to 0.18 mg/m^3 of fluoride (4 to 6 hours time weighted averages). The highest level was measured for a maintenance worker. All other levels were below 0.04 mg/m^3 (Brown 1985). A fourth publication mentions accidental peak exposure to HF mist of 150 to 200 ppm (100-133 mg/m^3) during 2 minutes (Lee *et al*. 1993). Confidential data from producers all show exposure levels below 1 mg/m^3 or exposure is described as being "below the occupational exposure limit" (3 ppm or 5 mg/m^3) (ICI 1994; Riedel de Haën 1994; Bayer AG 1994).

For inhalation exposure to vapours of highly volatile substances in closed systems the EASE model estimates (reasonable worst case estimates):

- without breaching: 0-0.1 ppm (0-0.08 mg/m^3);
- with breaching (= non dispersive use with LEV): 100-200 ppm (80-160 mg/m^3).

The limited exposure data found indicate that normal short term (10-15 minutes) inhalation exposure levels are generally below 2.5 mg/m^3. The EASE model results for "non dispersive use with LEV" appear to be excessively high, while the results for "closed systems, full containment" underestimate potential exposure levels. This is probably due to the fact that even closed systems that are not intentionally breached will still exhibit small, unintended leaks, leading to evaporation of relatively small amounts of HF. If larger leaks occur, toxic concentrations of HF can soon be reached, as shown by the reports on accidental exposures (Lee *et al*. 1993; Braun *et al*. 1984).

For normal working conditions a short term exposure level of 2.5 mg/m^3 will be used as a reasonable worst case estimate for this scenario. Full shift exposure levels will be lower. They are estimated to be up to about 0.5 mg/m^3 (calculated from a concentration of 2.5 mg/m^3 during somewhat less than 2 hours and no exposure during the remainder of the day) which may be reached if several activities that lead to exposure occur on one day.

Skin exposure to HF in this scenario is rather uncommon. Actual exposure to anhydrous HF or hydrofluoric acid solutions in high concentrations is very dangerous. The use of engineering controls to prevent leakage of HF is normal procedure. However, as shown by several case reports, accidental leakage of HF occurs occasionally, leading to inhalation as well as skin exposure (Braun *et al*. 1984; Chan *et al*. 1987). Furthermore, some activities require manual handling, in which case precautions will be taken to limit potential contact and the use of protective clothing is required. The commonly used skin exposure models are considered inapplicable for this substance.

Skin exposure is considered to occur only accidentally in this scenario.

The duration of exposure to HF cannot be concluded from the reported data. Generally exposure will occur through small leakages and occasional opening of valves and other manual handling. It is estimated that duration of inhalation exposure due to specific activities is low (1-2 hour/day), whereas 4-8 hours per day exposure to background concentrations may be possible. Frequency of exposure depends on work patterns, but daily exposure is possible.

Occupational scenario 2: Use of hydrofluoric acid solutions

This scenario includes several rather different exposure situations. Included are:

- the use of solutions for etching in the metal and glass industries;
- the use of products for rust removal and/or cleaning facades;
- the use of special products for other (small scale) uses, such as in dentistry.

Hydrofluoric acid solutions are used in the manufacture of electronic components for surface treatment (etching). It is usually purchased in concentrations of typically 49% and diluted to solutions of 1 to 10%. In a typical process it is pumped from drums through etching basins (EPA 1993). Other processes in which aqueous HF is used are metal pickling, glass etching and similar processes (EPA 1993).

The use of HF in industrial cleaning (e.g. in acid baths or cleaning products for facades of buildings) is mentioned in some sources (Luijk *et al*. 1989; Sheehy and Jones 1985; Marquart 1990; Van de Laar *et al*. 1994).

The use of HF for etching will mainly be in baths, tanks etc. Exposure is possible due to evaporation of HF from the baths, during dilution of concentrated preparations and during preparation of the baths with higher concentrated HF.

In cleaning activities, such as cleaning the facades of buildings, products in the form of liquids or pastes are used and are often removed after some time by washing with (copious amounts) of water. In some cases, e.g. in the cleaning of facades, the water may be applied by (high pressure) spraying. This may lead to the formation of aerosols. Skin contact is possible during the preparation of solutions, loading and unloading baths and equipment and during cleaning activities.

Some exposure data, mainly regarding etching, have been found in literature. Exposure levels (probably short term measurements) of up to more than 7.5 ppm (6 mg/m^3; = arithmetic mean + standard deviation) have been measured during etching of metal and glass in Finland (Finnish Registry 1995). Kono *et al*. (1987; 1990; 1992) report averages for several workshops of up to 5 ppm (4 mg/m^3). Another source reports levels up to 3 ppm (2.4 mg/m^3) (Burr *et al*. 1990). Levels from stationary full shift sampling by the INRS are up to 1.8 mg/m^3 (2.25 ppm) in usual conditions (INRS 1995). Measurements of HF by area sampling around acid baths have been reported. One sample was taken at the edge of a bath containing 13% HF. The concentration was 2.7 mg/m^3. At the edge of another bath (in a different facility) containing an unknown percentage of HF, 0.14 to 0.19 mg/m^3 was measured in 4 measurements. Duration of measurements was 2 to 8 hours (Sheehy and Jones 1985).

The applicable choices in the EASE model for this scenario are: non dispersive use and local exhaust ventilation. For estimating the exposure level, the vapour pressure of HF in the diluted solutions should be known. According to the HEDSET, a 40% solution has a vapour pressure of 6 hPa. Extrapolating from the data in the HEDSET, a solution of 10% has a vapour pressure of

approximately 26 Pa, whereas a solution of 1% has a vapour pressure of approximately 10 Pa. Solutions of less than 40% are clearly of "low volatility" in the EASE model. The estimated exposure level for non dispersive use and local exhaust ventilation is therefore 0.5-3 ppm (0.4-2.4 mg/m^3). If aerosol formation is to be expected, the model estimates an exposure level of 100-200 ppm (80-160 mg/m^3).

The EASE model estimations (disregarding the formation of aerosols) are in the same range as the results presented in the literature. The presented measured data mostly represent short term exposure levels, while the EASE model estimates full shift levels.

From the measured data it is estimated that reasonable worst case short term exposure levels in this scenario are up to 7.5 ppm (6 mg/m^3), while full shift levels may be up to 3 ppm (2.4 mg/m^3). In these estimates it is assumed that most measured exposure levels were short term levels. The data on full shift stationary sampling under typical conditions by INRS are in reasonable agreement with the estimate for full shift levels. Typical full shift levels are expected to be about 1/2 of the reasonable worst case levels (expert judgement).

The exposure during use of facade cleaners containing HF cannot be estimated. The EASE model results are probably overestimating exposure levels, since they are based on indoor measurements, while the cleaning of facades usually is outdoors, where ventilation is much higher. Furthermore, this type of use consists of manually applying pastes containing acids and (after some time) removing the pastes by means of high pressure cleaning. It is not clear whether this activity will lead to aerosols containing HF or whether all the hydrofluoric acid will have reacted with the components on the facades. The use of HF for this type of activity probably only constitutes a (very) minor use. However, under worst case conditions (e.g. cleaning virtually enclosed facades) this type of use may lead to relatively high exposure levels, depending on methods of use and amounts and percentages used.

The use of HF in dentistry concerns preparations with a percentage of up to 9% of HF. It is probably a very small scale use involving very small amounts of HF per day (KEMI 1997). Exposure will be substantially below the values estimated for other activities in this scenario. Some skin contact cannot be excluded. Duration of inhalation exposure may be up to 8 hours per day for certain operations, whereas in other cases duration of exposure will be less. Frequency of exposure may be up to 100 days per year.

Skin exposure to dilute solutions of HF is possible due to preparation of solutions, filling and emptying of baths, contact with treated objects and cleaning activities. It is generally known that even dilute solutions can lead to effects. Workers using solutions of HF daily will be aware of the potential effects and will thus try to prevent routine skin exposure. However, occasional skin and eye exposure does occur and is mentioned in several sources (El-Saadi *et al*. 1989; Burns and Paterson 1989; Stencel and Tobin 1987; LaDou 1991). Due to the irritating and corrosive properties of HF solutions workers must rely on protective clothing to prevent actual exposure, since potential exposure levels may be considerable, e.g. when handling material that has been in an acid bath. Incidentally workers may receive actual exposure due to faulty protective equipment, faulty work procedures or failure of the protective equipment.

In The Netherlands 16 cases of acute effects due to clearly identified skin contact with HF have been reported in a period of 9 months in 1993, mainly in cleaning activities for facades and metal products. The study was restricted to accidents due to the manual use of etching, cleaning and disinfecting agents. In 8 of these cases no personal protective equipment (gloves) were used

during (part) of the activities, mainly due to lack of knowledge regarding the products and its possible effects, or due to severe underestimation of the risks. In three of these cases the worker involved was aware of the dangers, but was not aware of some of the exposure sources (e.g. contaminated surfaces). Working under strict deadlines contributed to some of these cases. In 5 cases the personal protective equipment used was inadequate (holes, liquid getting inside of short gloves, wrong material). These data clearly show that there is a high potential of dermal contact if workers are not fully aware of the risks and if adequate personal protective equipment is not properly used. No quantitative information on exposure was available, except for data on the concentration of HF in the liquids. Mentioned concentrations were between 35 and 350 g/L (approximately 3.5-35%) (Van de Laar *et al*. 1994).

Since measured exposure data are lacking, exposure has to be estimated by modelling. Potential exposure is estimated using the EASE model for dermal exposure with the following assumptions. Exposure in the etching of metal and glass will be non-dispersive use with direct handling and incidental contact.

The area potentially exposed due to preparation of solutions (1-49% HF) and filling and emptying of baths is estimated to be a part of the fingers of a hand (100 cm^2). This leads to the following potential exposure levels (non-dispersive use, incidental contact):

- solution 49%: 0-5 mg/day;
- solution 1%: 0-0.1 mg/day.

Manual handling of 49% HF in this scenario is not considered to be a normal procedure.

The area potentially exposed due to the handling of wet surfaces (1-10% HF) will be higher. The estimated area (part of the fingers and palms of two hands) is 450 cm^2, leading to the following potential exposure levels (non-dispersive use, incidental contact):

- solution 10%: 0-4.5 mg/day;
- solution 1%: 0-0.45 mg/day.

Potential exposure due to manual cleaning (*e.g.* facades, metal parts of tank trucks and other objects) will be considerably higher. Unexperienced and not fully trained workers sometimes do not take sufficient precautions against direct and intensive contact with products containing HF. As shown in the Dutch study, reported above, this often leads to severe acute effects. Even when personal protective equipment is used, this may not be adequate, since the contamination of the inside of gloves is reported in several cases (Van de Laar *et al*. 1994). Assuming the use of products containing 3.5-35% HF, extensive contact, non-dispersive use and a contact area of 650 cm^2 (one hand and part of the forearms) the potential exposure is estimated to be approximately 23-1100 mg/day (1-5 $mg/cm^2/day \cdot 650 \cdot 0.035\text{-}0.35\%$).

In this scenario the exposure to a corrosive substance or a substance with acute serious effects on the respiratory tract is assessed. The models used to estimate the exposure levels are not specifically aimed at estimating exposure levels for such a situation. The total containment, a combination of technical and organisational measures and personal protective equipment, is in such a situation usually considerably better than average. Therefore, the results of the exposure estimate by the model are for this situation (by default) multiplied by a factor of 0.1 for use in risk characterisation. This factor is based on expert judgement. For this scenario the reasonable worst case exposure for a single day is calculated to be 0.5 mg/day for etching and 110 mg/day

for manual cleaning and facade cleaning using this default estimation method. Repeated exposure to concentrations that lead to corrosive effects is not to be expected. However, repeated contact with (very) diluted solutions, by penetration of protective equipment, or by contact with slightly contaminated surfaces is considered possible.

The concentration that will not lead to corrosive effects is unknown. Therefore, the lower limit of the range given above for single day exposure, including a factor of 0.1 for extra total containment, will also be used as an upper bound estimate of repeated dose exposure due to manual cleaning and facade cleaning: 0.2 mg/day (expert judgement). This level relates to concentrations of up to 3.5%, that lead to severe local effects. The upper bound estimate is therefore assumed to be a (severe) overestimation of true repeated dermal exposure levels.

The activities possibly leading to dermal exposure are expected to be done up to 100 days per year, with actual dermal exposure (even to low concentrations) probably being less frequent.

Scenario 3: exposure not resulting from the use of HF (indirect exposure)

This "scenario" consists of a group of very different work situations, practices and possible exposures that have one thing in common: exposure to HF is not the result of using HF or a product containing HF. Although these scenarios may not have to be evaluated for the purposes of the existing substances regulations, some data are included for comparison with the other scenarios.

In all of the work situations in this scenario HF is formed by heating of fluoride containing substances. The exact composition of the substances, the heating energy, duration of heating and exposure control measures will influence levels of inhalation exposure to HF. The work situations and exposure levels gathered in this scenario are given below.

Fertiliser production

Exposure is continuous, due to the processes used. Measured exposure levels are <1 to >10 mg/m^3 (probably short term measurements) (Hodge and Smith 1970; Hery *et al*. 1990).

Aluminium industry

Exposure is continual, due to the processes used. Measured exposure levels are <1 to >10 mg/m^3 and "levels above exposure limits" (Hodge and Smith 1970; Miszke *et al*. 1984).

Magnesium foundries and melting

The exposure is probably due to similar processes as in the aluminium industry. Measured exposure levels are <1 to >10 mg/m^3 (Hodge and Smith 1970).

Fire fighting

Exposure depends on the materials present in the fire. The use of fluorine containing fire-fighting foams is probably not very important for the exposure levels. Exposure levels measured are potential exposure levels. Actual exposure levels (inside respirators) will be very much lower. The use of personal protective equipment in fire fighting is standard procedure due to the possible presence of life threatening concentrations of several substances as well as the lack of

oxygen. Potential exposure levels measured are < 0.1-6.4 mg/m^3 (Jankovic *et al*. 1991). HF is not a very important risk factor in fire fighting compared to other factors.

Very low levels of HF were measured in:

- polymer treatment: <0.01 mg/m^3 (short term) (Echt *et al*. 1993);
- brazing, soldering and welding: <1 mg/m^3 (Hodge and Smith 1970).

These low levels are explained by the (very) small amount of fluorine that is available for conversion to HF and by the use of engineering controls, such as local exhaust ventilation. HF does not appear to be an important risk factor in these two situations.

The results presented by Hodge and Smith (Hodge and Smith 1970) are from measurements before 1970 and may not be valid for present conditions. However, from the scarce results it can be seen that in some situations where HF is not used, but is a pollutant resulting from the heating of fluoride containing components, exposure levels can be at least as high as in the other two scenarios.

Skin exposure in this scenario cannot be estimated. Some deposition of vapours or aerosols containing HF is to be expected. However, concentrations of HF on contacted surfaces and skin exposures due to contact with these surfaces are expected to be considerably below the values mentioned in scenario 2.

Duration and frequency of exposure depend on the frequency of heating of fluoride containing components leading to the production of fumes containing HF. In the fertiliser industry and the aluminium industry frequency may be daily and duration up to 8 hours per day.

Conclusions

Table 4.1 Conclusions of the occupational exposure assessment

Scenario / subscenario	Activity	Frequency (day/year)	Duration (hr/day)	Estimated inhalation exposure level; RWC		Estimated inhalation exposure level; typical		Estimated skin exposure level	
				(mg/m³)	Method	(mg/m³)	Method	(mg/cm²/day)	dose (mg/day)
1: chemical industry	general peak activities full shift[a]	100-200 100-200	*6-8* *1-2* 6-8	very low 2.5 0.5	EASE, measured measured calculated	not estimated		accidental	accidental
2: use of hydrofluoric acid solutions	etching: preparing and cleaning baths etching: full shift; manual cleaning/ facade cleaning: full shift	50-100 50-100 50-100	2-3 6-8 6-8	6.0 2.4 ne[c]	Measured and EASE Expert[b] 	 1.2 not estimated	 Expert[b] 	not estimated not estimated	0.5 (single day) 110 (single day) 0.2 (repeated[d])
3: indirect exposure	several	100-200	6-8	<1 - ca. 10[e]	Measured	not estimated			cannot be estimated[f]

[a] Full shift exposure calculated from 1.6 hour at 2.5 mg/m³ and negligible exposure during the remaining 6.4 hours. In practice the background exposure may be higher, but for compensation the duration of high exposure may be lower

[b] Expert judgement based on stationary measurements and on measured data that are probably short term data

[c] The inhalation exposure for manual cleaning and polishing is probably below the level of etching, due to the low volumes handled. The inhalation exposure due to facade cleaning cannot be estimated with the available information and methods

[d] The repeated exposure is an upper bound estimate that probably (severely) overestimates true exposure levels

[e] These are rough estimates based on measured data that were limited in quantity and quality and are only presented for comparison with the other 2 scenarios

[f] Cannot be estimated, but are considered to be clearly below the levels in scenario 2

4.1.1.3 Consumer exposure

The producers of HF stated that there is no consumer exposure since the historic uses for aqueous hydrogen fluoride e.g. rust cleaning agents have been discontinued (CTEF 1995). It appeared that consumer use only occurs in accidental cases e.g. workers use industrial products in private life or HF containing products are reformulated and/or marketed as consumer products.

However, Velvart (Velvart 1993) mentioned the use of aqueous HF in facade- and stone cleaning agents and in rust spot remover for textiles in concentrations of 10% and 10-15%, respectively, both products being available to consumers. In addition, in the Swedish product register 3 HF-containing products were mentioned as pickling agents (metal) for non-occupational uses (CTEF 1995).

Accidents were reported in the Netherlands after non-occupational use of an HF containing cleaning agent (Van de Laar *et al*. 1994). Other Dutch information mentioned 2 products available to consumers (facade cleaning (25% HF) and stainless steel polishing paste (4.5% HF) (Bragt 1995). Recently information was obtained from the Anti-poison centre in Belgium which shows that the use of aqueous hydrogen fluoride in rust cleaning and stone and wood cleaning agents, all available and marketed to consumers, is still common practice in Belgium (SZV&W, 1999). A significant number of accidents through the use of these products have been reported. An overview of the information collected by the Anti-poison Centre is given in Annex 4. Details about the concentration of HF in the products are not available but it is mentioned that solutions up to 75% are available in certain hardware stores.

4.1.1.4 Indirect exposure via the environment

As mentioned in previous sections hydrogen fluoride may enter the environment from both natural and anthropogenic sources. It is concluded in section 3.3.1 that the contribution of HF emissions from the HF producing and processing industry is limited compared to those from other industrial sources. In air, water and soil HF is transformed to a variety of other fluoride anion containing compounds.

4.1.1.4.1 Fluoride exposure from air

Local fluoride concentrations (PEC's) are calculated for the atmospheric compartment for 13 HF-producing plants (some are both producer and user) and 5 end-user plants (a-e).

The data are listed in **Tables 3.6**. In addition to the calculated atmospheric HF concentrations monitoring data are available for some plants. The measured data are listed in **Table 4.2** and range from 0.05 - 2.4 $\mu g/m^3$. The calculated local atmospheric HF concentrations for each production and end use plant are given in **Table 4.3** and range from 0 -3.2 $\mu g/m^{3.}$

Table 4.2 Summary of measured local

Plant	Air concentration [a] µg/m³	Actual intake µg/d
NL	0.1 1	2 20
D I	1.3	26
D II	2.4	48
UK I	0.06 0.23	1.2 4.6
EU	0.05-0.06	1-1.2

[a]For specific data see section 3.1.5.3

These data are of the same order of magnitude as the measure data. In both tables the actual inhaled amount in µg/day is calculated assuming an average respiration rate in an adult person of about 20 m^3 per day. The concentrations presented in **Table 4.3** are strictly related to local plant sites and are exclusive the background concentration.

Table 4.3 Summary of calculated local atmospheric PEC-values and actual intakes

Plant No.	Annual average Air concentration [1][2] (100 m) µg/m³	Actual intake µg/d	Year
1	0.091	1.82	1994
2	1.03	20.6	1994
	0.29	5.8	1995
	0.27	5.4	1996
	0.26	5.2	1997
	0.06	1.2	1998
3	2.36	47.2	1994
	1.60	32	1995
	1.0	20	1996
	0.91	18.2	1997
	0.95	19	1998
4	0.24	4.8	1995
	0.16	3.2	1997
5	0.13	2.6	1994
	0.12	2.4	1995
6	0.024	0.48	1994[3]
7	0.013	0.26	1994
8	0.30	6.0	1994
	0.037	0.74	1997
9	0[4]	0	1997
10	1.54	30.8	1994[3]
	0.03	0.7	1998
11	0.023	0.46	1994
12	0.023	0.46	1994
13	0.26	5.2	1994
	0.79	15.8	1996
14	0.26	5.2	?
	0.11	2.2	1997
a	0.03	0.6	1994
b	12.2	244	1994
	3.2	64	1998
c	0.016	0.32	1994
	0.012	0.24	1995
d	0.0038	0.076	1994
e	0.0099	0.20	1994

[1]Calculated with OPS (operational atmospheric transport model Priority Substances), which is also the air-model in the Technical Guidance Document

[2]Concentrations are strictly related to local plant sites and the ambient background concentration is not included

[3]Same for 1995

[4]Gas-washer installation

4.1.1.4.2 Comparison of inhalatory exposure to fluoride with intake via food and water

To get an impression of the relevance of the actual additional intake of fluoride via air in **Table 4.4** an overview is given of the fluoride exposure via food and drinking water.

The fluoride intake by adults from food and drinking-water has been estimated in several studies. In **Table 4.4** estimations of the average daily intake of inorganic fluoride via food and water are given for low and high fluoride areas with drinking water containing 400 μg F/l and about 1000 μg F/l, respectively. In the Netherlands where the drinking water is not fluoridated, fluoride drinking water levels range from 1180 - 5640 μg/l (Slooff *et al*. 1988).

Table 4.4 Fluoride exposure through food and water

Reference	Intake (low fluoride area) mg F/day	Intake (high fluoride area) μg F/day
WHO/IPCS (1984)	430 - 910	990 - 5400
CEPA (1993)	2212 -	- 3981

The concentration of 0.048 mg F/day for both the measured and calculated PEC-values (see **Tables 4.2** and **4.3**) rounded to 50 μg F/day is used as a realistic worst case situation of inhalatory exposure to fluoride of the population at large.

With respect to the intake via food and water the highest value of 5640 μg F/day has been taken into account as a worst case situation (see **Table 4.5**).

Human intake of fluoride may also include iatrogenic sources. Dental products that contain fluoride, such as toothpaste have been identified as significant sources of inorganic fluoride (CTEF 1995). It is assumed that 10% of toothpaste is ingested. At a daily consumption of 2.25 g of toothpaste, the ingested fluoride amounts to 0.2 - 0.3 mg F/day (Slooff *et al*. 1988). For the comparison 300 μg F/day is used.

The estimates for the total human fluoride exposure via all routes in fluoridated and non-fluoridated areas is given in **Table 4.5**.

Table 4.5 Estimates of total daily fluoride intake of adults

Route	Intake (μg F^-/day)
Food & drinking water	5640
Air (HF)	50
Toothpaste	300
Total intake	5990

From the data in **Table 4.5** it is concluded that HF contribution to total daily fluoride intake is negligible.

4.1.1.5 Combined exposure

See section 4.4.3.4

4.1.2 Effect assessment

4.1.2.1 Toxicokinetics, metabolism, and distribution

This section of the document is primarily concerned with the hazards associated with exposure to HF rather than exposure to inorganic fluoride. However, it should be noted that in studies aiming at the description of kinetic aspects of fluoride or HF it is always the F^- ion which is finally determined, usually by ion-selective electrodes or incidentally by highly sophisticated systems like flame-ionisation chromatography. None of these methods can discriminate between the nature of the original source of the determined fluoride.

Kinetics of fluoride have been extensively reviewed (e.g. WHO 1984; Thiessen 1988).

Absorption of any inorganic fluoride is thought to be a passive process. Inorganic fluoride of any source is thought to be transported across biological membranes primarily as molecular (non-ionic thus uncharged) HF. At physiological pH (in blood, intercellular fluid, mucus) free fluoride (thus not associated with e.g. proteins or lipids) exists primarily as fluoride ion (F^-); only 0.01% of the total free fluoride concentration exists as molecular HF in equilibrium with the ionic form (Anonymus 1996). The fate or effects of absorbed inorganic fluoride are independent of the fluoride source (Thiessen 1988).

Absorption

Inhalation

Experiments in which rats were head-only exposed to HF gas, demonstrated that over 99% of the inhaled HF does not reach the lungs but is rapidly absorbed via the lining of the upper respiratory tract. A linear relationship was observed between the HF concentration to which the rats were exposed and the plasma fluoride level. The virtually complete absorption of HF in the upper airways was determined in an experiment in which HF contents of the inhaled air was analyzed via an endotracheal tube (Morris, Smith 1982). Inhalatory uptake of fluoride has also been observed in humans and rabbits (Dinman 1976; Kirk-Othmer 1980; Largent 1960). For instance, human volunteers who breathed 1.16 to 3.9 mg HF/m^3 for period of 15 to 30 days excreted F^- in their urine in average daily amounts of 3.44 to 19.9 mg over the entire period of exposure. Lund *et al*. exposed human volunteers for 1 hour to constant concentrations of HF, ranging from 0.2 to 5.2 mg HF/m^3. From 0.7 mg/m^3 upwards, a linear relationship between exposure and increase in plasma fluoride levels was observed. Maximum plasma levels (ca. 18-80 ng/ml) were seen at 60 to 120 minutes after the start of the exposure (Lund *et al*. 1997).

Dermal

Dermal uptake of F^- from liquid HF in humans has been reported by Burke *et al*. (1973). A man, accidentally exposed to about 5 g of HF excreted 404 mg F^- in the urine over the first three days following the accident (Burke *et al*. 1973). From the reported data it is impossible to quantify the rate of absorption of HF after dermal exposure.

In rats which were dermally exposed to 2% HF (2 ml/kg b.w., under occlusion) in water for 1 or 4 hr, serum fluoride reached levels 3 to 6 times (0.78 - 1.42 mg/l) above the level in the controls (0.25 mg/l) at one hour after the exposure. The serum levels increased with exposure time and decreased to near normal values over the next 96 hr (Derenlanko *et al*. 1985).

Oral

Oral uptake of HF has not been studied. However, because of the rapid absorption of fluoride from the gastro-intestinal tract, it is conceivable that HF will be rapidly absorbed after oral administration (Wallace-Durbin 1954; Van Asten *et al*. 1996). The absorption of orally administered fluoride depends on the presence of fluoride-binding cations such as calcium, magnesium and especially aluminium (CEPA 1993; Janssen 1989; WHO 1984) and on the formulation of the fluoride [e.g. in pharmaceutical preparations (Van Asten *et al*. 1996)].

Distribution

After uptake fluoride is transported in the blood. 75% of the total blood fluoride concentration is present in the plasma; the remainder is associated with the red blood cells. About 50% of the fluoride in serum is bound to organic molecules, mainly in perfluoro-fatty acids (WHO 1984) and thus in a non-ionic form.

Fluoride distributes throughout all soft tissues, without particular accumulation in one of these. It may also cross the placenta and reach the unborn child. Sequestration of fluoride occurs in bone and teeth, in which it is incorporated into the mineral structures by exchange with hydroxyl groups. About half of the absorbed fluoride is deposited into bone structure. However, in younger humans and in the elderly, bone fluoride uptake is higher than in mid-age persons. Fluoride levels in plasma and in bone have been shown to be directly correlated to the level of exposure. (Morris, Smith 1982; WHO 1984; NTP 1990; Maurer *et al*. 1990; Maurer *et al*. 1993).

Elimination

The major route for excretion of fluoride is via the urine. In animals and humans excretion into urine occurs through the glomerular filtration after which reabsorption in the form of HF may occur in the renal tubules, especially after decreased urinary acidity. Minor routes of excretion are via faeces, saliva (partial re-absorption after ingestion) and perspiration. Excretion via the milk is no relevant route of elimination (Thiessen 1988).

In humans plasma half-lives of 2 to 9 hr have been reported (WHO 1984). Because soft tissue fluoride levels are in equilibrium with plasma levels for these tissues similar half-lives may be assumed. After cessation of exposure, fluoride in bone will be released and eliminated from the body. In humans the half-live for bone fluoride is reported to be in the range of 8 to 20 years. (WHO 1984).

Conclusion

Inhaled gaseous hydrogen fluoride is virtually completely absorbed in the upper airways. The extent of absorption via the dermal route cannot be specified. Fluoride from any inorganic source is absorbed as HF and circulates in the body as F^- or as organically bound fluoride. The distribution of this ion and its route of excretion do not depend on the way via which it enters the body. After oral, inhalatory or dermal exposure to HF, fluoride can be found in all tissues in the

body. Sequestration takes place in bone tissue in which about half of the absorbed fluoride is deposited. Secretion is mainly via the urine. In humans half-lives are in the range of 2 to 9 hr for plasma and in the range of 8 to 20 years for fluoride in bone deposits.

Remark

Although the form of fluoride to which one is exposed may influence the amount of fluoride which finally reaches the systemic circulation, the form of fluoride which circulates within the body is not dependent on the fluoride species one has contacted (e.g. Van Asten *et al*. 1996). Thus when data gaps for systemic effects are established for HF, these data gaps may be filled, using experimental results of other inorganic fluorides, even if these were administered via a route other than inhalation. Toxicity data on other inorganic fluorides will only be used for the hazard assessment of HF, when base set required data for HF are not available.

4.1.2.2 Acute toxicity

Animal studies

Several studies have been carried out with different species and with inhalatory and dermal exposure. The most relevant studies with inhalatory exposure to HF are summarised in **Table 4.6**.

Table 4.6 Acute inhalatory toxicity of Hydrgen Fluoride

Species	Protocol[1]	Results
mouse	other	1 hr LC_{50}: 279 mg HF/m^3 (Wohlslagel *et al*. 1976)
rat	other; GLP	1 hr LC_{50}: 1828-1909 mg HF/m^3 (Valentine 1990)
rat	other	1 hr LC_{50}: 1069 mg HF/m^3 (Rosenholtz *et al*. 1963)
rat	other	1 hr LC_{50}: 792 mg HF/m^3 (Vernot *et al*. 1977; MacEwan and Vernot 1976)
rat	other	1 hr LC_{50}: 1138 mg HF/m^3 (Wohlslagel *et al*. 1976)
guinea pig	other	15 min LC_{50}: 3540 mg HF/m^3 (Rosenholtz *et al*. 1963)
rhesus monkey	other	60 min LC_{50}: 1470 mg/m^3 (Darmer KI *et al*. 1972)

[1]For details see HEDSET

LC_{50} values for inhalatory exposure to HF are about 279 mg/m^3 (Wohlslagel *et al*. 1976) in mice and about 817 to 1900 mg/m^3 in rats after exposure for 1 hr (Valentine 1990; Rosenholtz *et al*. 1963; Wohlslagel *et al*. 1976; Vernot *et al*. 1977; MacEwan and Vernot 1976). In the mouse study signs of toxicity were eye and mucous membrane irritation, corneal opacity, skin erythema and respiratory distress, pulmonary edema and haemorrhage were observed at necropsy. In rats severe damage to the upper respiratory tract, respiratory distress, ocular and nasal discharge, corneal opacity and weight loss were observed. Dermal corrosion (necrotic lesions of nose face and ears) were commonly seen. Upon pathological examination, pulmonary congestion, intra-alveolar edema and thymic haemorrhage were seen as well. Irritation to the eyes and nose, body weight loss and respiratory distress were toxic effects observed in guinea pigs, histopathology was not performed (Rosenholtz *et al*. 1963). In rhesus monkeys an LC_{50} of 1470 mg/m^3 was determined after 60 minutes of exposure, further details were not reported (Darmer *et al*. 1972).

In rats, besides damage at the site of application, dermal application resulted in decreases in spontaneous ventilation and movement, tremor, loss of co-ordination, loss of righting reflex and death. Blood analysis showed a marked decrease in serum Ca levels and an increase in parathyroid hormone, as a result of dermal uptake of F^-. Simultaneously hyponatremia, hyperkalemia, an increase in serum phosphorus, a decrease in serum alkaline phosphatase accompanied by bradycardia were found. The authors stated that a dermal HF burn of only 1.7% of the total skin surface may result in fluoride poisoning and disturbances of calcium and other electrolyte homeostasis. Dermal application of 0.5 ml of a 50% HF solution for 5 min to rats (approx. 900 mg HF/kg b.w.) resulted in 80% mortality (Kono *et al*. 1982; Kono *et al*. 1988).

Human data

Fatalities with HF have occurred after accidental contact. Next to dermal contact in these cases inhalation of HF fumes will have occurred. In these studies severe dermal lesions and damage to the respiratory tract and lungs were reported (Kleinfeld 1965; Irving Sax 1984). It was noted that blood fluoride levels were comparable to those observed after fatal ingestion of fluorides (Greendyke, Hodge 1964).

In two human volunteers, exposure to HF for periods of several minutes or shorter caused mild smarting in the nose and eyes and respiratory tract irritation at concentrations of 26 mg/m^3. At 50 mg/m^3 marked conjunctival and nasal mucosae irritation occurred, while at 100 mg/m^3 also pain in the exposed skin was experienced with marked conjunctival and respiratory irritation. Indications of severe damage to the respiratory system were also reported in other studies (Machle *et al.* 1934).

Conclusion

The inhalatory 1 hr LC_{50} of HF amounts to about 280 mg/m^3 in mice and to 817 to 1900 mg/m^3 in rats. Oral and dermal LD_{50}s cannot be derived. Inhalatory and dermal exposure to HF may result in severe damage to eyes and airway epithelia and to damage to the skin. Systemic F^- results in disturbances in Ca and other electrolyte homeostasis and in cardiac arrhythmias.

In humans, dermal contact with HF either liquid or gaseous produces severe dermal lesions. Dermal contact with HF may result in systemic (cardiac) effects eventually resulting in death. Inhalatory exposure may damage the respiratory tract.

According to the EU guidelines HF is classified as Very Toxic (T^+);
R-phrases 26/27/28: very toxic by inhalation, in contact with skin and if swallowed.

Although studies were not performed according to OECD or EU guidelines, the rapporteur considers the studies submitted to have sufficient quality to allow for a proper evaluation of acute toxicity.

4.1.2.3 Irritation

Animal studies

Dermal

Severe damage to the skin (erythema, edema, blistering and coagulative necrosis down to the dermal muscular junction) was found in rats after application of 50 µl of a 70% solution of HF to the shaved skin for 60 s. The wound healed over the next 35 to 56 days (Bracken *et al.* 1985).

In rabbits, application of 2 ml/kg b.w. of a 2% solution of HF in water (approx. 40 mg HF/kg b.w.) to the shaved back skin for 1 or 4 hours under occlusive conditions results in severe dermal changes. No damage to the skin was seen at 2% applied for 1 min. Exposure to 2 ml/kg of solutions of 0.01, 0.1, 0.5 or 2% HF under similar conditions for 5 to 60 min all caused dermal lesions, which are considered to be related to contact with HF. However, at the lower end of the exposure range the dose-response relationship was rather weak. Additionally, at the highest dose level (for 1 or 4 hours) organ weights were determined and histological examination was carried out. The only effect observed was a reduced testes weight (40%) as compared to controls after 4 hours of exposure (observation time: 96 h after exposure). This reduction of testes weight was not associated with significant microscopic alterations (Derenlanko *et al*. 1985).

Skin irritation and corrosivity of HF has been studied in a test performed according to OECD Guideline 404. Application of 5 ml of a 5% solution to the rabbit's skin under a semi-occlusive patch for 4 h followed by a washing produced marked eschar formation and destruction of the underlying tissue, 24 hr after the exposure period. The lesions did not recover within the next 14 days. The lesions resulted in a Draize score of 4 in 2/3 animals (Bayer AG 1990).

No corrosivity or irritation of HF was observed when it was applied to the rabbit's skin in concentrations of 0.13 or 1.06% in a quantity of 0.5 ml for 4 h under semi-occlusive conditions (Thyssen and Lorke 1980).

Ocular

Eye irritation has been investigated in two studies in which HF solutions of 0.13 or 1.06% (Thyssen and Lorke 1980) or HF solutions from 0.5 up to 20% (McCulley *et al*. 1983) were administered in the rabbit's eye. A dose of 100 µl of an aqueous solution of 1.06%, but not 0.13% HF, caused corneal opacity, iritis, conjunctival oedema and redness (Thyssen and Lorke 1980). A solution of 20% (quantity unknown) causes immediate and extensive ocular damage (McCulley *et al*. 1983).

Inhalatory

In an Alarie test according to ASTM E981 (Schorsch 1995) six groups of 4 mice were exposed (nose and mouth, only) for 30 minutes to HF in concentrations of 30, 80, 170, 180, 190 and 250 mg/m^3 in air. From the time courses of the respiration rate an RD_{50} (for respiratory depression) of 110 mg/m^3 was computed. Despite several inconsistencies in the report, it was stated that the test was performed according to GLP.

In another Alarie-test (ICI 1990), an RD_{50} (for respiratory depression) of 151 ppm (123 mg/m^3) was computed after inhalatory exposure of mice to gaseous HF in concentrations of 78 to 172 ppm. However, a full report of this test does not exist.

Human data

In patients exposed to HF, causing second and third degree skin burns in approx. 2.5% of the body surface, plasma fluoride levels less than 300 µg/100 ml were seen. Changes in electrocardiograms were reported, which were reversible within three days after exposure (Burke et al. 1973).

In patients who came into contact with HF via the skin, skin burns may develop several days after the exposure, although severe pain is experienced shortly after exposure, already. These burns show a whitish discolouration after an erythematous stage, followed by rapid tissue destruction and necrosis. HF-wounds tend to heal very slowly (Moeschlin 1980; Irving Sax 1984). Van de Laar *et al*. (1994) reported 19 cases of people involved in various activities such as cleaning of walls and tiles, metal surfaces and cars, usually in some occupational setting. The cleaning agents contained 35 to 350 g HF/l. In most cases, dermal contact was on hands or fingers. Symptoms similar to the ones described above were reported. In two of the agents with low HF content (35 and 48 g/l) also other acids (phosphorus or nitric acid) were present, while in a third low HF formulation 50 g/l was present. However, the symptoms associated with HF-contact were seen in all cases (Van de Laar *et al*. 1994).

Lund *et al*. (1997) exposed human volunteers for 1 hour to constant concentrations of HF, ranging from 0.2 - 0.6 mg/m^3 (n = 9), 0.7 - 2.4 mg/m^3 (n = 7) and 2.5 - 5.2 mg HF/m^3 (n = 7). The following parameters were monitored by means of a questionnaire: eyes and upper airways (itching and soreness) and upper airways (chest tightness, soreness, expectoration, coughing and wheezing). Lung function was determined by measuring forced vital capacity (FVC), forced respiratory volume in 1 second (FEV_1) with a spirometer according to a European standardized method. HF concentration of ≥2.5 mg/m^3 resulted in increased symptoms scores of the upper airways (nose and throat). Significant increases in lower airways scores (chest tightness, soreness, coughing, expectoration and wheezing) were not observed. Lung function parameters (FVC and FEV_1) were not dose relatedly affected by exposure to HF (Lund *et al*. 1997). Almost all symptoms had disappeared four hours after the end of exposure.

Conclusion

When applied to the skin or the eye, HF produces severe lesions, even at low concentrations. According to EU guidelines HF is classified as corrosive (C); R-phrase: R35: causes severe burns. One dermal irritation study was performed according to OECD guidelines and no test according to OECD- or EU- guidelines for eye irritation has been submitted. However, the rapporteur considers the submitted data set to have sufficient quality to allow a proper evaluation of irritation and/or corrosivity of HF to skin or eyes. In mice, exposure to HF in a concentration of 110-123 mg/m^3 results in a respiratory depression of 50%. This range of exposure values was derived from two tests according to Alarie.

Like in animals, in humans dermal contact with HF causes second and third degree skin burns. Severe pain is experienced shortly after exposure, already and these burns tend to heal very slowly. After dermal exposure to HF, changes in electrocardiograms were reported, which were reversible within three days after exposure. Largent *et al*. (see 4.1.2.6: human data) found some irritation of eyes, skin and nasal mucosa at average HF concentration as low as 1.16 mg/m^3. In a study with human volunteers by Lund *et al*. (1997) increased upper airway symptoms (itching, soreness) were observed after one hour of exposure at 2.5 mg/m^3 and above.

Remark

It should be noted that in the studies mentioned under 4.1.2.2 "acute toxicity" severe damage to the skin was found when HF was applied dermally, too. Similarly, after inhalatory exposure extensive damage was found in the respiratory tract, especially in the nasal mucosa. In these studies, eye damage was found, similar to that observed after direct application of HF solutions to the eye.

In humans an amount of about 5 g anhydrous HF, causing second and third degree skin burns in approx. 2.5% of the body surface, will result in plasma fluoride levels less than 300 μg/100 ml but even these were though to be high enough to result in a life-threatening systemic intoxication (Burke *et al.* 1973).

Comparison of the ocular effects of HF with those observed after application of equivalent solutions of sodium fluoride, potassium fluoride or hydrogen chloride (pH equal to 8% HF) suggests that the severity of eye burns caused by HF depends on both pH and the toxicity of the F^--ion. Initial damage to the eye as a result of the acidity of HF facilitates the penetration F^- to the deeper tissue layers (McCulley *et al*. 1983) in which F^- produces severe lesions. The same may be true for skin damage (Derenlanko *et al*. 1985).

4.1.2.4 Corrosivity

Corrosivity of HF has been discussed under 4.1.2.3: Irritation.

Conclusion

It is concluded that HF is corrosive to skin and eyes. For classification see under 4.1.2.3: Irritation.

4.1.2.5 Sensitisation

Sensitisation studies with HF either with animals or with humans are not available.

Conclusion

A sensitisation test was not submitted, although such a test is a base-set requirement. It was argued that an assessment of skin sensitisation potential could only be done at relatively low concentrations, at which practical experience with humans has shown no indication of sensitising potential. Although such experience is in general unsuitable to demonstrate the absence of a sensitising potential and data were not available to the rapporteurs, either, its is agreed that no sensitisation test need to be performed. Physico-chemical properties of HF or F^- indicate that it is reasonable to assume that this substance is not sensitising.

Furthermore, both Dutch legislation and international guidelines recommend not to perform experiments which would provoke extreme distress and pain by corroding effects of the test substance and which would most probably result in the intercurrent death or killing of the animals for reasons of humanity. Additionally it is generally accepted that gross lesions, as are indicated by the corrosive properties of a compound, alter the physiological state of the test animal and thus affects any other biological activity.

4.1.2.6 Repeated dose toxicity

Only inhalatory studies are available.

Animal data

The results of the most reliable studies are summarised in **Table 4.7**.

Table 4.7 Repeated dose toxicity

Repeated dose toxicity	Species	Protocol	Results
Inhalatory	Rat	other: concentrations of 0 and 1 mg HF/m³; 6 hr/d; daily for 1 month	at 1 mg/m³ changes in dental enamel, airways; formation of irregular shaped bone cavities (Sadilova *et al.* 1974)
	Rat	like OECD 413; GLP; concentrations of 0, 0.082, 0.816 and 8.16 mg HF/m³; 6 hr/d; 5 d/wk; 91 days	nominal NOAEL 0.816 mg/m³ (actual value 0.72 mg/m³) clinical (incl. dental malocclusions) and haematological signs including death and body and organ weight changes at 8.16 mg/m³. (Placke and Griffin 1991)

Daily exposure of rats for 5 hr/d for 3 months to 1.6 µg HF/m^3 resulted in histological and/or histochemical changes in liver, lungs, heart or stomach. However, these changes were not properly reported and therefore impossible to interpret, especially with respect to quantitative aspects. Therefore, this study is not taken into account for the overall effect assessment of HF (Humiczewska *et al.* 1989).

Exposure of female rats of various age to 1 mg HF/m^3 for 1 months, 6 hr/d resulted in damage to the dental enamel. This effect was especially seen in young animals and in animals of 17.6 to 18.6 months of age. The respiratory organs of the young animals showed atrophy and local oedema of the bronchial mucosa, whereas airways in the older animals showed peribronchial hyperplasia. In animals of about 12 months formation of irregular shaped cavities in their bones was observed (Sadilova *et al*. 1974). Other tissues were not evaluated.

Study (Placke *et al*. 1990) is a range-finding test for study (Placke and Griffin 1991). This study was performed according to GLP standards. Inhalatory exposure of rats (both sexes) to 0, 0.816, 8.16, 20.4, 53.0 and 82 mg HF/m^3 (nominal values; actual values were 0, 0.816, 7.06, 17.78, 53.04 and 93 mg/m^3, respectively) for 6 hr/d and 5 d/wk for 14 days resulted in death of all female animals at 20.4 mg/m^3 and above and of all male animals exposed to 53.0 mg/m^3 and higher (Placke *et al*. 1990). At the lower levels of exposure no death occurred. At 0.816, and higher body weight changes and/or changes in absolute or relative organ weights (liver, heart, kidney, lungs) were reported as well as clinical signs of discomfort and nasal and ocular mucosal irritation. Dermal crust formation, ocular opacity and tremors were also observed.

In a 91 days subchronic study (Placke and Griffin 1991), also performed according to GLP with similarity to OECD 413 guideline, female and male rats (20/group) were exposed to 0, 0.082, 0.816 and 8.16 mg HF/m^3 (nominal concentrations; actual concentrations were: 0, 0.098, 0.72 and 7.52 mg/m^3, respectively) for 6 hours/d, 5 days/week.

Observations included clinical signs, body weight, organ weights of liver, kidneys, testes, ovaries, adrenals, heart, spleen, brain and lungs, haematology, blood biochemistry and complete

histopathology. In contrast to the range-finding study, death (five males, one female) was observed in the 8.16 mg/m^3 group. Clinical signs in this group were red-coloured discharge from eyes and nose, ruffled fur, alopecia and hunched posture. Body weights were depressed and in 9 males and 2 females dental malocclusions were observed. Increases in number of segmented neutrophils was seen in the high dose male group. Platelets were increased in the high dose males. Mid and high dose group males showed decreased numbers of lymphocytes and RBC were depressed in high dose males and females. Biochemistry showed decreased serum glucose in the high dose males. Additionally, decreases were seen in serum albumin (high dose males and females), A/G -ratio (mid and high dose males), and increases were seen in K^+ and P in both males and females of the high dose groups. Relative organs weights of kidneys, liver, lung, testes, spleen, brain, heart and adrenals were increased at the highest dose. Histopathological changes were not found. The decreases in serum A/G-ratio and lymphocytes in the male mid-dose group are too small to have a biological significance and are therefore not considered as adverse effects. Thus the NOAEL in this study is 0.72 mg/m^3 (actual value).

Human data

Volunteer studies

Largent *et al*. (1960) exposed 5 human volunteer to gaseous HF for 6 hr/d in concentrations ranging from 0.9 to 2 ppm (0.74 to 1.64 mg/m^3) for 15 days to 2.7 to 8.1 ppm (2.21 to 6.64 mg/m^3) for 50 days. Each individual was exposed to HF according to his or her own personal exposure schedule (time as well as concentrations). Systemic effects of any kind were not observed, but some discomfort in the form of a slight stinging sensation in eyes and facial skin and in slight irritation of the nasal mucosa were reported. No other effect was noted when the concentration of HF did not exceed 2 ppm (1.64 mg/m^3). At concentrations of 3.39 ppm (average concentration for ten days; 2.78 mg/m^3) and above, erythema and desquamation of the superficial epithelium of the facial skin were observed. Symptoms of discomfort disappeared after cessation of the exposure; while skin redness persisted only for a short time (Largent *et al*. 1960).

The results of this study have also been discussed in another journal (Largent *et al*. 1961), in which it was stated that an average concentration of 1.42 ppm was tolerated without noticeable effects. Because these two reports (Largent *et al*. 1960) and (Largent *et al*. 1961) are somewhat contradictory it is assumed, for safety sake, that at the lowest exposure level (0.74 to 1.64 mg/m^3; on average 1.16 mg/m^3 = 1.42 ppm) still some effects were observed.

Epidemiological data

Bearing in mind the equivalence of HF and other inorganic fluorides with respect to systemic toxicity, as discussed in the section on kinetics (see 4.1.2.1) in the following paragraphs the relevant studies on HF and an overview of the epidemiology on NaF are presented.

Exposure to HF

At an average occupational exposure to 1.03 ppm HF (0.82 mg/m^3) no alterations in pulmonary function were observed and no increase in respiratory complaints was noted among workers exposed to HF concentrations below 2.5 mg/m^3. However, HF induced a minimal increase in bone density after exposure to less than 4.3 ppm (3.5 mg/m^3; ACGIH 1984).

A number of studies on the epidemiology of skeletal fluorosis, occurring either after oral or inhalatory exposure to fluoride (F^- or other fluor-containing substances, among which HF), has been reviewed (CEPA 1993; ATSDR 1993). An early (pre-clinical) symptom in humans is an increase in bone mass. Sporadic pain and joint stiffness, chronic joint pain, osteosclerosis of cancellous bone, calcification of ligaments are symptoms of first and second clinical stages while in stage 3 limited movement of joints, skeletal deformities, intense calcification of ligaments, muscle wasting and neurological deficits are manifest (CEPA 1993: ATSDR 1993).

A marginally elevated occurrence of fluoride-induced osteosclerosis was observed in workers exposed to 2.5 mg/m^3 (duration corrected value: 600 μg/m^3; equivalent to approximately 170 μg/kg b.w./d in a 70 kg adult; Hodge and Smith 1970, Hodge and Smith 1977 cited in Slooff et al. 1988).

Chan-Yueng *et al*. (1983) studied health effects in 2066 workers in an aluminium smelter. The cohort comprised high and medium exposed potroom workers as well as low-exposed controls and a miscellaneous group. For each group exposure to particulate and gaseous fluoride and urinary fluoride excretion were determined. The number of workers in each group and the levels of exposure are presented in the table below:

Table 4.8 Exposure levels to workers

Group	Number exposed	Average total airborne fluoride (mg/m^3)	Average gaseous fluoride (mg/m^3)	Average particulate fluoride (mg/m^3)
controls	880	0.053	0.015	0.038
potroom/high	570	0.48	0.20	0.28
potroom/medium	332	0.12	0.057	0.062
miscellaneous	284	0.46	0.054	0.41

In addition an external control group of 372 railway repair workers was studied. Observations included musculoskeletal complaints and surgery, spine and sacroiliac joint examination, pelvic X-rays, urinary fluoride and blood haemoglobin, haematocrit, white cell count, total bilirubin, alkaline phosphatase, sASAT, total protein, BUN, creatinine, Ca^{2+} and phosphate. No overt signs of skeletal fluorosis were observed in workers exposed up to 0.48 mg F^-/m^3 (0.2 mg/m^3 for gaseous F^- and 0.28 mg/m^3 for fluoride dust) for up to ten years (duration corrected value: 114.2 μg/m^3; equivalent to 33 μg/kg b.w./d). The relevant blood biochemistry parameters did not indicate occurrence of hepatic or renal effects. Changes in haemoglobin and haematocrit and calcium, though (statistically) significant, were within the normal biological range. Serum calcium but not phosphate was increased in the highest exposure group (9.71 ± 0.44 mg% Ca^{2+} vs 9.62 ± 0.42 mg% in the controls). The changes in the respective blood parameters were considered of little relevance. Therefore, it is concluded that no overt signs of skeletal fluorosis or renal, hepatic or haematological effects were observed in workers exposed to 0.48 mg (total) fluoride/m^3 for up to ten years.

In a parallel study in the same aluminium smelter, as in the above study (Chan-Yeung *et al*. 1983), Chan-Yueng *et al*. (1983) reported on the association between working in potrooms and respiratory performance. The following respiratory parameters were studied: FEV_1[5], FVC,

[5] FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, $FEF_{25-75\%}$ = maximum mid-expiratory flow rate

$FEF_{25-75\%}$, chest X-ray and chest symptoms (cough, phlegm, wheeze, dyspnea, chronic bronchitis). 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 potrooms, n = 495), a medium exposed group (<50% of the working time in the potrooms, n = 302) and a control group (office and casting personnel, n = 713). The air in the smelter was analysed for the following contaminants by personal sampling devices:

Table 4.9 Concentrations of air contaminants in an aluminium smelter *(data taken from Chan-Yueng et al. 1983)*

Air contaminant	Potroom workers	Control workers
Particulate matter	3.55 ± 2.26 (n=22)*	1.45 ± 5.11 (n=33)
Fluoride		
total	0.48 ± 0.35 (n=1157)	0.05 ± 0.12 (n=102)
gaseous	0.20 ± 0.17	0.02 ± 0.03
particulate	0.28 ± 0.03	0.04 ± 0.1
Carbon monoxide	11.43 ± 5.49 (n=47)	6.23 ± 2.95 (n=45)
Sulfur dioxide	2.15 ± 1.66 (n=121)	0.54 ± 0.74 (n=29)
Benzo-[a]-pyrene	3.49 ± 7.11 µg/m³ (n=69)	0.16 ± 0.29 µg/m³ (n=4)

*Values are mean ± standard deviation of n samples. Units are mg/m³ unless stated otherwise

High exposure workers showed a statistically significant decrease in FEV_1 and $FEF_{25-75\%}$ with 2 and 5%, respectively and the incidence of cough and wheeze were statistically significant increased in the high exposure group by each 7% as compared to control workers. No changes in FVC were observed. The medium exposure group did not statistically deviate from the control group. Comparison of pre- and post shift respiratory parameters showed a similar decline in both control and high exposure workers. Most Chest X-radiographs were normal. Abnormalities (e.g. signs of previous pulmonary tuberculosis) did not show an association with any of the worker groups.

As potroom workers were exposed to several airway irritants at the same time, a definite conclusion about the cause of the changes cannot be drawn. Possibly, the effects are caused by the combined action of the air contaminants determined.

Exposure to NaF

Riggs *et al*. (1990) carried out a randomised placebo-controlled, double-blind clinical trial in postmenopausal osteoporotic women. At an average dose level of 0.48 mg F^-/kg b.w./d, administered orally as sodium fluoride for four years, an increase in the rate of non-vertebral bone fractures and a decrease in cortical bone density were observed. However, although an increase in cancellous bone density was seen, only an insignificant trend towards a decrease in the rate of vertebral bone fractures was found. Treated women reported significantly more side effects (gastric irritation, pain in lower extremities) than untreated women. Although well performed, this study may not be completely indicative for the risk of fluorosis resulting from

oral administration of fluoride, because bone and calcium homeostasis, and thus sensitivity to fluoride, may differ from that in non-osteoporotic persons.

CEPA (1993) cited various ecological studies in which the effects of fluoride intake via drinking water were investigated. According to this review, severe skeletal fluorosis has been reported in humans after prolonged intake of 15 mg/day (215 µg/kg b.w. day in an adult weighing 70 kg) and above. In one case, exposure to drinking water containing 8 mg/l fluoride for 37 years resulted in fluoride-induced bone changes, but not in clinical signs. In a community exposed to 4 mg fluoride/l in the drinking water (estimated to be equivalent to 72 µg/kg b.w/d) the relative risk for various bone fractures was 2.2 to 2.7 as compared to an "unexposed" control community which received 1 mg/l (Sowers *et al.* 1986). However, with respect to the latter study, CEPA (1993) stated that exposure in the high fluoride community was probably underestimated, while the calcium concentration in the drinking water of this community was about only 25% of that in the control group.

Other aspects

Numerous studies in the USA and in Europe have shown that a certain level of fluoride consumption, especially when it is continuous from earliest childhood, affords considerable protection for both permanent and milk teeth against carries, without exerting any unfavourable influence on the appearance of the teeth or on the periodontium. Fluoride is usually offered by the fluoridation of drinking water (about 1 mg F^-/l) or by fluoride dentifrices (Wagner *et al*. 1993).

Fluoride continues to deposit into the calcified structures after the other constituents of bone have already reached a steady state. Thus the major constituents - calcium, phosphorus, magnesium, carbonate, citrate - reach their maximum concentration early in life and remain essentially unchanged, even after administration of large amounts of the ion in question. Fluoride, on the other hand, showed a tenfold increase in bone following ingestion of drinking water with fluoride concentrations of <1.0 up to 4 mg/l. Calcification of bone is preceded by a nucleation process in the early deposition of calcium and phosphorus on the chief organic matrix of bone and collagen to form the mineral phase, generically called hydroxyapatite or $Ca_{10}(PO_4)_6(OH)_2$. The hydroxyl groups of apatite in calcified structures may be partially or completely substituted isomorphically by fluoride. Thus mixed crystals of hydroxyapatite and fluorapatite may be present (Wagner *et al*. 1993).

Conclusion

The available animal data set for HF permits the derivation of a NOAEL for repeated sub-chronic inhalatory exposure. No suitable studies are available for HF, for other routes of exposure. The over-all NOAEL for repeated inhalatory exposure is taken from the 91-day GLP study with female and male rats and amounts 0.72 mg HF/m^3 (actual value) for a 6 h per d 5 d per week exposure regimen. At this exposure no adverse effects were observed. At the next exposure level death, tissue irritation, dental malformations, haematological and biological changes and changes in several organ weights were observed.

Like in animals, in humans prolonged intake of fluoride results in skeletal fluorosis, an effect for which indications were found after both oral and inhalatory exposure.

Skeletal effects have been reported in some but not all studies of workers in aluminium plants who were exposed to levels of airborne inorganic fluoride considerably higher than those in the

general environment. Based on consideration of the collective data available from studies involving aluminium smelter workers, Hodge and Smith (Hodge and Smith 1970) concluded that the occurrence of fluoride induced osteosclerosis was elevated if workers were exposed to levels of airborne fluoride greater than 2.5 mg/m^3. In a more recent cohort study with workers in an aluminium smelter no overt signs of skeletal fluorosis or renal, hepatic or haematological effects were observed after exposure to 0.48 mg (total of which 0.20 mg gaseous and 0.28 mg particulate) fluoride/m^3 for up to 10 years. In a parallel study in the same plant signs of airway irritation were observed at the same exposure level, but this effect may have been caused by other (than HF) airway irritants as well.

In humans exposure to 1.16 mg HF/m^3 for 6 hr/d may result in some discomfort in the form of a slight stinging sensation in eyes and facial skin and in slight irritation of the nasal mucosa. This concentration can be considered as a LOAEL for inhalatory exposure.

Beneficial effects

There are indications that fluoride is an essential nutrient, which in any case plays a role in the dentition and the development of the skeleton, but conclusive evidence is still lacking. The question whether fluoride is an essential element cannot be satisfactorily answered because attempts to develop a diet which is sufficiently low in fluoride are hampered by the widespread occurrence of fluorides in dietary ingredients. The essentiality of fluoride can only be determined if such a low fluoride diet is available (Slooff *et al*. 1988, WHO 1984; National Academy of Sciences 1971).

Beneficial effects (prevention of dental carries, particularly in children) after low fluoride intake have been observed. On the other hand, excessive fluoride intake can cause dental fluorosis (dental lesions) and osteofluorosis (bone structural changes) as described above (Slooff *et al*. 1988).

Remark

It should be noted that many of the epidemiological studies (ecological or cohort studies) provide limited insight in actual exposure to fluoride via nutrition and other routes and that confounding factors (e.g. interfering exposure to other substances, extent of physical labour) are usually poorly characterised. The clinical studies focused on beneficial effects of fluoride, rather than adversity (cf. ref CEPA 1993).

4.1.2.7 Mutagenicity

With HF only a limited number of genotoxicity tests is available (see **Table 4.10**).

Table 4.10 Genotoxicity of Hydrogen Fluoride

Genetic toxicity		Species/system	Protocol	Results
4.1.2.7	***In vitro***			
	gene mutations (Ames)	Salmonella typhymurium	other[1]; GLP	negative; with and without S9 (Bayer AG 1987)
	In vivo			
	cytogenic effects	rat	other[1]	positive increase in chromosomal aberrations (predominantly hyperploidy) (Voroshilin *et al.* 1975)
	dominant lethality	mouse	other[1]	inconclusive; improperly reported (Voroshilin *et al.* 1975)
	SLRL test	Drosophila melanogaster	other[1]	reduced fertility in F1 after HF-exposure of F0; inconclusive (Gerdes *et al.* 1971; Gerdes 1970; Gerdes 1971)
	RL test	Drosophila melanogaster	other[1]	reduced viability of F2 homozygous for chromosome II after HF-exposure of F0; inconclusive (Mohamed 1971)

[1]See HEDSET for full description of the protocol

In vitro tests

An Ames test with HF, performed according to GLP, provided negative results (Bayer AG 1987).

In vivo tests

The *in vivo* tests with HF are either chromosomal aberration tests (Voroshilin *et al*. 1975; Zeiger *et al* 1994) or tests which may reveal the genesis of inheritable defects. The test for chromosomal aberrations in rats (Voroshilin *et al*. 1975) was positive, especially in older animals. It demonstrated that HF may induce hyperploidy. However, deletions were not counted. The dominant lethal test with mice (Voroshilin *et al*. 1975) could not be interpreted because of poor description of methodology and results.

HF was shown to induce sex-linked recessive lethality in *Drosophila melanogaster*, but the tests were not properly reported and their significance cannot be evaluated (Gerdes *et al*. 1971; Gerdes 1970; Gerdes 1971.

In another test (Mohamed 1971) HF was shown to reduce the viability in F2-offspring of *Drosophila melanogaster* when these were homozygous for chromosome II. The results of this test cannot be interpreted in terms of genotoxicity.

The data set on genotoxicity of HF is limited. Therefore it is difficult to reach a conclusion on the genotoxicity of this substance. However, because in toxicity tests, whether *in vivo* or *in vitro*, HF will reach its possible targets only as (partly organically bound) F^-, studies with other inorganic fluoride, such as NaF, will provide insight in fluoride genotoxicity also applicable for HF. This has been treated in the section on the kinetics of fluoride (see 4.1.2.1). Some representative mutagenicity assays with NaF have been summarised in **Table 4.11**.

In vitro tests

An Ames test with sodium fluoride did not reveal a potential of the fluoride ion to induce gene mutations (NTP 1990).

In *in vitro* tests with eukaryotic cell systems, sodium fluoride has shown a potency to induce gene mutations (NTP 1990) and chromosomal aberrations (NTP 1990; Tsutsui *et al*. 1984; Aardema *et al*. 1989; Aardema *et al*. 1989; Khalil 1995) as well as sister chromatid exchanges (NTP 1990) and DNA-repair (Tsutsui et *al.* 1984; Tsutsui *et al*. 1984). The substance was negative in a test for chromosome aberrations in human fibroblasts (Tsutsui *et al*. 1995). In four studies (Tsutsui *et al*. 1984; Aardema *et al*. 1989; Aardema *et al*. 1989; Khalil 1995) information was provided as to the nature of the aberrations. Especially gaps, breaks and deletions were observed.

Table 4.11 Genotoxicity of Sodium Fluoride

Genetic toxicity		Species/system	Protocol[1]	Results
	In vitro			
	gene mutations (Ames)	Salmonella typhymurium	other	negative; with and without S9 (NTP 1990)
	gene mutations	Mouse lymphoma assay	other	positive; with and without S9 (NTP 1990)
	SCE-test	CHO-cells	other	positive; with and without S9 (NTP 1990)
	UDS-test	human oral keratinocytes	other	positive; without activation (Tsutsui et *al.* 1984)
	UDS-test	human fibroblasts	other	positive; without activation (Tsutsui *et al*. 1984)
	chromosomal aberrations	human fibroblasts	other	positive; without activation (Tsutsui *et al*. 1984)
	chromosomal aberrations	CHO-cells	other	positive; with and without S9 (NTP 1990)
	chromosomal aberrations	CHO-cells	other	positive; with and without S9 (Aardema *et al*. 1989)
	chromosome aberrations	bone marrow cells	other	positive; without activation (Khalil 1995)
	chromosome aberrations	human fibroblasts	other	negative; without activation (Tsutsui *et al*. 1995)
	In vivo			
	cytogenic effects	mouse	other	negative for micronuclei in erythrocytes and for chromosome aberrations in bone marrow (Zeiger *et al* 1994)

[1]For "other" see details in HEDSET

In vivo tests

Zeiger *et al*. (1994) have exposed mice to NaF in their drinking water for 1 or 6 weeks, in a well-performed test for chromosomal aberrations. At 200 and 400 mg/l reduced body weight gain was observed, while in the 400 mg/l group several animals died, as well. Erythrocytes and other bone marrow cells were analysed for micronuclei or chromosomal aberrations. No indications for cytogenetic action of fluoride were obtained.

Jackson *et al*. (1994) found no increase in number of SCEs in a case-control study with osteoporotic women receiving as therapy 23 mg elemental F/d on average for approximately 18 months.

Additionally, the results of various other mutagenicity tests with fluoride have been reviewed (Li *et al*. 1988). These authors discussed the outcome of positive and negative *in vitro* and *in vivo* tests and reached the conclusion that no firm statement could be made as to the genotoxicity of fluoride. More recently, Zeiger *et al*. (1993) re-evaluated old and new literature data and concluded that the information as to fluoride's genotoxicity *in vivo* is still too incomplete to reach a final decision. It was further mentioned that in a number of *in vivo* tests, in which anaphase cells were studied positive results for cytogenic effects were obtained, while in tests studying metaphase cells no positive results were found. To their opinion (Zeiger *et al*. 1993), especially information is needed about the underlying mechanisms of action and the way F^- might have interacted in the *in vitro* studies with DNA and/or with DNA related proteins, enzymes or other cellular systems (Zeiger *et al*. 1993). It has been argued that genotoxicity in *in vitro* test systems occurs at levels above 4.5 mg F^-/l medium, a level which is higher than the steady state concentration found in human plasma and that F^- has no capacity to interact with DNA via a direct mechanism (Janssen and Knaap 1994).

Conclusion

The test results show that HF and NaF are both negative in a bacterial test system. In eukaryotic systems *in vitro* NaF induces SCE, UDS and chromosomal aberrations at levels of 4.5 mg F^-/l and above. Four *in vivo* tests with HF are available in which genotoxicity was studied. However, these four tests are inconclusive as a result of poor reporting or invalidated tests system. For reasons of similarity of toxicokinetics, there is no need to perform additional *in vivo* mutagenicity tests with HF because a well-performed *in vivo* assay with NaF is available. This test showed that fluoride did not cause chromosomal damage in mice. However, positive *in vivo* results were scored in anaphase cells, indicating a possible indirect effect. Since it is unlikely that F^- binds to DNA covalently, a prerequisite for DNA-adducts, the DNA damage observed in *in vitro* studies is probably not caused by a direct interaction of fluoride with DNA. It is concluded that inorganic fluoride does not induce chromosomal damage *in vivo*.

Remark

Although the CEPA (1993) recognised that the data on genotoxicity of fluoride are conflicting, it has been stated that fluoride is apparently not genotoxic when administered via an appropriate physiological route (i.e. orally). For inhalatory exposure no data are available but given the fact that fluoride does not interact with DNA in a direct way, it can be concluded that the substance is not genotoxic after inhalatory exposure either.

4.1.2.8 Carcinogenicity

Carcinogenicity studies with HF are not available[6]. Because in carcinogenicity studies HF will reach its possible targets only as (partly organically bound) F^-, studies with other inorganic fluoride, such as NaF, will provide insight in the possible (systemic) carcinogenicity of fluoride in general and thus in the carcinogenicity of HF. This has been treated in the section on the kinetics of fluoride (see 4.1.2.1). Four carcinogenicity studies performed with NaF are available.

[6] IARC (1992) has evaluated the carcinogenicity of mists of strong inorganic acids. From several occupational studies it was concluded that sufficient evidence was available to consider strong-acidic mists containing sulfuric acid to be a human carcinogen. HF was not included in this evaluation. It should be noted that HF is not a strong acid (pKa = 3.5; the pKa values of sulfuric and hydrochloric acid are ≤ 0) and that IARC concluded that for carcinogenicity HCl was not classifiable because of insufficient evidence in both animals and humans. Thus from this IARC evaluation no conclusion can be drawn as to the carcinogenicity of HF.

Animal data

Mice

Mice were exposed to NaF in their drinking water daily for two years in concentrations of 0, 25, 100 or 175 mg/l (NTP 1990). These concentrations were equal to average dose levels of 0, 1.27 , 5.11 and 8.50 mg F^-/kg b.w./d for the females and to 0, 1.08, 4.34 and 7.55 mg F^-/kg b.w./d for the males. The diet contained 8.66 mg F^-/kg (equivalent to 1.23 mg/kg b.w./d). Observations included clinical status, body and organ weights (liver, kidneys and brain at interim sacrifices), urinalysis, haematology, clinical chemistry (limited), and complete histopathology. Teeth showed dose-related discolouration and mottling in all groups including the controls, but at higher incidences and earlier in time in the exposed groups. Dental attrition was enhanced in the 175 mg/l dose groups; in the males slightly more pronounced than in the females. Dentine dysplasia was significantly increased in the 175 mg/l males group. Other non-neoplastic lesions were not found. Some neoplastic lesions (lymphomas, hepatocellular neoplasms, harderian gland adenomas, pituitary adenomas) were seen, but these lesions were either not treatment-related or of no biological significance (NTP 1990).

In a combined toxicity/carcinogenicity diet study, Maurer *et al*. (1993) exposed mice for two years to nominally 0, 4.0, 10, and 25 mg NaF/kg b.w./d (equal to 0, 1.79, 4.43 and 11.17 mg F^- /kg b.w./d, respectively). Through the (low-fluoride) diet the animals received 0.45 mg F^-/kg b.w./d. Observations included clinical status, body and organ weights (extensive) and histopathology (extensive). Dose related changes in teeth were found at 4 mg/kg b.w. and above comprising a.o. fractures, attrition and discolouration, which were accompanied by ameloblast dysplasia, cystic hyperplasia, degeneration and vacuolation. Various skeleton malformations (enostosis, osteosclerosis, hyperostosis) were observed at 10 mg/kg b.w./d and above. Ossification or mineralisation of stifle joints, occasionally together with arthritis were seen in males and females at 10 and 25 mg/kg b.w./d. Soft tissue lesions, though looked for were not reported. The dental and bone lesions were considered to be related to exposure to fluoride. Other changes in relative organ weights or tissues (including testes) were not found, but quantitative data were not provided. Especially in the high dose group an enhanced number of benign osteomas were observed in which a high density of retroviral particles were seen. The authors concluded that with respect to the occurrence of the osteomas the study is inconclusive because the presence of the retroviral infection might have enhanced the genesis of these tumours (Maurer *et al*. 1993).

Rats

Rats were exposed to NaF in their drinking water daily for two years in concentrations of 0, 25, 100 or 175 mg/l (NTP 1990). These concentrations were equal to average dose levels of 0, 0.59, 2.48, 4.29 mg F^-/kg b.w./d for the females and to 0, 0.50, 2.35 and 3.89 mg F^-/kg b.w./d for the males. The diet contained 8.66 mg F^-/kg (equivalent to 0.43 mg/kg b.w./d). Observations included clinical status, body and organ weights (liver, kidneys and brain at interim sacrifices), urinanalysis, haematology, clinical chemistry (limited), and complete histopathology. Teeth showed whitish discolouration and mottling with increasing incidences from 25 mg/l. At 100 mg/l and higher these colour changes were accompanied by dental attrition, deformities and malocclusion. In males at 25 mg/l and higher and in females at 100 mg/l and above increases in dentine dysplasia and ameloblast and odontoblast degeneration were found. The effects were more pronounced in male animals. In the females of the 175 mg/l group an increased incidence in osteosclerosis was observed. In male animals osteosarcomas were observed with incidences of 0/80, 0/51 1/50 and 3/80 in the 0, 25, 100 and 175 mg/l groups, respectively. Osteosarcomas

were not reported for the females. The authors considered the results equivocal with respect to the carcinogenic potential of NaF. No other indications for the formation of neoplastic lesions were obtained; neither were other treatment-related lesions found (NTP 1990).

In a combined toxicity/carcinogenicity study, Maurer *et al*. (1990) exposed rats for two years to 0, 4.0, 10, and 25 mg NaF/kg b.w./d (equal to 0, 1.81, 4.52 and 11.24 mg F^- /kg b.w./d, respectively). Through the (low-fluoride) diet the animals received 0.16 mg F^-/kg b.w./d. Observations included clinical status, body and organ weights (extensive) and histopathology (extensive), clinical chemistry (not specified), and urinalysis (not specified). Dental aberrations (ameloblast dysplasia and enamel hypoplasia) were dose-relatedly increased in all groups. Dental fractures and malocclusions were enhanced at 10 and 25 mg/kg b.w./d. The females were no less sensitive than the males. Subperiosteal hyperostosis was observed in particular in the bones of the skulls of males at 10 mg/kg b.w./d and above. In the females this effect was less pronounced. Relative and absolute stomach weight were significantly increased at 10 mg/kg b.w./d and above. Mononuclear cell infiltration of the glandular epithelium was dose-relatedly increased from 4 mg/kg b.w./d in the male and from 10 mg/kg in the females. Chronic inflammation and regeneration of the glandular mucosa occurred in the males at 10 mg/kg and above. In the females these effects were seen at 4 mg/kg and above and at 25 mg/kg b.w. respectively. In 24 other tissues (including testes) no lesions were reported, but quantitative data were not provided. In some animals neoplastic bone lesions were seen (sarcoma, osteosarcoma,chordoma, chondroma) but these lesions were incidental and randomly distributed among the groups. In the stomach of one control male a papilloma was found. Other soft tissue neoplasms were not reported in detail but it was stated that "there was no evidence that fluoride altered the incidence of preneoplastic and neoplastic lesions at sites of fluoride toxicity or at any other site in rats of either sex" (Maurer *et al*. 1990).

Human data

Based on epidemiological data IARC (1982) concluded that the evidence for carcinogenicity of orally taken fluoride in humans is inadequate. Several organisations have reviewed ecological studies into a relationship between oral exposure to fluoride (via fluoridated drinking water) and cancer mortality in humans. No reliable evidence of an association between consumption of fluoridated drinking water and increased incidence of mortality due to cancer could be established (CEPA 1993; Janssen and Knaap 1994). US-EPA, reviewing the epidemiological data for fluoride, stated that no conclusion can be drawn as to the carcinogenicity of fluoride after inhalatory exposure, because in all studies available, humans were exposed to other substances as well (Thiessen 1988).

Conclusion

Carcinogenicity studies, in which HF has been tested, are not available[7]. Studies with NaF may provide insight in the carcinogenicity of HF, especially for systemic tumours. With the latter substance 4 animal studies have been performed, 2 in which NaF was supplied in the drinking water to rats and mice, and two in which NaF was administered via the diet, again to rats and mice.

In the rat drinking water study, equivocal indications for osteosarcomas in males were obtained, but the rat diet study was negative, despite clear indications of fluoride intoxication. The mouse

[7] IARC (1992) has evaluated the carcinogenicity of mists of strong inorganic acids. From this IARC evaluation no conclusion can be drawn with respect to the inhalatory carcinogenicity of HF.

drinking water study was also negative. The mouse diet study was confounded by the presence of a retrovirus which may have (co)-induced the growth of benign osteomas thus thwarting the interpretation of the study. In the diet studies (Maurer *et al*. 1990; Maurer *et al*. 1993) bone fluoride levels were higher than in the drinking water studies (NTP 1990), while in the diet studies no indications for osteosarcomas were obtained. Furthermore, the osteomas were considered to be reminiscent of hyperplasias rather than true bone neoplasms. It was concluded that the available data is sufficient to suggest that fluoride is not a carcinogenic substance in animals (Janssen and Knaap 1994).

Based on epidemiological data IARC (1982) concluded that the evidence for carcinogenicity of orally taken fluoride in humans is inadequate. Recent studies (cited in CEPA 1993; Janssen and Knaap 1994) did not supply evidence of a relationship between fluoride in drinking water and cancer mortality, either. US-EPA, reviewing the epidemiological data for fluoride, stated that no conclusion can be drawn as to the carcinogenicity of fluoride after inhalatory exposure, because in all studies available, humans were exposed to other substances as well (Thiessen 1988).

Remark

It is especially noted that in none of the animal carcinogenicity studies effects on morphology of any of the reproductive organs were found.

4.1.2.9 Toxicity for reproduction

No reproduction studies are available for HF. However, effects on reproduction are systemic and HF occurs in the systemic circulation only as free ionic or as organically bound fluoride rather than as HF or NaF. This has been treated in the section on the kinetics of fluoride (see 4.1.2.1). Data on NaF that provide insight in the reproductive toxicity of fluoride may, therefore, also provide insight in the reproductive toxicity of HF.

Animal data

Studies with respect to reproduction and development/teratogenicity with NaF are summarised in **Table 4.12**.

Table 4.12 Reproductive and developmental toxicity

Reproduction & developmental toxicity		Species	Protocol	Results
4.1.2.9	A: fertility studies oral	mouse	Other; dose levels 0, 10, 20 mg NaF/kg b.w. for 30days	LOAEL; 10 mg NaF/kg b.w. (~4.52 mg F^-/kg b.w.); Reversible decreased sperm motility and sperm count and infertility. Abnormal sperm morphology. (Chinoy and Sequeira 1992) LOAEL; 10 mg NaF/kg b.w. (~4.52 mg F^-/kg b.w.); Reversible histological changes in testis, epididymis and vas deferens. (Chinoy and Sequeira 1989)
		rat	Other; dose levels 0, 100, 200 mg F^-/kg diet for 60 days	LOAEL: 100 mg F^-/kg; (~5 mg F^-/kg b.w./d) dental fluorotic lesions, changes in seminiferous tubules. decreased serum testosterone levels n.s, trend in decreased average litter size, (Araibi *et al* 1989)
		rat	Other; dose levels: 0, 5 and 10 mg NaF/kg b.w. /d for 30 days.	LOAEL : 5 mg/kg b.w./d (~2.26 mg F^-/kg b.w.) reduction of fertility, decreased sperm counts and motility, biochemical changes in testes, epididymis and prostate. (Chinoy *et al*. 1991)
		rabbit	Other; dose level 0, 20 and 40 mg NaF/kg b.w./d for 30 days	LOAEL: 20 mg NaF/kg b.w./d (9 mg F^-/kg b.w.); count, biochemical, morphological, numerical and motility changes in sperm cells. Irreversible loss of fertility. (Chinoy *et al*. 1992)
	B: generation studies	rat	Similar to OECD 416; dose level 0, 25, 100, 175 and 250 mg NaF/l.	NOAEL: 250 mg NaF/l; highest dose tested estimated to be about 10 mg F^-/kg b.w./d in adults. (Collins *et al*. 2001a, 2001b)
		rat	Other; dose level 0, 25, 100, 175 and 250 mg NaF/l.	NOAEL: 250 mg NaF/l; highest dose tested estimated to be about 10 mg F^-/kg b.w./d in adults. (Sprando *et al*. 1997, 1998; sub-study of Collins *et al*. 2001a, 2001b with special attention for male fertility)
		rat	Other; dose level 0, 25, 100, 175 and 250 mg NaF/l.	NOAEL: 250 mg NaF/l; highest dose tested estimated to be about 10 mg F^-/kg b.w./d in adults. (Sprando *et al*. 1997)
	C: embryo- and fetotoxicity/ teratogenicity studies	rat	Similar to OECD-414; 0, 50, 150 and 300 mg NaF/l drinking water from days 6 - 15 of gestation.	NOAEL for maternal effects: 150 mg NaF/l (~ 8.4 mg F^-/kg b.w./d). NOAEL for developmental effects: 300 mg NaF/l (~12.3 mg F^-/kg b.w./d) (Heindel *et al*. 1996)
		rat	Similar to OECD-414; 0, 10, 25, 100, 175 and 250 mg NaF/l drinking water daily throughout gestation	NOAEL for maternal toxicity and developmental effects: 175 mg NaF/l (~11.12 mg F^-/kg b.w./d) (Collins *et al*. 1995)
		rabbit	Similar to OECD-414; 0, 100, 200, and 400 mg NaF/l drinking water daily from days 6 - 19 of gestation	NOAEL for maternal effects: 200 mg NaF/l (~ 8.2 mg F^-/kg b.w./d. NOAEL for developmental effects: 400 mg NaF/l (~13.2 mg F^-/kg b.w./d) (Heindel *et al*. 1996)

Effects on male fertility

Chinoy *et al*. (1989; 1991; 1992 ; 1992) studied the effects of fluoride on the testes of mice, rats and rabbits with respect to reproductive impairment. In none of these studies the F^--content of the control diet was stated.

Male Swiss mice were exposed to 0, 10 and 20 mg NaF/kg b.w. (~ 4.52 or 9.05 mg F^-/kg b.w.) by gavage for 30 days. Observations included morphology and histocytometry of all male sex organs, electron microscopic evaluation of sperm cells and a fertility test. Reversible changes in sperm motility and counts and testis (decreased germinal epithelial cell height), epididymis (decreased epithelial cell height and absence or reduction in sperm cells) and histoarchitecture of vas deferens were observed. Sperm cells showed abnormalities in head, midpiece and tail, including deflagelation. No effects were found in seminal vessels and prostate gland. In a fertility test the males showed reversible loss of fertility. The LOAEL in these studies is 10 mg NaF/kg b.w./d (~ 4.52 mg F^- /kg b.w./d) (Chinoy and Sequeira 1992; Chinoy and Sequeira 1989).

Rats were orally dosed with 0, 5 or 10 mg NaF/ kg b.w. for 30 days. Impairment of fertility with decreased sperm motility and counts were seen at both exposure levels. Testicular succinate dehydrogenase was diminished in both exposure groups. The concentration of sialic acid as well as ATP-ase levels in both caput and caudal epididymis were lowered in the treated animals. At 10 mg/kg acid phosphatase and protein were increased in the ventral prostate. The LOAEL in this study is 5 mg NaF/kg b.w. ~ 2.26 mg F^-/kg b.w.) (Chinoy *et al*. 1991).

Rabbits received 0, 20 and 40 mg NaF/kg b.w./d for 30 days via the diet and were subsequently mated with untreated females. A satellite group receiving 40 mg NaF/kg b.w./d for 30 days was withdrawn from treatment and kept for another month. After 30 days of exposure, body weights were decreased in all dose groups. A complete loss of fertility was seen at 40 mg/kg b.w. and at 20 mg/kg a 70% reduction of fertility rate was found. This was accompanied by reduced sperm counts and motility at both dose levels. Decreases in seminal ATP-ase, succinate dehydrogenase, acid phosphatase, total protein Na^+ and K^+ levels were seen at both dose levels. None of the parameters returned to normal values after the period of recovery. The LOAEL in this studies is 20 mg NaF/kg b.w./d (~ 9.05 mg F^-/kg b.w.) (Chinoy *et al*. 1992).

Araibi *et al*. (1989) administered fluoride (as NaF) via the diet at levels of 0, 100 and 200 mg/kg to groups of male rats for 60 days. Serum testosterone levels, testes histology and male fertility were determined at the end of the study. Peritubular membrane thickness of seminiferous tubules, and relative numbers of sperm cell containing sperm tubes were significantly reduced at 200 mg/kg, while mean seminiferous tubular diameter was decreased in both exposure groups. At the highest dose numbers of pregnant females and newborns were reduced and a tendency to a decreased average litter size was observed at both levels. Serum testosterone was decreased at 200 mg/kg. The authors did not clearly state whether the fluoride levels in the food were calculated as free fluoride ion or as NaF. If it is assumed that the dose levels refer to F^- the LOAEL in this study is 100 mg F^-/kg feed (~5 mg F^-/kg b.w./d). The study was poorly reported and the F^--content of the control diet was not stated.

Shusheela and Kumar (1991) dosed male rabbits with 0 or 10 mg NaF/kg b.w./d for 18 or 29 months. Seven animals/group were killed after 18 months and the remaining 3 animals after 29 months of exposure. Testis, caput epididymis and vas deferens were examined by light and electron microscopy. After 29 months the spermatogenic cells in the seminiferous tubules were

disrupted, degenerated and devoid of spermatozoa. After 18 as well as after 29 months in the epididymis and vas deferens effects on the epithelial cilial cells were observed. The F^--content of the control diet was not stated. It is hard to believe that up to the 18th month of the experiment no effects were observed (in 7 animals) and that from month 18 through 29 spermatogenesis has ceased (as determined in three animals). Given the low number of animals and the rather time pattern of the changes, no credibility can be attached to this finding.

In the light of the above mentioned fertility studies, the US-FDA studied the effects of intratesticular injections of NaF (Sprando *et al*. 1996). The study was of proper design. Sodium fluoride (0, 50, 175 or 250 µg/µl) dissolved in saline, was injected once (50 µl/injection) in the left testicle. These levels were equivalent to 0, 0.71, 3.1 and 3.53 mg F^-/g testes tissue. The right testicle served as an intact control. Tissues were collected 24 h and 1, 2 and 3 weeks after treatment. Data on fluoride contents of the feed were not provided. According to the authors the exposure to the highest amount of injected fluoride was at least 100 times greater than that under normal conditions.

Observations included testis and epididymal weights, various morphological aspects of interstitial tissue, seminiferous tubules, Sertoli and germ cells, spermacytogenesis and meiosis. The only effects observed were signs of mechanical damage and occasional leucocyte infiltration which were related to the injections themselves rather than the exposure to fluoride. Other effects on testes morphology or on spermiogenesis were not seen. Although the study may indicate that direct exposure of testicular tissue to fluoride has no pronounced effect on testis morphology and sperm quality, is results cannot be interpreted in terms of safe or unsafe oral exposure to sodium fluoride, because extrapolation from direct testicular dosing to oral exposure is impossible.

Generation studies

In a 2-generation study female mice receiving 0, 50, 100 or 200 mg F^-/l as NaF in their drinking water were mated with untreated males. Control diet contained 0.1 to 0.3 mg F^-/kg. In the control group a progressive decline in litter production with successive litters occurred in both generations. By 6 weeks of exposure 50% of the females had died in the highest dose group and by week 17 of exposure all females in this group had succumbed. Also in the 100 mg/l dose group only nine litters were born over a 10 weeks period. Although the study is performed according to a limited design, it suggests that 50 mg F^-/l (approximately 7.5 mg F^-/kg b.w./d) is more adequate to maintain reproductive capacity than the low fluoride control diet without extra fluoride in the drinking water (Messer *et al*. 1973).

In a 3-generation study female mice of the first generation were orally exposed to 0 and 2 mg F^-/kg diet as NaF, equivalent to 0 and 0.3 mg F^-/kg b.w./d, respectively and mated with untreated males. The second and third generation females received 0, 2 and 100 mg F^-/kg diet. The control diet contained less than 0.5 mg F^-/kg. Relevant observations included among others, growth, reproductive response, litter size, pup weight and incidence of stillbirth. No compound-related effects on reproduction were observed. With respect to reproductive toxicity of fluoride, the protocol of this study is considered incomplete and an occurring kidney infection may have disturbed the sensitivity of the test. Therefore this study is not taken into account in the over-all assessment (Tao and Suttie 1976).

Aulerich *et al*. (1987) fed mink (6/sex/group) for 4.5 months up to 1 year diets to which 0, 33, 60, 108 , 194 or 350 mg F^- (as NaF)/kg were added (equivalent to 0, 8, 15, 27, 50 or 90 mg F^-/kg b.w.). After 4.5 months 5 male animals per group were sacrificed and in the high dose group brittle

skull bones were observed. After another 3.5 months females were mated with the one male belonging to their respective dose group. In the control and low dose group 80 and 50% of the females became pregnant, while in the other dose groups all of the females became pregnant. No substance-related effects on mean litter size, mean kit body weight at birth and kit growth were observed, but at 6 weeks post-partum in the high-dose group decreased pup survival (down to 14%) was seen. Female animals were kept until 382 days of age, after which in the high dose group only one animal survived. Survival in the other groups was not affected by fluoride exposure. In several females of the high dose group enlarged or deformed sagittal crests were noticed. Serum alkaline phosphatase was increased at 108 mg/kg and significantly increased at 194 mg/kg. (The one remaining female in the 350 mg/kg group had elevated alkaline phosphatase as well). Urinary fluoride was increased in all dose groups and bone fluoride was increased from 60 mg/kg onwards (both parameters dose related). Dental mottling, broken canine teeth and exostosis of jaws were observed in kits from the 194 and 350 mg/kg groups (Aulerich *et al*. 1987). The study is considered too incomplete for derivation of an overall NOAEL.

US-FDA has performed a two-generation study in rats in which NaF was administered via the drinking water. The results of this study have been published in four different papers, two by Collins *et al.* (2001a, 2001b) in which attention is paid to the conventional end points of such a study, and two by Sprando *et al.* (1997, 1998) in which attention is paid to the results of special incvestigations into the functionality of the sex organs of the males that were used in this two generation study. These four papers are discussed below in chronological order.

In a two-generation study in rats NaF was administered via the drinking water.at concentrations of 0 (<0.2), 25, 100, 175 and 250 mg NaF/l (Sprando *et al*. , 1997). Based on the reported average body weights of the adult P_0 males and an assumed daily water intake of 50 ml/d these concentrations are equivalent to approximately 0, 1.1, 4.4, 7.5 and 10 mg F^-/kg b.w./d, respectively. The low fluoride diet contained 7.95 mg F^-/kg (equivalent to 0.4 mg/kg b.w./d). Twenty-two days old P_0 males and females (Sprague-Dawley rats 12/sex/group) received fluoride for about 14 weeks (10 weeks pre-mating, 3 weeks mating and 1 week post-mating periods) and pregnant P_0-females continued to be exposed until the end of lactation. The F_1 generation remained within the same treatment groups as their parents. F_1 animals received F^- *in utero*, via lactation and via the drinking water to approximately 14 weeks after weaning. In the male rats the following parameters were monitored (both P_0 and F_1 generations): testes weight and histology (Leydig cell morphology, composition of interstitial cell population, seminiferous tubule morphology, Sertoli cell morphology, spermatid development), homogenisation-resistant spermatid counts, sperm cell production and production rate (per gram of testis tissue), secondary sex organ weights, serum LH, FSH and testosterone concentrations, body, liver, spleen, heart and adrenal weights. Only isolated statistical differences in various organ weights between treated and control groups or between P_0 and F_1 generations were observed. These differences were not treatment related and do not indicate toxicologically relevant effects. Testicular histological examination did not reveal any abnormalities. The NOAEL for effects on male reproductive organs and cells in this study is 250 mg NaF/l which is equivalent to approximately about 10 mg F^-/kg b.w./d.

In an additional paper (Sprando *et al*, 1998) the authors described the results of an electronmicroscopical morphometric analysis of testicular tissue of F1 generation males (5/group). The animals were taken from the same experiment as described above.

Seminiferous tubules comprised 89%, 87%, 88%, 88% and 88% of the total testis volume while the interstitial space occupied 9.3%, 11.2%, 10.2%, 9.8% and 9.9% of the total testis volume for

the 0, 25, 100, 175 and 250 mg NaF/l treatment groups, respectively. Statistically significant differences between control and NaF-treated rats were not observed with respect to absolute volume of the seminiferous tubules, interstitial space, Leydig cells, blood vessels boundary layer, lymphatic space, macrophages, tubular lumen or absolute tubular length and absolute tubular surface area, mean Sertoli cell nucleoli number per tubular cross-section, mean seminiferous tubule diameter and the mean height of the seminiferous epithelium. A statistically significant decrease in the absolute volume and volume percent of the lymphatic endothelium was observed in the 175 and 250 ppm NaF-treated groups and in the testicular capsule in the 100 ppm NaF-treated groups. The significance of this finding is unknown at the present time. Overall, the quantitative information obtained suggests that exposure to NaF at the doses used in the present study does not adversely affect testis structure or spermatogenesis in the rat.

A two-generation study according to a randomized design, with mating protocol and treatment in compliance with the OECD-416 guideline, performed under GLP, has been reported by Collins *et al.* (2001a). For the P generation, 48 rats per sex (strain: CD CRL:CD-BR) were assigned to groups receiving 0 (<0.2 mg F^-/l), 25, 100, 175 or 250 mg NaF/l via the drinking water. The animals were kept on a low fluoride diet containing 7.95 mg F^-/kg.

P animals were treated for 10 weeks before mating and subsequently mated (1:1) within each group until either pregnancy was determined by the presence of a sperm plug or for three consecutive weeks. After the mating P males were transferred to a follow up study for effects on the male reproductive system (see Sprando *et al.* (1997, 1998)). At day 20 of gestation 8 P females of each group were sacrificed. These dams and their offspring were examined in a separate study (Collins *et al.* 2001b). The remaining dams were allowed to litter. On postnatal day 4 the litters were culled to 10 pups per group by random procedure. The F1 animals remained within their respective treatment groups and at postnatal day 21, 36 F1 animals from each sex were randomly selected for further breeding. These F1 animals were kept for another 10 weeks and subsequently mated according to the same procedure as the P animals. At gestation day 20, F1 females were sacrificed and dams and their fertility and offspring was examined.

The following observations were made:

- feed and drinking water consumption, clinical observations, and growth and development in and F1 animals,
- pathology: 10 males and females from each group (P generation, F1 weanlings, F1 adults) gross lesions, body weights, organ weights of 14 tissues (among which male sex organs and ovaries), histopathology of 41 tissues in all animals and in addition histopathology of 17 extra tissues in the animals of the control and highest dose groups,
- reproductive performance: date of birth, litter size, mating-, gestation-, fertility- and viability-indices pup survival. Indicators for embryo/foetal toxicity and effects on foetal development (both skeletal and visceral) were reported separately (Collins *et al.* 2001b).

No dose-related clinical effects were observed. During the 10-week periods before mating, P males in the highest dose group consumed statistically significant less feed than the control P males. In the F1 females a negative dose-related trend in feed consumption was seen, but statistical significance was not reached. In the same period, P and F1 males and females consumed less drinking water than the control animals, possibly due to decreased drinking water palatability. P females and males showed a negative dose-related trend in body weight gain, but only in the males of the 250 mg/l group the reduction in body weight gain became statistically

significant. No effects on body weights were observed in the F1 animals. Absolute and relative organ weights of any of the organs studied were not affected.

F1 males and F1 females showed dose-related and statistically significant mild dental whitening at 100, 175 and 250 mg NaF/l but not at 25 mg NaF/l. Dental staining or mottling was not observed. In the 250 mg/l dose group, in all adult males and females of the P and F1 generations and in 8 female and 10 male F1 weanlings, an increase in the development of prominent growth lines (basophilic lines in dentin and dental enamel) was observed. In the same exposure group, dentin deposition in de pulpal cavity was observed in one P male and one P female and in four F1 males. Hyperkeratosis of the limiting ridge of the forestomach was observed in one P male and three P females of 100 mg/l group, in one P male of the 175 mg/l group, in one P male of the 250 mg/l group and in two F1 males and two F1 females of the 250 mg/l group.

No effects were observed on any of the following parameters indicative for reproductive performance or pup viability: mating index, fertility index, time to mating, and for the F1 generation number of implants, litter size, number of stillborn pups per litter, and pup survival and lactation indices. Runts were randomly distributed among control and treatment groups.

For the detection of developmental toxicity 8 pregnant P dams per group were sacrificed and their offspring was examined for gross appearance (Collins *et al.* 2001b). For each treatment group, 29 to 34 pregnant F1 dams were sacrificed and their offspring was studied extensively for skeletal and visceral abnormalities.

Neither in the 8 P dams nor in the F1 dams clinical signs of toxicity were observed during gestation. In the P dams and in the F1 dams at 100 mg/l and above a reduced average intake of drinking water was observed, which reached statistical significance in the P dams at 250 mg/l and in the F1 dams at 175 and 250 mg/l. Although in all treatment groups in both generations a reduced feed intake was observed, this effect showed no dose-response relationship. No dose response relationship was observed in body weight gain during pregnancy or in gravid uterine weight.

In both P and F1 generations, no effects were observed on female fertility parameters, or on parameters indicative for embryo- or foetotoxicity. Foetal body weights and lengths were not affected. No gross external malformations in the offspring of both generations were observed.

Upon examination for skeletal defects, in the offspring of the F1 dams no effects were observed with respect to sternebral variations. An increased incidence of retarded ossification of the hyoid bone in the 250 mg/l group was observed when the data were analysed on a total number of pups basis, but not on a per litter basis. In none of the other skeletal elements any indication for retarded ossification due to treatment with NaF was observed. No irreversible structural changes, neither in the skeleton nor in the soft tissues were found.

From the study (Collins *et al.* 2001a, 2001b) it can be concluded that no fertility effects occurred in rats exposed to NaF in the drinking water at concentrations up to 250 mg/l. The dose levels (expressed on a mg/kg b.w./d basis) for P and F1 animals were about equal, and based on drinking water consumption data and body weights, the exposure level of 250 mg/l is on average equal to 10.7 mg F^-/kg b.w./d or 12.5 mg F^-/kg b.w./d for males and non-pregnant females respectively. The NOAEL for developmental toxicity in this study is 250 mg NaF/l drinking water, which is equal to 11.7 mg F^-/kg b.w./d for the P generation and equal to 12.7 mg/l for the F1 generation. (dose level representative for the period of gestation).

Embryo-, feto- and developmental toxicity

As part of a more extended study into the kinetics and toxicity of fluoride administered as various salts, pregnant rats received 0, 51, 124 and 200 mg NaF/kg diet (equivalent to 0, 1.13, 2.74 or 4.41 mg F^-/kg b.w./d) from day 1 to day 20 of gestation. Observations with respect to reproduction included number of viable fetuses/litter, fetal and placental weight and resorptions. No effects were observed. This study is incomplete with respect to reproductive toxicity of fluoride because the offspring was not appropriately examined (Theuner *et al* 1971).

In another study, pregnant female rats (20/group) were exposed to 0 or 30 mg F^-/l as NaF (~ 0 or 3.36 mg F^-/kg b.w./d) through day 6-15 of gestation and killed at day 20. It was stated that in a preliminary study with 30, 40 and 50 mg F^-/l no maternal toxicity was observed at 30 mg/l. Observations included maternal weight, verification of fetal life, sex, macroscopic deformities, resorptions, corpora lutea, fetal histopathology and bone malformations. Enhanced numbers of congenital deformities (equimosis, bone formation deficiencies of sternum and skull bones) and runts were observed. The histological examination were reported to be normal, but specification about techniques and tissues were not given. The LOAEL in this study is 30 mg F^-/l (~ 3.36 mg/kg b.w./d. (Larez *et al* 1980). The study is inadequately reported and maternal toxicity was tested in an indirect way (no effect on maternal weight change in a pilot study). The relevance of the effect denoted by the term "equimosis" cannot be assessed.

Collins *et al*. (1995) have investigated the oral developmental toxicity of NaF in rats in an assay similar to OECD-414. The substance was administered via the drinking water (ultra pure) in concentrations of 0, 10, 25, 100, 175 and 250 mg NaF/l, daily throughout gestation. Groups of 33 to 37 females were mated with untreated males. Actual dose levels were 0, 0.63, 1.76, 7.06, 11.12 and 11.35 mg F^-/kg b.w. All animals received a low fluoride diet containing 7.95 mg F^-/kg feed which results in an additional exposure to approximately 0.6 F^- mg/kg b.w./d.

The observations included maternal toxicity (behavioral and clinical signs including dental mottling, feed and drinking water intake, body weight) and toxicity in the off-spring (numbers of live and dead foetuses, implantations, resorptions, numbers of corpora lutea, sex, weight, external examination, skeletal abnormalities and soft tissue abberations).

Clinical signs of toxicity in the dams were not seen, but at the highest two dose levels drinking water consumption and at the highest dose level feed intake were diminished. At 250 mg/l dams showed reduced growth. At the highest level of exposure, a slight reduction in corpora lutea, and number of implants per dam were seen but these observations were no effect of fluoride. No signs of retarded foetal development were obtained. At the highest dose level a limited but statistically significant increase in the number of foetuses with skeletal variations was found. The number of litters affected was not significantly increased. Thus this study did not reveal relevant reproductive or developmental toxicity resulting from fluoride at dose levels up to 250 mg/l. At this level maternal toxicity was observed. The NOAEL for maternal toxicity and developmental effects in this study is 11.12 mg F^-/kg b.w./d. (Collins *et al*. 1995).

In another study by NTP, similar to OECD-414, sodium fluoride was administered via the drinking water to rabbits and rats.

Groups of 26 female rats received 0 (≤0.6), 50, 150 or 300 mg NaF/l in deionised water from day 6 through day 15 of gestation. The feed contained about 12.4 mg/kg fluoride (average value). Actual intake of fluoride via the drinking water amounted to ≤0.3, 3.0, 8.4 and 12.3 mg F^-/kg b.w./d. Fluoride in feed resulted in an additional exposure of 1.0 mg F^-/kg b.w./d. With the

highest dose administered the authors aimed at the induction of some maternal toxicity while avoiding dehydration effects due to reduced water intake resulting from bad palatability of NaF solutions. Observations included maternal toxicity (clinical signs, weight gain, water and feed consumption, liver and kidney weights) and toxicity in the offspring (number of litters, corpora lutea, implantation sites, resorptions, late death, live fetuses, fetal body weights, sex ratio, external and skeletal and soft tissue malformations.

The only significant effect on the dams was a reduced water intake in the high dose group during the treatment. No indications for embryo-, feto- or developmental toxicity were obtained. The NOAEL in this study for developmental of fetotoxicity is therefore equal to the highest level tested being 12.3 mg/kg b.w./d (Heindel *et al*. 1996).

In the same study report (Heindel *et al*. 1996), the results of exposure of groups of 26 rabbits to 0 (≤0.6), 100, 200 and 400 mg NaF/l in the drinking water for day 6 through 19 of gestation have been described. Exposure via the drinking water amounted to ≤0.1, 4.7, 8.2 and 13.2 mg F^-/kg b.w./d, whereas exposure via food contributed about 0.8 mg F^-/kg b.w./d to the total fluoride intake. As with the rats observations included maternal toxicity (clinical signs, weight gain, water and feed consumption, liver and kidney weights) and toxicity in the offspring (number of litters, corpora lutea, implantation sites, resorptions, late death, live fetuses, fetal body weights, sex ratio, external and skeletal and soft tissue malformations. Dams exposed to the highest fluoride level demonstrated reduced water intake during the exposure period and a reduced feed intake on days 6 through 8 of gestation resulting in a reversible loss of body weight over these days. No (other) signs of maternal toxicity were obtained. Examination of uteri and offspring did not reveal any sign of embryo-, feto- or developmental toxicity. The NOAEL for reproductive effects in this study is therefore 13.2 mg/kg b.w./d (highest level tested).

In a preliminary study, only reported as an abstract, I.P. injection of 0 or 15 mg NaF/kg b.w. in rats (~ 0 or 6.79 mg F^-/kg b.w.) through days 7-14 or days 14-20 of gestation resulted in skeletal malformations and retardations in sternebrae and thoracic vertebrae with increased occurrence of 14^{th} rib. These aberrations were mainly observed in the 14-20 day dose group. Maternal toxicity was not observed. For a proper evaluation, the whole report should be made available. (Horvath 1989).

NaF was intraperitoneally or subcutaneously injected into pregnant rats from days 10 through 18 of gestation. A more or less dose-related increase in the frequency of necrotic placentas and dead fetuses was observed. Even the lowest dose level (1 mg NaF/kg b.w./d; equal to 0.45 mg F^-/kg b.w./d) elicited these effects, which were more pronounced after IP than after SC administration of NaF. Up to 9 mg F^-/kg b.w./d. no maxillo-facial malformations were seen. Other effects were not studied. (Deveto *et al*. 1972).

From the two generation studies by Collins *et al.* (2001a, 2001b; see section generation studies) a NOAEL for developmental toxicity of 250 mg NaF/l drinking water can be derived (highest dose tested).

Human data

A study into the impact of fluoride in drinking water on human fertility showed a decrease in total fertility rate (determined as number of birth per 1000 women) associated with increasing fluoride drinking water concentrations (Freni 1994). However, this epidemiological study was performed at population level, and a causal relationship between fluoride exposure and reduced fertility rate was not demonstrated. Too many confounding factors, which were not taken into

account, may be involved in the association between fluoride intake and the biological phenomenon. This study is unsuitable to derive a NOAEL.

Conclusion

No specific data with respect to the reproductive, developmental or embryo/feto-toxicity of HF have been reported. However, these effects are systemic and thus, because of similar kinetics and dynamics, data on sodium fluoride are used to give insight in the reproductive toxicity of HF.

Human data on reproductive toxicity of fluoride are inconclusive.

The available information from repeated dose toxicity studies as well as reproductive toxicity studies do not indicate a hazard for female reproduction in relation to exposure to fluoride. In several studies indications were obtained that oral exposure to fluoride may damage testicular tissue and reduce male fertility. The LOAEL for these effects was 2.26 mg F^-/kg b.w./d. In a study in which F^- (as NaF) was administered directly into the testes of rats no substance related effects were seen. In another recently completed two-generation study of high quality (US-FDA) which specifically focussed on damage to the male reproductive system, no testicular effects were seen at an exposure level of 250 mg NaF/l (equivalent to about 10 mg F^-/kg b.w./d).

The available results of the long-term studies, the test for the effects of F^- on testes after intratesticular injection and the reports of the two-generation study by US-FDA contradict the results of the tests which indicate that F^- may damage testes tissue.

For the establishment of an overall NOAEL/LOAEL the following considerations are taken into account:

- In all animal studies in which fertility effects were reported, NOAELs could not be found. It cannot be excluded that this is the result of some unknown contaminant.
- In these studies dose levels are generally below back-ground exposure, while concentrations in food or drinking water have not explicitly been determined. Therefore the relevance of the findings is highly questionable.
- These studies are very limited in design and technical realisation and of considerable less quality than the studies performed by US-FDA, their weight of evidence is therefore far less. In contrast, the US-FDA studies are technically well performed according to modern standards, while high maximum dose levels were used, with well-described background fluoride exposure.
- In a dermal irritation study (Derelanko *et al*. 1985) a reduced testes weight (with 40%) was found after 4 hours of exposure to 2% HF (~40 mg HF/kg b.w.) under occlusion (observation time: 96 h after exposure) without significant microscopic alterations, however, dermal lesions were already observed at 0.01 % HF (0.2 mg/kg b.w.).
- In the 90-days inhalatory toxicity test with HF in rats no specific effects on reproductive organs were seen up to the highest level of exposure (7.52 mg/m^3) which roughly corresponds to a systemic daily dose of 0.856 mg F^-/kg b.w.[8]
- In the NaF drinking water carcinogenicity studies by NTP (1990) with rats and mice weights of reproductive organs were not determined. However, at histopathology no effects on testes

[8]Calculated as follows: 0.856 mg/kg bw/d = Cair · t/24 · d/7 · Rr/bw, in which Cair = 7.52 mg/m^3, t = hours of exposure/day, d = exposure days/week, Rr = respiration rate = 0.223 m^3/d and bw = body weight = 0.35 kg. This calculation assumes 100% inhalatory bioavailability.

or ovaries were observed in these studies. In the NaF diet study on carcinogenicity with mice (Maurer *et al*. 1993) no changes in reproductive organ weights were seen; histopathology data were not available. In an identical study with rats (Maurer *et al*. 1990) neither weight changes nor histological changes of the reproductive organs were seen. (see 4.1.2.8). In none of these studies it was mentioned that sperm characteristics were evaluated.

Consequently, the NOAEL from the US-FDA two-generation study (250 mg NaF/l, equivalent to about 10 mg F^-/kg b.w./d) is used as a NOAEL for effects on fertility.

In the available studies on embryo- and developmental toxicity, some embryotoxicity was observed. From three studies similar to OECD-414, for NaF a NOAEL of 11.12 mg F^-/kg b.w./d for maternal toxicity and developmental effects is established, which was further confirmed in a two-generation study in compliance with the OECD-416 guideline. In this two generation study the observed maternal toxicity, if any, was limited to mild dental whitening, and changes in dentin and enamel structure, next to some hyperkeratosis in the upper gastrointestinal tract.

4.1.3 Risk characterisation

4.1.3.1 General aspects

The human population may be exposed to hydrogen fluoride, and indirectly to fluoride, predominantly at the workplace and indirectly via the environment (sections 4.1.1.1 and 4.1.1.3), but also via consumer products (section 4.1.1.2).

In the data set for HF animal as well as human studies were available. With respect to reproduction toxicity (base set requirement), mutagenicity and carcinogenicity data from studies carried out with sodium fluoride have been taken into account, since these studies provide insight in the possible hazard of fluoride and thus HF as has been explained in the sections on toxicokinetics.

Inhaled gaseous hydrogen fluoride 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. Secretion is mainly via the urine. In humans half-lives are in the range of 2 to 9 hr and in the range of 8 to 20 years for fluoride in plasma and bone deposits, respectively.

In animals HF is very toxic by inhalation, in contact with skin and if swallowed. According to the EU guidelines HF is classified as Very Toxic (T^+). When applied to skin and eye HF produces severe lesions, even at low concentrations. According to EU guidelines HF is classified as corrosive (C).

Signs of acute fluoride intoxication in humans resemble those observed in animals. Dermal contact with HF either as liquid or as gas produces severe dermal lesions. Dermal contact with HF may result in systemic (cardiac) effects including death. Inhalatory exposure is highly damaging to the respiratory tract. Exposure to HF in a concentration of 1.16 mg/m^3 will possibly result in some irritation.

Sensitisation studies with HF are not available. Although such a test is a base-set requirement it was agreed that based on the physico-chemical properties of HF and F^-, it is reasonable to assume that the substance has no sensitising properties.

The available animal data set for HF 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 a study with rats, changes in body and organ weights as well as haematological and clinical signs and death were seen at actual concentrations of 7.52 mg/m^3; 6 hr/d; 5 d/w for 90 days. This value is equal to a duration corrected value (DCV[9]) of 1280 μg/m^3. Based on actual exposure levels a NOAEL of 0.72 mg/m^3 is established. Because at higher dose levels apart from irritation also systemic effects occur, a duration corrected equivalent of this NOAEL is calculated. This duration corrected value (NOAEL) amounts to 128 μg/m^3.

In humans, prolonged oral intake of excess fluoride results in skeletal fluorosis, an effect for which indications were also found after inhalatory exposure. In epidemiological studies with workers exposed to 0.48 mg total fluoride/m^3 (of which 0.2 mg gaseous fluoride) no fluorosis was observed. This level can be considered as an inhalatory NOAEL for fluoride in humans.

The data set on genotoxicity of HF is limited, while carcinogenicity studies with HF are not available[10] at all. However, because in toxicity tests, whether *in vivo* or *in vitro*, HF will reach its possible targets only as (partly organically bound) F^-, studies with other inorganic fluoride, such as NaF, will provide insight in fluoride genotoxicity and carcinogenicity and will also be applicable to HF.

From genotoxicity studies with both HF and NaF, it is concluded that fluoride does not induce chromosomal damage *in vivo*. However, genetic damage is observed in *in vitro* studies.

From carcinogenicity studies with NaF in rats and mice it is concluded that fluoride is not considered to be carcinogenic in animals.

Reproduction studies with HF are not available. In some incomplete studies fluoride (as NaF) has elicited effects on male fertility in mice, rats and rabbits. The LOAEL for these effects was 2.26 mg F^-/kg b.w./d. In a two-generation study (leading to a NOAEL of 250 mg NaF/l; equivalent to about 10 mg F^-/kg b.w./d) and in an intratesticular injection study, fluoride did not induce any sign of impaired testicular functioning. In this two-generation study fluoride did not affect male or female fertility. The NOAEL of about 10 mg/kg b.w./d derived from the two-generation study will be used in the risk assessment.

From three well-performed embryo- and developmental toxicity studies with NaF an overall NOAEL for maternal toxicity and developmental effects of 11.12 mg F^-/kg b.w./d can be derived.

The duration corrected NOAEL of 128 μg/m^3 from the 90 days rat study will be used for the characterisation of the risk of human inhalatory exposure for the population at large.

The NOAEL of 0.48 mg total F/m^3 for systemic effects which was found in an epidemiological study is used as starting point for the occupational risk assessment.

[9] DCV: calculated as: Cair · h / 24 · d / 7; in which h and d are hours of exposure per day (=6) and number of days of exposure per week (=5), respectively

[10] IARC (164) has evaluated the carcinogenicity of mists of strong inorganic acids. From this IARC evaluation no conclusion can be drawn with respect to the inhalatory carcinogenicity of HF

It should be noted that in most studies background exposure to fluoride (e.g. control diet or/and drinking water fluoride level) has not been determined. This is especially problematic in oral studies in which systemic effects were investigated. Basically it would be correct to take this background exposure into account in the risk assessment for fluoride. An appropriate correction can only be carried out when sufficient data on bioavailability and concentrations in animal feed and drinking water are available. Animal feed for routine toxicity testing may contain as much as 20 mg fluoride/kg diet (approx. 1 mg/kg b.w./d). On the other hand, human diet will contain fluoride from natural sources as well. The risk-evaluation for the workers and population at large for systemic effects reflects only the additional risk resulting from exposure to fluoride above oral background. In this approach it is assumed that oral effects of fluoride in the diet are equally likely to occur in humans and in experimental animals.

4.1.3.2 Workers

Assuming that oral exposure is prevented by personal hygienic measures, the risk characterisation for workers is limited to the dermal and respiratory routes of exposure. Furthermore, it is assumed that adequate risk reduction measures are taken to prevent accidental exposure.

For risk characterisation, local effects of HF and systemic effects of the fluoride-ion after uptake of HF should be distinguished. Actually, for risk regarding systemic effects the total intake of F^- should be taken into account, i.e. F^--uptake via food and drinking water and the F^--uptake due to occupational exposure to HF. Data on background levels in the toxicity studies are not always reported. For occupational risk characterisation it is assumed that the impact of oral background uptake of F^- in the studies and for workers are comparable. Therefore, the estimated risk with regard to systemic effects reflects only the additional risk resulting from exposure to HF above oral background levels, unless data are available which allow a refinement (see 4.1.3.0).

Acute toxicity

Because it is generally known that HF is a very toxic and very strongly corrosive agent, high inhalation and dermal exposure levels are avoided in practice and the use of protective measures were taken into account in the exposure estimates. The LC_{50}-values (1 hr values 280-1900 mg/m^3) are much higher than the estimated short-term inhalation exposure levels (2.5 mg/m^3 in scenario 1, 6 mg/m^3 in scenario 2, up to circa 10 mg/m^3 in scenario 3). Risk reduction measures, additional to those already taken to prevent accidental exposure, are not indicated (**conclusion ii**).

Irritation and corrosivity

Exposure to HF is possible by dermal contact, and via the respiratory tract and the eyes. The risk for workers is characterised for exposure via these routes to liquid and to gaseous HF, and account is made for single as well as repeated exposure. It is noted that local effects to the skin might be caused by simultaneous exposure to gaseous and liquid HF

Skin, single exposure, liquid HF

HF is a strongly corrosive agent. A 5% solution of HF is corrosive to the skin of rabbits. Skin lesions were observed even after exposure of rabbit's skin to 0.01% solutions for 5 minutes.

In scenario 1 (chemical industry) dermal exposure will be limited to accidental events. As for scenario 2 dermal exposure levels to HF solutions with concentrations up to 35% cannot be

excluded. Because it is generally known that HF and HF solutions cause caustic skin effects, the exposure estimates for these two scenarios assume the use of protective measures. Dermal exposure levels cannot be estimated for scenario 3 (indirect exposure).

According to the information submitted by industry extensive risk reduction measures have been taken in industrial premises using HF (scenario 2) (Additional information of industry 1997). Despite this fact that risk reduction measures are taken to prevent accidental exposure, contact to the skin cannot be excluded in scenarios 2 and 3. Because of the strong corrosive properties, it is concluded that additional risk reduction measures are indicated for these scenarios (**conclusion iii**). It is possible that adequate worker protection measures are already being applied in (some) industrial premises.

Skin, single exposure, gaseous HF

In the LC_{50}-studies skin erythema and skin corrosion were reported. In these studies animals were exposed to high levels. In the human volunteer study of Lund *et al*. (1997) no skin effects were reported after exposure to concentrations up to 5.2 mg/m^3, but it is unclear whether skin observations were performed. The data available do not allow a risk estimation for local skin effects after single exposure to gaseous HF in occupational circumstances **(conclusion ii)**.

Skin, repeated exposure, liquid HF

There are no data on local skin effects due to repeated dermal exposure to HF liquid (solutions). Given the corrosive properties, repeated exposure to concentrations that lead to corrosive effects is not expected **(conclusion ii)**.

Skin, repeated exposure, gaseous HF

Exposure of human volunteers to gaseous HF in concentrations of 0.74 to 1.64 mg/m^3, average 1.16 mg/m^3, for 6 hr during 15 days resulted in slight facial irritation and slight irritation of the nasal mucosa. After exposure to 2.78 mg/m^3 and above during 50 days, erythema and desquamation of the skin were observed. Starting-points for the risk characterisation for workers repeatedly exposed to gaseous HF with respect to local dermal effects are (a) the LOAEL of 1.16 mg/m^3, and (b) the inhalation occupational levels (see chapter 4.1.1.1. and **Table 4.1**). Given the nature of effects it is reasonable to start with short-term exposure levels. The MOS between the LOAEL and these levels varies between 0.2 and 1.2 (see **Table 4.13**).

These MOSs can be evaluated by comparison with the minimal MOS (2). In Annex 3 this method is explained and assessment factors used to establish the minimal MOS are given (Table A3 in this Annex). If this method is used, then there is concern when the MOS is lower than the minimal MOS.

Given the risk assessment presented in **Table 4.13** it is concluded that workers are at risk with regard to local skin effects due to occupational exposure to gaseous HF and **conclusion iii**) is considered to be applicable for all scenarios. According to the information submitted by industry extensive risk reduction measures have been taken in industrial premises producing and/or using HF (scenario 1 and 2) (Additional information of industry 1997). It is noted that exposure levels in scenarios 1 and 2 are estimated for situations with protective measures. According to the industry (CTEF 1996), workplace experiences do not reveal adverse irritating effects in scenario 1. It is possible that in some industrial premises adequate risk reductions measures are already applied to avoid irritation.

Table 4.13 Occupational risk characterisation of HF for local effects on respiratory tract and skin after repeated exposure to gaseous HF

Occupational scenario	Risk characterisation for exposure to gaseous HF		
	Estimated inhalation exposure (mg/m^3) , short-term	MOS[a]	Conclusion[b]
1: Chemical industry	2.5	0.5	iii
2: Use of HF acid solutions	6	0.2	iii
3: Indirect exposure	ca. 10[c]	1.2	iii

[a]Based on a human LOAEL of 1.16 mg/m^3
[b]The conclusion is reached by considering the magnitude of the MOS, taking into account a number of additional parameters as described in the TGD. An approach to do so is given in Annex 3
[c]Rough estimate

Inhalation, single exposure

In the Alarie test an RD_{50}-value for mice of 151 ppm (124 mg/m^3) was established. However, the suitability of this test as starting-point for risk assessment is doubted (Bos *et al*. 1992). Apart from questions as reproducibility and interpretation of the time- and concentration-response curves of the Alarie test, for corrosive substance as HF the toxic effects probably interfere with nervus trigeminus stimulation.

Respiratory effects due to exposure to gaseous HF have been described in case reports (accidental exposure) and in volunteer studies. In the volunteer study of Lund *et al*. (1997) exposure to levels >2.5 mg/m^3 for 60 minutes resulted in subjective symptoms of the upper airways. Because of the estimated short-term occupational exposure levels (2.5 mg/m^3 in scenario 1, 6 mg/m^3 in scenario 2, up to circa 10 mg/m^3 in scenario 3) a risk cannot be excluded and risk reduction measures, additional to those already taken to prevent accidental exposure, are indicated (**conclusion iii**). According to the information submitted by industry extensive risk reduction measures have been taken in industrial premises using HF (scenario 2) (Additional information of industry 1997).

Inhalation, repeated exposure

In workers exposed to average concentrations of 0.82 mg/m^3 no alteration in pulmonary function were observed and no increases in respiratory complaints were recorded. The highest HF concentrations were below 2.5 mg/m^3. These data are in correspondence with the results from the human volunteer study of Largent *et al*. (1960) (described and used in the chapter 'skin, repeated exposure, gaseous HF') in which irritation of the nasal mucosa was observed after exposure to 1.16 mg/m^3 (average) for 15 days.

Starting-points for the risk characterisation for workers repeatedly exposed to gaseous HF with respect to local respiratory effects are (a) the LOAEL of 1.16 mg/m^3, and (b) the inhalation occupational levels (see chapter 4.1.1.1. and **Table 4.1**). Given the nature of the effects it is reasonable to start with short-term exposure levels. The MOS between the LOAEL and these levels varies between 0.2 and 1.2 (see **Table 4.13**).

These MOSs can be evaluated by comparison with the minimal MOS (2). In Annex 3 this method is explained and assessment factors used to establish the minimal MOS are given (**Table A3** in this annex). If this method is used, then there is concern when the MOS is lower than the minimal MOS.

Given the risk assessment presented in **Table 4.13** it is concluded that workers are at risk with respect to local respiratory effects due to occupational exposure to gaseous HF in all scenarios. **Conclusion iii**) is reached. According to the information submitted by industry extensive risk reduction measures have been taken in industrial premises producing and/or using HF (scenario 1 and 2) (Additional information of industry 1997) and workplace experiences do not reveal adverse irritating effects in scenario 1. It is possible that in (some) industrial premises adequate risk reduction measures are already being applied to avoid irritation.

Eye

Exposure to the eyes is possible via vapours (all scenarios) or accidentally by splashing of HF (solutions) in scenarios 2 and 3. Exposure to the eyes is possible via vapours (all scenarios) or accidentally by splashing of HF (solutions) in scenarios 2 and 3. However, eye protection is obligatory for activities where direct handling of HF occurs. If the required protection is strictly adhered to, exposure to liquid HF will occur only accidentally in scenarios 2 and 3, so **conclusion ii**) is justifiable. Given the effects observed in the acute eye irritation studies (exposure to HF solutions) and in human volunteer studies (repeated exposure to vapours gives slight irritation at 1.16 mg/m^3), it is concluded that HF is of concern for workers with regard to eye irritation after repeated exposure to vapours, and risk reduction measures are indicated for these scenarios (**conclusion iii**). It is noted that workers are not at risk for adverse eye effects after single exposure to gaseous HF, based on the study of Lund *et al*. (1997), in which no effects on eyes were observed after 60 minutes exposure to concentrations up to 5.2 mg/m^3.

Sensitisation

A sensitisation study with HF is not available (see 4.1.2.5). Given the physico-chemical properties of HF and F^- it is concluded that the substance is of no concern for workers with regard to skin sensitisation (**conclusion ii**).

Repeated-dose toxicity

Inhalation exposure, systemic effects

The occupational risk characterisation for local effects on the respiratory tract due to repeated exposure is mentioned in the chapter 'irritation'.

The occupational exposure levels to be used as starting-point for risk characterisation vary between 0.5 and 10 mg/m^3 (see chapter 4.1.1.1 and **Table 4.1**). As toxicological starting-point for systemic effects both the epidemiological study of Chan-Yeung *et al*. (1983) and the semichronic inhalation study with rats (Placke and Griffin 1991) can be used. In general, in epidemiological studies only limited parameters are studied as compared with animal studies. Therefore, the sensitivity of both starting-points should be weighed.

In the inhalation study with rats exposed to HF an NOAEL of 0.72 mg/m^3 was established. At the next higher dose level (LOAEL, 7.52 mg/m^3) both local effects on respiratory tract and systemic effects occur. These effects comprise changes in body and organ weights, as well as haematological effects, clinical signs and death. In the epidemiological study no signs of fluorosis were observed in workers exposed to up to 0.48 mg/m^3 for up to ten years. There were indications for liver and kidney lesions in this study, but the changes were within the normal range. Values for hematocrit and hemoglobin were reported to be slightly higher in workers of the highest exposure group (0.48 mg/m^3) but were within normal limits.

The following arguments are given to justify the use of the epidemiological study as starting point:

(a) the parameters studied in the epidemiological study (fluorosis, kidney and liver damage) were also affected in the rat study;
(b) the epidemiological study reveals early signs of liver and kidney damage;
(c) because of the large gap (factor 10) between LOAEL and NOAEL in the rat study, the critical systemic effect in rats could not be established;
(d) fluorosis in human is a more sensitive parameter than fluorosis in rats (CEPA 1993). They reported that rats are less sensitive to fluorosis than humans, because in contrast to humans there is little or no bone remodelling in rats;
(e) the exposure period in the epidemiological study is more adequate than that in the semichronic inhalation study with rats in relation to a 40-year worklife;
(f) occupational human data are generally preferred to animal data.

Therefore, the NOAEL from the epidemiological study is used as starting-point (0.48 mg/m^3). Given the estimated frequency of exposure (50-200 days/year) chronic exposure is assumed for risk characterisation. The MOS between the NOAEL and the inhalation exposure levels varies between 0.05 and 1 (see **Table 4.14**).

These MOSs can be evaluated by comparison with the minimal MOS (2). In Annex 3 this method is explained and assessment factors used to establish the minimal MOS are given (Table A4 in this annex). If this method is used, then there is concern when the MOS is lower than the minimal MOS.

Given the risk assessment for inhalation exposure as mentioned in **Table 4.14** it is concluded that systemic effects due to repeated inhalation exposure cannot be excluded for all scenarios. However given the magnitude of the MOS for scenario 1 occupational health risks are not likely to occur (**conclusion i).** This conclusion can also be reached based on the fact that the ratio between the minimal MOS and the MOS in scenario 1 is only 2, and the fact that the actual NAEL most likely is higher than the NOAEL on which the risk assessment is based, it is assumed that occupational health risks in scenario 1 are not likely to occur (**conclusion ii**), but risk reduction measures are indicated for scenarios 2 and 3 (**conclusion iii**). According to the information submitted by industry extensive risk reduction measures have been taken in industrial premises using HF (scenario 2) (Additional information of industry 1997).

Remarks

- The NOAEL used as starting-point is the highest concentration reported.
- The risk for systemic effects due to inhalation exposure to HF cannot be considered in isolation, because actually the risk of total fluoride uptake should be taken into account. The risk characterisation reflects only the additional risk above background levels of F^-.
- The additional uptake of F^- at the level of the HBORV-inh/syst/chronic (derived from the NOAEL 0f 0.48 mg/m^3 by application of an assessment factor of 2, assuming 100% respiratory absorption and a respiratory rate of 10 m^3/day; see also footnote below **Table 4.14**) amounts to 2.5 mg/day, i.e. 25-50% of the estimated oral background value of F^- (non-fluoridated areas).

Considering this contribution of exposure at the HBORV-inh/syst/chronic to the total fluoride intake more information about a dose-response relationship of the effects of fluoride is useful for a proper judgement of the additional risk due to occupational exposure.

Dermal exposure

There are no dermal repeated dose toxicity studies available. Starting-points for the occupational risk assessment for systemic effects due to dermal exposure are the NOAEL (0.48 mg F^-/m^3) from the epidemiological study of Chan-Yeung *et al*. (1983) by application of route-to-route extrapolation, and (b) the dermal occupational exposure levels (see chapter 4.1.1.1 and **Table 4.1**). Correction is made by worst case assumptions for differences between inhalation and dermal absorption. It is assumed that fluoride is completely absorbed in the upper respiratory tract and 100% dermal absorption cannot be excluded. Given the estimated frequency of exposure (50-200 days/year) chronic exposure is assumed for risk characterisation. The MOS between the NOAEL and the dermal exposure levels is 24 (scenario 2) or is unknown (scenario 3; because exposure levels cannot be estimated) (see **Table 4.14**).

These MOSs can be evaluated by comparison with the minimal MOS (2). In Annex 3 this method is explained and assessment factors used to establish the minimal MOS are given (**Table A4** in this annex). If this method is used, then there is concern when the MOS is lower than the minimal MOS.

Because skin exposure in scenario 1 is limited to accidental events, risk characterisation for repeated exposure is not relevant. Systemic effects due to occupational dermal exposure in scenario 2 are not expected. Because dermal exposure in scenario 3 cannot be estimated, systemic effects cannot be excluded. Therefore **conclusion iii**) may be applicable for scenario 3. It is considered possible that risk reduction measures already applied in this scenario are adequate.

Remarks

- The risk for systemic effects due to dermal exposure to HF cannot be considered in isolation, because actually the risk of total fluoride uptake should be taken into account. The risk characterisation reflects only the additional risk above background levels of F^-.
- The additional uptake of F^- at the level of the HBORV-derm/syst/chronic amounts to 2.5 mg/day (assuming 100% dermal absorption), i.e. 25-50% of the estimated oral background value of F^- (non-fluoridated areas).
- Considering this contribution of exposure to the HBORV-derm/chronic to the total fluoride intake more information about a dose-response relationship of the effects of fluoride is useful for a proper judgement of the additional risk due to occupational exposure.

Table 4.14 Occupational risk characterisation of HF for repeated dose toxicity (systemic effects)

Occupational scenario	Risk characterisation for inhalation exposure			Risk characterisation for dermal exposure		
	Estimated inhalation exposure (mg/m³) full shift values	MOS[a]	Conclusion[b]	Estimated dermal exposure (mg/d)	MOS[c]	conclusion[d]
1:Chemical industry	0.5	1	ii	accidental	not relevant (see text)	not relevant ii
2: Use of HF acid solutions	2.4	0.2	iii	0.2	24	ii
3: Indirect exposure	< 1 - ca. 10[e]	0.05-0.5	iii	unknown	unknown	iii

[a]Based on a human NOAEL of 0.48 mg/m³
[b]The conclusion is reached by considering the magnitude of the MOS, taking into account a number of additional parameters as described in the TGD. An approach to do so is given in Annex 3
[c]Based on a human NOAEL of 0.48 mg/m³ and a respiratory volume of 10 m³/day
[d]The conclusion is reached by considering the magnitude of the MOS, taking into account a number of additional parameters as described in the TGD. An approach to do so is given in Annex 3
[e]Rough estimates

Mutagenicity

The results from the mutagenicity studies give no indication that HF is of concern for workers with regard to mutagenicity (**conclusion ii**).

Carcinogenicity

There are no carcinogenicity studies with HF available. Since the results from the oral studies with NaF give no indications that fluoride has a carcinogenic potential in animals, and taking into account that HF is not mutagenic, there is no clear reason for concern for workers with regard to carcinogenicity of HF (**conclusion ii**).

Reproductive toxicity

Inhalation exposure

The occupational exposure levels to be used as starting-point for risk characterisation vary between 0.5 and 10 mg/m^3 (see chapter 4.1.1.1 and **Table 4.1**). As for the toxicological starting-points, there are no studies available on reproductive toxicity with HF. Therefore, the oral reproduction studies with NaF are used.

Given the effects observed in the developmental studies it is concluded that HF is of no concern with respect to these effects. Fluoride causes effects on the progeny only at maternally toxic dose levels.

The 2-generation study of the US-FDA is used as starting-point for risk characterisation. At the highest dose level tested (10 mg F^-/kg b.w./d) no effects on fertility were observed. Route-to-route extrapolation is applied with worst case assumptions for differences between inhalation and oral absorption. As mentioned in chapter 4.1.2.1 HF is completely absorbed in the upper respiratory tract. For oral absorption of fluoride 100% is used. The MOS between the NOAEL and the inhalation exposure levels varies between 2.5 and 50 (see **Table 4.15**).

These MOSs can be evaluated by comparison with the minimal MOS (36). In Annex 3 this method is explained and assessment factors used to establish the minimal MOS are given (**Table A5** in this annex). If this method is used, then there is concern when the MOS is lower than the minimal MOS.

Given the risk assessment presented in **Table 4.15**, it is concluded that the MOS is lower than the minimal MOS in scenario 3, indicating a risk for fertility effects. There are no indications for concern for the other occupational exposure scenarios.

Remarks

- The NOAEL used as starting-point is the highest dose level tested.
- The NOAEL in the study is 25 times the oral background value of fluoride in the diet.
- Fluoride uptake via occupational respiratory exposure to HF amounts to 5, 24 and <1-ca 10 mg/day for scenarios 1, 2, and 3, respectively (assuming 100% inhalation absorption and a respiratory rate of 10 m^3/day), i.e., approx. 1, 4 and <1-2 times the background value for fluoride uptake via food and drinking water in non-fluoridated areas (6 mg/d).

Given these remarks and the height of the MOS, it is concluded that this risk estimation indicates no additional risk for fertility effects resulting from occupational exposure above oral background levels for scenario 1 and 2, resulting in **conclusion ii**) for these scenarios. For scenario 3 health risk cannot be fully excluded, and **conclusion iii**) might be applicable for this scenario.

Dermal exposure

The occupational exposure levels to be used as starting point in risk characterisation are estimated in chapter 4.1.1.1 and summarised in **Table 4.1**. As for the toxicological starting-points, there are no dermal studies on reproductive toxicity with HF available. Reference is made to the chapter above ('reproductive toxicity, inhalation exposure') for the choice of the NOAEL to be used for the risk characterisation (10 mg F^-/kg b.w./d from the 2-generation reproduction study). Route-to-route extrapolation is applied with worst case assumptions for differences between dermal and oral absorption. Complete dermal absorption cannot be excluded. For oral absorption of fluoride 100% is used. The MOS between the NOAEL and the dermal exposure levels is 15 (scenario 2) or is unknown (scenario 3; because exposure levels cannot be estimated) (see **Table 4.15**).

These MOSs can be evaluated by comparison with the minimal MOS (36). In Annex 3 this method is explained and assessment factors used to establish the minimal MOS are given (**Table A5** in this annex). If this method is used, then there is concern when the MOS is lower than the minimal MOS.

Skin contact in scenario 1 is limited to accidental events, and therefore risk characterisation is not relevant in that case. Given the risk assessment presented in **Table 4.15** it is concluded that reproduction effects due to occupational skin contact are not likely to occur in scenario 2, but cannot be excluded in scenario 3.

Remarks

- The NOAEL used as starting-point is the highest dose level tested.
- The NOAEL in the study is 25 times the oral background value of fluoride in the diet, and at this level no effects on fertility were observed.
- Fluoride uptake via occupational dermal exposure to HF amounts to 0.5 mg/day for scenario 2, (assuming 100% dermal absorption) i.e., approx. 7% of the background value for fluoride uptake via food and drinking water in non-fluoridated areas (6 mg/d).

Given these remarks, it is concluded that this estimation indicates no additional risk resulting from occupational exposure above oral background levels in scenario 1 and 2 and **conclusion ii**) is applicable for these scenarios. Because dermal exposure in scenario 3 cannot be estimated, reproduction effects cannot be excluded, resulting in **conclusion iii**).

Table 4.15 Occupational risk characterisation of HF for reproduction effects

Occupational scenario	Risk characterisation for long-term inhalation exposure/reproduction toxicity[a]			Risk characterisation for long-term dermal exposure/reproduction toxicity		
	Estimated inhalation exposure (mg/m^3) full shift	MOS[b]	Conclusion[c]	estimated dermal exposure (mg/d)	MOS[d]	Conclusion[e]
1: chemical industry	0.5	50	ii	accidental	not relevant (see text)	ii
2: use of HF acid solutions	2.4	10	ii	0.2	15	ii
3: indirect exposure	< 1 - ca.10[f]	2.5->25	iii	unknown	unknown	iii

[a]Worst case assumption: 8 hr exposure/workday;
[b]Based on a NOAEL of 10 mg/kg b.w./d in the rat, and a bodyweight of the rat of 0.3 kg, a respiratory volume of the rat of 0.12 m^3/8 hr;
[c]The conclusion is reached by considering the magnitude of the MOS,
taking into account a number of additional parameters as described in the TGD. An approach to do so is given in Annex 3;
[d]Based on a NOAEL of 10 mg/kg b.w./d in the rat, and a bodyweight of the rat of 0.3 kg;
[e]The conclusion is reached by considering the magnitude of the MOS,
taking into account a number of additional parameters as described in the TGD. An approach to do so is given in Annex 3;
[f]Rough estimates

Occupational limit values

It is noted that the HBROEL of the Dutch Expert Committee on Occupational Standards (DECOS) amounts to 1 mg F^-/m^3 (Dutch Expert Committee for Occupational Standards 1989). This value is based on direct effects on the respiratory tract observed in human volunteer studies of Largent as reported by the WHO (1984), in which 'the probable NOAEL' is 2.1 mg HF/m^3. Irritation occurs at 4.2 mg HF/m^3. By using a 'safety factor' of 2-4 the proposed health-based recommended occupational exposure limit is 1 mg F/m^3 t.w.a - 15 min'.

The Scientific Expert Group on Occupational Exposure Limits (1993) states that 'the no adverse effect level of 2.5 mg F^-/m^3 could be a suitable limit to prevent any kind of acute response of the body to HF. The starting point for this level has not been clearly described, but it is assumed that the same human volunteer studies of Largent were taken as starting point. This level would also

prevent the effects on skeleton, the biological critical system, i.e. osteosclerosis, according to the most relevant data. An OEL should be set at 2.5 mg F^-/m^3 (STEL with skin notation).

In the UK a short-term occupational exposure standard (OES) of 3 ppm (as F) is established as a 10-minute time-weighted average (HSE 1993). Irritation is considered as critical effect with a human no-effect-level of 3 ppm. The study on which this NOAEL relies is not mentioned. An 8-hour OES was considered unnecessary.

4.1.3.3 Consumers

Information obtained from the Anti-poison centre in Belgium shows that a significant number of accidents have occurred through the use of rust cleaning and stone and wood cleaning agents, available to consumers. In the majority of cases symptoms concerned burned lesions of the hands. In all cases medical care was needed. An overview of the information collected by the Anti-poison centre is given in Annex 4.

Because of the strong corrosive properties of the substance and because of the fact that incidental dermal exposure of consumers through the use of the above mentioned products cannot be excluded it is concluded that risk reduction measures are needed (**conclusion iii**).

4.1.3.4 Man exposed indirectly via the environment

Inhalation exposure

Repeated dose toxicity

For the risk characterisation the ambient background F concentration in air has been added to the PEC values of **Table 4.3**. For the ambient background F concentration a value of 0.07 $\mu g/m^3$ is chosen (see paragraph 3.1.1.2).

In **Tables 4.16** and **4.17** all local estimates of HF air concentrations measured as well as calculated, respectively are compared with the NOAEL (DCV) of 128 $\mu g/m^3$ from the 90 day rats study (see 4.2.1.6 and 4.1.3.0). At this dose no irritation or systemic effects were observed. A marginal effect level for irritation in humans was established at 1.16 mg/m^3.

Table 4.16 Margin of Safety (from measured data)

Plant	Air concentration[a] $\mu g/m^3$	Margin of Safety
NL	0.1 1	1280 128
D I	1.3	98
D II	2.4	53
UK I	0.06 0.23	2133 557
EU	0.05-0.06	2560-2133

[a] For specific data see section 3.1.5.3

It is known that in healthy workers exposed to fluoride in air at a concentration of 114.2 μg/m^3 no fluorosis occurs after 10 years of exposure (Chan-Yeung *et al*. 1983). Because this NOAEL is approx. equal to the NOAEL (DCV) in the 90-day rat study a MOS of 100 is considered sufficient.

The margin of safety (measured data) for 2 plants in Germany indicate a concern for human safety following inhalatory exposure to HF, indirectly via the environment. These rather old (<1994) measured data, however, are assumed to be replaced by more recent emission figures that are used in the calculated PECs .

The margin of safety (calculated data) for end-user plant b indicate a concern for human safety following inhalatory HF exposure, indirectly via the environment **conclusion iii**). As stated in section 3.3.3 plant b has indicated that a) their fluoride emissions originate from unintentional HF formation (by-product) during the production of several organofluor compounds and b) they have taken release reduction measures which are expected to lead to substantial emission reduction.

For all other plants and end-users the MOSs indicates no concern **conclusion ii**).

Table 4.17 Margin of safety (from calculated data)

Plant No.	PEC[1] µg/m3	Margin of Safety	Year
1	0.16	800	1994
2	1.1	116	1994
	0.36	356	1995
	0.34	376	1996
	0.33	388	1997
	0.13	985	1998
3	2.43	53	1994
	1.67	77	1995
	1.06	121	1996
	0.98	131	1997
	1.02	126	1998
4	0.31	412	1995
	0.23	556	1997
5	0.2	640	1994
	0.19	674	1995
6	0.09	1422	1994[2]
7	0.08	1600	1994
8	0.37	346	1994
	0.11	1164	1997
9	0.07	1829	1997
10	1.61	80	1994[2]
	0.10	1280	1998
11	0.09	1422	1994
12	0.09	1422	1994
13	0.33	387	1994
	0.86	149	1996
14	0.33	387	?
	0.18	711	1997
a	0.1	1280	1994
b	12.3	10	1994
	3.3	37	
c	0.09	1422	1994
	0.08	1600	1995
d	0.07	1829	1994
e	0.08	1600	1994

[1]The PEC values are inclusive an ambient background concentration of 0.07 µg/m^3
[2]Same for 1995

Reproductive toxicity

The local estimates for HF air concentrations measured as well as calculated to be used as starting point for the risk characterisation are listed in **Tables 4.2** and **4.3**. There are no studies available on reproductive toxicity with HF. Therefore, the oral studies with NaF are used.

It is concluded that HF is of no concern with respect to developmental effects, since fluoride causes effects on the progeny only at maternally toxic doses (**conclusion ii**).

In the 2-generation study of US-FDA with rats, at the highest dose level tested (about 10 mg F^- /kg b.w./d) no effects on fertility were observed. By route to route extrapolation assuming complete oral and inhalatory absorption an inhalatory equivalent NOAEL of 35 mg/m^3 can be calculated for a continuously exposed person of 70 kg and a daily respiratory volume of 20 m^3. When comparing this inhalatory equivalent NOAEL with the measured and calculated local HF concentrations (see **Table 4.16** and **4.17**) all margins of safety are >>2800. Hence, it is concluded that this risk estimation indicates no additional risk for fertility effects (**conclusion ii**).

Intake via all media

In section 4.1.3.3.1 it is concluded that HF contribution to the total daily fluoride intake is considered negligible. Therefore no risk characterisation has been performed for humans after exposure to total fluoride.

4.1.3.5 Combined exposure

Since nearly all scenarios described in the previous sections caused concern for the environment/workers/public at large as discussed. It seems not useful to characterise the risk more specifically after combined exposure.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

HF is not flammable and not explosive. Oxidising properties are not expected in the sense of reaction with oxygen.

It is noted that hydrofluoric acid dilutions in water of 65% and lower react with metals (e.g. iron from steel drums or from reactors) under the formation of H_2. Dilution of concentrated HF with water may cause violent behaviour because of high dilution heat. There are no R- and S-sentences appropriate for these properties. **Conclusion iii**) is reached, because the general warnings on (1) the formation of H_2 by reaction of HF solutions of less than 65% with metals, and (2) on the violent behaviour upon dilution of concentrated HF with water, should be included in all MSDSs.

5 RESULTS

Environment

( ) There is need for further information and/or testing
( ) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied
(X) There is a need for limiting the risks: risk reduction measures which are already being applied shall be taken into account

Conclusion iii) is reached because:

- for a number of HF producing and HF using sites the local environmental risk characterisation points to risks for either 1) the aquatic compartment, or 2) the atmospheric compartment or 3) livestock and wildlife exposed via air.

Man indirectly exposed via the environment

( ) There is need for further information and/or testing
( ) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied
(X) There is a need for limiting the risks: risk reduction measures which are already being applied shall be taken into account

Conclusion iii) is reached because:

- for one HF using site the local environmental risk characterisation indicates a significant risk for humans indirectly inhalatory exposed via the environment

Consumers

( ) There is need for further information and/or testing
( ) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied
(X) There is a need for limiting the risks: risk reduction measures which are already being applied shall be taken into account

Conclusion iii) is reached because of concerns for skin irritation and/or corrosivity, depending on concentration, as a consequence of single exposure to the hydrogen fluoride liquid arising from the use of HF containing rust cleaning and stone and wood cleaning agents.

Workers

( ) There is need for further information and/or testing
( ) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied
(X) There is a need for limiting the risks: risk reduction measures which are already being applied shall be taken into account

Conclusion iii) is reached because:

- the general warnings on (1) the formation of H_2 by reaction of HF solutions of less than 65% with metals, and (2) on the violent behaviour upon dilution of concentrated HF with water, should be included in all MSDSs.

- concerns for skin and respiratory tract irritation and/or corrosivity, depending on concentration, as a consequence of repeated exposure to gaseous hydrogen fluoride at production and use as an intermediate in the chemical industry and use of aqueous HF-solutions.

- concerns for general systemic toxicity as a consequence of repeated inhalatory exposure arising from the use of aqueous HF-solutions.

- concerns for skin irritation and/or corrosivity, depending on concentration, as a consequence of single exposure to the hydrogen fluoride liquid arising from the use of aqueous HF-solutions.

- concerns for respiratory tract irritation and/or corrosivity, depending on concentration, as a consequence of single exposure to gaseous hydrogen fluoride at production and use as an intermediate in the chemical industry and at the use of aqueous HF-solutions.

Table 5.1 Overview of conclusions with respect to occupational risk characterisation

End-point	conclusions valid for the occupational scenario's			
	scenario 1		scenario 2	
	MOS	conclusion	MOS	conclusion
acute toxicity				
- dermal	na	ii	na	ii
- inhalation (LC_{50}, 1 hr, 280-1900 mg/m^3)	> 112	ii	> 47	ii
irritation and corrosivity, single exposure, liquid HF				
- dermal	na	ii	na	iii
irritation and corrosivity, single exposure, gaseous HF				
- dermal	na	ii	na	ii
- inhalation	na	iii	na	iii
- eyes	na	ii	na	ii
irritation and corrosivity, repeated exposure, liquid HF				
- dermal	na	ii	na	ii
irritation and corrosivity, , repeated exposure, gaseous HF				
- dermal (LOAEL 1.16 mg/m^3, human study)	0.5	iii	0.2	iii
- inhalation (LOAEL 1.16 mg/m^3, human study)	0.5	iii	0.2	iii
- eyes (LOAEL 1.16 mg/m^3, human study)	0.5	iii	0.2	iii
sensitisation	na	ii	na	ii
repeated dose toxicity, systemic effects				
- dermal (NOAEL 0.48 mg/m^3, epi-study workers)	not relevant	ii	24	ii
- inhalation (NOAEL 0.48 mg/m^3, epi-study workers)	1	ii	0.2	iii
mutagenicity	na	ii	na	ii
carcinogenicity	na	ii	na	ii
reproductive toxicity, developmental effects	na	ii	na	ii
reproductive toxicity, fertility effects				
- dermal (10 mg/kg b.w./d, oral 2-gen study with NaF)	not relevant	ii	15	ii
- inhalation (10 mg/kg b.w./d, oral 2-gen study with NaF)	50	ii	10	ii
flammability	na	ii	na	ii
explosive properties	na	ii	na	ii
oxidising properties	na	iii[a]	na	iii[a]

na = Not applicable

[a]Formation of H_2 by reaction of HF-solutions of less than 65% with metals, and violent behaviour upon dilution of concentrated HF with water

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GLOSSARY

Standard term / Abbreviation	Explanation/Remarks and Alternative Abbreviation(s)
Ann.	Annex
AF	assessment factor
BCF	bioconcentration factor
bw	body weight / *Bw*, *b.w.*
°C	degrees Celsius (centigrade)
CAS	Chemical Abstract System
CEC	Commission of the European Communities
CEN	European Committee for Normalisation
CEPE	European Council of the Paint, Printing Ink and Artists' Colours Industry
d	day(s)
d.wt	dry weight / dw
DG	Directorate General
DT_{50}	period required for 50 percent dissipation (define method of estimation)
DT_{50lab}	period required for 50 percent dissipation under laboratory conditions (define method of estimation)
DT_{90}	period required for 90 percent dissipation (define method of estimation)
$DT_{90field}$	period required for 90 percent dissipation under field conditions (define method of estimation)
EC	European Communities
EC	European Commission
EC_{50}	median effective concentration
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
EU	European Union
EUSES	European Union System for the Evaluation of Substances
f_{oc}	Fraction of organic carbon
G	gram(s)

PNEC(s)	predicted no effect concentration(s)
$PNEC_{water}$	predicted no effect concentration in water
(Q)SAR	quantitative structure activity relationship
STP	sewage treatment plant
TGD	Technical Guidance Document[11]
UV	ultraviolet region of spectrum
UVCB	Unknown or Variable composition, Complex reaction products or Biological material
v/v	volume per volume ratio
w/w	weight per weight ratio
w	gram weight
GLP	good laboratory practice
h	hour(s)
ha	Hectares / *h*
HPLC	high pressure liquid chromatography
IARC	International Agency for Research on Cancer
C_{50}	median immobilisation concentration or median inhibitory concentration 1 / *explained by a footnote if necessary*
ISO	International Standards Organisation
IUPAC	International Union for Pure Applied Chemistry
kg	kilogram(s)
kPa	kilo Pascals
K_{oc}	organic carbon adsorption coefficient
K_{ow}	octanol-water partition coefficient
Kp	Solids water partition coefficient
l	litre(s)
log	logarithm to the basis 10
$L(E)C_{50}$	lethal concentration, median
m	Meter
µg	microgram(s)
mg	milligram(s)

[11] Commission of the European Communities, 1996. Technical Guidance Documents in Support of the Commission Directive 93/67/EEC on risk assessment for new substances and the Commission Regulation (EC) No 1488/94 on risk assessment for existing substances. Commission of the European Communities, Brussels, Belgium.
ISBN 92-827-801[1234]

MOS	margins of safety
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
OECD	Organisation for Economic Co-operation and Development
OJ	Official Journal
pH	potential hydrogen -*logarithm* (to the base 10) of the hydrogen ion concentration $\{H^+\}$
pKa	-*logarithm* (to the base 10) of the acid dissociation constant
pKb	-*logarithm* (to the base 10) of the base dissociation constant
Pa	Pascal unit(s)
PEC	predicted environmental concentration

Annex 1 The occurrence of HF in products according to the Swedish product register (KEMI, 1995)

Table A1 Trades that use products containing HF and product functions

Trade	Product functions
Glass and glass products	Etching agents for glass Pickling agents (metals)
Office machinery and computers	Etching agents for glass
Electrical machinery n.e.c.	Etching agents for glass Intermediates
Wholesale of chemicals	Etching agents for glass Laboratory chemicals Pickling agents (metals) Intermediates
Manufacturing for export, export	Laboratory chemicals
Technical testing and analysis	Laboratory chemicals
Other chemical products	Metal surface treatment agents
Basic metals	Metal surface treatment agents Pickling agents (metals)
Metal products	Metal surface treatment agents Pickling agents (metals) Degreasing agents * High pressure cleaning agents *
Treatment and coating of metals	Metal surface treatment agents Pickling agents (metals)
Radio, television, communication equipment	Metal surface treatment agents Pickling agents (metals)
Transport equipment	Metal surface treatment agents Pickling agents (metals) High pressure cleaning agents *
Electricity, gas and water works	Pickling agents (metals)
Wholesale trade, except motorvehicles and motorcycles	Pickling agents (metals)
Transport, storage and communication companies	Pickling agents (metals)
Ceramic , bricks and tiles	Friction agents * Degreasing agents *
Publishers and printers, recorded media	Other paints and varnishes, solvent based *
Construction industry	Polishing agents *
Laundries, dry cleaning	Stain removers *

* There are less than three products in this product category

Annex 2 Measured Occupational exposure levels of HF measured

Table A2 Measured occupational exposure levels of HF measured

Industries and tasks	Exposure levels[1)] (mg/m³)		Remarks	References
	Full-shift	Short-term		
Manufacture and filling		15 samples < 0.25 0.43 + 0.46	Unclear whether personal sampling; duration of sampling not mentioned	120
Manufacture of inorganic fluorides		9 samples < 0.25 5 samples 0.27-0.62	Unclear whether personal sampling; duration of sampling not mentioned	120
Manufacture of organic fluorides		9 samples < 0.2	Unclear whether personal sampling; duration of sampling not mentioned	120
Manufacture		< 2	No details	106
Manufacture		< 5	No details	107
Alkylation plant		well below 2.5	abstract only; not very clear whether concentrations were actually measured at alkylation plant only; occasional symptoms	117
Refinery		only one sample approached 2.5	abstract only; not clear whether measurements where at alkylation unit	118
Oil refinery		100-133	accidental peak exposure, duration approx. 2 minutes	119
Oil refinery, alkylation unit, operators and maintenance workers	< 0.005-0.04 one value of 0.18		22 measurements of 4 to 6 hours duration; 10 measurements below 0.005 mg/m³	116
		1.9 ± 3.1	Arithmetic mean and standard deviation, it is assumed that these are short-term results; n = 52	125
Washing television tubes and etching semiconductors		averages per workshop: 0.2-3.3	Probably area samples; unclear description; number of samples unknown, but at least 40: 5 per workshop (8 workshops); measurements pre 1985	126-128

Table A2 continued overleaf

Table A2 continued

Industries and tasks	Exposure levels[1)] (mg/m³)		Remarks	References
	Full-shift	Short-term		
Glass manufacturing, etching department		0.34-3.0	abstract only, duration of measurements uncertain	129
Etching and polishing	< OEL		abstract only	118
Plating facility, acid baths	0.14-0.19 2.7		4 measurements at the edge of a bath with unknown percentage HF 1 measurement at the edge of a bath containing 13% HF	123
Bricks, tiles: (surface) treatment, cleaning, protection	0.6-1.3		4 samples, stationary sampling	130
Metal industry: treatment, assembly	< 0.04-16.1		9 samples of which 7 stationary, 4 non-detected including both personal samples; The highest value was clearly in an unusual situation	130
Metal industry: foundries	< 0.01		22 samples of which 12 stationary	130
Fertiliser manufacturing general * Superphosphate	< OEL's 50% > OEL's	Often > OEL's	No details; abstract only	115
Phosphate/fertiliser		< 1 to > 10	Five pre 1970 studies; no details	113
Superphosphate		< 1-8	One pre 1970 study; no details	113
Polymer fumes in a plastic department		0.003-0.005	Area samples; No details on sample duration; assumption: short-term; abstract only	114
Fire fighters		< 0.1-6.4	samples of 22 fires, sampling duration around 15 min.	111
Aluminium industry		< 0.1-3	Three pre 1970 studies; no details	113
Magnesium foundries and melting		< 1 to > 10	Four pre 1970 studies; no details	113
Brazing, soldering, welding		< 1	One pre 1970 study; no details	113
Electrolysis shop of an aluminium plant		6-22 times OEL or STEL	Probably area samples; abstract only	135

[1]Exposure levels are usually given as levels F^-.
1 mg/m³ = 1.25 ppm
1 ppm = 0.8 mg/m³

Annex 3 Establishment of the minimal MOSs used for the risk characterisation by the Netherlands[12]

In the tables below calculations of the minimal MOS-values via assessment factors are given. The assessment factors are based on the report of Hakkert et al. (1996).

Table A3 Assessment factors applied for the calculation of the minimal MOS for local effects on skin and respiratory tract due to single exposure to gaseous HF

Aspect	Assessment factors
Interspecies differences	1[1]
Intraspecies differences	1[1]
Differences between experimental conditions and exposure pattern of the worker	1
Type of critical effect	1
Dose-response curve	2[2]
Confidence of the database	1
Overall	2

[1]The inter- and intraspecies differences are assumed to be 1 for irritation effects
[2]Because a LOAEL instead of a NOAEL is used as starting point, a factor 2 is introduced

Table A4 Assessment factors applied for the calculation of the minimal MOSs for chronic inhalation and dermal exposure applicable on the NOAEL from the epidemiological study

Aspect	Assessment factors for inhalation risk assessment	Assessment factors for dermal risk assessment
Interspecies differences [1]	1	1
Intraspecies differences [1]	1	1
Differences between experimental conditions and exposure pattern of the worker [2]	2	2
Type of critical effect	1	1
Dose-response curve [3]	1	1
Route-to-route extrapolation	-	1[4]
Confidence of the database	1	1[5]
Overall	2	2

[1]A factor 1 is applied, because an occupational epidemiological study is used as starting-point
[2]For a conclusion on extrapolation from 10-years exposure (study) to occupational exposure during the whole work-life (40 years) it should be taken into account (a) that in general adverse effect levels will decrease with increasing exposure times, (b) that adverse effects may appear a long time after exposure has been stopped, and (c) other and more serious adverse effects may appear with increasing exposure times. A factor 2 is applied
[3]At the highest dose level no effects were observed. Therefore, the actual NAEL might be higher than the NOAEL used as starting point. However, based on the data available, no estimation can be made of the actual NAEL, and therefore, the default value of 1 is used
[4]For route-to-route extrapolation correction is made for difference between inhalation and dermal absorption. For the inhalation and dermal route of exposure both 100% absorption is taken into account
[5]Application of a factor higher than 1 for uncertainties inherent to route-to-route extrapolation is considered not to be necessary for the fluoride-ion. Apart from absorption differences, no significant differences are expected with respect to metabolic and kinetic aspects due to uptake via dermal and inhalation exposure

[12] This annex represents the views of the Netherlands. In particular it presents the approach used by the Netherlands to determine, in a transparent way, which conclusion is to be drawn for worker risk characterisation based on the magnitude of the MOS

Table A5 Assessment factors applied for the calculation of the minimal MOSs for inhalation and dermal exposure applicable on the NOAEL from the reproduction study

Aspect	Assessment factors for inhalation risk assessment	Assessment factors for dermal risk assessment
Interspecies differences [1]	3	4 · 3
Intraspecies differences	3	3
Differences between experimental conditions and exposure pattern of the worker	1	1
Type of critical effect	1	1
Dose-response curve [2]	1	1
Route-to-route extrapolation [3]	1	1
Confidence of the database [4]	1	1
Overall	9	36

[1]A factor for interspecies differences is required, because there is only one well-performed study with rats available extrapolation via caloric demands is applied, together with an uncertainty factor for calculation of the minimal MOS for dermal risk assessment, because comparison is based on dose levels. A factor for caloric demands is not included for the calculation of the minimal MOS to be used for inhalation risk assessment, because the MOS is calculated as the ratio of the NOAEL expressed as concentration and the inhalation exposure levels

[2]At the highest dose level no effects were observed. Therefore, the actual NAEL might be higher than the NOAEL used as starting point. However, based on the data available, no estimation can be made of the actual NAEL, and therefore the default value of 1 is used

[3]For route-to-route extrapolation correction is made for difference between oral and inhalation and between oral and dermal absorption. For the oral as well as for the inhalation and dermal route of exposure 100% absorption is taken into account.

[4]Application of a factor higher than 1 for uncertainties inherent to route-to-route extrapolation is considered not to be necessary for the fluoride-ion. Apart from absorption differences, no significant differences are expected with respect to metabolic and kinetic aspects due to uptake via oral and inhalation exposure

Annex 4 Information from the Anti-poison Centre in Belgium on accidents with HF containing products (as annexed to SZV&W, 1999)

Short overview of the telephone calls received by the Anti-poison Centre in 1998 and necessitating at least a treatment on the basis of calcium (percutaneous or via parenteral route), communicated by Dr. M. Mostin 1.10.99 (*shortened translation*).

Profile of the calls

Number of calls

Total number: 40
Number of victims: 41

Origin

11 calls from the public
29 from the medical profession.

Circumstances of exposure

Except for one suicide attempt, all exposures were accidental: in 10 cases due to professional exposure; in the remaining cases: domestic.

Route of exposure

Three via oral route; one contact via eye and skin; the 36 remaining via dermal route.

Age and sex of the victims

All adults. In 28 cases : male; in 11 cases: female. In two cases the sex of the victim was not registered.

Products

In case of professional use: aqueous HF solutions or preparations for cleaning trucks, cleaning aluminium surfaces (e.g. alloy wheels), facade or verandas cleaning.

Domestic accidents were due to solutions of HF (usage not registered or precised), or to marketed preparations e.g. rust cleaning of textiles, cleaning of aluminium surfaces, of stoneware, wheels, greenhouses, cleaning and lightening of wood and rust remover.

The labelling of several products does not mention the presence of HF in the preparation.

Time interval

The delay between exposure and the call was recorded in 29 cases. Delay: 1h: in 12 cases. Delay >1h to 12h.: 7 cases. Delay > 12h to 24h: 9 cases. Delay >24h: 1 case.

Severity of the exposure

All patients developed symptoms. In the majority of the cases it concerned burning lesions of the hands. In all cases medical care was needed. In total 37 patients were hospitalised directly at the moment of their call or sent to the hospital via the physicians of the Anti-Poison Centre.

Other data

The progressive development of the burning lesions is a cause of delayed medical care.

Solutions containing up to 75% HF are available in certain hardware stores.

In 1998 no accident in children was registered but several cases of poisoning are known from the literature.

Dr. M. Mostin, head of the Anti-Poison Centre concludes that the danger of those preparations justifies limiting their use to the well-informed skilled workers.

European Commission

EUR 19729 – European Union Risk Assessment Report hydrogen fluoride, Volume 8

Editors: B.G. Hansen, S.J. Munn, S. Pakalin, C.J.A. Heidorn, R. Allanou, S. Scheer, G. Pellegrini, S. Vegro, M. Luotamo, J. De Bruijn, F. Berthault, H. Loonen, K. Vormann, A. Naughton, V. Anfossi, L. Praderio

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The report provides the comprehensive risk assessment of the substance Hydrogen fluoride. It has been prepared by the Netherlands in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to man and the environment, laid down in Commission Regulation (EC) No. 1488/94.

The evaluation considers the emissions and the resulting exposure to the environment and the human populations in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined. For human health the scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.

The human health risk assessment for Hydrogen fluoride concludes that there is at present concern for workers, for consumers and for humans exposed via the environment. The environmental risk assessment for Hydrogen fluoride concludes that there is at present concern for the aquatic compartment and the atmospheric compartment at a number of HF producing and HF using sites, while no concern for the terrestrial ecosystem and for micro-organisms in the sewage treatment plant was concluded.

The conclusions of this report will lead to risk reduction measures to be proposed by the Commissions committee on risk reduction strategies set up in support of Council Regulation (EEC) No. 793/93.

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