European Union Risk Assessment Report

TRISODIUM HEXAFLUOROALUMINATE

CAS No: 13775-53-6

EINECS No: 237-410-6

CAS No: 15096-52-3

EINECS No: 239-148-8

Risk Assessment

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RISK ASSESSMENT

Draft of October 2008

Germany

Rapporteur for the risk assessment of **Trisodium hexafluoroaluminate** is Germany

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Foreword

This Draft Risk assessment Report is 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), now renamed Scientific Committee on Health and Environmental Risks (SCHER) which gives its opinion to the European Commission on the quality of the risk assessment.

This Draft Risk Assessment Report has undergone a discussion in the Competent Group of Member State experts with the aim of reaching consensus by interpreting the underlying scientific information, or including more data, but this work has not yet been totally finalised. The information contained in this Draft Risk Assessment Report does not, therefore, necessarily provide a sufficient basis for decision making regarding the hazards, exposures or the risks associated with the priority substance.

This Draft Risk Assessment Report is under the responsibility of the Member State rapporteur. In order to avoid possible misinterpretations or misuse of the findings in this draft, anyone wishing to cite or quote this report is advised to contact the Member State rapporteur beforehand.

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[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]

General introduction to risk assessment

The concern about workplace risks was the initial reason for putting cryolite on the third EU priority list. Nevertheless, the environmental assessment has shown to be challenging in methodological terms but also in indicating potential risks.

Due to the varying forms of fluoride emissions from cryolite producers and users and due to the dissociation behaviour of cryolite in the environment, two approaches are taken in the assessment. In the first approach called HF/F approach, risks arising from releases of HF to air and F to water have been evaluated using PNECs derived in the risk assessment of HF (European Commission, 2001). In this approach, the assessment has a common part with the Aluminiumfluoride (AlF_3)–risk assessment (European Commission, 2008). In aluminium smelters both AlF_3 and cryolite are used causing emissions of HF to air. These HF-emissions from aluminium smelters have been completely covered in the AlF_3-RAR, and that part has been merely copied in this assessment. A regional PEC for concentration of HF in air has been derived in the AlF_3-RAR on the basis of EPER-data. It is likely, that some of the HF-emissions of downstream uses of cryolite are not covered by EPER and hence there will be a need to adjust the present regional PEC when specific information on cryolite downstream uses becomes available.

Due to very high releases of F from cryolite producers and downstream users other than aluminium smelters to water, the aquatic assessment has been conducted, too. Assessment of aluminium smelters emitting dissolved fluoride to the aquatic compartment has been included for reasons of comparison to this assessment, although it has not been targeted in the assessment of AlF_3. It is noted, that at this phase the assessment of the aquatic compartment regarding risks arising from emissions of dissolved fluoride is necessary as demonstrated by the results from generic downstream user scenarios.

Aluminium industry and most probably also cryolite producers and other downstream users emit cryolite in particulate form. However, branch or site specific information on these emissions is available only from aluminium industry (and one producer site).

0 OVERALL RESULTS OF THE RISK ASSESSMENT[4]

CAS Number:	13775-53-6
EINECS Number:	237-410-6
IUPAC Name:	Trisodium hexafluoroaluminate

Environment

General

Conclusion (i) There is a need for further information and/or testing.

Information on downstream user industries (other than aluminium smelters), use volumes, life-cycle steps, emissions, pollution abatement techniques and processes should be provided to replace the generic exposure assessment with a more specific evaluation.

Furthermore, information on waste management and emissions from waste management step of all downstream uses should be provided. Especially aluminium smelters produce considerable amounts of cryolite waste. The amount of this waste, its management and potential emissions should be clarified.

Aquatic compartment (including sediment)

Conclusion (i) There is a need for further information and/or testing.

Conclusion (i) applies to production sites 2, 3 and 4 and downstream users other than aluminium industry. Risk ratios for the dissolved cryolite in surface water (not site 3) and in waste water treatment plants are > 1 (HF/F-approach). $PNEC_{water}$ and $PNEC_{stp,microorganisms}$ should be refined with additional testing. Long-term ecotoxicity tests on fish, daphnia and algae are needed to refine the $PNEC_{water}$.- A microbial inhibition test with higher test concentrations than in the available study is necessary for determining the actual $E(I)C_{50}$.

Conclusion (i) applies also to all downstream user sites regarding waste management (see chapter 3.3).

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to production sites 3and 5 for dissolved fluorides to aquatic environment (HF/F -approach). It also applies to aluminium smelter sites for the releases of fluorides to aquatic environment (HF/F -approach).

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[4]
Conclusion (i)	There is a need for further information and/or testing.
Conclusion (ii)	There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
Conclusion (iii)	There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Terrestrial compartment

Conclusion (i) There is a need for further information and/or testing.

This conclusion applies to a need of more specific emission data for the production sites 3, 4 and 5 and downstream user sites other than aluminium smelters. The sites should provide information on the amount of particulate cryolite emissions to air (*particulate cryolite approach*).

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

This conclusion applies for aluminium smelters and production site 2 regarding their emissions of particulate cryolite (*particulate cryolite approach*).

Atmosphere

Conclusion (i) There is a need for further information and/or testing.

Conclusion (i) applies to:

- Production sites 3, 4 and 5 should provide information on particulate cryolite emissions to air (*particulate cryolite approach*).
- to all downstream uses, except aluminium smelters (see “General”) (*HF/F approach and particulate cryolite approach*). It is expected, that also the PECregional for HF can be refined after specific information on these downstream uses becomes available.
- to all downstream user sites regarding waste management (see “General”) (*HF/F approach and particulate cryolite approach*).

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

This conclusion cover the production sites 2 and 4 as they contribute to the local ambient concentrations less than the regional background concentration of HF (*HF/F-approach*).

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iii) applies to the production sites 3 and 5 (*HF/F approach*).

Human health

Human health (toxicity)

Workers

Conclusion (i on hold) There is a need for further information and/or testing.

Conclusion (i on hold) applies for eye irritation due to insufficient data base.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iii) applies to repeated dose toxicity (local and systemic effects), and developmental toxicity. On the background of local effects in the airways air concentrations of cryolite dust at the workplace should be controlled to a level in the range of 0.1 mg/m^3 (critical exposure level for local effects after repeated exposure). In doing so also inhalation risks from other endpoints, especially systemic effects by fluorosis as result of repeated exposure and developmental toxicity are similarly and effectively mitigated.

Special attention should be given to skin contact. With respect to fluorosis and taking into account carcinogenicity the dermal exposure at the workplace should not exceed 92 mg/person/day (1.3 mg/kg/day). If this is difficult to ensure with risk management tools, dermal risk estimation might be refined by an additional suitable dermal absorption study.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

For the other toxicological endpoints the risk orientated conclusions result in no concern with the consequence that risk reduction measures are of low priority.

Consumers

Conclusion (i) on hold There is a need for further information and/or testing.

Conclusion (i) on hold applies due to insufficient data base for C&L decision.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iii) applies to repeated dose toxicity and eye irritation. Concern is expressed and risk reduction measures should be intiated for consumer use in pottery. Inhalative repeated dose treatment of cryolite can induced fluorosis at relatively low doses. Information on eye irritation indicates that cryolite may have a certain potential for eye irritation. Since eye protection measures of consumers does not exist there is concern for eye effects.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

This conclusion applies to all the other toxicological endpoints i.e. acute toxicity, irritation other than eye irritation, sensitisation, mutagenicity, carcinogenicity and reproductive toxcicty.

Humans exposed via the environment

Conclusion (i) There is a need for further information and/or testing.

Combined exposure

[keep only appropriate conclusion(s)]

Conclusion (i) There is a need for further information and/or testing.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion () applies to [click here to insert text in accordance with conclusion(s)]

Human health (physico-chemical properties)

[keep only appropriate conclusion(s)]

Conclusion (i) There is a need for further information and/or testing.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion () applies to [click here to insert text in accordance with conclusion(s)]

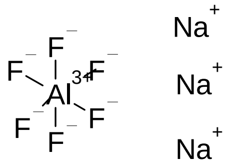
CONTENTS

Appendix A: Estimation of the concentration of particulate cryolite in air and deposition around aluminium smelters using OPS-Pro 4.1

TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number:	13775-53-6
EINECS Number:	237-410-6
IUPAC Name:	Trisodium hexafluoroaluminate
Molecular formula:	AlF_6Na_3
Structural formula:	
Molecular weight:	209.97 g/mol
Synonyms:	Aluminate (3-), hexafluoro-, trisodium Aluminium trisodium hexaflouride Cryolite Icestone Sodium aluminium fluoride Sodium hexafluoroaluminate Trisodium hexafluoroaluminate

Trisodium hexafluoroaluminate herein after referred to as cryolite is a mineral of very limited natural distribution. It was only found in large quantities on the west coast of Greenland, USA Canada and in the Urals. The composition is: 12.95 % aluminium, 54.29 % fluorine and 32.86 % sodium (Ullmann, 1988). Natural cryolite has the CAS-number 15096-52-3.

Today cryolite is produced synthetically. Synthetic cryolite has the CAS-number 13775-53-6.

Cryolite is the main constituent of the electrolytic bath in the production of aluminium (bath material) and is formed as a by-product during the electrolytic process containing 50 – 85 % cryolite. This by-product is listed as a UVCB-substance in EINECS with the CAS number 91696-24-1. It does not have same characteristics as CAS number 13775-53-6.

1.2 PURITY/IMPURITIES, ADDITIVES

Natural cryolite has a purity of 75 to 95 %. The principal impurity is siderite (< 20 %). Quartz occurs in quantities of < 5 %. Other impurities are galena, zincblende, pyrite, chalcopyrite and fluorine minerals in small quantitites (Roholm, 1937).

Synthetic cryolite has a purity of >95 %. Impurities are aluminium oxide, aluminium fluoride, lithium fluoride, magnesium fluoride, calcium fluoride (each ≤ 5 %), quartz (≤ 0.2 %), diiron trioxide (≤ 0.1 %). In Table 1.1 a short summary about the composition of the three forms of cryolite is given.

Table 1.1 Overview of the composition

Name	Natural cryolite	Synthetic cryolite	Flux remnant from the aluminium production
CAS number	15096-52-3	13775-53-6	91696-24-1
purity (%)	75-95	> 95	50 - 85
impurity (%)	siderite < 20 quartz < 5 galena, zinc blende, pyrite, chalcopyrite, fluorine minerals: each in small amounts	diiron trioxide (CAS no. 1309-37-1) ≤ 0.1 quartz ≤ 0.2 aluminium oxide (CAS-no. 1344-28-1), aluminium fluoride (CAS-no. 7784-18-1), magnesium fluoride (CAS-no. 7783-40-6), calcium fluoride (CAS-no. 7789-75-5): each < 5 %	n.n.

1.3 PHYSICO-CHEMICAL PROPERTIES

In the following table the physico-chemical properties of natural and synthetic cryolite are listed:

Table 1.2 Summary of physico-chemical properties for natural cryolite

Property	Value	Reference
Physical state	clear or white to yellowish, sometimes reddish or black solid monoclinic cube-like crystals	Roholm (1937)
Melting point	1009 – 1012 °C	Ullmann (1988)
Boiling point	No information available	
Relative density	2.97 at 29 °C	Ullmann (1988)
Vapour pressure	253 Pa at 1009 °C	Ullmann (1988)
Water solubility	0.39 g/l at 25 °C (pH unknown)	Roholm (1937)
	0.9 g/l at 20 °C (pH 4 – 7) 1)	Sjöberg (2002) 2)
	ca. 400-500 mg/l at 20 °C (pH 8)	Sjöberg (2002) 2)
	ca. 100-200 mg/l at 20 °C (pH 8.5)	Sjöberg (2002) 2)
	ca. 20-40 mg/l at 20 °C (pH 10)	Sjöberg (2002) 2)
	144 mg/l at 20 °C (pH 7.7-7.9)	IWL (1998) 2); after 24 h stirring; test medium of *Daphnia* ecotoxicity test (see section 3.2.1.1.2)
Partition coefficient n-octanol/water (log value)	not applicable (inorganic complex salt)	
Granulometry		
Conversion factors		
Flash point	not conducted (solid)	
Autoflammability	not determined (inorganic complex salt)	
Flammability	not determined (inorganic complex salt)	
Explosive properties	not determined (inorganic complex salt)	
Oxidizing properties	not determined (inorganic complex salt)	
Viscosity		
Henry's constant		
Surface tension	not determined (inorganic complex salt)	

1) Sjöberg calculated in his report the water solubility of cryolite as a function of the pH. The solubility is approximately constant in the pH range 4 – 7 and results to 4.5 mMol/l. This value based on cryolite forming about 25 % AlF_3, 55 % AlF_4^- and 19 % AlF_5^{2-} in water. In the acidic range the solubility increases due to the extensive formation of HF. With pH > 7.5 the solubility decreases due to the formation of $Al(OH)_3$. It is noted, that water solubility as calculated by Sjöberg is a theoretical maximum solubility. In figure 1.1 the predominance area diagram of the speciation as a function of pH and the free fluoride concentration as $\log[F^-]$ is visualised in an aquatic solution containing F and Al.

2) Water solubility is not specified for natural or synthetic cryolite.

Table 1.3 Summary of physico-chemical properties for synthetic cryolite

Property	Value	Reference
Physical state	white crystalline solid	
Melting point	1027 °C	Solvay (1997) [1)]
Boiling point	no information available	
Relative density	2.95 at 20 °C	Solvay (1997)
Vapour pressure	2.5 mbar (= 250 Pa) at 1027 °C	Solvay (1997)
Water solubility	0.41 g/l at 25 °C (pH unknown) 0.9 g/l at 20 °C (pH 4 – 7) [1] in table 1.1 See table 1.1 for other values	Rethmann (1996) Sjöberg (2002)
Partition coefficient n-octanol/water (log value)	not applicable (inorganic complex salt)	
Granulometry		
Conversion factors		
Flash point	not conducted (solid)	
Autoflammability	not determined (inorganic complex salt)	
Flammability	not determined (inorganic complex salt)	
Explosive properties	not determined (inorganic complex salt)	
Oxidizing properties	not determined (inorganic complex salt)	
Viscosity	6.7 mPa.s	Solvay (1997)
Henry’s constant		
Surface tension	not determined (inorganic complex salt)	

[1)] For the melting point, relative density and vapour pressure only data of a safety data sheet are available. In comparison with the data for natural cryolite and under consideration of the purity these values are acceptable.

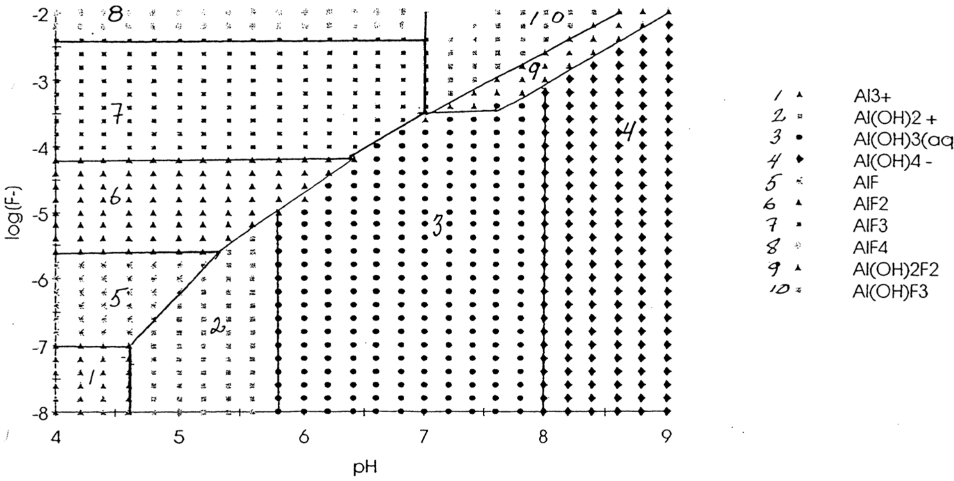


Figure 1.1. Predominance area diagram of the Al3+-F-.OH- system (Sjöberg, 2002)

1.4 CLASSIFICATION

1.4.1 Current classification

Classification according to Annex I of Directive 67/548/EEC:

T	Toxic	
	R48/23/25	Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed
Xn	Harmful	
	R20/22	Harmful by inhalation and if swallowed
N	Dangerous for the environment	
	R51-53	Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment

1.4.2 Proposed classification

T	Toxic	
	R48/23/25	Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed

On the basis of the data submitted, the current classification of cryolite is confirmed. The corroboration for classification is based on the hazard identification determined by the selected inhalation studies (90-day study and 5-months study, both in rats) according to the lowest concentration causing serious health effects. The toxic profile of cryolite is dominated by its systemic toxicity. The critical adverse effects for serious damage to health after prolonged inhalation or the oral route of exposure are distinct toxic effects on the bones and teeth. In a 5-month inhalation study with rats toxic effects on the bones and teeth were observed at ≥ 1 mg/m^3 cryolite (6h/d, 6d/week, whole body exposure (Plotko et al., 1973)). Local effect in rats after subchronic inhalation of predominantly respirable cryolite dust was lung toxicity seen as interstitial pneumonia at a low concentration of 1.04 mg/m^3 (0.001 mg/l) cryolite (90-day inhalation study, 6h/d, 5d/week (BG Chemie, unpublished report, 1997)). These identified concentrations are far below the cut-off value for attributing R48/20 (0.25 mg/l) in a 90-day inhalation study. The observed critical effect levels presented in experimental animals are comparable in magnitude to the effect dose concentrations described in man occupationally exposed to cryolite dust. In male pot room workers employed in aluminium plants skeletal fluorosis was observed at average fluoride concentrations of 2.4 to 6.0 mg/m^3 (on average 8h/d, with 36-50 % content gaseous fluoride) (Kaltreiter et al., 1972). In humans skeletal fluorosis was observed at 6 mg/m^3 and increased bone density was noted in workers of a phosphate fertilizer manufacturing plant exposed to concentrations of about 3.38 mg/m^3 fluorides in the form of dusts and gases over a period ranging from 4.5 to 29.9 years with an average of 14.1 years (Derryberry et al., 1963). In a more recent study skeletal changes were determined in workers employed at an aluminium plant in Poland exposed to hydrogen fluoride concentrations of 0.5 mg/m^3 (Czerwinski et al., 1988).

The critical effect following repeated dietary exposure to cryolite in experimental animals was fluoride accumulation and the appearance of its consequence: non-neoplastic bone disease - skeletal fluorosis - was observed in rats (males/females) from the lowest dose tested of 3.8/4.5 mg/kg bw/d and in dogs from 17 mg/kg bw/d upward, respectively (90-day studies, EPA 1996). Toxic effects on the bones and teeth were also reported in early repeated dose toxicity studies in rats. Findings on the teeth were noted at 1 mg/kg bw/d, and development of abnormally structured osseous tissue and renal effects at 5 mg/kg bw/d (Roholm, 1937a,b). These identified dose levels are far below the cut-off value for attributing R48/22 (50 mg/kg bw/d) in a 90-day study. Comparable effect dose levels were also described in man. In occupationally exposed workers 20-80 mg of fluoride per day caused skeletal effects (Roholm, 1937 a,b). Long-term intake of fluoride in water and foodstuffs is the primary causative factor for endemic skeletal fluorosis in humans. Very high intakes have been observed in areas world-wide in which the environment is rich in fluoride and where humans consume groundwater containing high concentrations of fluoride. There is clear evidence from India and China that significant skeletal effects are seen at a total intake of 14 mg fluoride/day, equivalent to about 0.2 mg/kg bw/d calculated on a assumed body weight of 70 kg person (WHO 2002).

Thus, classification and labelling with T, Toxic, R48/23/25 (Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed) is confirmed.

Xn Harmful

R20 Harmful by inhalation

After inhalation of cryolite an acute LC_{50} of 4470 µg/l was estimated in rats (4-h exposure). Therefore, a classification as harmful and labelling with R20 is appropriate.

Based on the results of available tests on acute oral toxicity, cryolite shows no relevant acute oral toxicity with LD50 values for rats > 5000 mg/kg bw. Therefore, labelling with R22 is not appropriate.

Xi Irritating

R36 Irritating to eyes

Scarce data on eye irritation indicate a moderate potential of cryolite to induce eye irritation, but due to a low quality of available data, a final assessment is not possible. In order to avoid additional animal testing, a precautionary classification with R36 is proposed.

Xn; Repr.Cat.3; R63 Possible risks of harms to the unborn child

On the basis of the data submitted (two-generation reproduction toxicity study with rats) cryolite needs to be classified and labelled as a reproductive toxicant. The critical adverse effects that had been revealed were impairment of postnatal growth evidenced by significantly decreased pup body weights during lactation as well as gross pathological changes in several organs (kidney, liver, heart) of the pups resulting from dose levels without any significant systemic toxicity.

Cryolite is at present included in Annex I of Directive 67/548/EEC with a classification N; R51-53 for the environment.

The present classification is according to ECB (ECB/61/95-Add 22) based on a LC_{50}(98h) of 47.0 mg/l for rainbow trout (Johnson and Finley, 1980), EC50(48h) of 5 mg/l for *Daphnia pulex* (Sanders and Cope, 1966) and NOEC(96h) of > 5000 mg/l for algae (Bayer AG data; as cited in ECB/61/95-Add 22). First two of these values have been assigned by the Rapporteur a reliability grade of 4 (not assignable; see section 3.2) and for the third value no documentation at all has been available to the Rapporteur.
Reliable acute ecotoxicity test results are available for algae ($EC_{\mu50}$ = 8.8 mg l^{-1})(Solvay Pharmaceuticals, 2008b), invertebrates (EC_{50} = 156 mg l^{-1})(IWL, 1998) and fish (LC_{50} > 100 mg l^{-1}) (Solvay Pharmaceuticals, 2008a). Due to the sensitivity of algae, the present classification R51/53 is confirmed.

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

2.1.1 Production processes

Synthetic cryolite can be obtained by reaction of hydrofluoric acid with aluminium hydroxide to form fluoroaluminium acid. After treating H_3AlF_6 with NaCl cryolite precipitates:

$$6HF + Al(OH)_3 \rightarrow H_3AlF_6 + 3H_2O$$

$$H_3AlF_6 + NaCl \rightarrow Na_3AlF_6 + 3HCl$$

In addition, H_2SiF_6 can be used as starting material in a similar reaction where the precipitated silicic acid is separated from the reaction solution:

$$H_2SiF_6 + 2\,Al(OH)_3 \rightarrow 2\,AlF_3 + SiO_2 + 4\,H_2O$$

$$2\,AlF_3 + 6\,NaCl \rightarrow 2\,Na_3AlF_6 + 6\,HCl$$

Cryolite is put on the market according to the producers in powder form. No information on the size of the particles was provided with the exception of the use of words “grinded”, “granular”, “flour“ and “fine” to distinguish different particle sizes.

Natural cryolite (CAS 15096-52-3) was extensively mined in the early 20th century with substantial amounts found in Greenland and smaller ores in Russia and US. Today natural sources are essentially exhausted and synthetic cryolite is used instead (Ullmann's, 1985; Römpp, 1997).

Cryolite is the main constituent of the electrolytic bath in the production of aluminium (further description on aluminium production in Chapter 3.1.2.3.1). During the electrolytic process cryolite is also formed as a by-product. Alumina (calcinated metallurgical grade Al_2O_3), the raw material of aluminium, contains normally 0.2 – 0.5 % Na_2O w/w which reacts with aluminium fluoride present in the electrolytic bath:

$$3\,Na_2O + 4\,AlF_3 \rightarrow 2\,AlF_3 \cdot 3\,NaF + Al_2O_3$$

This reaction is separate from the reduction reaction of alumina to aluminium in Hall-Héroult process, which is the only smelting process used today industrially. Based on the molar masses of Na_2O and cryolite, approximately 2 times the mass of Na_2O of excess cryolite results, if no other sources of sodium are available and if losses of cryolite are excluded. In this case, one tonne of alumina fed to the process would produce normally ca. 4-10 kg excess cryolite. According to EAA (2007a), two tonnes of alumina is reduced to one tonne of aluminium. Hence, one tonne of primary aluminium is based on the assumptions above accompanied by ca. 8-20 kg (0.8-2 % w/w) of excess cryolite as by-product.

In modern smelters excess bath material is tapped from time to time. Concentrations of bath components vary within and between the sites depending on the alumina quality, other substances are added to the bath and on other process parameters. An example of the contents of bath material has been provided by Alcoa (Solvay, 2007):

Cryolite	51-53 %
Al_2O_3	45 % (WS: insoluble or < 1 mg/l according to IUCLID
AlF_3	7 % (WS: 5.3-9.4 at pH 5.9, European Commission, 2008)
CaF_2	3 %
MgF_2	1.2 %
Carbon	0.8 %
Fe_2O_3	0.27 %
SiO_2	0.25 %
Moisture	0.25 % (Rapporteur assumes H_2O is meant by this)

It is noted, that the Rapporteur considers that bath material has another identity than cryolite. Already based on the very low water solubility of the substantial constituent Al_2O_3, properties of cryolite do not resemble the properties of bath material.

2.1.2 Production capacity and tonnage

Intended production

Cryolite is produced at four sites in the EU-15. All sites provided information on exposure. Sites 2, 3 and 4 updated their information in 2006. Production volume of these four sites is 23,561 t/a of which 11,500 t a^{-1} is exported. The volume for the European market is thus 12,061 t/a. Production capacity was provided by three companies and it makes 43,200 t/a.

Table 2.1 Production sites of synthetic cryolite in the EU-15

Company	Location
Derivados del Fluor S.A.	Spain, Onton
Fluorsid S.p.A.	Italy, Assemini (Cagliari)
I.C.I.B. S.p.A.	Italy, Treviglio (BG)
Solvay Fluor und Derivate	Germany, Bad Wimpfen

By-production in aluminium smelters

Eleven aluminium smelters have provided information under Regulation 93/793/EEC. Four of these sites reported not to sell bath material on a regular basis or to use it completely for own purposes. One site reported to have imported cryolite. Total production volume of the eleven sites involved is 4,500 t/a (as cryolite). Of this amount, 700 t/a is sold to the EU market and 3,800 t/a exported. These volume estimates are based on the information from the years 1996-1998.

Table 2.2 presents the primary aluminium production sites located in European countries. Primary aluminium production in the year 2005 amounted to 3,101,000 t/a in the EU-27. The total aluminium production volume for the EU-15 and Norway was 3,758 kt/a in 2003 (EAA, 2006a).

The production rate of excess bath as cryolite is ca. 0.5-2 % w/w of aluminium produced. This range is derived from the estimates of three smelters which provided infomation under Regulation 93/793/EEC and agrees with the estimation approach presented in chapter 2.1.1. However, according to the information of industry, this rate may not apply to all sites as the process conditions vary largely from site to site. Multiplying the EU-15+NO volume of primary aluminium production (3,758 kt /a) by the production rate of excess bath formed gives a volume of 19,000 – 75,000 cryolite, which is considerably higher amount than the reported production volume from notified smelter sites (4,500 t/a). There may be several reasons for the difference in these volumes. EAA (2008a) has provided an estimate of 24,000 t/a cryolite in the excess bath material produced at the European aluminium smelter sites.

2.2 USES

2.2.1 Introduction

All sites producing cryolite intentionally and all aluminium smelters which provided information under Regulation 93/793/EEC provided information on uses and their shares of the volume sold.

The main volume of intentionally produced cryolite is used as bath material in aluminium smelters. Table 2.2 lists the primary aluminium production sites in Europe. Both synthetic cryolite and bath material from own by-production is used in the European smelters for the cryolite bath when new or relined aluminium pots are taken to use. The bath volume used for aluminium production can be increased, e.g., by the use of own excess cryolite. However, the volume is increased only if the aluminium production volume is increased. The volume of bath material in use in pots was reported only by six of the eleven smelter sites which notified under 93/793/EEC (9,350 t in total). The excess bath material is either stored for later use or sold to third parties for use in other aluminium smelters.

Cryolite is also used as filler in synthetic resins for abrasives and as binding agent for cutting or grinding discs. Closer information on the industrial categories for these uses is not available and hence the categories indicated in table 2.3 are assumed for the assessment.

Minor uses are the use as opacifier in glass and enamel industry, in pyrotechnics and in ceramic industry. According to the producers these uses make together ca. 13 % of the use volume. No further information was provided on these uses. These uses are covered in the assessment by the industrial category “others” (IC 15).

Cryolite is used in the United States as a plant protection product (insecticide) for i.a. vegetables and fruits (U.S.EPA, 1996). This use is not registered in the EU.

The SPIN (2006) database indicated for the four included Nordic countries that a volume of 2240.2 t in total in altogether 43 preparations were on the market in the year 2004 (Danish data from the year 2003). The most recent use data (Finland and Norway for the year 2004) indicate a use of 1853.3 t in the industrial category “manufacture/industry of basic metals” (83 % of total amount). The other industrial categories between the years 2001 and 2004 have been “industry for fabricated metal products, except machinery and equipment”, “industry for other non-metallic mineral products” and “manufacture of chemicals and chemical products”, whereas the use categories were “raw materials for production of metals”, “others”, “fillers” “process regulators” and “flux agents for casting”. This information is in accordance with the data provided by industry.

Table 2.2 Primary aluminium production sites in Europe (EAA 2006b). Some of the sites were closing by 2006.

Company	Location(s)
Elkem Lista	Norway
Elkem Mosj.	Norway
Hydro Årdal	Norway
Hydro Høyan	Norway
Hydro Karm	Norway
Hydro Sund	Norway
Søral AS	Norway
Trimet Aluminium	Germany
[Hydro Stade]	[Germany]*
Hydro Neuss	Germany
HAW	Germany
Corus Voerde	Germany
Aluminium Delfzijl	Netherlands
PNL Vlissingen	Netherlands
Anglesey Al.	United Kingdom
Alcan Lynem	United Kingdom
Alcan Lochab	United Kingdom
Nordural	Iceland
Alcan Isal	Iceland
Kubikenborg AB	Sweden
Talum	Slovenia
Slovalco	Slovakia
Aluminium of Greece	Greece
[Alcan Lannemezan]	[France]*
Alcan Dunkirk	France
Alcan St. J. De Maurienne	France
Alcoa San Ciprian	Spain
Alcoa Aviles	Spain
Alcoa La Coruna	Spain
Alcoa P. Vesme	Italy
Alcoa Fusina	Italy
[Alcan Steg]	[Switzerland]*

* Activity stopped according to EAA (2007b,c).

Table 2.3 Known uses of cryolite from intended production.

Industry category*	Use category*	Quantity used t/a	Percentage of total use
Aluminium smelters (primary and recycled; IC 8)	Flux agent (UC 24)	5,343	44.3
Engineering industry (IC 16)	Filler in synthetic resins for abrasives (UC 55/0)	3,750	31.1
Metal extraction, refining and processing industry (IC 8)	Binding agent in cutting or grinding discs (UC 2)	1,353	11.2
Pyrotechnic industry Glass industry Ceramics industry (IC 15/0 = others)	Colouring agent, opacifier (UC 10).	684	5.7
Metal extraction, refining and processing industry (IC 8)	Opacifier in enamel production (UC 10 assumed)	931	7.7
Total		12,061	100

* Descriptions of uses and IC/UC numbers provided by the notifiers are not consistent and partly lack information on volumes. The contents of the table is therefore an interpretation of the Rapporteur. Background information on the compilation of the table is confidential.

2.2.2 Scenarios

The assessment focuses on the following local scenarios:

Intended production of cryolite: for this life-cycle step, four specific site scenarios are presented.

Use as flux agent and by-production in aluminium smelters (IC8/UC24/processing): this life-cycle step is considered to be a processing step. Thirty two specific sites are included (also the non-EU European smelters). No downstream uses exist for the by-production, because the production of excess cryolite not used for own purposes is sold to other smelters for the start of a new or renewed pot. Instead, waste containing cryolite and other fluoride compounds is produced. Spent pot linings (cathode coal), anode butts and scrubber waste (water) contain fluorides (EAA, 2007a). A considerable part of fluoride is recovered at the site and used at the site. A part of waste is either disposed of into designated landfills or recycled externally.

Use as filler in synthetic resins for abrasives (IC16/UC55 or UC0): no specific information regarding this use has been provided. It might be possible, that this use could be allocated under plastics industry (IC 11), for which an emission scenario document (ESD) is available. The ESD would result lower releases than if the use is allocated to IC 16. However, as the producers have not indicated that the use would occur in plastics industry, but use in “abrasives industry” and IC 16 have been reported, it is decided to use IC 16 for this assessment until more specific information will be provided. A generic scenario is derived based on the assumption that the first life cycle-step for this use is *formulation* followed by industrial use (*processing*). The step “processing” covers also possible releases during service life in industry. TGD foresees for IC 16 also a *private use* step. It is considered that more information on the possible uses in abrasive articles is needed before releases from consumer use are estimated.

Use as binding agent in cutting or grinding discs (IC8/UC2): no specific information for this use has been provided. Therefore a generic scenario is derived based on the assumption that the first life cycle-step for this use is *formulation* followed by industrial use (*processing*).

Use as colouring agent or opacifier (IC15 or IC 0/UC10): no specific information for this use has been provided. The life-cycle for the four industries reported (glass industry, pyrotechnics, ceramics industry, metal industry) are covered by the same generic scenarios. Since no adequate information regarding the shares of these uses of the total volume has been provided, no difference is made between the four branches (collective use volume) and a common generic scenario is derived. We assume that the first life cycle-step for this use is *formulation* followed by industrial use (*processing*). It can be expected that the products of these industries are object of wide dispersive use. Therefore, scenarios for consumer use and waste management may be necessary. However, in order to develop sufficient exposure estimation for these life-cycle steps, more specific information is needed.

2.3 TRENDS

No information on recent trends in production volume is available. The production trends of bath material in the aluminium smelters can be assumed to be correlated with the trends in primary aluminium production. According to the European Aluminium Association (EAA, 2006), primary aluminium production has increased steadily during the last ten years whereas the increase from the year 2000 to the year 2001 was 2.2 %.

2.4 LEGISLATIVE CONTROLS

The Directive on Integrated Pollution Prevention and Control (IPPC; 96/61/EC) regulates chemicals industry, primary aluminium production and recycling, glass industry and ceramics industry. IPPC reference documents for Best Available Technology (BREFs) have been compiled for all these industrial categories. In addition, these industries have to report their emissions on certain pollutants over the Member State authorities to the European Pollutant Emission Register (EPER). Fluoride and HF –emissions are covered by the reporting requirements (with certain reporting thresholds).

Germany has derived under the Directive 76/464/EEC implementation a surface water quality standard for fluoride, which is 1 mg F l^{-1} (annual mean) (LAWA, 2003). The German ground water quality standard for fluoride is 0.750 mg l^{-1} (LAWA, 2004).

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 General discussion

The dissociation behaviour of cryolite poses a specific challenge for the risk assessment. A scientifically most sound approach to evaluate potential risks caused by cryolite production and uses would be to define first in realistic worst case environmental conditions few most relevant transformation products of cryolite. Fate of these transformation products would be modelled and PECs and PNECs for each of the transformation species would be derived. RCRs for each transformation product would result. Such an approach would need a very large amount of test data (of which a part would need to be generated) and a very complicated exposure assessment. In addition, the amount of relevant transformation products might be too high to make such an assessment feasible. Furthermore, the most abundant forms are not necessarily identical for all compartments.

Instead, a simplistic approach is taken in this report which is named “HF/F-approach”. It covers all gaseous HF- and dissolved F-emissions reported to be released by the known sites. In addition, for the generic scenarios the releases are assumed to be at the point of release in form of free fluoride ion (or in air as HF). PECs for HF and F are calculated based on their properties and compared to PNECs derived for F and HF.

In addition, risk assessment is conducted separately for particulate cryolite. This form is, however, considered relevant only for terrestrial compartment in a limited way.

The production and use of cryolite causes releases of aluminium (complexes). Risks to aluminium have been reviewed by WHO/IPCS (1997) and its risks should be assessed in the EU in a separate risk assessment. In line with the assessment of aluminium fluoride (CAS 7784-18-1) under Regulation 93/793/EEC, aluminium is not the focus of this assessment.

3.1.2 Environmental releases

A part of cryolite is released according to site specific data in already dissociated/transformed form into the environment. The form at the point of emission can be expected to depend i.a., on the temperature, pH as well as on the abundance and type of other substances and particles in the emission. The generic emission factors of the TGD reflect the losses of the parent substance from the life-cycle step in question and the releases estimated for the generic scenarios are therefore related first to cryolite. In the HF/F approach, 1 kg cryolite release corresponds to 0.54 kg F$^-$ or 0.57 kg HF formed (applied to generic scenarios).

The specific emission data of the producer sites have been provided in a variety of forms of F (“HF”, “particulate F”, “F$^-$“, or unspecific “total F” or “F”). Hence, emissions presented for the production sites in the following chapters are in reality not in all cases directly comparable with each other. However, in the lack of detailed information on the form of emitted F, assumptions have been made (as denoted in table 3.3)

Other anthropogenic sources than producers and downstream users of cryolite are contributing to the emissions of fluoride compounds significantly. Tables 3.1 and 3.2 denote the emissions reported to the European Pollutant Emission Register (EPER) by sites subject to the IPPC-Directive and exceeding the reporting thresholds (2 t F/a to water; 5 t F or HF/a to air). It is noted, that due to the rather high reporting thresholds, the total releases covered by EPER may not reflect the total European releases of fluoride and fluorine compounds.

Table 3.1 Fluorine emissions from EU-15 (Ireland not included) to air from the activities covered by the IPPC-Directive in the year 2001. Number of sites included is 238 (EEA 2006).

Activity	Emission to air (t HF a^{-1})
Combustion installations > 50 MW	6,361.15
Metal industry and metal ore roasting or sintering installations, Installations for the production of ferrous and non-ferrous metals	3,462.38
Installations for the production of cement clinker (>500t/d), lime (>50t/d), glass (>20t/d), mineral substances (>20t/d) or ceramic products (>75t/d)	1,682.89
Basic organic chemicals	12.11
Basic inorganic chemicals or fertilisers	295.54
Installations for the disposal or recovery of hazardous waste (>10t/d) or municipal waste (>3t/h)	26.70
Installations for the disposal of nonhazardous waste (>50t/d) and landfills (>10t/d)	97.00
Industrial plants for pulp from timber or other fibrous materials and paper or board production (>20t/d)	7.00
Total	**11,944.77 t**

Table 3.2 Emissions of fluoride and inorganic fluoride compounds from EU-15 (Ireland not included) to water and waste water (external wwtp) from the activities covered by the IPPC-Directive in the year 2001. Number of sites emitting F is 198 (EEA 2006).

Activity	Emission to water (t F a^{-1})	Indirect release to water (transfer to an off-site waste water treatment) (t F a^{-1})
Combustion installations > 50 MW	255.92	4.13
Mineral oil and gas refineries	185.62	-
Coke ovens	-	48.10
Metal industry and metal ore roasting or sintering installations, Installations for the production of ferrous and non-ferrous metals	2,230.52	63.90
Installations for the production of cement clinker (>500t/d), lime (>50t/d), glass (>20t/d), mineral substances (>20t/d) or ceramic products (>75t/d)	11.75	-
Basic organic chemicals	1,784.76	128.28
Basic inorganic chemicals or fertilisers	5,567.97	90.66
Biocides and explosives	7.00	3.40
Pharmaceutical products	12.70	5.17
Installations for the disposal or recovery of hazardous waste (>10t/d) or municipal waste (>3t/h)	58.29	11.13

Activity	**Emission to water (t F a^{-1})**	**Indirect release to water (transfer to an off-site waste water treatment) (t F a^{-1})**
Installations for the disposal of non-hazardous waste (>50t/d) and landfills (>10t/d)	24.71	4.77
Industrial plants for pulp from timber or other fibrous materials and paper or board production (>20t/d)	2.13	-
Slaughterhouses (>50t/d), plants for the production of milk (>200t/d), other animal raw materials (>75t/d) or vegetable raw materials (>300t/d)	-	2.30
Installations for surface treatment or products using organic solvents (>200t/y)	81.95	55.80
Total	**10,223.32**	**417.63**

In the category of metal industry, 48 facilities are included in EPER as emitting fluorine and its compounds to air.

3.1.2.1 Release from production

Three of four production sites provided data on their emissions to the Rapporteur. Site 3 did not provide any data on exposure. The sites did not always indicate in which form the release is emitted. For the emissions to air the form HF and for the emissions to WWTP or surface water F^- are assumed for these sites. The production sites have been identified under the EPER (EEA 2006) to belong to the activity of “basic inorganic chemicals or fertilisers”. This category corresponds to the IC 2 of TGD. According to the process descriptions of the producers, production takes place in a continuous process. The whole production volume is isolated and transported off-site to the customers. Accordingly, the main category 1b is applied.

Releases of by-production from aluminium smelters are covered by the releases from use of cryolite (see chapter 3.1.2.3).

Table 3.3 Site specific emissions from intended production to air and aquatic compartment based on reported values from the sites or based on generic estimates.

Site nr.	Emission to air (kg HF a^{-1})	Particulate cryolite emission to air (kg F a^{-1})	Release to waste water (kg F^- a^{-1})	Emission to surface water (after treatment) (kg F a^{-1})	Nr. of emission days (2)	Notes
2	18 (2)	102 (2)	NA (1)	576 (2) 3,280 (3)	60	Continuous, wet process (2). Wet scrubber assumed on the basis of description. The site specific information available on release to surface water is assumed to be the amount of dissolved F. The EPER –value is assumed to be the total F-release including dissolved and particulate F. The form of particulate release to air is assumed to be kg F a^{-1} for further calculations. Gaseous emission to air was reported as kg F a^{-1} (2); The form HF will be assumed for the assessment. The emissions cover also other sources of the site (2).
3	5,322.5 (4)	NA (5)	NA (1)	12,000 (3)	120	Continuous, wet process (2).The site has also other releases of F (2) but the share of cryolite was not reported. Effluent is treated and released to open sea (2). EPER does not differentiate between dissolved and particulate F -release.
4	69.4 (2)	NA (5)	NA (1)	115,000 (3)	170	Continuous process, wet scrubber involved (2). Release to wwtp cover also other sources than cryolite production but the share of cryolite from the total F release is high (2). EPER does not differentiate between dissolved and particulate F -release.
5	5,600 (2); year 1996	NA (5)	4,260 (3)	5,100 (2); year 1996	330	Continuous, wet process and wet scrubber. Waste water transferred to external wwtp for industrial waste waters (2). Release to wwwtp cover also releases from AlF_3 –production (2). Effluent released to sea (2). EPER does not differentiate between dissolved and particulate F -release. The form of emission to air was not given by the site. The value is assumed to be gaseous HF.

(1) NA = no site specific information is available.

(2) Information provided by the site

(3) Estimate from EPER for the year 2004 (EEA, 2007). These values are used for the exposure estimation of dissolved F in recipient water. Information on the emissions of particulate F or more specifically of particulate cryolite should be provided.

(4) No site specific information is available. The cryolite release is estimated using the generic emission factor: EF(air) = 0.005 from table A.1.1 of TGD is applied based on vapour pressure of HF (1033 hPa; EU, 2001) and MC 1b. The resulting release is converted to HF according to the conversion factor of 0.572 kg HF/kg cryolite.

(5) Information on the release of particulate cryolite to air should be made available.

3.1.2.2 Release from formulation

Table 3.4 Total releases of four cryolite uses including formulation step (generic assessment).

MC/IC/UC	Use	Release to air (t cryolite a^{-1})	Release to waste water (t cryolite a^{-1})
3/16/55 or 0	Filler in synthetic resins for abrasives	93.8 (53.5 as HF)	11.3 (6.1 as F)
3/8/2	Binding agent in cutting or grinding discs	33.8 (19.3 as HF)	4.05 (2.2 as F)
3/15 or 0/10 contains also 3/8/10	Colouring agent, opacifier	40.4 (23.0 as HF)	4.85 (2.6 as F)

Assumptions:

Formulation process employs a volume of formulation ≥ 1,000 t a^{-1} The emission factor for air has been chosen by using the PC-properties of HF.

Table A 2.1: EF(air) = 0.025; EF(wastewater) = 0.003

3.1.2.3 Release from industrial/professional use

3.1.2.3.1 Aluminium smelters

Following general information on releases has been gathered directly from exposure information forms and accompanying reports: releases emerge mainly from the pots, where alumina in powder form is fed onto the cryolite bath where it melts gradually. Bath temperature is around 950 ºC. The aluminium resulting from electrolysis settles to the bottom of the pot from and it is tapped from time to time. The pots are hooded tightly and the release to air is sucked off and treated in all sites in a scrubber before the release to air. Sites using wet scrubber cause releases to waste water, whereas sites with dry scrubbers do not have releases from the process to aquatic environment.

Both gas (mainly hydrogen fluoride) and dust (carbon dust, fluorides, aluminium oxides) are released from the pots to air. Water has to be avoided in the electrolysis due to risk of explosion. Some sites have reported to use only dry cleaning methods for pots in order to avoid water. It is assumed that all other sites use dry cleaning as well. Releases to pot room air are caused when the hoods are removed for renewal of anodes, for relining the pot, for tapping aluminium or excess cryolite and for adding bath constituents to the bath.

Emissions from European primary aluminium production sites to air and water in 2002 are presented in table 3.5. The data was provided by EAA (2006a) and the same data is used in the risk assessment of AlF_3 (European Commission, 2008). According to EAA (2006a), the emissions cover both the use of AlF_3 and cryolite. The risk assessment of AlF_3 has carried out the assessment for emissions of HF to air and the results are presented in this report as a direct copy for these parts. EAA (2007b) has provided newer data on HF and total F emissions to air, but these values are presented as information only. In this report, fluoride emissions to surface water and particulate emissions to air (and water if possible) are covered. Despite the fact that AlF_3 risk assessment did not cover the aquatic compartment due to its irrelevancy for aluminium smelters, the aquatic compartment is covered in this assessment for reasons of comparison. The aquatic assessment is necessary to conduct for the producers and other downstream users due to the very high aquatic fluoride emissions.

The particulate emissions to air in Table 3.5 are the total fluoride emissions subtracted by HF emissions. Particulate emission to air contains bath material and aluminium oxide. According to EAA (2008b), the gases collected from the cell contain varying amounts of cryolite, atmolite and chiolite, depending on the local conditions.

To find out the fraction of cryolite in particulate F –releases, sampling of dust for analysis of cryolite has taken place at 8 plants (sites no. 6, 7, 14, 18, 20, 22, 23 and 25). The samples were collected from roof constructions or at the exit from the roof ventilators in order to be representative of dust being emitted to the air. The reason for collecting dust in these locations instead of taking air samples is the large quantity of dust required for this analysis, generally more than 25 g. The analysis was carried out with X-ray diffractometer. The first step of the analysis is a scan showing the X-ray patterns of the crystal phases, including phase diagram analysis and identification of cryolite phase. After this, a semi quantitative calculation was performed taking into account that the samples have nano-crystal phases and amorphous patterns (EAA, 2008b).

Individual measurements for 12 samples showed an average cryolite content of 10,5% with a minimum value of 5% and a maximum at 21%. Results from three plants are not included, as they did not separate different sodium aluminium fluoride compounds present. The discarded results from three plants showed a fraction of 22 to 29 % for total sodium aluminium fluorides (including cryolite, atmolite and chiolite). A sample of suspended solids in water effluent from one of the few plants using sea water for ventilation air scrubbing showed no cryolite in the dust (0,00005%). In the clean gas from a dry scrubber the cryolite concentration was for all samples lower than 9%, in most cases 1-2% (EAA, 2008b).

It is noted, that only a summary of the study was provided without analytical background documentation. Additionally, the two largest emitters were not included in the study. However, it is considered based on the study summary, that the fraction of 21 % of cryolite in particulate emissions to air is plausible enough as a realistic worst case fraction for this assessment as well as that no particulate cryolite is emitted to water from water scrubbers.

An exposure assessment of particulate cryolite is conducted for the sites with largest and smallest particulate emissions to air.

The emissions to surface water have been reported as total F –emission. In the absence of more detailed data than provided in table 3.5, aquatic exposure is calculated for the HF/F-approach further assuming that the total emission is in the form of free fluoride ion.

Table 3.5 Aluminium production capacity in 2005 (EAA, 2006b) and emissions of fluoride compounds to air and water from aluminium smelters (EAA, 2006d).

Location number	Production capacity (t Al a^{-1})	Total F-emission to air (t F a^{-1})	HF - emission to air (t HF a^{-1})	Particulate F emission (= Total F-emission to air – HF emission to air) (t F a^{-1})	Particulate emission of cryolite to air; 21 % of total particulate F-emission is assumed to be cryolite (t Al F_6Na_3 a^{-1})**	Total fluoride emission to surface or marine water (after treatment) (t F a^{-1})
1	300,000	86.7	50.8	35.9	13.89	59
2	281,000	124	47.2	76.8	29.71	
3	255,000	119.3 (126*)	68 (86*)	40	15.47	
4	229,000	154.8	136.8*	18	6.96	240 (188)*
5	224,000	118.6 (106*)	35 (49*)	57	22.05	338
6	222,000	60.2	53.2*	7	2.71	
7	219,000	174 (102*)	86 (40*)	62	23.98	
8	185,000	73.6	47.8	25.8	9.98	72
9	176,000	97.9	69.4	28.5	11.02	
10	169,000	188	140	48	18.57	
11	166,000	246.7	193.4	53.3	20.62	
12	164,000	85.9 (60*)	63.2 (46*)	14	5.42	159
13	158,000	30.1	26.6	3.5	1.35	
14	151,000	30	10	20	7.74	
15	150,000	505 (250*)	286 (152*)	98	37.91	
16	145,000	76.1	50.4	25.7	9.94	
17	135,000	81.3	51.5	29.8	11.53	
18	134,000	59.8	52.9	6.9	2.67	
19	117,000	1,360 (790*)	420 (340*)	450	174.05	
20	110,000	103	84	19	7.35	1.7

Location number	**Production capacity (t Al a^{-1})**	**Total F-emission to air (t F a^{-1})**	**HF - emission to air (t HF a^{-1})**	**Particulate F emission (= Total F-emission to air – HF emission to air) (t F a^{-1})**	**Particulate emission of cryolite to air; 21 % of total particulate F-emission is assumed to be cryolite (t AlF_6Na_3 a^{-1})****	**Total fluoride emission to surface or marine water (after treatment) (t F a^{-1})**
21	102,000	67.5	10	57.5	22.24	280
22	93,000	39.1	16.7	22.4	8.66	187
23	90,000	79.2	41	38.2	14.78	
24	90,000	41	29.1	11.9	4.60	
25	89,000	288	111	177	68.46	
26	86,000	145.7	66.2	79.5	30.75	
27	76,000	39.7 (24*)	21.6 (20*)	4	1.55	97 (70)*
[28]****	[69,000]	[110]	[12]	[98]	[37.91]	
[29]****	[50,000]	[215]	[129]	[86]	[33.26]	
30	45,000	91.5	29	62.5	24.17	
[31]****	[44,000]	[13.9]	[12.3]	[1.6]	[0.62]	
32	41,000	23.4	13.3	10.1	3.91	
Total	4,402,000	3646	2063	1582	612	1,354.7

* the updated values of total F emission to air and HF emission to air were provided by EAA (2007). HF is covered by the risk assessment of AlF_3 and the updated values are for reasons of comparability kept in parenthesis as until they are included in the AlF_3-RAR. The updated values are used for the exposure estimation of particulate cryolite.

**** According to the indication of EAA (2007b,c), these sites have ceased their activity. The sites are kept as a part of the risk assessment for reasons of comparability wtih AlF_3-RAR.. The sites are not included in the “Total”.

For the regional PEC-calculations of aerosol bound cryolite, 10 % of the total particulate cryolite release of 596 t $Al\ F_6Na_3\ a^{-1}$ when excluding two sites in Iceland (due to their far location) is chosen to represent the regional release. This amounts to 59.6 t $AlF_6Na_3\ a^{-1}$. Considering that the 90th percentile of local emissions (37.4 t $AlF_6Na_3\ a^{-1}$) is lower than the regional release calculated above, it is considered that the value of 10 % of total releases represents better the realistic worst case regional emission than if the highest local emission would be allocated to the region.

3.1.2.3.2 Other uses

Table 3.6 Total releases of four other cryolite uses from processing step (generic assessment).

MC/IC/UC	Use	Release to air (t $AlF_6Na_3\ a^{-1}$)	Release to waste water (t $AlF_6Na_3\ a^{-1}$)	Note
3/16/55 or 0	Filler in synthetic resins for Abrasives	365 (208.1 as HF)	2730 (1474 as F)	(1)
3/8/2	Binding agent in cutting or grinding discs	328 (187 as HF)	656 (354 as F)	(2)
3/15 or 0/10 contains also 3/8/10	Colouring agent, opacifier	157 (89.5 as HF)	1180 (637 as F)	(3)

(1) EF(air) = 0.1 using VP > 10,000 Pa; EF(wastewater) = 0.75 using water solubility >= 1,000 mg l-1 and VP < 10 Pa (Table A 3.16 of TGD).

(2) EF(air) = 0.25; EF(wastewater) = 0.5 from Table A 3.7.

(3) EF(air) = 0.1 using VP > 10,000 Pa; EF(wastewater) = 0.75 using water solubility >= 1,000 mg l-1 and VP < 10 Pa (Table A 3.16 of TGD).

The releases have been calculated applying the use volume for each use subtracted by the total release in the formulation step.

3.1.2.4 Release from private use (service life of consumer products)

The use as filler in synthetic resins for abrasives (IC16) and the use as opacifier and colouring agent (IC 15) cause according to TGD releases, whereas point releases are in B-tables estimated only to occur to waste water. No information has been provided by producers on the existence of private use of cryolite. In addition, no specific information on the type of industry involved in the preceeding steps is available. Hence, it is considered that more information is needed on the uses under these use categories before the releases are estimated.

3.1.2.5 Release from disposal

Aluminium smelters

Primary aluminium smelting pots have a carbon lining which has a lifetime of 5-7 years. After that used lining is removed and replaced with new lining. In average, 25-35 kg spent pot linings (SPL) are produced per tonne of aluminium. SPL could according to aluminium industry be used in the production of cement, mineral wool or steel. Due several difficulties, major parts of SPL are at the present deposited (IAI 2005).

Following information on waste was compiled from exposure information provided to the Rapporteur by the smelters: cryolite has penetrated SPL when taken out of use and (cryolite) fluoride content can be up to ca. 10 % w/w. In addition, spent anodes, which are changed in smelters with pre-bake technology approximately once in a month, contain cryolite. Anodes are cleaned from bath material mechanically (anode coal scrap, contains cryolite several per cent w/w) before they are sent back to anode baking sites. Gas cleaning scrubber waste contains also fluorides and aluminium oxide.

Some smelters have indicated to deposit all waste material into designated landfills, whereas other have reported to have recovery units for cryolite or to dispense the waste to third parties for use. Emissions from handling of waste at smelter sites are included in the processing step. No information on downstream use of waste material was provided.

It is noted, that based on the slightly contradictory information from the smelter sites and EAA (2007a) on the content of waste fractions, a more explicit description on specific waste fractions and their content of cryolite and other fluorides and their use and/or disposal is necessary for determining potential releases of especially particulate cryolite.

Other uses

Disposal may be a relevant source of cryolite, HF or F for other downstream uses than aluminium production. The relevance can be assessed only after more specific information on downstream uses is available.

3.1.2.6 Summary of releases

Following table summarises the releases from production, aluminium smelters and other downstream uses it should be noted, that releases to waste water and direct releases to surface water could be summed up due to the assumption that fluoride is not adsorbed into sludge (see chapter 3.1.3).

Table 3.7 Overview of releases from known sources; HF and F screening assessment.

Source	Emission to air (t HF a^{-1})	Release to surface water (t F^- a^{-1}) *
Production	11	135.4
Other uses (formulation)	95.8	10.9
Aluminium smelters (processing)	2,063	1,354.7
Other uses (processing)	485	2,465
Total	**2,655**	**3,966**

*Refers to total F as far as possible to report based on site specific data

Total (H)F-emissions covered by this assessment make only a small part of emission to air and release to waste water and surface water covered by EPER (see Tables 3.1 and 3.2). The total HF emissions to air from point sources producing or using cryolite is ca. 26 % of HF-emissions covered by EPER. The corresponding ratio for F –emissions to surface or sea water is ca. 60 %. It must be noted that especially for emissions to surface water the downstream user activities contribute the largest share, whereas these emission estimates will be probably lower after specific information is gained from these activities. In addition, diffuse sources contribute to fluoride concentration in the environment.

3.1.3 Environmental fate

Environmental fate of cryolite is for relevant parts connected to the form in which it is released and to the fate of its dissociation and transformation products. Dissolution, dissociation and speciation of dissociation products of cryolite is influenced by concentration of especially Al(III)-complexes, free F^-, other (organic and inorganic) ions and pH. All transformation products have different physical-chemical properties and their ecotoxicity is different.

As inorganic compound, cryolite is not biodegraded but abiotic dissociation and subsequent interactions occur instead. There is no information available on biotransformation of cryolite by micro-organisms.

3.1.3.1 Atmospheric degradation

No information is available on the behaviour of aerosol bound cryolite in air. Some dissolution and transformation (see chapter 3.1.3.2) could be expected to occur while particulates are washed down with wet deposition but the amount cannot be predicted. For the assessment, particulate bound cryolite is not assumed to react in the atmosphere.

3.1.3.2 Dissolution, dissociation and speciation

Sjöberg (2002) has modeled dissociation and speciation of cryolite in aqueous solutions using a chemical equilibrium modeling software SOLGASWATER of Umeå University. The author estimated water solubility in pure water as a function of pH and concluded that water solubility was relatively constant within the range $4 \leq pH \leq 7.5$ amounting to 4.5 mM (= ca. 0.9 g l^{-1}). At such concentrations near saturation, dominating species of Al(III) would be AlF_3, AlF_4^- and AlF_5^{2-}. At environmentally relevant loading rates and pH range, the dominating species of aluminium would be aluminium hydroxide $Al(OH)_3$, followed by AlF_2^+, AlF_3 and AlF_4^- . Consequently, a major part of fluoride would be in form F^-. At low pH (around 4), AlF_2^+, AlF_3, AlF_4^- and AlF_5^{2-} are predicted to dominate where the dissociation degree depends on the cryolite loading rate (F^- activity). This prediction is in line with the observations that fluoride mobilizes in low pH aluminium. With increasing cryolite loading at pH around 7, $Al(OH)_3$ precipitate as gibbsite, whereas with increasing pH, speciation is shifted towards dominance of more water soluble $Al(OH)_4^-$ followed by fluoride complexes of aluminium hydroxide. Between pH 0f 8.5 and pH 9, Sjöberg (2002) predicts that the dissolution has decreased to approximately one tenth (= ca. 90 mg l^{-1}) of the plateau at $4 \leq pH \leq 7.5$.

Preliminary results are available on a dissolution study using a sample with particulate size as follows: median = ca. 7.8 µm; 90-P = 18.3 µm; max = 45-63 µm. Solubility reached so far at the higher pH (7.5-7.9 reached instead of 8.5-9.0 aimed despite several trials with different buffers) is 161 mg/l and at the lower pH (6.5-6.6) is 614 mg/l (Solvay, 2008). Further samples were planned to be analysed due to an upward solubility trend with time. These preliminary results would indicate, that particulate form cryolite dissolves in water approximately in the same way as when loaded molecule by molecule. The result would support also the finding of aluminium industry, that no particulate cryolite is present in waste water from scrubber.

Hence, it is considered, that particulate cryolite is not a relevant form of exposure in the aquatic environment. Similarly, a rapid dissolution is expected when cryolite gets into contact with soil porewater.

A complementing way to understand dissociation of cryolite in aquatic environment is to look speciation and solubility of aluminium in pure water. At $pH < 5$, Al^{3+} is predominant species, at $5 < pH < 6$, $Al(OH)_2^{+}$, at around pH 7 the undissociated $Al(OH)_3$ form, which is nearly insoluble, predominate and above pH 7 $Al(OH)_4^{-}$ predominates. Solubility of aluminium hydroxide is correspondingly lowest around pH 7 (Drever, 1982). Aluminium can also form complexes with silica, which are not soluble in pH around 7. The aluminium speciation is far more complex in natural water, where also other ligands than OH/H or fluorides, are present. At a $pH > 5.5$, naturally occurring aluminium compounds exist predominantly in an undissolved form such as gibbsite, $Al(OH)_3$, or, e.g., as aluminosilicates except in the presence of high amounts of dissolved organic material or fulvic acid, which binds with aluminium and can cause increased dissolved aluminium concentrations in streams and lakes (e.g., Drever, 1982, Hem, 1970; IPCS/WHO, 1997).

According to the reviews of Slooff et al. (1989) and IPCS/WHO (2002) free fluoride ion is the main form of dissolved fluorides in surface and marine waters. In addition, a review of EPRI (1984) concluded that free fluoride ion is the only dominant species of fluorides in ground water above pH 5.5.

3.1.3.3 Adsorption and precipitation

Adsorption and precipitation properties of cryolite in **dissolved or gaseous** form depend on the species formed. Therefore the properties are very dependent on i.a., pH, redox and contents of ions in the matrix. Due to the absence of data on cryolite, data compilations of other fluoride and aluminium species have been reviewed.

No information on adsorption coefficients of fluorides in aqueous environment is available. From measured total and dissolved concentrations of fluorides in fresh water and seawater (reviews in Slooff et al., 1989; IPCS/WHO, 2002), it can be concluded that most of fluorides are present in dissolved form. For fluoride screening assessment, solid-water partitioning coefficients of aquatic compartment were set arbitrarily to $0.01\ l\ kg^{-1}$.

According to the review of EPRI (1984), adsorption behaviour of fluoride in soils is strongly dependent on pH. Fluoride ion has the same size and charge with OH^{-} and it has been proposed that exchange with OH^{-} on clay minerals and hydrous oxides is a relevant retention mechanism in soils. Most adsorption studies have observed increase of pH in soil solution following adsorption of F^{-}· It has been also suggested by several authors that removal of fluoride from solution occurs rather via chemical reaction of soil molecules (EPRI, 1984). From the point of view of risk assessment, the way of removal from soil solution is not relevant, because partitioning coefficients have to be derived on the basis of measurements for inorganic substances. A compilation of variable measured Langmuir adsorption constants for fluoride in several soils have been presented by EPRI (1984). For the HF/F -approach, no soil-water partitioning coefficient was derived as it was not deemed necessary (see chapter 3.1.5).

Adsorption –desorption process of aluminium has been reviewed by EPRI (1984). Adsorption of Al is governed by complexation with organic matter or exchange on soil clays. Haidouti (1995) conducted laboratory scale leaching experiments of three soils (contaminated, uncontaminated acidous, uncontaminated calcareous) with cryolite, KF, NaF, distilled water, HCl and KCl. He concluded that fluoride containing solutions induce substantial losses of aluminium, whereas losses were largest from Al –contaminated soil.

For the assessment of **particulate cryolite**, dissolution and sorption processes are not taken into account in the exposure assessment. Koc was arbitrarily set to 10,000,000 for the EUSES –calculations.

3.1.3.4 Volatilisation

For inorganic metal compounds like cryolite in aquatic solution, volatility under environmental conditions is considered negligible. This assumption is in line with recommendation of TGD for metal assessments. After transformation of cryolite to various Al- and F –species, volatilisation is species dependent. For example, HF has very high volatility according to its vapour pressure of 1033 hPa at 20 ºC (European Commission, 2001) but it is miscible with water in all portions and therefore not volatile from aquatic solution. In addition, once entering water, its volatility depends on its speciation.

3.1.3.5 Distribution in wastewater treatment plants

No information is available regarding the elimination rate of dissociated cryolite/fluorides in wastewater treatment plants. For the HF/F-approach it is assumed that all fluoride ends up in the effluent without elimination.

3.1.3.6 Accumulation and metabolism

Due to the dissociation behaviour of cryolite, its bioaccumulation cannot be assessed. The accumulation and metabolism behaviour of the main species present in aqueous solutions have been reviewed in the Environmental Health Criteria (IPCS/WHO, 1994 and IPCS/WHO, 2002). In addition, accumulation of fluoride is considered in the risk assessment of HF (EU, 2001).

3.1.3.7 Natural occurrence and natural background concentrations

Two sampling sites in headwater branches (Altbach and Prims) of the River Rhine are considered as reference sites in the German surface water quality monitoring net (LAWA), reflecting as far as possible natural background concentrations. In the years 2003 and 2004, the range of fluoride concentrations at these sites was 0.05-0.08 mg l^{-1} measured as total concentration for dissolved forms (LAWA, 2006).

Fluoride concentration in natural surface waters which are receiving runoff from F-containing rock formations is in the range 0.01-0.3 mg l^{-1}. In seawater, fluoride belongs to the macro-components and its concentration is above 1 mg l^{-1}. Dissolved fluoride is divided to F^-(51 %), MgF^+ (47 %) and CaF^+ (2%) (Slooff et al., 1989).

Background concentration with no anthropogenic influence in soil was identified in the draft risk assessment of AlF_3 in the Netherlands to be for total fluoride concentration 364-720 mg kg^{-1} and for water extractable fraction 3.6-4.6 mg kg^{-1}.

3.1.4 Aquatic compartment (incl. sediment)

3.1.4.1 Predicted environmental concentrations (PEC_{local})

Due to setting the partitioning coefficients arbitrarily low all fluoride goes in the HF/F approach through waste water treatment plant without adsorption into sludge. In addition, sediment and suspended matter concentrations remain low. Some companies provided information on their waste water treatment method. However, no information on elimination rates was presented by any site.

3.1.4.1.1 Calculation of PEC_{local} for production

Sites 2 to 5 have emissions to surface water. Estimation of C_{local} is carried out using emission data from table 3.3 and either site specific information or defaults of TGD. The exposure assessment was done with the HF/F-approach.

Table 3.8 Site specific concentrations in surface water for producers, HF/F-approach.

Site nr.	$Clocal_{water}$ (mg F l^{-1})	$PEClocal_{water}$(mg F l^{-1})	$PEC_{stp,micro-organisms}$(mg F l^{-1})	Note:
2	0.4 (E)	0.6	4.1 (E)	Default D = 10 used; Effluent flow = 2332.8m^3 d^{-1} The site did not provide river flow rate. Measured concentration in effluent: a value 4 mg kg^{-1} reported but it was not specified whether F or cryolite is referred to or whether it is total or dissolved conc. Hence, the calculated value is used.
3	0.5 (E)	*	50 (E)	Defaults used: D = 100, effluent flow = 2000 m^3 d^{-1} Effluent is discharged to the sea
4	0.6 (E)	0.8	112 (E)	Effluent flow = 6048 m^3 s^{-1}; river low flow rate 13.3 m^3 s^{-1}, D = 191; hardness: 1.92-4.61 mmol/l (= 192-461 ppm $CaCO_3$; pH: 7.7-8.6
5	0.04 (E)	* 5 (M)	4.2 (E) for $C_{effluent}$	Default D = 100 used; Effluent flow = 3110.4 m^3 d^{-1} No biological treatment at WWTP. Effluent is discharged to the sea.

(E) = estimated; (M) = measured

* Natural concentration of dissolved fluoride in seawater is assumed to be 1 mg l^{-1} or above. The site does not contribute significantly to the local PEC in seawater.

Sites 2, 3 and 4 have not provided information whether they are using only a physical-chemical treatment or additionally also biological treatment. Hence it is assumed that biological treatment is in place.

3.1.4.1.2 Calculation of PEC_{local} for formulation

Local concentration in surface water was calculated for the formulation step of other uses than use in aluminium smelters. TGD defaults for dilution factor (10) and waste water effluent flow (2000 m^3 d^{-1}) were applied resulting following concentrations. The values of fraction of main source and number of emission days have been chosen as indicated in the notes of Table 3.9. Due to the partitioning assumptions described in chapter 3.1.3, no elimination in stp and no partitioning to suspended matter in the recipient water occur.

Table 3.9 Estimated concentrations in surface water and in raw waste water for formulation (HF/F-approach).

MC/IC /UC	Use	Local release of a generic site (kg F d^{-1})	$Clocal_{water}$ (mg F l^{-1})	$PEClocal_{water}$(mg F l^{-1})	$PEC_{stp,micro-organisms}$(mg F l^{-1})	Note
3/16/0	Filler in synthetic resins for abrasives	16.2	0.81	1.22	8.1	(1)
3/8/2	Binding agent in cutting or grinding discs	7.3	0.37	0.57	3.7	(2)
3/0/10	Colouring agent, opacifier	8.7	0.44	0.70	4.4	(2)

(1) Formulation volume of 3500-10000 assumed. Fraction of mainsource = 0.8, T = 300 (Table B2.3 of TGD).

(2) Formulation volume of < 3500 T a-1 assumed. Fration of mainsource = 1, T =300 (Table B2.3 of TGD).

3.1.4.1.3 Calculation of PEC_{local} for industrial/professional use

Aluminium smelters

Local concentrations in water were estimated for the sites which reported to have releases to the aquatic environment. According to EAA (2007b), all smelters having aquatic emissions except site 20 are emitting to seawater. In addition, none of the sites possess waste water treatment plants. Hence, no assessment on stp microorganisms is conducted for these sites. No partitioning to suspended matter is assumed to occur.

Table 3.10 Estimated site specific concentrations in surface water and raw waste water for aluminium smelters (HF/F-approach). The effluent (scrubber water) volumes were updated by EAA (2007b).

Site nr.	$Clocal_{water}$ (mg F l^{-1})	$PEClocal_{water}$(mg F l^{-1})	Note
1	0.01	***	D = 100 and effluent flow 86 000 000 m^3 a^{-1} (235 616 m^3 d^{-1}) used.
4	0.19	***	D = 100 and effluent flow 10 000 000 m^3 a^{-1} (27 397 m^3 d^{-1})used.
5	0.17	***	D = 100 and effluent flow 19 729 645 m^3 a^{-1} (54 054 m^3 d^{-1})used.
8	0.03	***	D = 100 and effluent flow 25 400 000 m^3 a^{-1} (69 589 m^3 d^{-1})used.
12	0.06	***	D = 100 and effluent flow 24 694 440 m^3 a^{-1} (67 656 m^3 d^{-1})used.
20*	0.002	0.2*	River flow rate was given as 245 m^3 s^{-1} resulting a low flow rate of 81.7 m^3 s^{-1}. Default effluent flow 2000 m^3 d^{-1} is used. Dilution rate was set to the maximum (1000).
21	0.05	***	D = 100 and effluent flow 54 900 000 m^3 a^{-1} (150 411 m^3 d^{-1})used.
22	0.05	***	D = 100 and effluent flow 39 200 000 m^3 a^{-1} (107 397 m^3 d^{-1})used.
27	0.04	***	D = 100 and effluent flow 16 000 000 m^3 a^{-1} (43836 m^3 d^{-1})used.

* For site 20, ambient fluoride background concentration of 0.2 mg F l^{-1} is applied as regional PEC. Clocal does not contribute significantly to the PEClocal.

**EAA (2007c) proposes to use for this site a dilution factor of 500 with the reasoning that the site is an "exposed coastal site": This level of background information is considered as not appropriate to change the dilution factor from 100 to 500.

*** Clocal for the sites at sea does not contribute significantly to the (natural) concentration of F in seawater.

The Clocal –values for the sites at sea are far below the natural dissolved fluoride concentration of seawater (≥ 1 mg F l^{-1}).

Other downstream uses

Local concentration in surface water and waste water was calculated for the processing step of other uses. B-tables have been applied to the use volume of the processing step (volume for the use minus the release in the formulation step) to obtain the fraction of main source and number of emission days (see table notes). The TGD defaults for dilution factor (10) and waste water effluent flow (2000 m^3 d^{-1}) are applied resulting following concentrations. Due to the partitioning assumptions described in chapter 3.1.3, no elimination in stp and no partitioning to suspended matter in the recipient water occur.

Table 3.11 Estimated local concentrations in surface water and in raw waste water for processing (HF/F-approach).

MC/IC /UC	Use	Local release of a generic site (kg F d^{-1})	Clocal_{water} (mg F l^{-1})	$\mathrm{PEClocal}_{water}$(mg F l^{-1})	$\mathrm{PEC}_{stp,micro-organisms}$(mg F l^{-1})	Note
3/16/0	Filler in synthetic resins for abrasives	3,937	197	198.3	1970	(1)
3/8/2	Binding agent in cutting or grinding discs	1,399	70.0	70.5	700	(3)
3/0/10	Colouring agent, opacifier	1,971	65.7	99.1	657	(4)

(1) Fraction of mainsource = 0.6, T = 225 (Table 3.14 of TGD)

(3) Fraction of mainsource = 0.8, T = 203 (Table 3.6 of TGD)

(4) Fraction of main source = 0.75, T = 242 (Table 3.14 of TGD)

3.1.4.2 Sediment

Assessment of sediment could not be carried out, because recent measured data was not available and partitioning coefficients are not available. In addition, older data is also very scarce (the only information available is from the late 70's and they are reviewed in Slooff et al.,1989).

In the HF/F_approach, fluoride is assumed to hardly partition to sediment. Based on the information on speciation in water, it could be expected, that fate of dissolved cryolite entering from the emission the aquatic compartment would be approximately same as fate of free fluoride. Equilibrium partitioning method as presented in TGD is not applicable for an inorganic substance like cryolite. Speciation and availability in sediment may be very different from speciation and availability in water because pH, redox and ion concentrations are not same.

Altough a relevant part of initial releases to waste water can be assumed occur in particulate form, it is expected based on the tentative results of the dissolution study and based on the study of aluminium smelters regarding the fraction of particulate cryolite in waste water, that particulate cryolite will dissolve in waste water

3.1.4.3 Comparison between predicted and measured levels

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3.1.5 Terrestrial compartment

HF/F-approach

Fluoride is in this approach not adsorbed to sludge in waste water treatment plants. Hence, fluoride is not released via sludge to soil from the generic downstream user sites, although these sites can be assumed to be connected to municipal sewer. The only input of fluoride comes via deposition of HF. In the risk assessment of AlF_3 (European Commission, 2008), it was observed that risk characterisation for terrestrial compartment results lower RCRs than risk characterisation for air and that possible terrestrial risks would hence be covered by risk characterisation for air. In the line with this conclusion, the assessment of terrestrial compartment for the HF/F –approach is not carried out further.

Particulate cryolite

For particulate cryolite, deposition flux was predicted using OPS-Pro 4.1 (see chapter 3.1.6.1.3 and Appendix A). Due to the dissolution of cryolite according to the tentative results of the dissolution study, soil matrix can be expected to be exposed with dissolved species of cryolite (different fluoride and aluminium species). These in turn can be expected to bind to soil. No PECsoil is calculated for cryolite, but the estimates of particulate cryolite deposition are shown, because cryolite applied in particulate form is used in the U.S. as an insecticide (see section 3.2).

3.1.5.1 Calculation of PEC_{local}

3.1.5.1.1 Calculation of PEC_{local} for production

Producer site 2 reported on particulate F emission (102 kg F a^{-1}) to air. No further information was provided and it is assumed for the assessment that the F-emission is solely consisting of cryolite. Converted to cryolite (187.9 kg AlF_6Na_3 a^{-1}) and considering that number of emission days is 60, a source strength of 0.04 g AlF_6Na_3 s^{-1} results, which is in the range of the source strengths of aluminium smelters. Hence, the assessment of aluminium smelters for soil cover also the particulate assessment of production site 2. Due to the fact that site 2 has rather low HF-emission compared to sites 3, 4, and 5 and considering the reported process and pollution abatement technique information, it is concluded that also sites 3, 4 and 5 should provide data on particulate emissions of cryolite to air.

3.1.5.1.2 Calculation of PEC_{local} for formulation

The assessment of aluminium smelter emissions for compartments soil and air cover also the emissions and source strengths of other downstream uses.

3.1.5.1.3 Calculation of PEC_{local} for industrial/professional use

Aluminium smelters

High releases of particulate fluorides to air have been reported to be caused by aluminium smelters. Among these, cryolite is released. The calculation of atmospheric concentrations and deposition fluxes of particulate cryolite was carried out with OPS-Pro 4.1 (details in chapter 3.1.6.1.3 and Appendix A) using 365 days/year for number of emission days. Deposition flux was calculated as the average over the area reaching from 0 to 1000 m distance around the edge of the source (square of 500m*500m).

Table 3.12 Particulate cryolite deposition for the aluminium smelters with highest, lowest and mean particulate F-emissions. The fraction of cryolite of particulate F-emissions is assumed to be 21 %.

	Highest source strength (site 19)	**Mean source strength**	**Lowest source strength (site 31)**
	5.52 g AlF_6Na_3 s^{-1}	**0.68 g AlF_6Na_3 s^{-1}**	**0.02 g AlF_6Na_3 s^{-1}**
Deposition within 1000 m (mg m^{-2} a^{-1})	755.3	92.9	27.4
Deposition within 1000 m (mg m^{-2} d^{-1})	2.1	0.26	0.07

Other downstream uses

The assessment of aluminium smelter emissions of particulate cryolite for compartments soil and air cover also the emissions/source strengths of other downstream uses in this phase of the assessment.

3.1.5.2 Measured levels

No data on measured environmental concentrations were provided.

3.1.5.3 Comparison between predicted and measured levels

No data on measured environmental concentrations were provided.

3.1.6 Atmosphere

3.1.6.1 Calculation of PEC$_{local}$

Most of the sites already reported their emissions in form of HF. The known HF-emissions and estimated cryolite emissions (converted to HF) from downstream uses other than aluminium smelter sites were used to determine local HF-concentrations in air. Concentration in air at a distance of 100 m from the source was calculated with EUSES 2.0.3 for all scenarios corresponding with the default source and model characteristics described in TGD (equation 40 and assumptions therein).

In addition, **particulate cryolite** concentration in air was estimated for aluminium producer sites. There is no information on particulate cryolite emissions of other downstream users. If assuming that the releases estimated for other downstream uses in sections 3.1.2.2 and 3.1.2.3.2 would be completely emitted as particulate cryolite, the local emissions from generic local sites would be in the range of the particulate cryolite emissions estimated for aluminium smelter sites in section 3.1.2.3.1. Therefore the assessment of particulate cryolite for aluminium smelters covers in an exemplary way also the potential exposure posed by other downstream uses in this phase of the assessment.

3.1.6.1.1 Calculation of PEC$_{local}$ for production

Concentrations of HF were estimated based on emissions and number of emission days in table 3.3.

Table 3.13 Site specific concentrations in air at producer sites (HF/F-approach).

Site nr.	**Clocal$_{air}$ (µg HF m^{-3})** Estimated (E) Measured (M)	**PEClocal$_{air}$(µg HF m^{-3})**	**Clocal$_{air}$(µg HF m^{-3}), annual average**
2	0.08 (E) ≤50,000 (M)	0.28	0.01
3	12.3 (E)	12.5	4.06
4	0.11 (E)	0.31	0.05
5	4.73 (E)	4.93	4.27

The estimation of PEC$_{air}$ for particulate cryolite is covered in this phase of the assessment by the PEC$_{air}$ –estimation for aluminium smelters.

3.1.6.1.2 Calculation of PEC$_{local}$ for formulation

Concentrations were estimated based on emissions and number of emission days in table 3.4.

Table 3.14 Site specific concentrations in air for formulation step (generic scenarios, HF/F-approach).

MC/IC/UC	**Use**	**Clocal$_{air}$ (µg HF m^{-3})**	**PEClocal$_{air}$(µg HF m^{-3})**	**Clocal$_{air}$(µg HF m^{-3}); annual average**

MC/IC/UC	Use	Clocal$_{air}$ (µg HF m^{-3})	PEClocal$_{air}$(µg HF m^{-3})	Clocal$_{air}$(µg HF m^{-3}); annual average
3/16/0	Filler in synthetic resins for abrasives	39.6	39.8	32.6
3/8/2	Binding agent in cutting or grinding discs	17.9	18.1	14.7
3/0/10	Colouring agent, opacifier	21.4	21.6	17.6

The estimation of PEC$_{air}$ for particulate cryolite is covered in this phase of the assessment by the PEC$_{air}$ –estimation for aluminium smelters.

3.1.6.1.3 Calculation of PEC$_{local}$ for industrial/professional use

Aluminium smelters

Concentrations of HF in air were estimated in the risk assessment of AlF_3 (European Commission, 2008).

Table 3.15 Total F and HF emissions for all EU primary aluminium smelters for the year 2002, including estimated local air concentrations based on model calculations (EUSES 2.0.3 and OPS-Pro 4.1) (European Commission, 2008).

Location number	**Production capacity (t aluminium a-1)**	**Total F-emission (t a-1)**	**HF emission (tonnes/yr)**	**HF emission (kg HF/ taluminium)**	**EUSES derived: C_{local} HF ($\mu g/m^3$)**	**OPS-Pro 4.1 derived:* C_{local} HF ($\mu g/m^3$)**
1	300,000	86.7	50.8	0,17	39	3.3 (5)***
2	281,000	124	47.2	0,17	36	3.1
3	255,000	119.3	68	0,27	52	4.4
4	229,000	154.8	136.8**	0,60	100	8.5 (3)***
5	224,000	118.6	35	0,16	27	2.3
6	222,000	60.2	53.2**	0,24	41	3.5
7	219,000	174	86	0,39	65	5.5
8	185,000	73.6	47.8	0,26	36	3.1
9	176,000	97.9	69.4	0,39	53	2.4
10	169,000	188	140	0,83	110	9.4
11	166,000	246.7	193.4	1,17	150	13
12	164,000	85.9	63.2	0,39	48	4.1
13	158,000	30.1	26.6	0,17	20	1.7
14	151,000	30	10	0,07	7.6	0.65
15	150,000	505	286	1,91	220	19
16	145,000	76.1	50.4	0,35	38	3.2
17	135,000	81.3	51.5	0,38	39	3.3
18	134,000	59.8	52.9**	0,39	40	3.4
19	117,000	1,360	420	3,59	320	27
20	110,000	103	84	0,76	64	5.4
21	102,000	67.5	10	0,10	7.6	0.65
22	93,000	39.1	16.7	0,18	12.7	1.1
23	90,000	79.2	41	0,46	31	2.6
24	90,000	41	29.1	0,32	22	1.9
25	89,000	288	111	1,25	85	7.2
26	86,000	145.7	66.2	0,77	50	4.3
27	76,000	39.7	21.6	0,28	16	1.4
28	69,000	110	12	0,17	9.1	0.77
29	50,000	215	129	2,58	98	8.3
30	45,000	91.5	29	0,64	22	1.9
31	44,000	13.9	12.3**	0,28	9.4	0.80
32	41,000	23.4	13.3	0,32	10	0.85
Total	4,565,000	4,929	2,208	0,48		

* Calculations based on emission over a surface of 500x500 m. and an emission height of 25 m.; ** No data on HF: HF was estimated from location number 13 for which (26.6/30.1) 88.4% (realistic worst-case) of total fluoride emission was reported to be HF; *** Between brackets: the HF concentration indicated by the NILU (µg/m^3) at circa 500m. distance from the plant

Concentration of **particulate cryolite** in air was estimated for the highest, mean and lowest emitter of particulate F. The emission of particulate F was converted to cryolite in the ratio of molar weights and source strengths were calculated assuming that nr. of emission days is 365. The exposure estimates were derived using OPS-Pro 4.1 with the assumption that 21 % of particulate F emitted is cryolite. In line with the risk assessment of AlF_3 (European Commission, 2008), the source size of 500 m * 500 m and chimney height of 25 m were used. Particle size was assumed to be "coarse" as defined by the program. Average weather conditions of the Netherlands were applied from year 2002. $Clocal_{air}$ at the distance of 100 m from the edge of the source was calculated for practical reasons as the average concentration within the area from 0 to 100 m distance from the source (the value was calculated by the program) as it was considered that the average of the concentrations over this recipient area would not differ from an average of concentrations at the edge (this should have been calculated manually using values of each lattice point). An example of the calculation and further details on settings used are presented in Appendix A.

Theoretical regional concentration of cryolite in air caused by the releases of only aluminium smelters is 0.0037 µg AlF_6Na_3 m^{-3} . This concentration does not have influence on the PEC_{air} of any emitter.

Table 3.16 Concentration of particulate cryolite in air in 100 m distance from aluminium smelters.

	Highest source strength **(site 19)**	**Mean source strength**	**Lowest source strength** **(site 31)**
	5.52 g AlF_6Na_3 s^{-1}	**0.68 g AlF_6Na_3 s^{-1}**	**0.02 g AlF_6Na_3 s^{-1}**
Clocalair, 100 distance (mg m^{-3})	0.011	0.001	0.04×10^{-3}
PEClocalair, 100 m distance (mg m^{-3})	0.011	0.001	0.04×10^{-3}

Other downstream uses

Concentrations of HF were estimated based on emissions and number of emission days in table 3.6.

Table 3.17 Estimated concentrations in air for processing step (generic scenarios; HF/F-approach).

MC/IC/UC	**Use**	**$Clocal_{air}$ (µg HF m^{-3})**	**$PEClocal_{air}$(µg HF m^{-3})**	**$Clocal_{air}$(µg HF m^{-3}); annual average**
3/16/0	Filler in synthetic resins for abrasives	154	154.2	94.9
3/8/2	Binding agent in cutting or grinding discs	204	204.2	114
3/0/10	Colouring agent, opacifier	183	183.2	121

The estimation of PEC_{air} for particulate cryolite is covered in this phase of the assessment by the PEC_{air} –estimation for aluminium smelters.

3.1.7 Secondary poisoning

Concentration in air and plants was recognized in the risk assessment of HF to be in connection with each other. Therefore HF-concentrations in air obtained in chapter 3.1.6 are used for the non-compartment specific exposure assessment. Cryolite itself is not expected to be accumulated in food chain as it dissolves to different aluminium and fluoride species.

3.1.8 PECregional

Due to the manifold anthropogenic point and diffuse sources contributing to fluoride exposure and because of the variety of fluoride compounds emitted, measured data should be pursued for the derivation of PECregional. Unfortunately, only a limited amount of recent measured data is available at the moment.

HF/F approach

German ambient surface water concentrations are measured by LAWA monitoring network. LAWA-sites reflect overall pollution load and are thus comparable with PECregional. Newest data available for fluoride is for the years 2003 and 2004 (LAWA, 2006). Soluble fluoride was measured at 27 sites in 15 rivers. Total number of measurements in these years is 1585. Minimum frequency of sampling was 12 measurements a year (one for each month), whereas at some sites even five samples per month are collected. Values of single measurements were in the range 0.05-0.6 mg $F^- l^{-1}$. The 90th percentiles of each sampling site for each year are in the range 0.08-0.5 mg $F^- l^{-1}$, whereas mean of these 90th percentiles is 0.2 mg $F^- l^{-1}$. The method used in LAWA for soluble fluoride analysis (DIN, 1984) covers free fluoride ion but also some soluble complexes of fluoride (with e.g., Al). It can be, however, expected that most of soluble fluoride is in form of free fluoride ion. The 90th percentiles are used as PECregional in the risk characterisation. If recent monitoring data from other Member States become available, geographically more specific $PECregional_{water}$ –values may be derived.

$PECregional_{air}$ of 0.2 µg HF m^{-3} and from HF -deposition caused $PECregional_{soil}$ 0.044 mg F^- kg wwt^{-1} were derived in the draft risk assessment of AlF_3 (European Commission, 2008) and they will be applied for this assessment. It should be noted that the regional concentration in air has been derived based on fluoride emissions to air from European point sources subject to IPPC-Directive (EPER-register). Hence, it reflects the emissions from cryolite production sites but does not necessarily incorporate emissions from all cryolite downstream use activities. It is considered not appropriate to derive a $PECregional_{air}$ at this phase as the releases calculated on a generic basis for downstream uses would dominate the result. Generic downstream use scenarios alone result using TGD defaults (100 % of the releases allocated to region) a $PECregional_{air}$ of 0.23 µg HF m^{-3}. However, it could be expected, that after more specific information on downstream uses will be available, the final regional concentration of HF in air can be derived .

Particulate cryolite

$PECregional_{air}$ and regional deposition flux for aerosol bound cryolite was calculated based on the regional release (10 % of EU-27+NO) from aluminium smelters. Other sources of particulate cryolite may be the producers and other downstream uses. However, no information on such releases is available (except from production site 2). The estimation was carried out with OPS-Pro 4.1 with average meteorological data for 2002 in the Netherlands, a source area of 500 m * 500 m, a chimney height of 25 m and a receptor area of 200*200 km (grid size 1000 m). Also for this calculation it is assumed that aerosol bound cryolite does not react in any ways in air. The particle size was assumed to be “coarse” as defined by the program (see Appendix A). It is noted, that in program runs varying the particle size class, no significant differences were observed in results for cryolite with these assumptions. In addition, the regional source strength is lower than the source strenght of the highest emitters.

Table 3.18 Regional PECair and regional deposition flux for aerosol bound cryolite as calculated with OPS-Pro 4.1.

	Regional source strength 1.89 g AlF_6Na_3 s^{-1}
$PECregional_{air}$, (mg AlF_6Na_3 m^{-3})	0.0037×10^{-3}
Deposition flux (mg AlF_6Na_3 m^{-2} a^{-1})	0.49

3.2 EFFECTS ASSESSMENT: HAZARD IDENTIFICATION AND DOSE (CONCENTRATION) - RESPONSE (EFFECT ASSESSMENT)

3.2.1 Aquatic compartment (incl. sediment)

Cryolite dissociates after dissolving in water to sodium ions and to different species of aluminium and fluoride (see chapter 3.1.3). Ecotoxicologically relevant are the species of aluminium and fluoride. In order to be able to compare approximately “like with like” in risk characterisation, factors influencing water solubility of cryolite and transformation of aluminium and fluoride species in aqueous media (especially pH throughout the test and hardness) should be well documented in test reports. In ideal case, also the concentration of free fluoride ion but also concentrations of other major species like aluminium species should be analysed during the test.

3.2.1.1 Toxicity test results

3.2.1.1.1 Fish

Acute toxicity

Johnson and Finley (1980) report in their handbook on a 96 –hour LC_{50} of 47.0 mg l^{-1} for rainbow trout and $LC_{50} > 400$ mg l^{-1} for bluegill. Very little information on test conditions has been provided and hence the results are considered not reliable (validity = 4).

Solvay Pharmaceuticals (2008a) carried out a static acute toxicity test according to OECD 203 with zebra fish (*Brachydanio rerio*) under GLP. Based on the results of a preliminary study, the study was conducted as a limit test at nominal concentrations of 0, 100 and 150 mg/l. One aquarium was prepared per test concentration containing 4 litre test solution and 8 zebra fish. The test was terminated after 96 hours of exposure.

Cryolite was not completely soluble in the standard culture medium (Rapporteurs note: probably due to a formation of an insoluble aluminium complex from dissolved/dissociated cryolite and the salts in the medium). For this reason, test solutions were prepared from a stock solution of 150 mg l^{-1} that was continuously stirred for four days at 20°C. On the day of test initiation the solution was filtered with filter paper (S&S 595 1/2) to remove undissolved/precipitated particles. The final test solutions were clear and no particles were visible. The fluoride content of the test solutions was analysed at 0 h and 96 h by measuring with cuvette test LCK 323 (Dr. Lange, Tiel, The Netherlands). The recovery at 0 hours was 71.5 mg l^{-1} (lower exposure level) and 96.4 mg l^{-1} (higher exposure level) and at 96 hours 70.8 mg l^{-1} (lower exposure level) and 98.3 mg l^{-1} (higher exposure level). Hence, although the recovery at both exposure levels was lower than 80 %, the exposure concentrations remained stabile during the test. Test temperature was 22.8-23.8 ºC, pH 8.3 at 0 h and oxygen content 8.3 mg l^{-1} at 0 h. At the termination of the test pH in all aquaria was 7.1 and oxygen concentration 8.0-8.3 mg l^{-1}.

No mortality was observed in the control aquarium. No mortality or effects on behaviour and general appearance were observed at both exposure levels. Hence, the measured higher exposure level is considered as NOEC. Based on the test results no LC_{50}.96h -value could be established but in the absence of any mortality or aberrant behaviour at 97 mg l^{-1}, it can be concluded that the LC_{50} 96h >100 mg l^{-1}.

The study is documented according to the test guideline. A slight problem for the interpretation of the results is caused by the low solubility and low recovery of cryolite in the test medium and by the fact, that cryolite itself cannot be analysed from the medium but the actual exposure was monitored by means of fluoride analysis. Nevertheless, it is noted that the exposure concentration was stabile. Based on the solubility model results of Sjöberg (2002) and other information available on the speciation, it can be expected, that cryolite was dissociated when dissolved and the aluminium precipitated with the salts of the medium. This phenomenon represents also the reactions in the environmentally relevant conditions, and hence the results are considered reliable (validity = 1).

Other results

IBACON (2003a) has conducted a test according to OECD 203 under GLP with *Brachydanio rerio*. However, the test substance was not cryolite, but bath material of Alcoa (consistence provided in section 2.1.1). Also IWL (2001a) has carried out a test according to OECD 203 under GLP with *Leuciscus idus* melanotus L. but using as a test substance bath material of VAW Aluminium AG.

In both tests the dissolved test material concentration could not be related to cryolite. Already due to the very low solubility of the substantial constituent Al_2O_3 the behaviour of bath material in test medium can be expected to be very different from the behaviour of cryolite. It is not possible to use the results to replace ecotoxicity testing for cryolite.

Long-term toxicity

Long term toxicity tests with fish were not available to the Rapporteur.

3.2.1.1.2 Aquatic invertebrates

Acute toxicity

Test 1

EC_{50} for *Simocephalus serrulatus* was reported by Sanders and Cope (1966) to be 10 mg l^{-1} with 5 % confidence limits of 7.6-13.0 mg l^{-1}in a 48 –hour static immobilisation test. For *Daphnia pulex*, EC_{50} of 5 mg l^{-1} with 5 % confidence limits of 3.6-6.8 mg l^{-1} was obtained in the same study. Several pesticides were tested simultaneously, and therefore description of test conditions and results are not provided as detailed as required at the present (e.g., in 67/548/EEC Annex V C.2.). Information on controls and pH during and at the end of test is not available, which is crucial regarding speciation and water solubility. In addition, test temperature is lower than required at the present for a valid test. Therefore this test is considered not valid (validity = 3). It is noted, that the results are included in the U.S.EPA Ecotox database with the indication of pH 7.4-7.8. These values were reported by the authors for all tested substances, and as cryolite is likely to change the pH of the culture medium, it is considered, that the data provided are not specific enough for cryolite.

Test 2

Cryolite was employed by IWL (1998) in a 48-h immobilisation test with *Daphnia magna* Strauss. Test was conducted according to the OECD 202 test guideline. Organisms were obtained from own culture and they were 6-24 h old. Five instars per test vessel, 50 ml each, four vessels per test concentration were run. Test temperature was kept at 20 ± 2 ºC and pH was in the 50 ml test vessels at the start 7.7-7.9 and at the end of the test 8.2-8.5. Oxygen level was at the start 8.0-9.1 mg l^{-1} and 8.7-9.3 mg l^{-1} at the end. In addition, KCr_2 was used as reference substance (EC_{50} of 1.8 mg l^{-1}). Tap water, which was used for cultures, was also used as test water. Control of dissolved concentration of cryolite was carried out by measuring concentration of dissolved aluminium in stock solution which an eluate prepared from test water and 10 g cryolite l^{-1} according to DIN (1984). Aluminium concentration in this eluate corresponded with concentration of 144 mg cryolite l^{-1} representing also water solubility of cryolite in test media. Authors noted that water solubility of cryolite in the test was lower than available water solubility data from literature probably due to sodium contained already in test water. Test concentrations were diluted from the stock solution to give 72, 86, 108, 115, 122, 130 and 144 mg l^{-1} .

Immobilisation in control vessels (0 mg l^{-1}) remained under 10 %. EC_{50} of 156 mg l^{-1} (above observed water solubility) was extrapolated from the test. Correspondingly, EC_{100} was not achieved up to the water solubility limit, whereas 45 % immobilisation was observed at the highest test concentration and EC_0 was determined to 72 mg l^{-1}.

This test is considered valid with restrictions, while no analytical monitoring of test concentrations was carried out, hardness was not measured, constitution of tap water is not known and temperature variation was one degree Celsius higher than required in 67/548/EEC Annex V C.2 (validity = 2).

Other data

Johnson and Finley (1980) report in their handbook on 48-hour EC_{50} of 5.0 mg l^{-1} for *Simocephalus* and EC_{50} of 10.0 mg l^{-1} for *Daphnia pulex*. Very little information is given about the test conditions and the results are not considered reliable (validity = 4).

IBACON (2003b) conducted according to OECD 202, Part 1, 1984 and draft OECD 202, 2000; under GLP a test with *Daphnia magna* but used as test substance bath material of Alcoa (consistence provided in section 2.1.1). Bath material is due to its consistence not comparable as test material to cryolite. Additionally, the dissolved test material concentration could not be related to cryolite and the result cannot be therefore used for cryolite.

Long-term toxicity

Long term toxicity tests with aquatic invertebrates were not available to the Rapporteur.

3.2.1.1.3 Algae

No test reports were available to the Rapporteur.

Acute toxicity

The acute toxicity of cryolite to green algae *Selenastrum capricornutum* was tested according to OECD Guideline 201 under GLP (Solvay Pharmaceuticals, 2008b). Based on the results of a preliminary study, the definitive test was conducted at nominal concentrations of 0, 1.0, 2.2, 5.0, 11 and 25 mg l^{-1}. Algae were exposed for three days using 250 ml sterile Erlenmeyer flasks containing 100 ml test solution. Three replicates of each exposure concentration and six control vials were run. Cryolite was not completely soluble in the standard algal medium (Rapporteurs note: probably due to a formation of an insoluble aluminium complex from dissolved/dissociated cryolite and the salts in the medium). For this reason, test solutions were prepared from a stock solution of 100 mg l^{-1} (cryolite in the test medium) that was continuously stirred for four days at 20°C. On the day of test initiation the solution was filtered with filter paper (S&S 595 1/2) to remove undissolved/precipitated particles. All final test solutions were clear and no particles were visible. The fluoride content of the test solutions was analysed on days 0 and 3 by measuring with cuvette test LCK 323 (Dr. Lange, Tiel, The Netherlands). The difference between the nominal and the mean measured concentrations was < 20% (measured concentrations were 98-110 % of nominal).

The cell density (initially 1.0×10^4 cells ml^{-1}) increased 80 times in the controls, which meets the validity criterion of a minimal 16 times increase. The cell density was measured by means of absorption at 750 nm (the calibration of the method is documented). The pH was measured on day 0 only in the controls and it was 7.7. On day 3 the pH was in all vials 7.6-7.7. Test temperature was 21-23 ºC. Using linear interpolation, with mean measured concentrations on a logarithmic scale (base = 10), the EC_{50}(0-72h) for biomass integral and growth rate were 3.2 and 8.8 mg l^{-1}, respectively. The NOEC based on biomass integral at test termination, was determined with Williams' Test to be 1.0 mg l^{-1}.

The study is documented according to the test guideline. Few punctual slightly exceeding values of temperature were recorded but they are considered as not relevant by the Rapporteur. A slight problem for the interpretation of the results is caused by the low solubility of cryolite in the test medium and by the fact, that cryolite itself cannot be analysed from the medium but the actual exposure was monitored by means of fluoride analysis. Based on the solubility model results of Sjöberg (2002) and other information available on the speciation, it can be expected, that cryolite was dissociated when dissolved and the aluminium precipitated with the salts of the medium. This phenomenon represents also the reactions in the environmentally relevant conditions, and hence the results are considered reliable (validity = 1).

Other data

IBACON (2003c) conducted a test according to OECD 201 under GLP with *Desmodesmus subspicatus* (green algae). However, they used as test substance bath material of Alcoa (consistence provided in section 2.1.1). Bath material is due to its consistence not comparable as test material to cryolite. The concentration of dissolved test material could not be related to concentration of cryolite in the study. It is not possible to use the results to replace ecotoxicity testing of cryolite.

Long-term toxicity

No data available.

3.2.1.1.4 Microorganisms

Solvay Pharmaceuticals (2008c) determined the effect of cryolite on activated sludge according to OECD Guideline 209 under GLP. The test was conducted at concentrations of 5.0; 10; 20; 40; 80 and 160 mg l^{-1}. The respiration rate of an activated sludge suspension (4.0 g dw l^{-1}) fed with a standard amount of synthetic wastewater was measured after a contact time with the test substance of 30 minutes and 3 hours. The respiration rate was monitored by oxygen consumption. Two controls were included.

A reference test was conducted at concentrations of 5.0; 10 and 20 mg 3,5-dichlorophenol per litre. In the test with 3,5-dichlorophenol the $E(I)C_{50}$ value after 30 minutes of incubation was estimated to be 6.2 mg l^{-1}. After 3 hours of incubation the $E(I)C_{50}$ value was 6.3 mg l^{-1}, which was in the range of the required sensitivity of the activated sludge.

At the highest test concentration of 160 mg l^{-1} the respiration inhibition was -1.8 and -24%, respectively, after 30 minutes and 3 hours incubation. The difference between the two controls was < 15%. The $E(I)C_{50}$ value after 30 minutes and 3 hours of incubation was >160 mg l^{-1}.

The study was reported according to the guideline requirements and it is considered as valid (validity = 1).

3.2.1.1.5 Amphibians

No data are available on amphibian toxicity.

3.2.1.2 Calculation of Predicted No Effect Concentration (PNEC)

It is noted, that the U.S. Ecotox database contains several acute ecotoxicity results of aquatic organisms for cryolite. However, the lowest acute value provided is the EC50 of 5 mg l^{-1} for *Daphnia pulex*, which is not considered valid by the Rapporteur. Also for the other data specific information on the pH is not provided and hence the values are considered as not reliable.

Reliable acute test results are available for fish, invertebrates and algae. In the 96 hour test according to OECD 203, an $LC_{50} > 100$ mg l^{-1} was found for fish. For *Daphnia magna*, an EC_{50}(48 h) of 156 mg l^{-1} was found in an OECD 202 –test (water solubility of cryolite in the test medium was 140 mg l^{-1}). The most sensitive species was green algae *Selenastrum capricornutum*, which showed an $EC\mu_{50}$ (72 h) of 8.8 mg l^{-1} in a test according to OECD 201. The last value is used for the calculation of the PNEC and an assessment factor of 1000 is applied in the absence of any chronic data. Consequently, a PNEC of 8.8 µg l^{-1} results. The PNEC expressed as fluoride is 4.8 µg F l^{-1} and this value is used for the HF/F-approach. This PNEC is applied as it is assumed, that the fluoride exposure in this assessment originates initially from dissolved cryolite.

For comparison, a PNEC for dissolved fluoride has been derived in the risk assessment of HF (European Commission, 2001). This PNEC = 0.9 mg F^{-} l^{-1} for normal waters and 0.4 mg l^{-1} for soft waters. For both PNECs long-term data were available from three trophic levels (AF of 10 used). Furthermore, in the HF -risk assessment acute $L(E)C_{50}$ –values ranged for fish between 51 and 340 mg l^{-1}, for daphnids from 97 to 352 mg l^{-1} and for algae from 43 to 122 mg l^{-1} (fluoride). If the acute toxicity results of the HF –assessment and this assessment are compared (when both are expressed as fluoride), it seems that at least algae are more sensitive to cryolite than to those forms of fluoride used for the tests in the HF –risk assessment.

$PNEC_{stp,microorganisms}$ is based on the $E(I)C_{50}$ of > 160 mg l^{-1} from the respiration inhibition test according to OECD 209. For this result an assessment factor of 100 is applied and a $PNEC_{stp,microorganisms}$ of 1.6 mg l^{-1} results for cryolite. This corresponds to a PNEC of 0.87 mg F l^{-1}.

For comparison a $PNEC_{stp,microorganisms}$ of 51 mg F^{-} l^{-1} was derived in the risk assessment of HF .

3.2.1.3 Toxicity test results for sediment organisms

No data on sediment toxicity are available.

3.2.1.4 Calculation of Predicted No Effect Concentration (PNEC) for sediment organisms

Equilibrium partitioning method is not directly applicable for cryolite and fluorides. In addition, test data on sediment toxicity are not available. Therefore it was not possible to carry out the assessment of sediment toxicity. Due to the dissolution of cryolite in water, it is expected, that risk assessment of water compartment covers the realistic worst case situation also for sediment.

3.2.2 Terrestrial compartment

Cryolite is used in the United States as pesticide. The following information has been extracted from the Registration eligibility decision of U.S.EPA (1996).

The target sites are variety of food crops such as melons, all types of squash, fruiting vegetables (pepper, broccoli, cabbage, lettuce, kohlrabi), pears, orange, tomatoes and potatoes. In addition, cryolite is applicable also on several non-food crops. Target pests are in example, cabbage looper, colorado potato beetle, cutworms, flea beetles, armyworm and tobacco budworm.

Cryolite products are provided mainly in formulations of dust, wettable powder and water dispersible granules. The product may be applied by hydraulic ground sprayers and/or aircraft. The maximum single application rate is 30 lbs A^{-1} (3.36 g m^{-2}), applied as a liquid suspension to citrus and ornamentals. The maximum seasonal application rate from multiple applications is 154 lbs A^{-1} (17.3 g m^{-2}).

3.2.2.1 Toxicity test results for terrestrial organisms

3.2.2.1.1 Plants

For cryolite exposure via soil (uptake from soil matrix), no data are available. However, it is noted, that due to the dissolution behaviour, it can be expected, that cryolite is not taken up by plants as such, but in form of different dissolved fluoride and aluminium species.

3.2.2.1.2 Earthworm

3.2.2.1.3 Microorganisms

3.2.2.1.4 Other terrestrial organisms

Test 1

A leaf dip bioassay was conducted to test the effects of Kryocide (96 % cryolite) and five other insecticides on beet armyworm *Spondoptera exigua*, which is a major lepidopterous pest on iceberg salad (Yee and Toscano, 1998). Neonate, 3rd instar and 5th instar larvae were fed with lettuce leaf discs dipped to suspensions of cryolite in deionized water. Test concentrations of the dip suspension were 50 mg l^{-1} (all larval stages tested) 1,000 mg l^{-1} and 10,000 mg l^{-1} (8 day old 3rd –instar tested). Approximately ten larvae were fed in each test. Leaves were left to air dry for 10-15 minutes. Leave disks were fed to larvae which were contained individually in covered cups on bacto agar. The frass was removed after 24 h and new leaf discs were inserted. Dosing of leaves exceeded the consumption of all or most (90 %) larvae. Feeding of each larval stage was continued until prepupation or death of the larvae (4 to 16 days depending on the stage and treatment). Several different control trials for area shrinkage were made in addition to feeding controls without test substance. Leaf consumption (measured by means of leaf area), length of larval stage, survival and time to death were followed as main end points. Feeding temperature was 27.5 ºC and photoperiod 16:8 (L:D).

Cryolite did not show significant effects on leaf consumption or length of larval stage in 50 mg l^{-1} treatment in any of the larval stages. 56 % of neonate larvae (N = 9) survived to prepupation (in control 89 % survival, N = 9). However, this difference was not considered significant by the authors, who used ANOVA for the analysis of all results. In other two stages, no effect to survival was observed. In the 1,000 mg l^{-1} treatment, 38 % or 3rd instar larvae (N = 8) survived (in control 88 % survival, N = 8). Larval stage was slightly longer (4.1 d) than in control (4.5 d). The treatment of 10,000 mg l^{-1} caused death of all (N= 8) larvae (in control 100 % survival, N = 8). Length of larval stage was 2.4 d (in control 3.8 d). Hence, a clear dose-response was observed for survival and length of larval stage. The authors also consider that obviously cryolite needs to be consumed by *S. exigua* to exert its effects, although it may also be topically active against some insects.

The results of the test are not directly applicable to the risk assessment, because the actual exposure cannot be quantified. In addition, the amount of replicates is low although reliability/comparability was on the other hand enhanced by testing six pesticides simultaneously (comparative target species testing is recommended for pesticides). Nevertheless, the results show proper dose response for three exposure levels, of which two are clearly above water solubility. Hence, the study indicates that particulate form of exposure causes effects due to its particulate form when fed to an invertebrate.

Test 2

In a similar study of Prasad, et al. (2000), third instar larvae of tobacco caterpillar (*Spodoptera litura*) were fed with castor leaves dipped to suspensions of 2000 mg l^{-1} or 6000 mg l^{-1} (considered as LC_{50} by the author) cryolite. The frass was replaced by fresh leaves every 24 hours and the total exposure duration was three days. Five replicates of each test concentration were conducted using 10 larvae in each were used and test temperature was 28 +/- 2 ºC. Leaf consumption, growth rate of larvae were followed as main end points over the three days of exposure and four days thereafter. The authors conclude that cryolite significantly suppressed consumption at both treatment levels and that growth rate was concentration dependent.

The test conditions were not documented in detail, the statistical analysis of results is missing and it remains unclear how growth rate was measured in this study. However, also this study provides supporting evidence on that digestion is relevant uptake route and that the particulate form of exposure causes increasing dose-response.

Test 3

Potential hazard of several pesticides on honeybee (*Apis mellifera*) was investigated by Atkins and Kellum (1986). Well established, free colonies were used for the test. Tests were carried out for larvae in age of 1-2 days, 3-4 days and 5-6 days. For every age group, 1-3 dilutions of test substance in acetone or acidified acetone were tested. The test substance was introduced as a single dose (droplet) directly into comb cells. The droplet was directed to the food in the bottom of the cell. Each treatment was applied to horizontal bands of the comb including approximately 100 larvae in 5-7 rows. In addition, control was included in each test. The brood comb was returned after the ca. 20 minutes lasting treatment to the hive. After the treatment the colony was not disturbed until the brood cells had been capped. At that time the number of treated and untreated larvae surviving to the capping stage was recorded.

The data for all dilutions used on each age-group and the data for the combined age-groups were analyzed statistically using linear regression. For the whole dataset (ages combined), a LD_{50} of 2,245 µg/larva was determined. A dose expressed as µg/larva equals according to the authors the application rate of the pesticide in kg ha^{-1}. The corresponding LC_{10} was 147.8 µg/larva and LD_{90} 34,000 µg/larva. Of the larval age groups, the 1-2 day old group was the most sensitive. LD_{10} of 45.73 µg/larva, LD_{50} of 189.6 µg/larva and LD_{90} of 4,366 µg/larva were derived. The authors concluded that cryolite was essentially non-toxic to bees at the usual application levels.

The study is considered as an acute test because the dose was administered as single dose and because less than one animal generation is followed. The test conditions are well described and increasing response with increasing dose was reported to all substances tested.

Test 4

Forsythe and Collins (1994) reported on a field application study employing early instar blueberry flea beetle larvae (*Altica sylvia*) on 20 ft * 20 ft plots in a pruned blueberry field. Two treatment levels of cryolite, 240 ounces $acre^{-1}$ (= 16.7 kg ha^{-1}) and 400 ounces $acre^{-1}$ (= 28 kg ha^{-1}) were applied in 3 replications per treatment using conventional pesticide application apparatus (recorded). Control fields (no pesticide) and fields with two other pesticides were also included. The larvae were sampled 1 day before treatment and on days 1, 2, 3, 5, 7 and 9 after application. On sample dates, 10 sweeps with a standard 12-inch sweep net were taken from the center of each plot. The larvae were counted and then released over the same plot. The authors report the amounts of larvae/10 sweeps as a mean of each treatment for each day.

The number of larvae in the sweeps of the control plots decreased considerably at days 7 and 9 but the authors stated that this was due to the migration of the larvae into the litter for pupation. They also conclude that cryocide provided at both application rates an excellent control of the population. The mean number of larvae per 10 sweeps of the days 1 to 5 is 102 (SD = 19) for controls. The mean for the lower application rate is 32 larvae/10 sweeps (SD = 30) and for the higher application rate the mean is 28 larvae/10 sweeps (SD = 29). A proper statistical analysis cannot be conducted to test whether the two treatments caused effects at same level or not (raw data not available). However, it can be concluded that the EC_{50} –level for this field test was likely to be reached already at the application rate of 16.7 kg ha^{-1}.

3.2.2.2 Calculation of Predicted No Effect Concentration (PNEC)

HF/F

A $PNEC_{soil}$ of 11 mg F^- kg wwt^{-1} was derived for fluoride ion in the risk assessment of HF (EU, 2001). This PNEC will be applied for the HF/F-approach.

Particulate cryolite

Based on the information of U.S.EPA (1996), cryolite is applied in dust and in suspension form where much of cryolite can expected to remain in particulate form. Ingestion of cryolite is expected to be the relevant route of exposure. The substance is considered to act predominantly as stomach poison while it releases fluoride ions (U.S.EPA, 1996). Fluoride ions in turn form complexes with metal containing enzymes in stomach (Corbett et al., 1974). The available two studies on target organisms (Test 1 and 2) provide evidence on that ingestion as route of exposure and particulate form as form or exposure in combination cause increased response to increased dose.

Tests 3 and 4 could be used in a tentative manner for PNEC –derivation related to exposure similar to insecticidal application. The honeybee brood LD50 of 224.5 g AlF_6Na_3 m^{-2} is related to the application rate as well as the results of the Test 4 (LD50≤ 1.67 g AlF_6Na_3 m^{-2}). Target species blueberry flea beetle in the Test 4 (short term field test) seemed to be more sensitive than honeybee brood in Test 3. Despite of the uncertainty regarding to whether a proper dose-response resulted in Test 4, the lower application rate of 1.67 g m^{-2} from the study is considered as the critical acute effect value and an assessment factor of 100 is chosen for the risk characterisation. This factor is deemed appropriate due to following reasons:

- two short-term field studies are available on invertebrates; one of them has used target species, the other has employed sensitive larval stages of a non-target species (honey beetle);
- a variety of plant species are not expected to show effects at application levels of cryolite as insecticide hence excluding the apparent need to test plants in this assessment.

With the above given assumptions, a tentative PNEC related to the exposure route deposition, “no-effect-deposition” ($NE_{dep)}$ of 17 mg AlF_6Na_3 m^{-2} is obtained. It should be noted, that although the units refer to exposure via air, this value reflects effects caused by cryolite deposited from air into soil or onto plants’ surface. It is considered not relevant to derive from the critical deposition $PNEC_{soil}$, because cryolite can be expected to dissolve as soon as it gets into contact with porewater. It is also noted, that the “no-effect-deposition” could be related to short-term exposure.

3.2.3 Atmosphere

A $PNEC_{plant-air}$ of 0.2 µg m^{-3} was derived HF in the risk assessment of HF (EU, 2001). This PNEC will be applied for the HF/F-approach. For particulate cryolite, no $PNEC_{air}$ was derived. The exposure route from air to vegetation is due to the particulate form same as discussed in the previous chapter. No effects on a variety of plant species have been observed with an exposure corresponding approved application levels of cryolite as insecticide.

3.2.4 Secondary poisoning

3.2.4.1 Effect data

Test 1

Schafer (1972) reported on a study where effects of 369 substances had been tested on red-winged blackbirds (*Agelaius phoeniceus*) or starlings (*Sturnus vulgaris*). A dose of 100 mg kg^{-1} or less had been dosed by gavage with suspensions or solution of the test chemical in propylene glycol. Wild-trapped birds were preconditioned to captivity for 2-6 weeks before dosing. No further details on test conditions are provided but methods of other authors are cited. Cryolite was listed by the authors among those chemicals which were not observed to be toxic at the dose level of 100 mg kg^{-1}. Due to the lacking documentation of the test conditions, the results can be used for background information only (validity = 4).

3.2.4.2 Calculation of PNEC$_{oral}$

NOECs of 0.8 µg m^{-3} and 0.3 µg m^{-3} for grazing and winter season, respectively, were derived in the risk assessment of HF (EU, 2001) for livestock effects due fluoride exposure via feed as it was observed that fluoride concentration in air correlated with concentrations in plants. NOECs were used directly without an assessment factor. The lower of these values (for winter season) is taken forward to the HF/F-approach.

Due to the dissolution of cryolite, it is expected, that no secondary poisoning occurs but exposure caused by cryolite is covered by the PNECoral for fluoride above.

3.3 RISK CHARACTERISATION [5]

Cryolite dissociates in the environment and its transformation is especially dependent on pH, on the prevailing relations in the Al-OH-F –system of the receiving environment but also on environmental levels of substances which cause precipitation of fluoride (silica and phosphorus complexes). This means that fate of cryolite is very complex to simulate and that a comparison of cryolite exposure to the effects of cryolite from laboratory tests is hardly ever a comparison of “like with like”. It was decided to take two separate assessment approaches. These are “HF/F-approach”, where exposure is estimated for HF (air) and fluoride (water, soil) and compared with corresponding PNECs. Aluminium exposure (Al complexes without F) is not accounted for in this assessment. The second approach covers risks caused by particulate cryolite exposure via deposition.

Information for conducting a specific exposure assessment is needed for all downstream uses other than aluminium industry. Information on the exact downstream user industries and volumes used at sites, life-cycle steps (including possible consumer uses), emissions (in form HF, dissolved F and particulate F), pollution abatement techniques and process descriptions should be provided.

Information on waste management and emissions from the waste management step of all downstream uses should be provided to the Rapporteur. Especially aluminium smelters produce considerable amounts of cryolite waste. The amount of this waste, its management and possibility of emissions should be clarified.

3.3.1 Aquatic compartment (incl. sediment)

HF/F-approach

Local concentrations of fluoride were estimated assuming that all site specific emission amounts reported are in form of free fluoride ion and in case of generic assessment cryolite emission was converted to corresponding amount of dissolved fluoride ion. Solid-water partitioning coefficients were kept low arbitrarily. Regional concentration was derived from measured data. PNEC$_{water}$ of 8.8 mg AlF_6Na_3 l^{-1} is available, which corresponds to a PNEC$_{water}$ of 4.8 mg F l^{-1}. PNEC$_{stp,microorganisms}$ of 1.6 mg AlF_6Na_3 l^{-1} is available, and it corresponds to a PNEC$_{stp,microorganisms}$ of 0.87 mg F l^{-1}. It is noted, that although the PNEC –

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[5] Conclusion (i) There is a need for further information and/or testing.
Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

values expressed as fluoride are used for the risk characterisation, the initial exposure is presumed to occur in the form of cryolite.

PNEC$_{sediment}$ was not derived because there is no information available on sediment toxicity of cryolite, dissolved fluoride ion or other relevant cryolite transformation products. Due to different pH, redox and ionic conditions in sediment than in water column, it can be expected that speciation and partitioning of fluorides differ from corresponding water column processes. Therefore, equilibrium partitioning method is not applicable. However, as fluoride exposure in water is in this approach calculated as realistic worst case approach assuming no partitioning to particulate matter, it is assumed, that risks to sediment are covered by the risk characterisation of the water compartment.

Table 3.19 Risk characterisation for aquatic compartment, production sites.

Site nr.	**PEClocal$_{water}$(mg F l^{-1})**	**RCR**	**PEC$_{stp,micro-organisms}$(mg F l^{-1})**	**RCR**
2	0.6	125	4.1	4.7
3	1.5* (Clocal = 0.5)	< 1*	50	57.5
4	0.8	167	112	128.7
5	1.04* (Clocal = 0.04)	< 1*	**	

* The sites are releasing to sea. The contribution of the local release to the local concentration is not significant compared to the natural dissolved fluoride concentration of seawater is above 1 mg l^{-1}.

** The site does not have biological waste water treatment.

Table 3.20 Risk characterisation for aquatic compartment, downstream uses, formulation.

Use	**PEClocal$_{water}$(mg F l^{-1})**	**RCR**	**PEC$_{stp,micro-organisms}$(mg F l^{-1})**	**RCR**
Filler in synthetic resins for abrasives	1.01	210	10.2	11.7
Binding agent in cutting or grinding discs	0.57	119	3.7	4.3
Colouring agent, opacifier	0.64	133	5.0	5.7

Table 3.21 Risk characterisation for aquatic compartment, aluminium smelters.

Site nr.	**Clocal$_{water}$(mg F l^{-1})**	**RCR**
1	0.01	< 1
4	0.19	< 1
5	0.17	< 1
8	0.03	< 1
12	0.06	< 1
20	0.002	< 1
21	0.05	< 1

Site nr.	Clocal$_{water}$(mg F l^{-1})	RCR
22	0.05	< 1
27	0.04	< 1

For the site 20 (located in inland), ambient fluoride background concentration of 0.2 mg F l^{-1} is applied as regional PEC. Clocal does not contribute significantly to the resulting PEClocal (0.202 mg l^{-1}). The other sites release directly to the sea and, similarly, their releases do not contribute significantly to the PEClocal because the natural fluoride concentration of seawater is equal or higher than 1 mg l^{-1}.

Table 3.22 Risk characterisation for aquatic compartment, downstream uses, processing.

Use	PEClocal$_{water}$(mg F l^{-1})	RCR	PEC$_{stp,micro-organisms}$(mg F l^{-1})	RCR
Filler in synthetic resins for abrasives	122	25417	1981	2277
Binding agent in cutting or grinding discs	70.1	14604	703	808
Colouring agent, opacifier	65.9	13729	659	757

Conclusions to the risk assessment for the aquatic compartment:

Conclusion (i) There is a need for further information and/or testing.

Conclusion (i) applies to production sites 2, 3 and 4 and downstream users other than aluminium industry. Risk ratios for the dissolved cryolite in surface water (not site 3) and in waste water treatment plants are > 1 (HF/F-approach). PNEC$_{water}$ and PNEC$_{stp,microorganisms}$ should be refined with additional testing. Long-term ecotoxicity tests on fish, daphnia and algae are needed to refine the PNEC$_{water}$.- A microbial inhibition test with higher test concentrations than in the available study is necessary for determining the actual E(I)C$_{50}$.

Conclusion (i) applies also to all downstream user sites regarding waste management (see chapter 3.3).

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to production sites 3and 5 for dissolved fluorides to aquatic environment (HF/F -approach). It also applies to aluminium smelter sites for the releases of fluorides to aquatic environment (HF/F -approach).

3.3.2 Terrestrial compartment

HF/F screening approach

Terrestrial risks to fluoride via deposition were not separately evaluated (see chapter 3.1.5).

Particulate cryolite

No conventional $PNEC_{soil}$ for cryolite was derived.. It can be expected, that when cryolite is mixed to soil matrix and gets in contact with pore water, it is dissolved to different aluminium and fluoride species and no exposure to dissolved cryolite occurs in soil. The EPM-approach is not applicable due to the speciation behaviour of cryolite.

A tentative "PNEC", a "no-effect-deposition" (NE_{dep}) of 17 mg m^{-2} was derived for the exposure route ingestion of particulate cryolite deposited or applied to soil. For this value, results from pesticide studies on target organisms were used. This value was not converted to a conventional $PNEC_{soil}$ because the route of exposure is deposition -> ingestion. This threshold value is rather representative of short-time exposure, whereas due to the dissolution of cryolite long-time exposure is expected to be negligible.

The annual deposition from aluminium smelters ranges from 27 to 755 mg AlF_6Na_3 m^{-2} with an annual mean of 93 mg AlF_6Na_3 m^{-2} . If the estimated annual deposition amounts are compared with the NE_{dep}, **RCR –values between 1.6 and 44.4 result (for mean 5.4).** This type of comparison of PNEC derived from single application tests with annual deposition may overestimate the risks. The comparison with respective daily deposition values provides **RCR-values of 0.004-0.12 (min-max) and 0.02 (mean source strength)**.

The maximum allowed seasonal application rate for cryolite in the United States is 17.3 g AlF_6Na_3 m^{-2} (U.S.EPA, 1996), which is 23-fold compared to the annual deposition around the most emitting aluminium smelter. It is therefore considered, that particulate deposition of cryolite does not cause risks in the vicinity of the aluminium smelters.

There is no information on the amount of particulate emissions of cryolite to air from the producer sites no. 3, 4 or 5 or from any downstream user sites other than smelters. It is necessary, that these sites provide information on particulate cryolite emissions to air in order to estimate whether development of a further terrestrial assessment is necessary.

Conclusions to the risk assessment for the terrestrial compartment:

Conclusion (i) There is a need for further information and/or testing.

This conclusion applies to a need of more specific emission data for the production sites 3, 4 and 5 and downstream user sites other than aluminium smelters. The sites should provide information on the amount of particulate cryolite emissions to air (*particulate cryolite approach*).

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

This conclusion applies for aluminium smelters and producer site 2 regarding their emissions of particulate cryolite (*particulate cryolite approach*).

3.3.3 Atmosphere

HF/F-approach

PNEC$_{plant\text{-}air}$ of 0.2 µg m^{-3} was derived in the risk assessment of AlF_3 (European Commission, 2008). Also a PECregional$_{air}$ of 0.2 µg m^{-3} has been derived in the same assessment and it has been used for this assessment. It is, however, noted, that this regional concentration does not necessarily incorporate all emissions from cryolite downstream uses, because it can be expected, that part of these uses are not covered by EPER reporting requirements. EPER was used by NL for deriving/choosing the regional PEC. However, specific information on downstream uses of cryolite is lacking and incorporation of the releases (estimated by means of generic scenarios) in to a calculation of PECregional$_{air}$ in this phase would result an unbalanced picture of the regional concentration. Downstream uses (other than aluminium smelters) alone result a generic PECregional$_{air}$ estimate of 0.23 µg m^{-3}. The final PECregional$_{air}$ will be calculated only after more specific data on downstream uses becomes available.

Production

Sites 2 and 4 reported their emissions as HF. For site 3 the release was calculated based on generic emission factor assuming that all cryolite is emitted in the form of HF. Site 5 did not specify the form of reported emission and it was assumed that the form is HF.

Table 3.23 Risk characterisation for plant-air exposure and predicted environmental concentrations, production.

Site nr.	PEClocal$_{air}$(µg HF m^{-3})	RCR
2	0.28	1.4
3	12.5	62.5
4	0.31	1.55
5	4.93	24.65

Other uses, formulation step

Table 3.24 Risk characterisation for plant-air exposure and predicted environmental concentrations, formulation.

MC/IC/UC	Use	PEClocal$_{air}$(µg HF m^{-3})	RCR
3/16/0	Filler in synthetic resins for abrasives	39.8	199
3/8/2	Binding agent in cutting or grinding discs	18.1	91
3/0/10	Colouring agent, opacifier	21.6	108

Aluminium smelters (processing)

The HF –releases from primary aluminium smelters cover all HF –releases of the sites regardless of the source. The risk ratios derived in the frame of the risk assessment of AlF_3 (European Commission, 2008) cover hence also the by-production and processing of cryolite.

Table 3.25 Atmospheric local F-concentrations, PEC-values and PEC/PNEC-ratios for all EU primary aluminium smelters (European Commission, 2008).

Location number	**OPS-Pro 4.1 derived: C_{local} HF (µg/m^3)/ year)**	**PEC_{local} (µg/m^3)**	**RCR**
1	3.3	3.5	18
2	3.1	3.3	17
3	4.4	4.6	23
4	8.5	8.7	44
5	2.3	2.5	13
6	3.5	3.7	19
7	5.5	5.7	29
8	3.1	3.3	17
9	2.4	2.6	13
10	9.4	9.6	48
11	13	13	65
12	4.1	4.3	22
13	1.7	1.9	9.5
14	0.65	0.85	4.3
15	19	19	95
16	3.2	3.4	17
17	3.3	3.5	18
18	3.4	3.6	18
19	27	27	135
20	5.4	5.6	28
21	0.65	0.85	4.3
22	1.1	1.3	6.5
23	2.6	2.8	14
24	1.9	2.1	11
25	7.2	7.4	37
26	4.3	4.5	23
27	1.4	1.6	8.0
[28]	[0.77]	[0.97]	[4.9]
[29]	[8.3]	[8.5]	[43]
30	1.9	2.1	11
[31]	[0.80]	[1.0]	[5.0]
32	0.85	1.1	5.5

Other uses, processing step

Table 3.26 Risk characterisation for plant-air exposure and predicted environmental concentrations, processing.

MC/IC/UC	Use	PEClocal$_{air}$(µg HF m^{-3})	RCR
3/16/0	Filler in synthetic resins for abrasives	154.2	771
3/8/2	Binding agent in cutting or grinding discs	204.2	1021
3/0/10	Colouring agent, opacifier	193.2	966

Particulate cryolite approach

Local concentrations of particulate cryolite in air were derived in section 3.1.6.1.3 for aluminium smelters. It is noted that the estimated local concentrations (as cryolite) are significantly lower than estimated local concentrations in air for HF and even lower than the regional PEC for HF. The air to plant route is considered for particulate cryolite to represent the identical exposure route with deposition of particulate cryolite. This route is covered in this report by the terrestrial assessment.

Conclusions to the risk assessment for the atmosphere:

Conclusion (i) There is a need for further information and/or testing.

Conclusion (i) applies to:

- Production sites 3, 4 and 5 should provide information on particulate cryolite emissions to air (*particulate cryolite approach*).
- to all downstream uses, except aluminium smelters (see chapter 3.3 for information requirements) (*HF/F approach and particulate cryolite approach*). It is expected, that also the PECregional for HF can be refined after specific information on these downstream uses becomes available.
- to all downstream user sites regarding waste management (see chapter 3.3) (*HF/F approach and particulate cryolite approach*).

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

This conclusion covers the production sites 2 and 4 as they contribute to the local ambient concentrations less than the regional background concentration of HF (*HF/F approach*).

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iii) applies to the production sites 3 and 5 (*HF/F approach*).

3.3.4 Secondary poisoning

A $PNEC_{oral}$ of 0.3 (µg HF m^{-3}) for livestock via feed is applied for the risk characterisation. Due to a limited area of plant feed source for livestock, the risk characterisation is based on local concentrations only. As this PNEC is related to the plant-air exposure route, the risks covered by the risk characterisation for atmosphere cover also this route.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General discussion

Cryolite is the double fluoride of sodium and aluminium (Na_3AlF_6) with a melting point of about 1010°C.

Natural cryolite (CAS No.: 15096-52-3) has been found in substantial quantities only in Greenland but it is practically exhausted and abandoned in favour of synthetic cryolite (CAS No.: 13775-53-6). Synthetic cryolite can be produced by reacting hydrofluoric acid with an alkaline sodium aluminate solution. Cryolite is also produced directly in reduction cells by the reaction of soda impurity in the feed alumina with added aluminium fluoride (Ullman, 1998) and it can also be recovered from used pot linings in the aluminium industry. The lining is crushed and treated with dilute sodium hydroxide solution to dissolve fluorides.

There are approx. 26.000 t cryolite produced per year in several production sites (5 producers in the EU-15), about 16.000 t is exported outside the EU. The aluminium industry produced approx. 4.500 t/a (as cryolite), 700 t are sold in the EU the other are exported.

Cryolite is mainly used in the aluminium metallurgy as a component in fluxing agents (lowers the melting point), protective and refining salts (56 % of the European annual production volume). Cryolite is also used as a filler in synthetic resins for abrasives (12 % of the European annual production volume), as a binding agent in cutting and grinding discs (8 %) and as a raw material for chemicals used in foundries (16 %). Minor uses are the use as a colouring agent and an opacifer in the pyrotechnic-, glass- and ceramic industry (8 % of the European annual production volume).

Detailed information see chapter 2 (general information on exposure).

For workers the inhalation and dermal routes of exposure are likely to occur.

In the Swedish product register no products are listed as consumer use. Due to information of the European Aluminium Association, cryolite is used in ceramic and metal processing. In the US, cryolite is used as a pesticide for terrestrial food and feed and terrestrial non-food sites, predominantly by commercial growers. It is not registered for greenhouse use. In the European Union, cryolite is not registered for this purpose and there is no indication for such uses in the EU.

4.1.1.2 Occupational exposure

Industrial activities using cryolite present opportunities for occupational exposure. Exposure ranges depend on the particular operation and the risk reduction measures in use.

There are no occupational exposure limits established in the EU (Ariel, 2005).

The exposure assessment generally aims at assessing exposure levels representing the reasonable worst case situation. The reasonable worst case is regarded as the level of exposure which is exceeded in a small percentage of cases over the whole spectrum of likely circumstances of use for a specific scenario.

The assessment of inhalation exposure is mainly based on measured exposure levels from which – if possible – 90th or 95th percentiles are derived as representing reasonable worst case situations. If available, only data measured later than 1990 are used in exposure assessment. Scenarios are clustered as far as possible to make the description transparent. If quantitative exposure data are not available, model estimates are taken.

Beside inhalation exposure, dermal exposure is assessed for each scenario. Two terms can be used to describe dermal exposure:

Potential dermal exposure is an estimate of the amount of a substance landing on the outside of work wear and on the exposed skin.

Actual dermal exposure is an estimate of the amount of a substance actually reaching the skin.

Within the framework of existing substance there is an agreement between the EU member states, to assess - as a rule - dermal exposure as exposure to hands and parts of the forearms. In this, the main difference between both terms – potential and actual - is the protection of hands and forearms by work wear and – more important – the protection by gloves. Within this exposure assessment, the exposure reducing effect achievable by gloves is only considered if information is provided indicating that, for a certain scenario, gloves are a widely accepted protective measure and that the gloves are fundamentally suitable for protection against the substance under consideration. As a measure for the latter, tests according to DIN EN 374 are taken as a criterion. For most downstream uses it is commonly known that gloves are not generally worn. In these cases, dermal exposure is assessed as actual dermal exposure for the unprotected worker. Since quantitative information on dermal exposure is often not available, the EASE model is usually used for assessing dermal exposure.

The following scenarios are regarded to be relevant for occupational exposure:

Scenario 1: Production of synthetic cyrolite (4.1.1.2.1)
Scenario 2: Use of cryolite in the aluminium industry (4.1.1.2.2)
Scenario 3: Use of cryolite in other industries (e.g. production of abrasives, glass-ceramic industry, foundries) (4.1.1.2.3)
Scenario 4: Use of abrasives and grinding discs (containing cryolite) (4.1.1.2.4)

4.1.1.2.1 Production of synthetic cryolite (scenario 1)

Inhalation exposure

Natural cryolite is an ore, which is widely exploited since the early days of commercial aluminium production, but now practically exhausted and abandoned in favour of synthetic cryolite. Until recently, natural cryolite ore occurred in considerable quantities in Ivigut, Greenland, and crushing and refining took place at a facility in Copenhagen, Denmark. Eight male workers at a cryolite concentrator participated in a 4-day study in 1990. Total dust exposures (personal sampler) varied between 0.16 and 21.2 mg/m^3 for the 4-hour periods. The major part of the dust was assumed to be cryolite (Grandjean, 1990).

Synthetic cryolite is produced in a closed reactor, with continuous processes. There are two methods described, one method is to dissolve aluminium hydrate under stirring in 15-25 % HF solution. Fluoroaluminic acid is formed. This acid is treated in another reactor with natrium chloride solution. Sodium fluoroaluminate precipitates, it is filtered, centrifuged, dried and bagged (Fluorsid, 1997). Another method is the conversion of hexafluorosilicic acid with aluminium hydroxide. The aluminium fluoride remains dissolved, is separated from the precipitated silicic acid and converted with a mixture of natrium chloride solution and hydrofluoric acid to form cryolite. In the second step cryolite is dried and packed (Solvay, 1997).

Cryolite is marketed as granular and milled cryolite qualities. Smaller quantities are micronized for technical applications, such as abrasives. The median particle distribution of cryolite powder is between 5-20 µm (Solvay, 1997).

Cryolite is packaged and delivered in many different forms, depending on the customer's requirement: small bags (plastic or paper) of 25 or 50 kg, big bags of 1000 or 1500 kg, bulk in sea containers, silo trucks and rail tank cars. About ¾ of the produced cryolite are exported outside the EU.

Exposure associated with transporting the chemical would result from loading, unloading, coupling, uncoupling and drumming operations. For the large-scale chemical industry high standards of control at the workplace are assumed to be practiced even if the containment is breached, e.g. during filling, cleaning, maintenance, repair works and taking of samples. Inhalation exposure in other fields is normally minimized by technical equipment (e.g. special designed filling stations, local exhaust ventilation (LEV)).

Measured data

Table 4.1.1.2.1: Total dust exposure at workplaces during production (scenario 1) (provided by 3 producers)

Job category / activities	Years of measurement	Number of samples	Measurement data [mg/m^3]	50th percentile [mg/m^3]	95th percentile [mg/m^3]
8 h TWA					
Production	1994 1997	11 13	0.1 – 11.1 0.1 – 0.93	- -	9.7 0.85
Packaging into big bags, granular	1996	1 (p)	2.1	-	-
Packaging into big bags, fine	1996	1 (p)	0.5	-	-
Packaging into big bags, flour	1996	1 (p)	5.8	-	-

p: personal sampling

For the purpose of measuring cryolite in the air at the workplace the gravimetric sampling method for the inhalable dust fraction was used. The measurements of total dust were performed with personal and stationary samples. Because two companies provided a few measured values model estimation is performed.

According to information provided by manufactures in the production of synthetic cryolite approx. 30 workers are employed. Workers normally use PPE (personal protective equipment, here gloves, eye glasses, dust masks) and, during cleaning activities, respiratory protection in addition.

Modelled data

EASE for Windows 2.0, Aug. 1997 was used.

a) EASE estimation for the use of powdery cryolite at workplaces with local exhaust ventilation (LEV):

Input parameters: T = 20 °C, exposure-type is dust, dry manipulation, LEV present

Level of exposure: 2 - 5 mg/m^3

b) EASE estimation for the use of dust-suppressed (granular) cryolite:

Input parameters: T = 20 °C, exposure-type is dust, low dust technique, LEV present

Level of exposure: 0 - 1 mg/m^3

Summary/statement of the exposure level

During the production of cryolite, exposure to dust in the area of bagging of powder in sacks or big-bags is regarded to be the main source of exposure.

For the assessment of health risks of daily inhalation exposure to cryolite an 8 h time weighed average concentration (8 h TWA) of 5.0 mg/m^3 (EASE-estimation) should be taken to represent a reasonable worst case situation. It is to be assumed, that exposure is lower, if granular cryolite is used. In this case an 8 h time weighed average concentration (8 h TWA) of 1.0 mg/m^3 (EASE-estimation) should be taken.

It is to be assumed that the substance is processed daily. Consequently, the duration and the frequency of exposure to cryolite are assumed to be daily and for the entire length of shift.

Dermal exposure

When producing cryolite (powder) dermal exposure could occur during activities like bagging, sampling, cleaning, maintenance and repair work.

Modelled data

For the unprotected worker, according to the EASE model, potential dermal exposure is assessed as follows:

Input parameters: Non dispersive use, direct handling, intermittent, non-aggregating-dust

Level of exposure: 0.1 – 1 mg/cm^2/day.

Considering an exposed area of 420 cm^2 (palms of hands) the model yields an exposure level of 42 - 420 mg/person/day.

For assessing actual dermal exposure levels, it has to be considered that the substance is manufactured primarily in closed systems and that the use of personal protection equipment (PPE, here gloves and eye protection) is highly accepted in the large-scale chemical industry. The extent of protection by PPE (here gloves) depends inter alia on the suitability of the recommended material with regard to the permeation properties of substance. For the handling of powdery substances, as a rule, the suitability of the gloves can be assumed. As a rough estimation, a protection efficiency of 90 % achieved by suitable gloves is taken resulting in dermal exposure of 4.2 – 42 mg/person/day. The upper value is regarded to represent the reasonable worst case situation.

Summary of the exposure level

For assessing the health risks from daily dermal exposure in the area of production (scenario 1), an exposure level of 42 mg/person/day should be taken. This exposure assessment is based on the assumption that gloves are suitable for the protection against powder.

Exposure to the eyes is largely avoided by using eye protection.

4.1.1.2.2 Use of cryolite in the aluminium industry (scenario 2)

The production of aluminium takes place in pots (electrolyses furnaces). The raw material (aluminiumoxide) is dissolved in the molten bath material (970°C) and splitted (in a continuous process) into aluminium and oxygen. The aluminium resulting from electrolysis settles on the bottom of the pot form and is tapped from time to time. The pots are hooded tightly and the release to air is sucked off and treated in all sites in a scrubber before the release to air. The working place is ventilated 40 times an hour (Aluminium Delfzijl, 1997). According to literature releases to pot room air are caused when the hoods are removed for renewal of anodes, for relining the pot, for tapping aluminium or excess cryolite and for adding bath constituents to the bath. ‘Fresh’ cryolite is used only for the start up of new or repaired pots. The cryolite is delivered in 25 kg paperbacks and feed to the pots by charging the closed paperback in the melted bath (Hoogovens, 1999).

In the aluminium electrolysis cells molten cryolite is the main component of the electrolysis bath. The cryolite is not being consumed in this process, but due to the temperature and presence of humidity, fluorides are evaporating from the bath and also being entrained with the gases sucked off from the cell to the gas treatment equipment. In the gases escaping from the cell there are varying amounts of cryolite, depending on the local conditions. Sampling of dust for analysis of cryolite has taken place in 8 plants. The samples referred to in the results have being collected from roof construtions or at the exit from the roof ventilators in order to be representative of dust being emitted to the air. A few samples have also been collected in the clean ga from the dry scrubber. Individual measurements for 12 samples showed an average cryolite content of 10.5 % with minimum value 5 % and maximum 21 %. In the clean gas from the dry scrubber the cryolite concentration was for all samples lower than 9 %, in most cases 1 - 2 % (EAA, 2008).

On the other side the aluminium industry is a producer of bath material (CAS No.: 91969-24-1) which contains approx. 20-85 % cryolite. Cryolite is formed in the bath through the reaction of aluminium fluoride (an excess of aluminium fluoride in relation to cryolite is needed) with soda impurity in the feed alumina.

The direct exposure to bath material is not a constant exposure as bath material stays in the pots most of the time and is only handled directly in connection with bath removal and with anode change. Handling of bath material in connection with anode change is automated and the main exposure is HF emissions and not cryolite. Workers in aluminium smelters do not handle cryolite except for rare occasions of charging extra cryolite on the pots (EAA, 2008).

During the above described activities an inhalation exposure of workers to dust is to be expected. The exposure is continuous during the working time.

Old pots and used anodes are taken out of service after 5 to 7 years of operation. In average, 25 – 35 kg spent pot linings (containing 5 - 8 % cryolite) are produced per tonne of aluminium. The tapped and collected bath material has to be crushed and is sold to third parties. The production of bath material depends on the production parameters and raw material composition (approx. 0.5 % of the aluminium production capacity) (Aluminium Delfzijl, 1997).

No downstream uses exist for the by-production, because the production of excess cryolite not used for own purposes is sold to other smelters for the start of a new or renewed pot. Spent pot linings (cathode coal), anode butts and scrubber waster contain cryolite. A considerable part of it is recovered at the site and used at the site.

Exposure associated with charging cryolite to the pots, removing old pots and crushing of collected bath material.

Inhalation exposure

Measured data

At the handling of bath material which contains 20% cryolite 25 total dust measurements (1991-1996) are available. The measured values are between 0.4 – 5.1 mg/ m^3 (VAW, 1997).

Total dust measured (personal monitoring, 1999) for anode changing in prebake potrooms show maximum concentration of 2 mg/m^3 (EAA, 2008).

In 2003 the Norway project “Survey of occupational exposure of importance in developing occupational asthma by production of primary aluminium” started with collection of personal exposure in 6 Norwegian Aluminium smelters (Skaugset, 2008). For both Prebake and Soderberg potrooms, the main contribution to the occupational exposure in this industry is caused by episodes, typically short timed and with high concentrations. The personal exposures in Prebake potrooms were significantly higher than the mean exposure in Soderberg potrooms.

The personal measurements have been done for similar groups of workers within the potrooms and as full shift samples. The geometric mean values for total dust (n = 1893) varied between 1.2 mg/m^3 (95 % CI: 1.0 mg/m^3; 2.5 mg/m^3) to 4.7 mg/m^3 (95 % CI: 4.2 mg/m^3; 5.4 mg/m^3). The range of all total dust measurements is 0.13 – 119 mg/m^3. The work categories with the highest dust exposure are anode changing (GM: 9.5 mg/m^3, max. 65 mg/m^3) and metal tapping (GM: 3.6 mg/m^3, max. 119 mg/m^3).

For the purpose of assessing inhalation exposure levels, the measurement result for anode changing of 9.5 mg/m^3 (geometric mean) is taken. For the calculation of cryolite in the air a concentration of 21 % cryolite as the worst case scenario is considered. Taking all information into account, 2 mg/m^3 is regarded to represent the reasonable worst case.

Modelled data

EASE for Windows 2.0, Aug. 1997 was used.

EASE estimation for the use of cryolite at workplaces with local exhaust ventilation (LEV):

Input parameters: T = 20 °C, exposure-type is dust, dry manipulation, LEV present, non-aggregating-dust

Level of exposure: 2 - 5 mg/m^3

Summary of the exposure level

Inhalation exposure has to be assessed for use of cryolite in the aluminium industry.

For the assessment of health risks of daily inhalation exposure to cryolite during the production of aluminium an 8 h time weighed average concentration (8 h TWA) of 2.0 mg/m^3 (workplace measurements) should be taken to represent a reasonable worst case situation.

It is to be assumed that the production of aluminium is processed daily. Consequently, the duration and the frequency of exposure to cryolite are assumed to be daily and for the entire length of shift.

Dermal exposure

When cryolite use in the aluminium industry dermal exposure could occur during activities like charging, removing old pots, crushing, cleaning, maintenance and repair work.

Modelled data

For the unprotected worker, according to the EASE model, potential dermal exposure is assessed as follows:

Input parameters: Non dispersive use, dry manipulation, intermittent

Level of exposure: 0.1 – 1 mg/cm^2/day

Considering an exposed area of 840 cm^2 (hands) the model yields an exposure level of 84 - 840 mg/person/day.

For assessing actual dermal exposure levels, it has to be considered that the use of personal protection equipment (PPE, here gloves and eye protection) is accepted in the aluminium industry. The extent of protection by PPE (here gloves) depends inter alia on the suitability of the recommended material with regard to the permeation properties of the substance. For the handling of powdery substances, as a rule, the suitability of the gloves can be assumed. As a rough estimation, a protection efficiency of 90 % achieved by suitable gloves is taken resulting in dermal exposure of 8.4 – 84 mg/person/day. The upper value is regarded to represent the reasonable worst case situation.

Summary of the exposure level

For assessing the health risks from daily dermal exposure in the aluminium industry (scenario 2), an exposure level of 84 mg/person/day should be taken. This exposure assessment is based on the assumption, that gloves are suitable for the protection against cryolite.

Exposure to the eyes is largely avoided by using eye protection.

4.1.1.2.3 Use of cryolite in other industries (e.g. production of abrasives, glass-ceramic industry, foundries) (scenario 3)

Cryolite is used as a component in several applications, such as filler in synthetic resins for abrasives (resin-bonded products contains up to 20 % cryolite), as binding agent in cutting and grinding discs and as colouring agent (opacifier) in the pyrotechnic-, glass- and ceramic industry. Closer information on the industrial categories for these uses is not available.

For the use as raw material in casting agents only one company indicated that this use occurs in the steel industry. No further information regarding to the use has been provided. More information on this use is needed to complete the assessment.

For this assessment, a generic scenario is derived based on the assumption that this formulation followed by industrial use (processing).

All applications have in common that solid cryolite is handled. The exposure to cryolite mainly takes place when the compound is added (weighing, dosing, charging or mixing) as a solid.

At the end of the processing the cryolite is bound in the final products, e.g. abrasives, grinding discs, glassware or pottery. At the handling of the final products an exposure against cryolite is not considered. One exception is the use of grinding discs or abrasives at mechanical processing (grinding, sanding). At these activities dust exposure is possible. Therefore a separate scenario is described (see 4.1.1.2.4)

For the above mentioned work places it must be assumed, that LEV is not generally present and protective gloves are not regularly worn. The duration and the frequency of exposure are not known for the particular case but it is estimated to be at maximum 1 hour per day.

It can be expected that the products of these industries are object of wide dispersive use. However, in order to develop sufficient exposure estimation, more specific information would be needed.

Inhalation exposure

Measured data

Workplace measurements are no available.

Analogous data

The NL provided results of a study relating to dumping of powdery goods in different formulating facilities (Marquart et al., 1999). The study was aimed neither at very good nor at very bad equipment. The measurements were taken during continuous dumping of powders into mixers equipped with LEV. A variety of powders were loaded generally from 25 kg bags, but in some cases also from big bags or drums. Exposure levels of inhalable dust averaged over all loading tasks of one worker ranged from 1.9 to 27.6 mg/m^3. Full-shift exposure levels to inhalable dust measured ranged from 0.8 to 12.1 mg/m^3. For bag dumping “reasonable worst-case” estimates in the presence of LEV with limited effectiveness were deduced from literature of 10 mg/m^3 total dust concentration.

A statistical evaluation of data which raised from “Berufgenossenschaftlichen Meßsystem Gefahrstoffe” (BGMG) in 21 branches of the ceramic and glass industry shows inhalable dust concentration of 7 mg/m^3 (95 % values, 324 personal measurements, 8-h TWA’s, 1996-1999). In the area of production of abrasives (compounding, pressing plant, finishing) shows the statistical evaluation inhalable dust concentration of 4.5 mg/m^3 (95 % values, 42 measurements, 8-h TWA’s, 1996-1998) (Barig, 1999).

Modelled data

EASE for Windows 2.0, Aug. 1997 was used.

EASE estimation for the use of powdery cryolite at workplaces without local exhaust ventilation (LEV):

Input parameters: T = 20 °C, exposure-type is dust, dry manipulation, without LEV, non-aggregating-dust

Level of exposure: 5 - 50 mg/m^3

Considering a duration of 1 hour an inhalation exposure of 0.63 – 6.25 mg/m^3 results.

Summary of the exposure level

Inhalation exposure has to be assessed for use of cryolite in the production of formulations and products, e.g. resin abrasives, ceramics.

The analogous data and the EASE estimation are in the same order of magnitude. For the assessment of health risks of daily inhalation exposure to cryolite during the formulation an 8 h time weighed average concentration (8 h TWA) of 10 mg/m^3 (analogous data) should be taken to represent a reasonable worst case situation.

If granular cryolite is used it is to be expected that lower exposure will occur.

It is to be assumed that the producing of formulations processed daily. Consequently, the duration and the frequency of exposure to cryolite are assumed to be daily and for 1 hour per day.

Dermal exposure

Dermal exposure is possible when cryolite is added into mixers or reactors (weighing, dosing, mixing, and charging) and by contact to contaminated surfaces.

Analogous data

Measurement results on dermal exposure are not available. As an analogy exposure scenario, dumping of powders in a formulation company is taken (Lansink et al., 1996). The field study includes manual dumping of calcium carbonate (several grades) from bags into paint mixers in ten paint producing facilities (n = 19). Calcium carbonate is a relatively dusty powder. The dumping lasted for 1 – 15 minutes and 2 – 24 bags, containing 10 – 1000 kg calcium carbonate were dumped. Local exhaust ventilation was generally used during dumping. Bags were cut open using a knife and the powder was allowed to flow into the mixer. Exposure is due to direct contact with the flow of powder. Furthermore, deposition of the dust and subsequent contact with contaminated surfaces occurs including contact to the outside of the bags. The 90th percentile of the data is used as the basis for the reasonable worst case (RWC) value. The exposure was determined as 1.9 mg/cm^2 and a total exposure of 3000 mg/person/day.

The dermal exposure is assessed for the unprotected worker.

Summary of the exposure level

For assessing the health risks from daily dermal exposure in the area of (scenario 3), an exposure level of 3000 mg/person/day should be taken. This exposure assessment is based on the assumption, that gloves are not worn.

Exposure to the eyes is largely avoided by using eye protection.

4.1.1.2.4 Use of abrasives and grinding discs (containing cryolite) (scenario 4)

Cryolite is used as binding agent in resin bounded grinding discs or abrasives. The content of cryolite in products amounts to 20 %. The grinding discs are used in metal processing industry. These activities generate dust which contents also cryolite. According to information from industry 90 % or more of the particulates of the dust during the grinding operation come from the material being ground and about 10 % is from the grinding tools (Future Abrasives, material data sheet). Based on this information, the resulting cryolite concentration in dust amounts to 2 %.

At grinding activities a high dust exposure is to be expected and therefore a further consideration is needed.

Inhalation exposure

Measured data

Workplace measurements are not available.

Analogous data

Dust exposure at metal grinding was investigated in 2004 in 8 companies. The result of inhalable dust concentration was 0.15 – 7.3 mg/m^3 (n=16 personal and stationary measurements, 8-h TWA's; 90th percentile: 5 mg/m^3) with LEV present. Two values of 22.7 mg/m^3 and 24 mg/m^3 were measured without LEV. As a result of this project it is stated that the „Allgemeine Staubgrenzwert“ of 10 mg/m^3 (hygiene value for inert dust) by effective LEV is definitely adhered (Amt für Gesundheit und Verbraucher-schutz, 2006).

In a Finnish study (Mäkinen, 2004) from 2003 grinding and finishing of steel parts was done with a hand-held grinding machine or a band-grinder. The work areas were usually equipped with local exhaust systems. The results of the breathing zone measurements for inhalable dust (average sampling time: 138 min) show a range of 0.5 - 300 mg/m^3 (n=28; average sampling time 138 min (range 47-214 min); arithmetic mean: 27.4 mg/m^3; median: 10.9 mg/m^3)

In a NIOSH health hazard evaluation report (No.: 96-0020-2610) a time–weighed average (TWA) exposure concentration of 10 mg/m^3 for total particulates was described. The air sample was collected in the breathing zone while performing a metal grinding activity (NIOSH, 1996).

Modelled data

EASE for Windows 2.0, Aug. 1997 was used.

EASE estimation for the use of abrasive discs (content 2 % cryolite) at workplaces without local exhaust ventilation (LEV):

Input parameters: T = 20 °C, exposure-type is dust, dry crushing and grinding, without LEV

Level of exposure: 50 - 200 mg/m^3

Consindering 2 % cryolite leads to 1 - 4 mg/m^3.

EASE estimation for the use of abrasive discs (content 2 % cryolite) at workplaces with local exhaust ventilation (LEV):

Input parameters: T = 20 °C, exposure-type is dust, dry crushing and grinding, with LEV

Level of exposure: 2 - 10 mg/m^3

Considering 2 % cryolite leads to 0.04 – 0.2 mg/m^3.

Summary of the exposure level

Inhalation exposure has to be assessed for grinding with abrasive discs which contain cryolite. The dust exposure at these activities varied widely depending on the workplace situation (with or without LEV).

The analogous data and the EASE estimation are in the same order of magnitude. In the case that LEV is absent 50 mg/m^3 (EASE estimation) is taken. On account that grinding activities are not performed during the whole shift and based on the information from the analogous data the lower value of the EASE estimation is feasible. For LEV present the value of 5 mg/m^3 (analogous data, 90th percentile of workplace measurements) is considered.

Taking into account that the cryolite content in dust is approximately 2 % (see above) the assessment of health risks of daily inhalation exposure to cryolite during grinding an 8 h time weighed average concentration (8 h TWA) of 1.0 mg/m^3 without LEV (EASE estimation) and 0.1 mg/m^3 with LEV (analogous data) should be taken to represent a reasonable worst case situation.

For short time and under unfavourable conditions higher inhalation exposure values are possible.

Dermal exposure

During grinding potential dermal exposure occure. The generated dust contains cryolite (estimated 2 %).

Modelled data

Dermal exposure is assessed for the unprotected worker using the EASE model:

Input parameters: Wide dispersive use, direct handling, extensive
Level of exposure: 5 – 15 mg/cm^2/day.

Considering a cryolite content in abrasive dust of 2 % and an exposed area of 840 cm^2 (hands) the model yields an exposure level of 84 - 252 mg/person/day.

The upper value is regarded to represent the reasonable worst case situation.

Summary of the exposure level

For assessing the health risks from daily dermal exposure during the use of abrasives (scenario 4), an exposure level of 252 mg/person/day should be taken, when considering a content of 2 % cryolite in abrasive dust.

4.1.1.2.5 Summary of occupational exposure

Cryolite is produced and imported as a powder by several companies in the EU. The consumption of cryolite is widely spread. Four scenarios were established:

Scenario 1: Production of synthetic cryolite

Scenario 2: Use of cryolite in the aluminium industry

Scenario 3: Use of cryolite in other industries (e.g. production of abrasives, glass-ceramic industry, foundries)

Scenario 4: Use of abrasives and grinding discs (containing cryolite)

The production of cryolite as a powdery substance is realized in a closed system. Therefore the inhalation exposure is relevant when the system is opened for drumming of the cryolite powder. For handling the pure substance the use of suitable gloves is considered leading to reduced dermal exposure.

Scenario 2 describes the handling of powdery cryolite or bath material. Filling, recycling, repairing, maintenance activities are to be considered. Because only a few measurement data are available, an estimation of the inhalation exposure is undertaken using the EASE model. The assessment of dermal exposure is performed by EASE and takes into account that suitable gloves are worn.

For scenario 3, a generic scenario is derived based on the assumption that formulation is followed by industrial use (processing). All applications have in common that solid cryolite is handled. The exposure to cryolite mainly takes place when the compound is added (weighing, dosing, charging or mixing) as a solid. For the dermal exposure estimation dumping of powdery cryolite is considered. The assessment of the exposure level is performed by analogy for the unprotected worker.

In Scenario 4 cryolite is used as binding agent in resin bounded grinding discs or abrasives. The content is about 20 %. The grinding discs are used at metal working processes. These activities generate dust which contains cryolite in amount of approximately 2 %. The assessment of the inhalation exposure differs between presence and absence of LEV. The estimation without LEV is performed using EASE and with LEV present using analogous data. For the assessment of dermal exposure the EASE model is taken and the assessment is performed for the unprotected worker.

The relevant inhalation and dermal exposure levels are given in table 4.1.

Table 4.1 Conclusions of the occupational exposure assessment

				Inhalation		Dermal	
				Reasonable worst case		Reasonable worst case	
Scenario	**Activity**	**Frequence Days/year**	**Duration Hours/day**	**Unit mg/m³**	**Method**	**Unit mg/person/day**	**Method**
Production							
1) Production of synthetic cyrolite	drumming, bagging	daily	shift	a) 5.0 b) 1.0	EASE (dusty material) EASE (granular material)	42	EASE (suitable gloves)
2) Aluminium industry	charging, removing used pots, crushing	daily	shift (assumed)	2.0	Workplace measurements	84	EASE (suitable gloves)
Formulation							
3) Use in other industries (e.g. production of abrasives, glass-, ceramic industry, foundries)	dumping, charging	daily	1 hour	10	Analogous data	3000	Analogous data
Uses							
4) Use of abrasives and grinding discs (content 20 %)	grinding	daily	shift (assumed)	a) 1.0 b) 0.1	EASE (without LEV) Analogous data (with LEV)	252	EASE

4.1.1.3 Consumer exposure

Cryolite is used for glazes in pottery and in grinding of metal. Both uses are possible to occur in the consumer area (hobby) which may lead to exposure by inhalation of dust containing cryolite (http://ceramic-materials.com/cermat/education/276.html). Since no measured data are available the basis for modelling exposure is lacking. According to the technical guidance document only qualitative assessment of consumer exposure is possible. For the selected quantitative assessment modelled EASE values regarding workplace had been modified for consumer use. For uses in pottery the 1 hour value for inhalation exposure of 6.25 mg/m^3 without local exhaust ventilation as a worst case scenario was selected for risk characterisation (see chapter 4.1.1.3).

Acute exposure to cryolite is deriving use of grinding and pottery by inhalation of dust containing cryolite. The magnitude of acute exposure cannot be estimated due to missing data but may reach similar levels as occupational exposure (compare chapter 4.1.1.2.3, modelled data).

4.1.1.4 Humans exposed via the environment

General

Downstream uses other than aluminium smelters are according to section 3.1.2 and 3.1.3 causing the highest releases and the highest local concentrations in the environment and hence represent the highest (estimated) local exposure situations for man via environment. Site and use specific exposure information for these other uses was required by TC NES III'07, but as no further information was provided by the deadline of 31.12.2007, the exposure information requirement has been included into the present draft Article 10(2)-Regulation. It is therefore not possible to provide at present realistic worst case exposure estimates for man via environment, but conclusion (i) is drawn in analogy with the environmental assessment:

Conclusion (i) There is a need for further information and/or testing.

Information on downstream user industries, use volumes, life-cycle steps, emissions, form in which cryolite is released, pollution abatement techniques, and processes should be provided to replace the generic exposure assessment with a more specific evaluation. Information on waste management and emissions from waste management step of all downstream uses should also be provided.

4.1.2 Effects assessment: Hazard identification and dose (concentration)-response (effect) assessment

In the following effect assessment the term cryolite is used for natural and synthetic trisodium hexafluoroaluminate. Although the water solubility of cryolite is rather low dissolution of cryolite is possible after in vivo uptake depending on the conditions. Dissolution of cryolite leads to the formation of fluoride according to the following equation:

$$Na_3AlF_6 \rightarrow AlF_4^- + 2\ F^- + 3\ Na^+$$

It has been stated that cryolite serves as a source of fluoride and is essentially metabolized as free fluoride. Released in aqueous solution, the fluoride is deposited primarily in teeth and bone (Pennwalt Corporation, 10/28/88) cited from CalEPA (1995) (031 071324) The original study was not available to the rapporteur). Therefore, fluoride concentrations in tissues and excreta have been used as a measure and a biomarker of cryolite exposure. In order to support the data obtained from cryolite, data from other fluorides (i.e. substances that release fluoride ions) have been integrated as far as appropriate (i.e. as far as physico-chemical properties and physical state were comparable to cryolite. It was regarded as inappropriate to include data from the gas hydrogen fluoride which mainly acts via its corrosive properties). The AlF_4-ion was not taken as a biomarker, because almost all of the studies did not measure AlF_4. Due to the fact, that adverse health effects of Cryolite are dominated by the action of fluoride, the focus is on fluoride. The toxicity of aluminium and aluminium containing compounds is dependent on speciation (i.e. the chemical form of the ingested compound and concurrent exposure to dietary chelators). As the Al^{3+} ion forms stronger complexes with OH^- ions than with F^- ions, Al(III) speciation might be dominated by the formation of a series of $AlF_n^{(3-n)+}$ complexes. Adverse health effects of aluminium containing complexes (which might be overwhelmed by the toxicity of the fluoride anion in the case of cryolite) have been summarized in comprehensive reports (e.g. http://www.inchem.org/documents/ehc/ehc194.htm (WHO (1997) or http://www.atsdr.cdc.gov/toxprofiles/tp22.html). Therefore, with respect to the aluminium containing moiety of cryolite, reference is given to these reports.

4.1.2.1 Toxicokinetics, metabolism and distribution

4.1.2.1.1 Studies in animals

In vivo studies

Inhalation

There are no toxicokinetic investigations concerning inhalation exposure in animals. However, from studies of repeated inhalation exposure (see 4.1.2.6.1.) it can be concluded that cryolite can be absorbed by the inhalation pathway.

Dermal

No data available.

Oral

An aqueous suspension of natural cryolite (9 g/kg bw) was administered orally to two rats. The larger portion of the ingested fluoride was eliminated with the faeces (about 48 – 58 % within 24 h, about 62 – 69 % within 4 d). At day 5 after dosing, fluoride excretion in faeces was back at baseline levels. The excretion via urine was 0.1 to 0.2 % of the dose within 4 days, an increase in urinary fluoride excretion could be observed during the first two days after administration (Largent, 1948).

An aqueous suspension of natural cryolite (3 g/kg bw) was administered orally to two rabbits. Fluoride was determined daily in blood, faeces and urine starting four days before application of cryolite and ending 13 days after application of cryolite. Elevated fluoride concentrations in blood, faeces and urine could be observed for up to two weeks after treatment with cryolite, but most of the administered fluoride was excreted during the first 4 days after administration. Within 13 days, 90 – 96 % of the applied amount of fluoride were excreted via faeces and 0.64 – 1.4 % of the applied fluoride was excreted via urine. Furthermore, it could be demonstrated, that there was no correlation between fluoride content in blood and urine after oral administration of an aqueous suspension of cryolite (9 g/kg bw) (Largent, 1948).

One dog (no further details) was given daily doses of 65 mg fluoride, which was mixed into its food in the form of cryolite over a period of approximately 4.5 years. A further dog served as a control. During this period, fluoride excretion was determined 6 times, with quantities excreted in the urine varying from 4.6 to 11.1 mg/day (mean value 7.8 mg/day) and quantities excreted in the faeces varying from 13.1 to 57.2 mg/day (mean value 43.3 mg/day). In the control dog, fluoride excretion was determined 3 times, with urinary excretion ranging from 0.8 to 6.8 mg/day (mean value 3.1 mg/day). At the end of the study, fluoride levels were determined in various organs and tissues. Fluoride accumulation occurred predominantly in the bones. The fluoride concentrations found in the femur and the ribs were 1320 mg/kg (control 380 mg/kg), respectively. The fluoride levels in the lungs, the kidneys and liver of the cryolite treated dog were about twice the levels in the control dog (1.18, 1.12 and 0.71 mg/kg as compared with 0.56, 0.52 and 0.37 mg/kg in the control). Examination of the dog by x-ray yielded no indication of any changes in bone structure. The fluoride levels in the blood, stomach, liver, heart, brain and muscle tissue of the cryolite-treated dog were lower than those in the control dog (0.03 to 0.54 as compared with 0.13 to 0.97 mg/kg (Largent, 1954, cited from BG Chemie 2005, the original publication was not available to the rapporteur.

Six male albino rats received cryolite with the diet for 7 consecutive days (mean intake of fluoride over the 7-day period: 8.7 mg). Urine and faeces were collected over the 7 day period and the fluoride content in urine and faeces was determined. At the end of the experiment, kidneys and left femurs were dissected for determination of the fluoride content. 30 % of the amount of fluoride that had been taken up with the diet was excreted with the urine, 15 % was excreted with faeces and approximately 55 % were retained (Wright and Thompson, 1978). The percentages excreted via faeces and urine differ considerably from the values obtained by Largent (1948). From the Work of Wright and Thompson (1978) it can be concluded that approximately 85 % of the amount of fluoride that has been orally taken up in the form of cryolite, will be systemically bioavailable. Nevertheless, fluoride retention and fluorine excretion from the basal diet (total cumulative fluorine intake from the basal diet over 7 days was 0.11 mg) has not been regarded in this publication.

In vitro studies

No data available.

4.1.2.1.2 Studies in humans

In vivo studies

Inhalation

Autopsies of two cryolite workers who had been exposed to cryolite dust by inhalation for 25 and 9 years showed an accumulation of fluorine in lung tissue (10.8 and 79.2 mg fluoride/100 g dry weight; unexposed control: 0.73 mg fluoride/mg dry weight) (Roholm, 1937a;b).

In workers, who were occupationally exposed to dust from natural cryolite, plasma concentrations and urinary excretion of fluoride and aluminium were determined (Grandjean et al., 1990) during a 4-day working week. Cryolite exposure was monitored by personal filters and varied between 0.16 and 21.2 mg/m^3. Urine was collected before work began and during two 4 hr periods. Preshift urine fluoride concentrations increased during the week. Fluoride concentrations in postshift urine and serum both correlated with the dust exposures. Serum fluoride concentrations decreased with a half-life of 3.3 to 6.9 hr after work. Fluoride clearance was 40.5 to 76.5 ml/min at urinary flow rates of 0.89 to 2.21 ml/min. Median preshift aluminium concentrations were 1.2 µmol/l in serum and 2.4 µmol/l in urine and were relatively high compared to levels during the working week (range of medians for serum: 0.8 - 0.9 µmol/l and range of medians for urine: 3.8 - 4.7 µmol/l). Workers with the highest dust exposure on a certain day had the highest serum aluminium concentrations at the end of the shift and the highest aluminium excretion after the shift. Aluminium and fluoride concentrations in the urine were significantly related. On a molar basis, almost 100 fold more fluoride (compared to aluminium) was excreted during a 24 hour period.

Based on the amounts of urinary excreted fluoride, exposure time, dust concentration and average minute volume it could be calculated, that approximately 31 % of the inhaled amounts of fluoride were excreted in the urine. From oral studies it could be observed, that approximately comparable amounts of the absorbed fluoride are retained in the body and excreted via urine. From other fluorides it has been described, that approximately half of the absorbed amount of fluoride is deposited in bones and teeth (WHO, 2002). Therefore, it might be justified to assume that approximately twice the amount that appeared in the urine, have been absorbed, which is 62 %. Absorption of cryolite dust is dependent on the particle size, but Grandjean et al. (1990) gives no information about particle size. Therefore, it should be taken into consideration that not the total amount of cryolite dust might have been consisting of respirable particles so that even higher absorption values might be possible. Due to the uncertainties concerning particle size, respirable fraction and deposition in bones and teeth, a default value of 100 % for inhalation absorption will be taken for risk characterisation.

Dermal

No data available.

Oral

Investigations with cryolite

Machle and Largent (1943) investigated absorption, retention and excretion of fluoride from solid cryolite (and other fluorine containing salts and compounds such as sodium fluoride, calcium fluoride (solid and in solution) and bone meal) after repeated oral exposure of a single human volunteer. Between periods of intake of fluoride containing compounds, there were periods of several weeks, in which there was no fluoride intake except for fluoride from food and fluid intake. Solids were administered after each meal in small gelatine capsules, solutions were prepared in distilled water. Fluoride ions were determined by titration. Absorption of fluoride was defined as the difference between total fluoride intake and faecal excretion. Retained amounts of fluoride were calculated by the difference between the amount absorbed and the amount excreted via urine. Fluoride balance was calculated by the difference between fluoride intake and excretion. Excretion via saliva or perspiration was neglected in the investigations. All results were presented as average daily values and are presented in the **table 4.1.2.1.2**. After oral administration of 6 mg fluoride from cryolite per day for three weeks, 77 % of fluoride (from cryolite and uptake via food and fluid intake) was absorbed and 37 % fluoride was retained. 40 % of the fluoride intake was excreted via urine 23 % was excreted via faeces. When compared with values that had been obtained with sodium fluoride, with solid calcium fluoride and with calcium fluoride in solution it could be demonstrated that both absorption and retention are higher (and correspondingly faecal excretion is lower), when readily soluble fluoride salts (e.g. NaF) are given as solids or when solutions of sparingly soluble sodium salts (e.g. CaF_2) are administered. It should be mentioned here, that cryolite used for the investigations contained approximately 5 % sodium fluoride and about 5 % of inert material.

Largent and Heyroth (1948) investigated absorption, excretion and retention of fluoride from cryolite after repeated (daily, on alternate days or on every 3rd day) oral exposure to cryolite. Average daily intakes of fluoride were 25.4 mg/day for cryolite solution (administered daily for 5 weeks) and 36.4 mg/day (administered daily for 3 weeks), 18.4 mg/day (administered daily for 6 weeks), 12.4 mg/day (administration every third day for 3 weeks) and 6.41 mg/day (administration an alternate days for 4 weeks) for solid cryolite. Solid cryolite was administered after each meal in small gelatine capsules as dry substance; cryolite solution was prepared in distilled water. Fluoride concentrations were corrected for the average dietary fluoride intake that had been determined previously (Machle et al., 1942). Fluoride determination was performed by titration. All calculations were performed based on daily average amounts. The results are presented in the **table 4.1.2.1.2**. When solid cryolite was ingested, 62.2 - 70 % of the average daily intake was absorbed on the average per day. With cryolite solution, the average daily absorbed amount was 93 %. With solid cryolite 34.1 - 45.4 % of the average daily intake was retained in the body. With cryolite solution, retention was 37 %. Urinary and faecal excretion of fluoride was dose-dependent. With solid cryolite, 29.9 - 37.9 % of the fluoride intake was excreted via faeces on a daily average basis and 36 - 45 % was excreted via urine. With a cryolite solution, lower faecal (7 %) and higher urinary (59 %) excretion levels could be observed. Other possible pathways of excretion of fluoride (e.g. via saliva or sweat) were not regarded by the authors.

McClure et al. (1945) have shown that elimination of fluoride from orally applied cryolite also occurs via sweat (in addition to faecal and urinary excretion) when volunteers spent eight hours each day of a five-day test period in experimental chambers where either "comfortable" (temperature: 28 - 30 °C, relative humidity 49 - 52 %) or "hot-moist" (temperature 37 - 38 °C, relative humidity 66 - 70 %) conditions existed. Five men aged 19 - 27 years received either synthetic or natural cryolite together with food so that total intake of fluorine (from cryolite, food and drinking water) was 4.5 (natural cryolite, comfortable conditions), 5.9 (natural cryolite, hot-moist conditions) and 5.7 mg (synthetic cryolite, hot-moist conditions). Within 24 hours, 44.4 % (natural cryolite, comfortable conditions), 28.8 % (natural cryolite, hot-moist conditions) and 29.8 % (synthetic cryolite, hot-moist conditions) of the fluorine intake was excreted via urine. Fluoride excretion of natural cryolite via faeces was 31.9 % of the intake under comfortable and 33.3 % of the intake under hot-moist conditions. During a 8-hour perspiration period, 16 % of the fluorine intake was perspired under comfortable conditions, whereas 25 - 27 % of the fluorine intake was perspired under hot-moist conditions.

Table 4.1.2.1.2: Overview about uptake, absorption and excretion of fluoride from different sources after oral administration to a human volunteer

Compound and experimental conditions (solid or solution; duration)	Total intake of fluoride [mg/day] (corresponding to 100 %)	Faecal excretion of fluoride [percent on a mg/day basis]	Urinary excretion of fluoride [percent on a mg/day basis]	Amount of absorbed[1)] fluoride [percent on a mg/day basis]	Amount of retained[2)] fluoride [percent on a mg/day basis]	Reference
Bone meal, 5 weeks[*)]	6.31	63.23	17.11	36.76	19.64	Machle and Largent, 1943
Sodium fluoroborate, solid, 2 weeks	6.4	1.56	100	excretion higher than intake	excretion higher than intake	Largent and Heyroth, 1948
NaF, solution, 14 weeks	6.47	2.94	37.40	97.00	59.66	Machle and Largent, 1943
NaF, solution, 2 weeks	12.4	3.62	51.13	96.37	45.24	Largent and Heyroth, 1948
NaF, solution, 2 weeks	19.4	3.76	50.26	96.24	45.98	Largent and Heyroth, 1948
CaF_2, solution, 4 weeks	6.25	4.32	34.72	95.68	60.96	Machle and Largent, 1943
CaF_2, solid, 3 weeks	6.43	37.95	27.68	72.00	44.62	Machle and Largent, 1943
Cryolite, solid, 3 weeks	6.61	22.99	40.02	77.00	36.76	Machle and Largent, 1943

Cryolite, solid, 6 weeks	18.4	29.89	38.23	70.05	31.81	Largent and Heyroth, 1948
Cryolite, solution, 5 weeks	25.4	6.89	58.83	92.94	34.11	Largent and Heyroth, 1948
Cryolite, solid, 3 weeks	36.4	34.45	35.82	65.54	29.75	Largent and Heyroth, 1948
Cryolite, solid, 3 weeks, intake every 3rd day	12.4	32.5	44.52	67.50	22.98	Largent and Heyroth, 1948
Cryolite, solid, 4 weeks, intake every 2nd day	6.41	37.91	40.72	62.09	21.37	Largent and Heyroth, 1948

1) amount absorbed = total intake - faecal excretion

2) amount retained = amount absorbed - urinary excretion

*) no statement whether applied as solid or in solution

Investigations with fluorides other than cryolite

Sodium fluoride (NaF)

Ekstrand et al. (1977) investigated uptake and excretion of fluoride in 8 men after single (3, 6 and 10 mg fluoride) and repeated (4.5 mg fluoride every 12 h for 6 d or 3 mg every 6 h for 6 d) doses of sodium fluoride in drinking water. In all single dose experiments performed, the peak plasma fluoride concentration was reached 30 min after intake. The plasma half-life increased with dose and was between 2 and 9 h. The plasma clearance ranged between 0.12 and 0.20 l/kg/h and there was no systematic change with dose. The elimination half-life obtained by a non-linear fitting to a three-compartment model ranged from 5.4 to 8.3 h. The steady-state concentrations after multiple dosing ranged between 54 and 145 ng/ml. About 50 % of the given dose were recovered in the urine. The ratio between fluoride concentrations in saliva and plasma was 0.64.

Two adult human volunteers ingested 1 mg NaF together with 5 µCi ^{18}F in 250 ml water. Fluoride contents in the plasma were 0.13 and 0.17 ppm. Maximum plasma radiofluoride concentration was reached within 60 min. Fluoride renal clearance always exceeded chloride clearance (which had also been determined) by manifold, but fluoride clearance was lower than creatinine clearance at all time points investigated. Measurement of uptake and release of the radioisotope by soft tissues and by the skeleton showed characteristic differences of radiofluoride retention in these tissues. Skeletal tissues retained the isotope but in soft tissues radioactivity decreased within 4 hr after ingestion. Less than 1 % of the absorbed fluoride appeared in saliva (Carlson et al. 1960).

Fluoride balances (the difference between fluoride intake and excretion) and the influence of inorganic elements (calcium, magnesium, phosphorus and aluminium) on fluoride balance has been investigated after oral uptake of NaF by male human volunteers (Spencer et al., 1981). It could be demonstrated, that the amounts of urinary fluoride correspond to 48 - 62 % of the intake (4 - 45 mg fluoride/d). Amounts of fluoride excreted via faeces were low, corresponding to 6 - 10 % of the intake. Both urinary and faecal excretions increased with increasing intake of fluoride. Approximately 1 mg of fluoride was retained per day when the average dietary fluoride intake was 4.3 mg/day. When fluoride was ingested in dosages of 10, 20, or 45 mg/d (in the form of NaF) in addition to the dietary fluoride content (which ranged between 1.2 and 1.5 mg/day), only a very small fraction of the previously retained amount of fluoride was excreted after the fluoride intake had stopped. During the intake of 10 mg fluoride per day, the fluoride balance was high, averaged 4.6 mg/d within the first 6 days of fluoride administration compared to an average of 1.6 mg/d prior to the intake of fluoride supplements. During a higher intake of 20 mg/d, the fluoride balance increased to approximately 8 - 10 mg/d within the first 6 days, depending on the retention of the respective individual and fluoride retention persisted throughout the 3 months of high fluoride intake. When the fluoride intake was increased further, to 45 mg/d for 3 months, the retention of fluoride increased further to levels between 12 and 18 mg/d. After fluoride intake had stopped, very small amounts of fluoride were excreted in the following days. When a 10 mg dose of fluoride was given daily for 32 days, a total of 114 mg fluoride was retained. After discontinuation of the fluoride supplement, a total of 5.1 mg fluoride was excreted with the urine within the first 6 days. From day 7 to day 12, further 2.6 mg of fluoride was excreted and from day 13-18, 0.3 mg fluoride was excreted. Only 8 % of the previously retained amount of fluoride were excreted via urine and faeces (9.2 mg fluoride had been excreted with faeces) within 18 days. After this period of time, fluoride excretion in urine and faeces returned to baseline levels. The excretion via sweat had not been determined in these investigations. Inorganic elements such as calcium, phosphorus and magnesium, which decreased intestinal absorption of fluoride in animals, were ineffective in humans. Aluminium on the other hand, which had been given in the form of aluminium hydroxide, markedly decreased intestinal absorption of fluoride.

Other data

Perspiration is a pathway of fluoride elimination. At temperatures between 28 and 30 °C and at humidities around 50 %, up to 16 % of the fluoride intake from orally applied cryolite can be perspired within 8 hours. Even higher amounts might be perspired when temperature and humidity are higher. Only a minimal amount of fluoride makes its way into breast milk (Ekstrand et al., 1982), but fluorides can pass through the placental barrier. Serum concentration in the mother has a direct relationship to that in the fetus (measured in umbilical blood): the level in umbilical blood is about 75 % of that in the mother (Shen and Taves, 1974, cited from NIWL (2005), the original publication was not available to the rapporteur). In the fetuses, fluoride is taken up in mineralized tissues (bone and teeth) (Whitford, G (1996), cited from NIWL 2005, the original publication was not available to the rapporteur.

In vitro studies

No data available.

4.1.2.1.3 Summary of toxicokinetics, metabolism and distribution

In animals and humans, Cryolite can be absorbed after oral and inhalative exposure. There are no data on dermal absorption of Cryolite.

Prerequisite for Cryolite absorption is the solubility of the substance. Water solubility of cryolite is rather low. The report by CalEPA (1995) makes the following statements concerning the solubility of cryolite at different pH values: cryolite hydrolyses in vitro to produce fluoride anion instantaneously under acidic (pH 5: 15.5 % F^-), neutral (pH 7: 36.8 % F^-) or basic (pH 9: 43.3 % F^-) conditions. The same effect probably also occurs in vivo, based upon the rapid assimilation into the bone as well as it's efficient membrane permeability ("Cryolite animal metabolism" (Pennwalt Corporation, 10/28/88) cited from CalEPA (1995) (031 071324) The original study was not available to the rapporteur). Dissolution of cryolite leads to the formation of fluoride according to the following equation:

$$Na_3AlF_6 \rightarrow AlF_4^- + 2\ F^- + 3\ Na^+$$

Therefore, fluoride concentrations in tissues and excreta have been used as a measure and a biomarker of cryolite exposure.

Oral uptake

Due to the acidic and aqueous conditions in the stomach, fluoride ions, which are liberated from cryolite, are present in the form of hydrogen fluoride and then behave as fluoride from any other inorganic source. Hydrogen fluoride easily penetrates biological membranes by passive diffusion both in stomach and intestines (NIWL, 2005; WHO, 2002). However, the presence of fluoride-binding cations, such as Ca^{2+}, can reduce the absorption of fluoride as has been demonstrated in animal experiments. In humans, on the other hand, lower intestinal absorption of fluoride could be observed in the presence of aluminium ions, but not in the presence of calcium, phosphorus or magnesium.

As has been demonstrated in human and animal studies, the way in which oral administration takes place, influences the amount of absorption of fluoride ions from cryolite: when administered in solution or via drinking water, higher rates of absorption can be found compared to intake of the solid material via diet. In animal experiments it could be demonstrated, that an up to 20 % higher absorption of cryolite is possible when administration via drinking water is compared with administration via the diet. In addition, the type of cryolite (synthetic cryolite versus natural cryolite, cryolite which is fine ground versus cryolite consisting of larger particles) also influences the amount of oral absorption. In animal experiments, fine ground synthetic cryolite lead to higher retention than commercial natural cryolite consisting of larger particles. With regard to these factors, which influence cryolite absorption, a maximum of 95 % absorption is taken for risk characterisation in humans based on the study of Largent and Heyroth (Largent and Heyroth, 1948). For animals, 85 % oral absorption is taken for risk characterisation in animals (rats) based on the study of Wright and Thompson (1978) (the oral absorption figure in animals was taken from Wright and Thompson (1978) because Largent (1948) used very high and non realistic oral dosages and because analytical determination of fluoride as applied by Wright and Thompson is more sophisticated (they used a specific ion electrode whereas Largent (1948) employed perchloric acid distillationand thorium-nitrate-back-titration procedures). A 95 % absorption value in humans differs only slightly from 97 % absorption that had been observed for the readily water-soluble salt sodium fluoride.

After uptake into the blood, where ionic and non-ionic (as perfluoro fatty acid-derivatives) forms of fluoride are present in the plasma [the mean concentration of fluoride in the blood plasma of 30 residents of communities in the USA served by drinking-water containing low concentrations of fluoride (i.e., <0.1 mg/l) was 0.4 µmol/l, while the mean concentration in plasma from individuals consuming drinking-water containing higher amounts of fluoride (i.e., 0.9–1.0 mg/litre) was reportedly 1 µmol/l (WHO, 2002 and literature cited therein)], fluoride is rapidly distributed to all tissues of the body (the biological half-live for fluoride in blood after oral intake of sodium fluoride is reported to be about 4 hours, although it seems to vary with the amount of intake (Ekstrand, 1977)). Considerable amounts of fluoride that had been absorbed from cryolite are retained in the body. In rats, approximately 55 % of the fluoride intake is retained in the body. Lower levels of retention may result when cryolite administration does not occur continuously, in the presence of increased calcium intake or when cryolite is administered in solution (and not as a solid). In humans, up to 37 % of fluoride from cryolite was retained in the body. Most of the retained fluorine (approximately 96 % in animals) is deposited in bones (most probably in the form of fluoride apatite), the remainder is deposited in teeth and soft tissues. In occupationally cryolite exposed humans, elevated levels of fluorine were determined in lungs and kidneys (data summarized in BG Chemie, 2005). The most important elimination pathway of fluoride from cryolite is via the kidneys. In rats, approximately 30 % of the fluoride intake is excreted via urine, in humans, up to 59 % of the applied amount of fluoride from cryolite is excreted via urine. Therefore, the amounts of fluoride which are excreted after oral intake of cryolite resemble those amounts of fluoride, that are excreted via urine after intake of other fluoride containing compounds (in general, general, 40 - 60 % of the daily fluoride intake is excreted via the kidneys (NIWL, 2005 and literature cited therein; WHO, 2002 and literature cited therein). Dependent on the pH in the urine, urinary excretion occurs either as F^- or as HF. In humans, up to 38 % of the intake of fluoride from cryolite was eliminated via faeces. Faecal fluoride excretion was higher after cryolite intake compared to other, better soluble fluoride containing salts (such as NaF), where faecal excretion is between 5 - 10 % of the daily fluoride intake (NIWL, 2005 and literature cited therein). Both urinary and fecal excretion of fluoride is dose-dependent. After single administration, elevated urinary and fecal fluorine concentrations can be observed up to four days after application. After repeated intake of high amounts of fluoride, fluoride concentrations in urine and faeces return to baseline levels after a maximum of approximately 18 days. However, only minor amounts of the retained fluoride are excreted within this period of time.

Inhalative uptake

Evidence that cryolite can be absorbed via inhalation comes from the occurrence of toxicological effects which have been observed in animals and humans after inhalative exposure to cryolite (e.g. dental or skeletal fluorosis (Roholm, 1937a;b)). Furthermore, elevated concentrations of fluoride have been determined in the plasma and urines of workers occupationally exposed to cryolite dust (Grandjean et al., 1990).

Particle size of cryolite dust plays a critical role in the pulmonary uptake of cryolite. Pulmonary absorption is favoured at particle sizes of approximately 5 µm and lower. From an inhalative study with cryolite workers it can be deduced, that up to 31 % of the inhaled amount of fluoride from cryolite is excreted via urine (Grandjean et al., 1990). From oral studies it could be observed, that approximately comparable amounts of the absorbed fluoride are retained in the body and excreted via urine. From other fluorides it has been described, that approximately half of the absorbed amount of fluoride is deposited in bones and teeth (WHO, 2002). Therefore, it might be justified to assume that approximately twice the amount that appeared in the urine, might have been absorbed, which is 62 %. Absorption of cryolite dust is dependent on the particle size, but Grandjean et al. (1990) gives no information about particle size. Therefore, it should be taken into consideration, that not the total amount of cryolite dust might have been consisting of respirable particles so that even higher absorption values might be possible. Due to the uncertainties concerning particle size, respirable fraction and deposition in bones and teeth, a default value of 100 % for inhalation absorption will be taken for risk characterisation.

Very little is known about the absorption and bioavailability of the aluminium-containing moiety of cryolite. Urinary and serum levels of aluminium have been determined in workers occupationally exposed to cryolite dust (in addition to fluoride levels). Due to the different excretion pattern of fluoride and aluminium it was hypothesized that the pulmonary retention time of aluminium was higher compared to fluoride. Furthermore, although the chemical species of aluminium has not been identified, it was hypothesized, that aluminium would not be present in form of the AlF_6^{2-} complex (Grandjean, 1990).

Dermal uptake

Data on dermal uptake of cryolite are not available. Based on the low solubility and the type of compound (inorganic salt), dermal absorption of cryolite could be anticipated to be quite low. Cryolite is insoluble in organic solvents and thus will not easily pass the lipophilic stratum corneum of the skin. Factors that may promote oral uptake of fluoride like the slightly alkaline environment in the small intestine and the presence of ions like Ca, Ba, Mg and Fe that can form soluble chelate with cryolite are absent for the dermal route. Furthermore, salts are usually poorly absorbed via the dermal route. Therefore, dermal absorption of cryolite probably does not exceed 10% and may even be lower then 10%. Therefore, a value of 10 % is taken for risk characterisation by the dermal uptake route for animals and humans. Nevertheless, an in vitro dermal absorption study, taking into account the actual human exposure conditions, may give more information on the actual dermal absorption figure.

4.1.2.2 Acute toxicity

[click here to insert text]

4.1.2.2.1 Studies in animals

In vivo studies

Inhalation

An inhalation LC_{50} of 4470µg/l (S.D. 850 µg/l) was obtained for Sprague-Dawley rats after a 4-hour continuous whole-body exposure to synthetic cryolite (slightly ground, high purity of approximately 99 % with a minor impurity of aluminium trichloride; Huntingdon Research Centre, 1993, appendix Bayer AG). This study was conducted in compliance to OECD TG 403. Three groups of 5 male and 5 female rats each, were exposed to cryolite (particulate aerosols of the test substance) for a period of 4 hours. The test groups were exposed to 4.34 mg/l (MMAD of 4.3 µm and 67.9 % of respirable particles), 2.83 mg/l (MMAD of 3.2 µm and 78.0 % of respirable particles) and 1.33 mg/l (MMAD 3.8 µm and 77.8 % of respirable particles). A fourth group was exposed to air only. The rats were observed continuously for signs of reaction to the test substance during exposure and at least twice daily throughout the observation period of 21 days. After a 4-hour exposure to 4.34 mg/l 5/5 male and 1/5 female rats died within 10 days; after a 4-hour exposure to 2.83 mg/l 1/5 male (on day 4) and 0/5 female rats died; after an exposure to 1.33 mg/l no mortality was observed. Clinical signs during the exposure to cryolite dust were considered to be consistent with inhalation of an irritant aerosol: partial closing of the eyes in the highest dose, exaggerated respiratory movements in the medium group and no signs in the lower group. The majority of rats dying as a result of exposure to 4.34 mg/l cryolite showed signs of lethargy for 1-5 days prior to death. Other signs observed prior to death were hypothermia, piloerection and the adoption of a hunched posture; surviving animals recovered within 15 days of the observation period. At necropsy, a high lung weight to bodyweight ratio was found for all deceased rats and survivors. Macroscopic pathology demonstrated swollen and severe congestion of the lungs in decedents. Abnormalities seen in rats that survived the exposure were subpleural foci in the lungs and congested lungs. Histological examination was confined to the lungs, liver and kidneys (kidneys demonstrating unspecific findings): in the lungs, increased alveolar macrophages with/without alveolar septal fibrosis adjacent to alveolar ducts, sometimes with focal alveolar epithelialisation was observed in all cryolite exposed rats. There was some evidence of a dose-related effect on the severity of the observed lesions. Alveolar congestion/haemorrhage was recorded in all decedents treated with cryolite at the high and intermediate dose levels, and in 4/9 rats in the intermediate and 2/10 in the low dose groups killed at termination. A dose-related effect on severity was noted. Alveolitis was reported in 4/6 decedent rats and 1/4 terminal rats in the high dose group, 1/1 decedent and 1/9 terminal rats in the intermediate group. This change was not seen in any rat in the lower dose group.

Prominent goblet cells in the bronchiolar epithelium were recorded in 2/6 decedent and 3/4 terminal rats in the high dose and in 1/9 terminal rats in the intermediate dose group. Changes seen only in decedent rats include hyaline membranes with/without alveolar oedema in all high and intermediate dose rats, bronchiolar epithelium basophilia and hyperplasia in 4/6 decedents and early thrombus in pulmonary artery in 2/6 decedents in the high dose group. Pleural inflammation was seen in a single decedent rat, and alveolar macrophages containing brown pigment in a single terminal rat in the high dose group. In the liver, centrilobular hepatocyte necrosis/degeneration with sinusoidal congestion was seen in all decedent rats in the high dose group. Prominent mitotic figures were seen in a single rat in the high dose group killed at termination. These changes were not seen in the control group, nor in any other group treated with cryolite (Huntingdon Research Centre, 1993).

According to EPA (1996) the LC_{50} for technical cryolite after inhalation exposure to rats is >2060 µg/l and <5030 µg/l (table from EPA (1996), no further details and no reference provided).

Dermal

According to EPA (1996) the LD_{50} for technical cryolite after dermal exposure to rabbits is >2100 mg/kg bw (table, no further details and reference provided).

Oral

In a study compliant to OECD TG 401 using Wistar rats, an oral LD50 > 5000 mg/kg was derived. Cryolite, described as a white powder (no data on purity), was suspended in peanut oil and administered in a single dose intragastrically to 5 male and 5 female rats, using a rigid metal stomach tube. None of the animals died within an observation period of 14 days. The clinical signs observed were piloerection and increased salivation. No pathological findings were obtained after necropsy (Bayer AG, 1987).

No mortality was observed within an observation period of 14 days in a limit test according to OECD guideline 401 using 5 female and 5 male Sprague Dawley rats. The animals were treated with 5000 mg/kg of synthetic cryolite (no data on impurities) suspended in water. Some of the treated animals showed piloerection starting 6 hours after administration. This effect lasted up to day 5. One male rat showed diarrhoea, with short duration, at the 6 hour observation. All the animals achieved recovery within day 6. At necropsy, no treatment-related macroscopic findings were observed (RBM, 1990).

In a screening study on acute toxicity (no details on method were provided) no mortality was observed in rats after oral administration of synthetic cryolite (purity not given) up to 2500 mg/kg. Five groups of 15 male rats each (strain not given) were dosed with 100, 250, 500, 1000 and 2500 mg/kg cryolite (no data on impurities) using cremophor as vehicle; the observation period was 14 days. Reduction of overall appearance and laboured breathing was observed in all rats dosed with 250 mg/kg and higher within 5 days after administration. No pathological findings were presented (Bayer, 1972).
According to EPA (1996) the LD_{50} for technical cryolite after oral exposure of rats is >5000 mg/kg bw (no further details provided).

In vitro studies

no data available

4.1.2.2.2 Studies in humans

no data available

4.1.2.2.3 Summary of acute toxicity

In a well conducted and guideline-compliant rat inhalation study, a LC_{50} of 4470 µg/l was derived. Hence, existing classification of cryolite with R 20, 'harmful by inhalation', is appropriate. For assessment of dermal acute toxicity only a rabbit screening assay is available, suggesting an LD_{50} of >2100 mg/kg. Hence, no classification and labelling is required for acute dermal toxicity. After oral administration to rats, an LD_{50} exceeding 5000 mg/kg was derived in several studies. Clinical signs observed in these studies were consistent with those reported from acute oral studies with other fluorides (WHO, 1984), which demonstrated lower LD_{50}s (IARC, 1982; Whitford, 1990, as referenced in WHO/ IPCS 2002), indicating a lower bioavailability for cryolite. In consequence, existing classification with R 22 is not supported.

4.1.2.3 Irritation

4.1.2.3.1 Skin

Studies in animals

In a well conducted, guideline-compliant guinea pig maximisation test (GPMT), 0.5 mL of an up to 50 % cryolite (purity > 95 %) solution in 1 % aqueous carboxymethyl-cellulose was dermally applied for 24 hours (pretest, occlusive patch) to the flank of guinea pigs. After termination of exposure, the treated skin areas were cleaned from residual test substance and assessed for irritation 24 and 48 hours after exposure. No dermal reactions were reported at all (NOTOX, 1998). For more details of the test, refer to 4.1.2.5.1.

According to EPA (1996) technical cryolite was not irritating to the skin of rabbits (table, no further details and reference provided).

Synthetic cryolite (purity and quantity not given) was applied for 8 or 24 h, respectively, to the inner earlobes of two rabbits. No effects were observed during an observation period of 7 days (Bayer AG, 1972).

Studies in humans

no data available.

4.1.2.3.2 Eye

Studies in animals

In a poorly reported Draize eye irritation test, 50 mg of synthetic cryolite (purity not given) was instilled into the eyes of two rabbits. Within an observation period of one week, no conjunctiva, sclera and cornea findings were reported. No further details are provided (Bayer AG, 1972).

According to EPA (1996) technical cryolite was moderately irritating to the eyes of rabbits (table, no further details and reference provided). EPA Chemical Fact Sheet 6/83 (EPA 1983) states for primary eye irritation in rabbit: “moderate conjunctiva irritation that disappeared within 7 days (Tox Category III)”. Similar results were obtained for AlF_3, which shows comparable physico-chemical properties. In a Material Safety Data Sheet of Alufluor is reported: “The product has been tested for eye irritation. Chemosis, redness and discharge occurred, but 72 hours after termination of exposure no abnormalitites were observed” (Scantox Report, 2001, referenced in Alufluor, 2003). Since no further details are available, also these results cannot be used to conclude on classification of cryolite.

Studies in humans

no data available.

4.1.2.3.3 Respiratory tract

Studies in animals

After a 4-hour continuous whole-body exposure to synthetic cryolite (slightly ground, high purity of approximately 99 % with a minor impurity of aluminium trichloride; Huntingdon Research Centre, 1993, appendix Bayer AG), clinical signs were observed which are indicative of respiratory irritation: partial closing of the eyes was observed after exposure at 4.34 mg/l, exaggerated respiratory movements were noted at 2.83 mg/l and no signs were detected at 1.33 mg/l. For more details, refer to section 4.1.2.2.1.

In two 2-week range finding inhalation toxicity studies (repeated dose toxicity studies, for details, refer to section 4.1.2.6.1), also signs indicative for repiratory tract irritation were observed. After repeated exposure to 470 mg/m³ (6 hours/day) in the first study, histopathology reported findings indicative for respiratory tract irritation, i.e. inflammatory reactions in the respiratory epithelia (BG Chemie, unpublished report, 1994a). In the second study the mean exposure levels were 5.1 mg/m^3 (low dose) or 13.6 mg/m^3 (high dose). Various inflammatory lesions were detected in alveolar parenchyma, and lymphoid hyperplasia was reported in the tracheobronchial and mediastinal lymph nodes of the treated male and female rats (BG Chemie, unpublished report, 1994b).

Studies in humans

no data available.

4.1.2.3.4 Summary of irritation

On the basis of the available data it can be concluded that cryolite does not have skin irritating properties. Scarce data on eye irritation indicate a low to moderate potential of cryolite to induce eye irritation, but due to a low quality of available data, a final assessment is not possible. In a well-conducted acute rat inhalation study using cryolite aerosol, a 4-hour whole body exposure in the range of the LC_{50} was performed (for details, refer to 4.1.2.2.1 inhalation). Clinical signs included closure of eyes upon start of exposure, which was also reported in a repeated dose toxicity study (for details, refer to 4.1.2.6). Since no other effects were reported for the eyes, these findings support the conclusion, that cryolite is not a strong eye irritant. Accordingly, cryolite was characterized as a moderate irritant by US EPA. However, these data are also not sufficient to exclude a moderate potential of cryolite to cause eye irritation, which may require classification and labelling according to EU-regulations. Overall, a data gap remains that may require additional testing. Results obtained from rat inhalation studies, do not require classification as a respiratory irritant.

4.1.2.4 Corrosivity

Data from skin and eye irritation studies do not indicate any corrosive potential of cryolite.

4.1.2.5 Sensitisation

4.1.2.5.1 Studies in animals

<u>Skin</u>

In vivo studies

In a fully guideline-compliant Magnusson Kligman Test (GPMT), 10 treated and 5 control guinea pigs (Dunkin Hartley strain) were used to assess the potential of cryolite to induce skin sensitisation. The substance tested was described as an off white solid with a purity of > 95 %. 1 % aqueous carboxymethyl cellulose was used as a vehicle. For intradermal induction 0.1 ml of a 10 % test substance formulation was injected into the skin of the scapular region. Since no dermal reactions were observed after topical induction in the pretest (cryolite concentration up to 50 %), local irritation of the shaved skin of the flank was induced by topical epidermal treatment with 0.5 ml 10 % sodium laurylsulfate in vaseline on day 7. On day 8, 0.5 ml of a 50 % formulation of cryolite in 1 % aqueous carboxymethyl cellulose was occlusively applied to the shaved flank for 48 hours. Challenge was conducted at the induced flank sites on day 22 with a 50 % substance formulation. Control animals received the vehicle only during inductions (day 1 and day 8) and a 50 % substance formulation at challenge. After challenge, not any skin reactions were observed in treated and control animals (NOTOX, 1998). Hence, cryolite was clearly shown not to cause skin irritation and sensitisation, respectively.

In vitro studies

no data available.

Respiratory tract

no data available.

4.1.2.5.2 Studies in humans

no data available.

4.1.2.5.3 Summary of sensitisation

In a Magnusson Kligman Test with guinea pigs, no skin sensitisation was observed. Human data and data on respiratory tract sensitisation are not available. In conclusion, no classification is proposed.

4.1.2.6 Repeated dose toxicity

4.1.2.6.1 Studies in animals

In vivo studies

Inhalation

14-day studies (rat)

There are two 2-week range finding inhalation toxicity studies (in conformance with requirements of the standard repeated dose toxicity testing protocols) in rats available. The data were used to establish exposure concentrations for use in a 90-day investigation. Cryolite (purity: 98.9 %) was administered to Sprague-Dawley CD rats for 6 hours a day, 5 days a week for 2 weeks by inhalation of particulates of the test substance using a whole body exposure system. A further group of rats (5/sex) acting as a control was exposed to air only. In both range finding studies, no treatment-related mortalities were reported.

In the first study, groups of rats (5/sex/group) were exposed to cryolite concentrations of 60 mg/m³ (low dose), 130 mg/m³ (mid dose), or 470 mg/m³ (high dose). With exception of closed or half-closed eyelids in high dose rats no other treatment-related clinical signs were seen. Haematology showed an increase of red cell numbers in high dose males, and increased neutrophil numbers in low dose females and in both sexes of the mid and high dose groups. In mid dose males, and in both sexes from high dose groups analysis of clinical chemistry revealed a decrease in blood protein concentration as compared with controls. Lung weights were increased in all regimen groups. At necropsy, pale mottled and oedematous lungs were observed in all dose groups except males exposed to 60 mg/m³. All cryolite exposed rats showed enlarged tracheobronchial and mediastinal lymph nodes. At histopathology, treatment-related findings were reported in the lungs, larynx, and tracheobronchial and mediastinal lymph nodes. Microscopic examination of the lungs revealed effects in all cryolite exposed groups of male and female rats. These changes were extensive in the high dose male and female rats. They involved the lumen of large bronchioles, bronchiolar-alveolar junction and lung parenchyma. Intraluminal inflammatory exudate in larger bronchioles was seen in mid and high dose males and in high dose females. It tended to be associated with prominent goblet cells in the bronchiolar epithelium. Bronchiolitis of terminal bronchioles and a granulomatous inflammatory reaction in the alveolar duct were observed in all cryolite exposed groups of male rats and in mid and high dose females. Focal pneumonitis was present in all treated groups of male and female rats. In high dose rats the lesion was more extensive and was associated with cell debris and polymorphs. Macrophages containing debris and pigment were seen in some high dose male and female rats. Peribronchiolar and perivalcular inflammatory cells, alveolar macrophages and intraalveolar oedema were observed in all exposed groups of male and female rats. In some animals, the macrophages were predominantly large and foamy. These findings were usually more marked in the high dose groups than in low or mid dose rats. Subepithelial inflammatory cells were reported in the larynx of some exposed male and female rats. Reactive hyperplasia and prominent sinusoidal macrophages, sometimes pigmented, were reported in the tracheobronchial and mediastinal lymph nodes of all cryolite exposed male and female rats (BG Chemie, unpublished report, 1994a).

In the second study with identical group arrangement the mean exposure levels were 5.1 mg/m^3 (low dose) or 13.6 mg/m^3 (high dose). There were no treatment-related findings between the groups with respect to clinical observations. A dose-related increase in lung weights was seen in male and female rats, statistically significant in the high dose group. All cryolite exposed rats showed enlarged tracheobronchial and mediastinal lymph nodes. Various inflammatory lesions were detected in alveolar parenchyma, and lymphoid hyperplasia was reported in the tracheobronchial and mediastinal lymph nodes of the treated male and female rats (BG Chemie, unpublished report, 1994b).

No relevant treatment related systemic effects were found in both studies. Therefore, the NOAEC for systemic effects in rats was 13.6 mg/m^3. The NOAEC for local effects was not established for both studies. So, the lowest concentration tested in both 2-week range finding inhalation toxicity studies was set as LOAEC. The LOAEC for lung effects of these studies was 5.1 mg/m^3 (BG Chemie, unpublished report, 1994a, 1994b).

90-day study (rat)

In a 90-day inhalation study according to OECD TG 413 (the recovery period was extended to 13 weeks) groups of Sprague-Dawley CD rats (10/sex/group) were snout-only exposed to cryolite (purity 98.9%) concentrations of 0, 0.21, 1.04, and 4.6 mg/m^3 for 6 hours a day, 6 days a week for a period of 13 consecutive weeks. An additional group of rats was exposed to a (study mean analysed) concentration of 5.7 mg/m^3 sodium fluoride, as a comparative control. The particulate aerosols employed in the study contained 86 to 89% respirable particles with diameters < 7 µm. Rats in the air control group, sodium fluoride dose group, and high dose cryolite group were maintained in their holding cages for a 13 week period following the last exposure. There were no treatment-related premature deaths. No effects of treatment were evident in clinical signs, body weight gain, and food or water consumption during exposure.

Haematology, biochemistry and urinalysis investigations did not reveal any treatment-related findings up to and including 4.6 mg/m^3. At termination, increased inorganic fluoride concentrations in urine, bones, and teeth were evident for rats in the high dose cryolite (4.6 mg/m^3) and the sodium fluoride dose group. Aluminium concentrations in the urine were increased in both sexes in the high and mid dose cryolite group, and in females in the low dose cryolite group. However, a dose relationship was not evident for this effect. Fluoride concentrations in bones and in tooth samples were increased in rats of both sexes of high dose cryolite group. Analysed values for aluminium in bones and teeth were below the limit of detection for the method of analysis used. After 13 weeks of recovery the fluoride levels and the aluminium concentrations in the urine and the fluoride concentration in the teeth of all groups returned to the control range, whereas the fluoride concentration in bones remained unchanged compared to terminal concentrations (no evidence for recovery was seen). Since the increased aluminium and inorganic fluoride excretion via urine could not be correlated to toxic effects, these findings were not considered to be toxicologically adverse.

At termination, increased lung weights were present in rats of both sexes of the high dose cryolite group. A similar but less obvious effect was present following 13 weeks of recovery. The necropsy protocol was in line with recommendations in OECD TG 413. However, bones and teeth, considered likely to be target organs, were excluded from light microscopic examination. Pulmonary inflammatory lesions were observed in a majority of animals receiving cryolite at the high dose, and to a lesser degree, in some animals from the mid dose group. In the majority of animals from the high dose cryolite group, treatment-related findings in the lungs have comprised varying degrees of macrophage aggregation which contained brown pigmented material around alveolar ducts and alveolitis with thickening of alveolar duct walls. In addition, perivascular inflammatory infiltration with increased collagen in the alveolar duct walls and extension of bronchiolar epithelium into alveolar ducts were observed. No treatment-related changes were seen in animals from the low dose cryolite group. Macrophages containing brown pigmented material were present in the tracheobronchial and mediastinal lymph nodes of the high dose cryolite rats. The observed lung changes in cryolite exposed rats were typical of a non-specific reaction over time to a particulate with irritant properties, and attempts at clearance of deposited material via the lung macrophage/lymph node routs. No treatment-related laryngeal changes were seen in cryolite exposed animals. The treatment-related changes had, with the exception of the increased lung weights and the presence of small foci of brown pigmented alveolar macrophages, resolved after the recovery period. Following exposure to sodium fluoride at 5.7 mg/m^3, 6 out of 19 animals exhibited aggregations of alveolar macrophages in the lung parenchyma and around the alveolar ducts, 16 out of 19 animals had laryngeal epithelial hyperplasia and 9 out of 19 animals had subepithelial inflammation of the larynx. No treatment-related changes were seen in the lymph nodes of sodium fluoride exposed animals.

Overall, the response of respiratory tract inhalation exposure to sodium fluoride differed from the response to exposure to cryolite at a similar concentration and particle size. In rats exposed to sodium fluoride, lesions were noted in the larynx, whereas in rats exposed to cryolite, lesions were in the lungs. The reasons for the differences in localisation of the respiratory tract lesions may be related to the relative solubility of cryolite and sodium fluoride. Sodium fluoride is more soluble than cryolite and may not remain in the lungs in particulate form for a period of time sufficient to cause the degree of response seen with cryolite.

For cryolite, the NOAEC for systemic effects in male and female rats was 4.6 mg/m^3 and the NOAEC for local toxic effects on the respiratory tract in rats was 0.21 mg/m^3 (BG Chemie, unpublished report, 1997).

5-month studies (rat)

In a chronic toxicity study, groups of 30-35 adult albino rats were exposed to cryolite (synthetic, purity not given) by whole body exposure to concentrations of 0, 0.5 (0.5 ± 0.01), 1 (0.99 ± 0.03), or 3 (2.98 ± 0.06) mg/m^3 6 hours/day, 6 days/week for up to 5 months followed by a 4-week recovery period. This long-term inhalation study was not in full agreement with the requirements needed for the base set studies of existing chemicals (no data on sex and rat strain). The animals were regularly observed, weighed, feed intakes were determined, and clinical laboratory investigations of blood samples were performed. In addition, functional observations and motor activity were assessed, dental enamel, and the excretion of fluoride were examined. At termination, histopathological examinations were performed using 6 animals per dose group.

There were no treatment-related mortalities. During the first 2 months of the study exposed animals appeared in a good physical condition, thereafter rats exposed to 1 or 3 mg/m^3 cryolite exerted general and specific toxic effects. Animals showed reduced locomotion activity, a permanent stiffness, disturbation in chronotaxy of flexor and extensor muscles, tremor, hunched posture, rough coat and fur unkempt. These findings were not reversible after the 4 week-recovery period. In the high and mid dose group, carbohydrate metabolism and acetylcholinesterase activity in plasma were statistically significantly decreased compared to the controls. In addition, inhibition of SH-groups, and a decrease of vitamin C level in adrenal glands were measured. The fluoride contents in urine, bones and teeth were increased (threefold in the high dose group, twofold in the mid dose group and 1.5-fold in the low dose group compared to controls). At 3 mg/m^3, a loss of normal tooth coloration (mottled teeth), and enamel defects were observed. The surface of the enamel showed irregularities, partly due to restricted pitting areas, partly due to real corrosion of the enamel. In animals from the high and mid dose group (3 and 1 mg/m^3), the bone structure of the femur tended to thicken, and blurred, and a reduction of the marrow volume occurred. The periosteum of the spinal column revealed gaps and fissures. Microscopic examination revealed increased lysis of osteocytes, formation of an abnormally structured osseous tissue and a reduced and irregular calcification of the osteoid tissues, with a tendency towards a granular precipitation of the calcium salts. Histologically, degenerative changes were observed in the enamel epithelium of the incisors, which was replaced by a hyperplastic, defectively calcified enamel and dentine. Microscopic examination of the lungs from animals from the high and mid dose groups revealed hyperaemia and various inflammatory lesions in the alveolar parenchyma, focal bleeding, increase in the number of eosinophil leukocytes in the alveoli, and lymphoid hyperplasia in the tracheobronchial lymph nodes. In the liver, single cell necrosis and focal degenerative changes of hepatocytes, single cystic bile ducts and small amounts of bile duct hyperplasia and areas of fatty degeneration were observed. Further observations were necrosis of proximal renal tubules, slightly bleeding, focal inflammatory infiltration in the submucosa of the glandular stomach, hypaeremia of the mucosa of the small intestine, inflammatory perivascular infiltration of the brain, and proliferation of neuroglia cells. No toxicologically relevant systemic effect was detected in rats at 0.5 mg/m^3 cryolite.

Overall, chronic inhalation of cryolite dust caused distinct general toxic and specific effects in rats. Exposure concentrations of ≥ 1 mg/m^3, 6 hours/day, 6 days/week for up to 5 months revealed dystrophic lesions on the bones and teeth. There were also adverse effects in the respiratory tract, stomach, liver, kidney and brain. Based on data presented, 0.5 mg/m^3 is considered as NOAEC for systemic effects, although fluoride concentrations in urine, bones and teeth were already elevated at this concentration. Since no overt adverse effects were identified at this concentration, the NOAEC for systemic toxic effects was set at 0.5 mg/m^3. Therefore, the NOAEC for systemic toxic effects in bones, teeth and lungs and for local effects on the respiratory tract was 0.5 mg/m^3 (Plotko et al., 1973).

In order to determine the effects of cryolite exposure on the unspecific immune function, phagocyte activity of white blood cells was determined in albino rats (no data of number, sex and rat strain), whole-body exposed to cryolite (synthetic, purity not given) concentrations of 0, 0.5, 1, and 3 mg/m^3, or to a mixture of cryolite (0.5 mg/m^3) and hydrogen fluoride (0.35

mg/m^3) (6 hours/day, 6 days/week) for up to 5 months followed by a 4-week recovery period. At termination, rats exposed to 1 or 3 mg/m^3 cryolite or to the mixture of cryolite and hydrogen fluoride the phagocytic index of leukocytes was decreased up to 56 %. Activity returned to normal values after inhalation was discontinued.

The leukocytic phagocytosis of rats exposed to 0.5 mg/m^3 was decreased to 33 %. Therefore, authors of this study required a lower level for the maximum permissible concentration of insoluble fluoride compounds in the air of workplaces.

A NOAEC for leucocytic phagocytosis was not determined (Egorova and Sadilova, 1971).

Dermal

No relevant data available.

The following repeated dose dermal toxicity study with synthetic cryolite (CAS-No. 15096-52-3) was submitted only in summary form (cited by EPA-738-R-96-016, Reregistration Eligibility Decision (RED) – Cryolite, p 9, August 1996). A detailed full report of this study is not available, but requested by the rapporteur. Up to now a complete study report is not available; therefore no final evaluation can be made.

There is a 21-day subacute dermal toxicity study in rabbits. However, this 21-day dermal toxicity study is unacceptable because the test substance was likely ingested during the study.

Synthetic cryolite (purity 96 %) was administered dermally to 5 New Zealand White rabbits/sex at dose levels of 0, 25, 250, and 1000 mg/kg bw/d for 6 hours a day, 5 days per week for a period of three consecutive weeks. The following signs were probably due to inadvertent oral exposure (animals were observed licking their fur during the study). Signs of toxicity included: at 1000 mg/kg bw/d mortality in males (3/5) and females (1/5); thin appearance and hypoactivity; actual decreases in absolute body weight (up to 400 g) throughout the study; anaemia and changes in several clinical chemistry parameters. At 250 mg/kg bw/d, body weight was only decreased on day 5 with weight gain returning to normal for the duration of the study. It can be assumed that clinical signs and mortality observed in the study were probably due to oral ingestion. Therefore, the systemic LOAEL and NOAEL due to dermal exposure can not be determined (Wilkinson et al., 1989 cited by EPA, 1996, MRID 41224801).

Oral

Diet studies

The following repeated dose toxicity studies with synthetic cryolite (CAS-No. 15096-52-3) were submitted only in summary form (cited by Federal Register, Vol. 61, No 90, p 20782, May 8, 1996, p 20783 and by EPA, EPA-738-R-96-016, Reregistration Eligibility Decision (RED) – Cryolite, pp 8ff, August 1996). A detailed full report of these studies is not available, but requested by the rapporteur. Up to now complete study reports are not available; therefore no final evaluation can be made.

Cryolite (synthetic product), marketed as insecticide, consisting of 47% fluorine and as a second compound, calcium fluoride, were fed in diet and drinking water to albino rats (10 females and 14 males/treatment group) at 0.58 mg/kg for 14 weeks. Several of the rats, irrespective of treatment groups showed hematuria lasting 1 or 2 days in the first week. Striations in tooth enamel began to appear during the 8th week of treatment and were visible in all rats by the end of the 10th week. Data demonstrate, that the action of fluorine from cryolite is indistinguishable from that of calcium fluoride when both are administered in aqueous solutions at the rate of 0.58 mg/kg bw daily. Approximately 96 % of the fluorine retained (13 ppm in food) is deposited in the skeleton, while the rest is equally divided between teeth and soft tissues ("The comparative toxicity of fluorine in calcium fluoride and in cryolite" (University of Illinois, 3/29/39) cited from CalEPA (1995) (031 071325). The original study was not available to the rapporteur).

Albino rats (10 females and 2 males/group) were fed cryolite in the diet (10 ppm fluorine (approx. 0.7 mg fluorine/kg bw/d)) or administered in solution (9.1 mg cryolite/l (approximately 0.9 mg fluorine/kg bw/d) for 19 or 20 weeks. Hematuria was observed in animals receiving cryolite in drinking water. Growth was reduced due to frequent food refusal. Refusal was twice as frequent for rats receiving cryolite solution than for those with cryolite in the diet. However there was no effect upon the method of fluorine administration upon body growth or appearance of teeth striations. A greater concentration of fluorine was found in bone, teeth and soft tissues of all rats receiving cryolite in water. Retention of fluorine was 18.6 % less for rats fed cryolite in diet versus solution. This is apparently due to decreased absorption in the alimentary tract ("A Comparison of the toxicity of fluorine in the form of cryolite administered in water and food" (University of Illinois, 3/29/39) cited from CalEPA (1995) (031 071326). The original study was not available to the rapporteur).

Albino rats were fed fluorine (as cryolite) in diet at 4, 6.5 and 12.5 ppm (1 male and 2 females per group; approximately 0.3, 0.455 and 11 mg/kg bw/d fluorine) for 22 - 32 weeks, depending upon respiratory impairment. Samples of urine and faeces were collected after 27, 56 and 70 days of feeding. Collection periods lasted from 6 to 14 days. At termination, body length, empty weight (of carcass) and fluorine content of skeleton, teeth and soft tissues were determined. Results showed that growing rats adapt themselves to continuous ingestion of low levels of fluorine by increasing their excretion of fluorine in faeces and urine. Rate of adaptation decreases with time but maximum adaptation is 60 - 100 % in proportion of ingested fluorine eliminated by kidneys and intestine. The greater the proportion of fluorine in the consumed food, the lesser the efficiency of adaptation. As fluorine consumption increases, the concentration deposited in teeth becomes greater than in bone ("Adaptation of the growing rat to the ingestion of a constant concentration of fluorine in the diet" (University of Illinois, 1/8/40) cited from CalEPA (1995) (031 071327). The original study was not available to the rapporteur).

Twelve pairs of littermate rats (sex/group not specified) were fed 1.4 ppm fluorine in diet for approximately 20 weeks (approximately 0.1 mg/kg bw/d fluorine). Additionally, one rat/pair was administered 1 ml of an aqueous solution containing cryolite (18 ppm fluorine)/ 3 grams of food (approximately 0.4 mg/kg bw/d fluorine). Every 3rd day the other rat was provided, in diet, with as much as cryolite as its pair mate received from aqueous dosage, so that the total intakes of fluorine by pair mates was equalized every three days for the total 3 day period. When fluorine is continuously administered as synthetic cryolite to growing rats, there is a greater retention of fluorine in bones and possibly teeth than when cryolite is administered intermittently (in the same quantity) ("The comparative assimilation of fluorine by growing rats during continuous and intermittent dosage" (University of Illinois, 7/2/40) cited from CalEPA (1995) (031071328). The original study was not available to the rapporteur).

Growing albino rats, 12 pairs of littermates (unspecified sex; average weight 120 g) and 8 pairs of younger littermates (44 g) were fed in diet cryolite (9.4 ppm fluorine, 0.23 % calcium; approximately 0.08 mg/kg bw/d fluorine for 120 g animals and approximately 0.03 mg/kg bw/d fluorine for the younger littermates). One rat per pair received this low calcium ration (Ca:P = 0.44 to 1), while the other rat received a diet containing 0.73 % calcium (Ca:P = 1.40

to 1). Feeding was terminated when each rat had consumed 1 kg of food. Result: a heavier dry fat-free skeleton was obtained as dietary calcium increased. Fluorine retention was decreased 10 - 13 %, especially in teeth and soft tissues. Data suggested that lower assimilation of fluorine with increased dietary calcium was greater in the younger group (Experiment I). When phosphorus content varied in the diet (experiment II), fluorine retention and distribution was not affected. It was concluded that calcium appears to protect against dietary fluorine by impairing assimilation in teeth and soft tissues ("The effect of dietary calcium and phosphorus on the assimilation of dietary fluorine" (University of Illinois, 1/3/41) cited from CalEPA (1995) (031 071329). The original study was not available to the rapporteur).

Weanling albino rats (35 - 45 g, 5 animals per dose) were fed 0.1105, 0.0554 or 0.0276 % cryolite; 0.132, 0.066, 0.033 or 0.0154 % NaF; 0.259, 0.1295 or 0.0648 % $AlCl_3$ + 6 NaF for 12 weeks. Three groups of weanling rats (5 animals per group) were given distilled water or 4 ppm of fluorine as aqueous cryolite or sodium fluoride for 8 weeks. At the end of each experiment femurs and tibiae were removed for fluorine analysis. Results showed at 4 ppm in drinking water, sodium fluoride or cryolite resulted in identical storage of fluorine in the bones of growing rats. At higher dosages, less fluorine was found in the skeleton when fed as cryolite or as sodium fluoride plus aluminium chloride, than when fed as sodium fluoride ("A study of the comparative toxicity of cryolite fluorine and sodium fluoride for the rat" (University of Wisconsin) cited from CalEPA (1995) (031 071335). The original study was not available to the rapporteur).

Lactating Holstein cows (3 per group) were fed 0, 50, 150 and 500 ppm krycocide (97.3 % synthetic cryolite, 52.8 % fluoride) (10.35 g krycocide/kg premix) for 28 days. Results showed no major changes in fluoride levels due to treatment with krycocide. Treatment with 500 ppm krycocide produced an increase in liver fluoride from 0.91 to 1.21 ppm and kidney fluoride increased from 1.99 ppm to 2.32 ppm ("A feeding study with diary cows using Krycocide insecticide (synthetic cryolite) (Pennwalt Corporation 1/10/86) cited from CalEPA (1995) (031 071336). The original study was not available to the rapporteur).

Leghorn laying hens (8 groups with 5 animals/group) were given krycocide (97.3 % synthetic cryolite, 52.8 % fluoride) in feed at 0, 8.6, 26 or 86 ppm (duplicate groups) for 35 days. krycocide in diet did not affect egg production. Level of fluoride in eggs was < 0.01 ppm (no increase over normal levels). No increase was found in tissue levels of fluoride after treatment (control = 0.27 - 1.01 ppm; high dose group = 0.32 - 1.07 ppm) ("A feeding study with chickens using krycocide insecticide (synthetic cryolite) (Wil Research Laboratories, Inc., 10/24/85) cited from CalEPA (1995) (031 071339). The original study was not available to the rapporteur).

Twelve pairs or trios of rats, depending on the number on rations to be compared, were selected on the basis of sex, litter membership and body weight and fed equal amounts within the pairs or trios. Initially, 1 - 4 animals/litter were sacrificed for base level of fluorine. Experiment I: Domestic synthetic cryolite (particle size ≤ 1 µm, 44.9 % fluorine) and natural Greenland cryolite (commercial form, ≤ 5 µm, 46.2 % fluorine; specially ground form ≤ 1 µm, 50.5 % fluorine) was fed (9.4 ppm fluorine (approximately 0.7 mg /kg bw/d)). Results showed that fluorine of synthetic cryolite is retained significantly more than fluorine from natural cryolite, probably due to solubility. Experiment II: Peaches sprayed with coarsely ground natural cryolite or finely ground special natural cryolite and un-sprayed peaches (dried and ground to fine powder) were found to contain 100, 94 and 1.5 ppm fluorine respectively. The two sprayed-peach powders were put into diet (fluorine = 9.6 ppm (approximately 0.7 mg/kg bw/d)). Results showed the degree of fineness to which cryolite is ground may modify the assimilation of the contained fluoride. Weathering of natural Greenland cryolite on sprayed fruit does not affect its assimilation in rats. Experiment III: Weathered synthetic cryolite was sprayed on apples in one group and the other group had unweathered synthetic cryolite mixed with unsprayed apple powder. Sprayed apples were dried and powdered then both diets were fed to rats (6.8 ppm fluorine (approximately 0.5 mg /kg bw/d)). Results showed weathering on fruit of synthetic cryolite lower the assimilation of its fluorine. Possibly, the more soluble compounds of fluorine contained in cryolite are leached out by weathering. Experiment IV: Freshly picked sprayed apples (using synthetic cryolite) were dried and ground to a powder. Sprayed apples allowed to age at a warm temperature and "wax up" for several weeks were then dried and ground. Rats were fed the two diets containing 11 ppm fluorine (approximately 0.8 mg /kg bw/d). Results showed the development of a wax coat on apples sprayed with cryolite may decrease the assimilation of fluorine (("The assimilation of fluorine by rats from natural and synthetic cryolite and from cryolite-sprayed fruits" (University of Illinois, 6/30/41) cited from CalEPA (1995) (031 071330). The original study was not available to the rapporteur).

28-day study (rat)

In a subacute feeding study, groups of 5 Sprague-Dawley rats were administered synthetic cryolite (purity 97.6%) at dose levels of 0, 250, 500, 1000, 2000, 4000, 10000, 25000, and 50000 ppm in the diet (representing approximately 0, 25, 50, 100, 200, 400, 1000, 2500, and 5000 mg/kg bw/d). The teeth were whiter and the enamel became soft and granular at all dose levels compared to controls. There was a dose-response relationship. The LOAEL was 250 ppm (representing 25 mg/kg bw/d) based on dental fluorosis. A NOAEL was not determined (cited by Federal Register, 1996; EPA 1996, MRID 00128109).

90-day study (rat)

In a 90-day feeding study in Charles River Crl:CD(SD)BR rats, synthetic cryolite (purity 96%) was administered to groups of 40 male and 40 female rats in the diet at dose levels of 0, 50, 5000, and 50000 ppm (corresponding to 0, 3.8, 399.2, and 4172.3 mg/kg bw/d in males and 0, 4.5, 455.9, and 4758.1 mg/kg bw/d in females). At 50000 ppm male and female rats exhibited reduced body weights and decreases in haemoglobin and haematocrit. At necropsy the stomach of male and female rats receiving ≥5000 ppm exhibited thickened walls, dark contents, raised focal areas, glandular thickened walls, non-glandular light focal areas, glandular dark focal areas and red glandular areas. Microscopical examination revealed submucosal lymphoid foci, epidermal hyperplasia, hyperkeratosis/acanthosis, erosion/ulcerations, mucosal atrophy and chronic submucosal inflammation. Fluoride accumulated in bones and teeth at all dose levels. The LOAEL for fluoride accumulation for male and female rats was 50 ppm, representing 3.8/4.5 mg/kg bw/d. The NOAEL for this effect could not be determined in this study. The LOAEL for lesions observed in the stomach was 5000 ppm (399.2 mg/kg bw/d in males and 455.9 mg/kg bw/d in females). The NOAEL for stomach effects in rats was 50 ppm, representing 3.8 mg/kg bw/d in males and 4.5 mg/kg bw/d in females (Weltman 1985 cited by Federal Register, 1996 and by EPA, 1996, MRID 00158000).

90-day study (dog)

In a 90-day feeding study in dogs, synthetic cryolite (purity 97.3%) was administered to groups of 7 male and 7 female dogs at dose levels of 0, 500, 10000, and 50000 ppm (corresponding to 0, 17, 386, and 1692 mg/kg bw/d). One male and one female dog/group were interim sacrificed after 45 days. At 50000 ppm, there were decreases in food consumption, body weight, body weight gain and red blood cells, haemoglobin, haematocrit, mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH). Fluoride accumulated in bone at all dose levels. The LOAEL for fluoride accumulation in male and female dogs was 500 ppm, representing 17 mg/kg bw/d. The NOAEL for this effect could not determine in this study. The NOAEL for effects other than fluoride accumulation was 10000 ppm, representing 368 mg/kg bw/d (Hagen and Strouse, 1986 cited by Federal Register, 1996 and by EPA, 1996, MRID 00157999).

1-year study (dog)

Synthetic cryolite (purity 97.3-97.4%) was tested in a one-year chronic feeding study in Beagle dogs (4/sex/group) at dose levels of 0, 3000, 10000, and 30000 ppm, representing 0, 95, 366, and 1137 mg/kg bw/d in males and 0, 105, 387, and 1139 mg/kg bw/d in females (in terms of fluoride the doses are 0, 51, 198, and 614 mg/kg bw/d for males and 0, 57, 209, and 615 mg/kg bw/d for females). At 3000 ppm, there were slight increases in the incidence of emesis in both males and females (vomiting, white and yellow froth). Body weight gain was increased in males at 30000 ppm. Haematology showed nucleated red cells in males receiving 3000 ppm; decreased red cell count, haemoglobin, haematocrit, MCV, MCH, mean corpuscular haemoglobin concentration (MCHC), and platelets; and an increased incidence of specific alterations of red blood cell morphology (anisokaryocytes, microcytes, macrocytes, target cells, hypochromic cells, nucleated red cells, basophilic strippling, and Howell-Jolly bodies) in both males and females at 10000 ppm, increased leukocytes (primarily segmented neutrophils and eosionphils) were observed only in females. Regarding clinical chemistry, a decrease in total serum protein and calcium in males and in serum albumin in females were noted at 10000 ppm. Increased lactate dehydrogenase was determined in both males and females, and decreased blood sodium was observed in males at 30000 ppm. In females receiving 3000 ppm a decrease in specific gravity of the urine was seen. Microscopic examination showed renal lesions at ≥3000 ppm. Regeneration of the tubular epithelium, interstitial fibrosis, tubular dilation, interstitial infiltration with lymphocytes was observed in two males and in females at 3000 ppm. Dilation of Bowman’s space was observed in one male and one female receiving 10000 ppm. At the same dose level haematopoiesis in the liver and spleen, megakaryocytosis in the spleen, and myelofibrosis in the bone marrow were observed in both genders. The LOAEL was 3000 ppm (95 mg/kg bw/d in males and 105 mg/kg bw/d in females) based on increases in emesis, nucleated cells in males, renal lesions and a decrease in urine specific gravity in females. The NOAEL could not be determined in this study (Tompkins, 1992 cited by Federal Register, 1996 and by EPA, 1996, MRID 42575101).

Other/further information

There are numerous repeated dose toxicity studies in experimental animals by oral administration which were not performed according to modern standard repeated dose toxicity testing protocols. Most of the data presented are early studies with limited quality. These studies also revealed toxic effects in bones and teeth. In several experiments cited data such as specification and purity of the test substance used - natural or synthetic cryolite - current fluoride content of the test substance were incomplete and a detailed recording of the experiment was not given. Most of them have been focused on selected parameters. However, main findings of these studies showed good consistency and therefore, they were also considered for the effect assessment. In the following early reports on oral administration of cryolite to rats are summarised. To complete the database these studies were reported here:

Gavage study

10-day study (rat)

Two rats/group (no data of sex and rat strain) received by gavage 8 g/kg bw/d of an aqueous suspension of natural and synthetic cryolite (purity not given) for 10 consecutive days or three times/week for a total of 10 applications. One rat died after the administration of the sixth dose of synthetic cryolite. Post-mortem examination failed to reveal the cause of death. All other animals survived for at least 21 days without exhibiting any noteworthy symptoms. No body weight changes were observed in both dose groups with natural cryolite. Observed decreases of body weight in both groups with synthetic cryolite were reversible. Gross examination of the organs revealed no significant abnormalities in all regimen groups. Data on histopathology were not available (Largent, 1948).

Diet studies

5- to 10-week studies (rat)

Effects of several concentrations of synthetic commercial cryolite (purity not given) in the diet upon the production of striations on the teeth were studied in young healthy albino rats (no data on number and sex, and strain). Animals were administered dose levels of approximately 4 mg/kg bw for 5 or 6 weeks, 7 mg/kg bw for 5, 6, or 10 weeks, and 11 mg/kg bw for 5 weeks. The incisors were examined each week for presence or absence of striations, so-called bleached areas. In addition, at termination each other tooth was examined for the presence or absence of striations, and the fluoride contents of the teeth were measured. At 4 to 7 mg/kg bw fluoride, no increased incidence of striations of the teeth was visible, and the fluoride-contents of the teeth were not significantly different from that of the controls. At 11 mg/kg bw fluoride in the basal diet for 5 weeks, faint striations of the teeth of rats and increased fluoride-content of the teeth and bones were observed. No duration-related effect of cryolite in the diet was seen.

The NOAEL for the teeth effects was 7 mg/kg bw/d (Marcovitch et al., 1937).

Results of another study showed growth retardation and poor utilisation of food when rats were given natural cryolite (purity not given) at 2260 ppm in diet (approximately 250 mg/kg bw/d fluoride) for up to 20 weeks. With 36000 ppm cryolite in the diet (approximately 1900 mg/kg bw/d fluoride) a marginal increase in mortality after 9 to 11 days of treatment was recorded (Smith and Leverton, 1934).

In the following some brief reports on experience by oral administration in rats to cryolite are summarised in the report of Roholm (1937a,b). In several experiments cited data on the specification of the test substance used - natural or synthetic cryolite, actual fluoride content of the test substance - were incomplete, detailed records of the investigations and duration of experiments was not given.

Cryolite (natural or synthetic not specified) was orally administered to young rats (no data on number and sex, and rat strain) at doses of 6.3, 11.8, or 23.1 mg/kg bw/d for 16 weeks. Administration of cryolite caused distinct toxic effects in rats at 23.1 mg/kg bw/d. Animals showed reduced food consumption, growth retardation, poor general appearance and behaviour, reduced reproduction, and typical dental changes such as mottled enamel of the teeth. In the histological examination, degeneration of liver and inflammatory changes in the kidney was found. Oral administration of cryolite to rats (11.3 mg/kg bw/day for 16 weeks) caused doubtful symptoms of intoxication (no more data).

No symptoms of intoxication were seen at 6.3 mg/kg bw/d (Smyth and Smyth, 1932).

After repeated daily intake of 243 ppm (approximately 1-2 mg/kg bw/d fluoride) cryolite (not specified whether natural or synthetic) in the diet first symptoms of degenerative tooth changes appeared in rats. Bleaching was seen on the incisors (DeEds and Thomas, 1934).

In addition, the publication of Roholm (1937a,b) listed further data on repeated dose toxicity studies with fluoride without information on the duration or any other study data, summarised in the following Table 4.1.2.6.1-A Summary table: Animal toxicity data after repeated oral administration of cryolite (natural or synthetic not specified) reported in early literature.

Table 4.1.2.6.1-A

Summary table: Animal toxicity data after repeated oral administration of cryolite (natural or synthetic not specified) to rats as reported in early literature

DOSE (mg/kg bw/d)	**EFFECT**
1	bleaching on the incisors
5	development of abnormally structured osseous tissue and renal effects
15	first symptoms of disturbance of general condition, slight inhibition of growth and behaviour
25	reduced vitality, unthrifty appearance, loss of weight, and certain morphological changes in parenchymatous organs
100	rapid loss of weight, and death after some weeks

From animal studies, the main toxic effects of cryolite are summarised in the following Table 4.1.2.6.1-B Summary table: Relevant animal toxicity data after repeated exposure to cryolite (for key to symbols, see end of the table).

Table 4.1.2.6.1-B

Summary table: Relevant animal toxicity data after repeated exposure to cryolite

Study design: **Species/Strain** **(male/female)** **Exposure route** **Exposure duration** **Test substance** **Dose**	**Findings, non-neoplastic effects (selected)** **NOAEL/NOAEC (effect)** **LOAEL/LOAEC (effect)**	**Reference**
Sprague-Dawley (CD) rat (10m/10f) **Inhalation** snout only exposure 90-day, 6 hours/day, 5 days/week, 13 weeks recovery cryolite (CAS 13775-53-6) 0, 0.21, 1.04, and 4.6 mg/m³; + extra group receiving 5.7 mg/m³ sodium fluoride No histopathology on bones and teeth	<u>4.6 mg/m³ (m/f):</u> (↑) inorganic fluoride concentration in urine, bones, and teeth (↑) Aluminium concentration in the urine ↑* lung weight (abs) <u>tracheobronch/mediast lymph nodes:</u> accumulation of laden macrophages <u>≥1.04 mg/m³ (m/f):</u> <u>lung:</u> alveolitis with trace interstitial thickening (fibrosis) of alveolar duct walls <u>0.21 mg/m³ (f):</u> (↑) Aluminium concentration in the urine NOAEC: 4.6 mg/m³ for systemic effects NOAEC: 0.21 mg/m³ for local effects (lung)	BG Chemie, unpublished report 1997

Study design: **Species/Strain** **(male/female)** **Exposure route** **Exposure duration** **Test substance** **Dose**	**Findings, non-neoplastic effects (selected)** **NOAEL/NOAEC (effect)** **LOAEL/LOAEC (effect)**	**Reference**
rat (no data on sex, and strain), 30-35 animals **inhalation** whole body, 5-month, 6 h/d, 6 d/wk, 4 weeks recovery synthetic cryolite 0, 0.5, 1, 3 mg/m^3	≥1 mg/m^3: permanent stiffness, ↓ motor activity ↓ plasma acetylcholinesterase activity ↑ fluoride content in urine, bones, teeth bone: periostal/ostal dystrophic/osteolytic lesions teeth: enamel defects lung: alveolitis tracheobronchial lymph nodes: hyperplasia liver: fatty degeneration of hepatocytes, single cell necrosis kidney: necrosis of the proximal renal tubules glandular stomach: focal submucosal inflammation brain: inflammatory perivascular infiltration, proliferation of neuroglia 0.5 mg/m^3: ↑ fluoride content in urine, bones, teeth No morphologic effects on bones and teeth NOAEC: 0.5 mg/m^3 for systemic and local effects No toxic effects on bones and teeth	Plotko et al. 1973
rat (no data on number, sex, and strain) **oral** (diet) synthetic cryolite 4 mg/kg bw for 5 or 6 weeks 7 mg/kg bw for 5, 6 or 10 weeks 11 mg/kg bw for 5 weeks	11 mg/kg bw/d: tooth: faint striations ↑ fluoride-content of teeth and bones NOAEL: 7 mg/kg bw/d for tooth effects	Marcovitch et al. 1937

Study design: **Species/Strain** **(male/female)** **Exposure route** **Exposure duration** **Test substance** **Dose**	**Findings, non-neoplastic effects (selected)** **NOAEL/NOAEC (effect)** **LOAEL/LOAEC (effect)**	**Reference**
rat (no data on number, sex, and strain) **oral** (diet) 16 weeks natural or synthetic cryolite not specified 6.3; 11.8; 23.1 mg/kg bw/d	11.3 mg/kg bw/d: doubtful symptoms of intoxication (no more data) NOAEL: 6.3 mg/kg bw/d For no systemic effects	Smyth and Smyth 1932
Sprague-Dawley rat (5m/5f) **Oral** (feed) 28-day synthetic cryolite (97.6%) 0; 250; 500; 1000; 2000; 4000; 10000; 25000; 50000 ppm (representing 0; 25; 50; 100; 200; 400; 1000; 2500; 5000 mg/kg bw/d)	≥25 mg/kg bw/d: tooth: change in coloration and physical property LOAEL: 25 mg/kg bw/d for dental fluorosis	Federal Register, 1996 EPA 1996, MRID 00128109
Crl:CD(SD)BR rat (10m/10f) **Oral** (feed) 90-day synthetic cryolite (96%) 0; 50; 5000; 50000 ppm (representing m: 0; 3.8; 399.2; 4172.3 mg/kg bw/d, f: 0; 4.5; 455.9; 4758.1 mg/kg bw/d)	≥50 ppm (3.8/4.5 mg/kg bw/d): fluoride accumulation (m/f) ≥5000 ppm (399.2/455.9 mg/kg bw/d: lesions in the stomach (m/f) LOAEL (m/f): 50 ppm (3.8/4.5 mg/kg bw/d) for fluoride accumulation	Weltman 1985 cited by Federal Register 1996 EPA 1996, MRID 00128109

Study design: **Species/Strain** **(male/female)** **Exposure route** **Exposure duration** **Test substance** **Dose**	**Findings, non-neoplastic effects (selected)** **NOAEL/NOAEC (effect)** **LOAEL/LOAEC (effect)**	**Reference**
rat (no data on strain; 10f/14m) **oral** (feed and drinking water) 14 weeks Synthetic cryolite (consisting of 47% fluorine, and calcium fluoride) 0.58 mg/kg bw/d	<u>0.58 mg/kg bw/d:</u> striations in tooth enamel from 8th treatmentweek LOAEL (m/f): 0.58 mg/kg bw/d for dental fluorisis	"The comparative toxicity of fluorine in calcium fluoride and in cryolite" (University of Illinois, 3/29/39) cited from CalEPA (1995) (031 071325); original study not available
Beagle dog (7m/7f) **Oral** (feed) 90-day; 1m/1f/group interim sacrificed at 45 days synthetic cryolite (97.3%) 0; 500; 10000; 50000 ppm (representing 0; 17; 386; 1692 mg/kg bw/d)	<u>≥500ppm (m/f):</u> fluoride accumulation in the bone <u>50000 ppm (m/f):</u> ↓ food consumption, body weight, body weight gain, RBC, HB, HCT, MCV, MCH NOAEL (m/f): 10000 ppm (368 mg/kg bw/) for effects other than fluoride accumulation LOAEL (m/f): 500 ppm (17 mg/kg bw/d) for fluoride accumulation	Hagen and Strouse 1986, cited by Federal Register 1996 EPA 1996, MRID 00128109
Beagle dog (4/sex/group) **Oral** (feed) one-year Synthetic cryolite (97.3-97.4%) 0, 3000, 10000, 30000 ppm (representing 0, 95, 366, 1137 mg/kg bw/d in males and 0, 105, 387, 1139 mg/kg bw/d in females; in terms of fluoride the doses are 0, 51, 198, 614 mg/kg bw/d for males and 0, 57, 209, 615 mg/kg bw/d for females)	<u>3000 ppm:</u> ↑ incidence of emesis, vomiting, white and yellow froth (m/f); ↓ specific gravity of the urine (f); ↑ nucleated red cells (m) <u>≥3000 ppm:</u> renal lesions (m/f) regeneration of the tubular epithelium, interstitial fibrosis, tubular dilation, interstitial infiltration with lymphocytes (2m/2f) <u>10000 ppm:</u> ↓ RBC; HB; HCT; MCV; MCH; MCHC; platelets; ↑ incidence of specific alterations of RBC morphology, anisokaryocytes, microcytes, macrocytes, target cells, hypochromic cells, nucleated red cells, basophilic strippling, and Howell-Jolly bodies, (m/f); ↑ leukocytes, primarily segmented neutrophils and eosionophils (f); ↓ serum albumin (f); ↓ total serum protein, calcium (m); dilation of Bowman's space (1m/1f); haematopoiesis in the liver and spleen, megakaryocytosis in the spleen, and myelofibrosis in the bone marrow (m/f) <u>30000 ppm:</u> ↑ body weight gain (m); ↑ lactate dehydrogenase (m/f); ↓ blood sodium (m) LOAEL: 3000 ppm (95 mg/kg bw/d in males and 105 mg/kg bw/d in females) for increases in emesis, nucleated cells in males, renal lesions and a decrease in urine specific gravity in females	Tompkins 1992 cited by Federal Register 1996 EPA 1996, MRID 00128109

↑: INCREASE COMPARED WITH CONTROLS, NO DATA OF STATISTICAL ANALYSIS; ↑*: STATISTICALLY SIGNIFICANT INCREASE

COMPARED WITH CONTROLS (P<0.01); (↑): INCREASE COMPARED WITH CONTROLS, NO STATISTICALLY SIGNIFICANT BUT POSSIBLY OF TOXICOLOGICAL RELEVANCE; ↓: DECREASE COMPARED WITH CONTROLS, NO DATA OF STATISTICAL ANALYSIS; M: MALE; F: FEMALE; RBC: RED BLOOD CELL COUNT; HB: HAEMOGLOBIN; HCT: HAEMATOCRIT; MCV: MEAN CORPUSCULAR VOLUME; MCH: MEAN CORPUSCULAR HEMOGLOBIN; MCHC: MEAN CORPUSCULAR HEMOGLOBIN CONCENTRATION; ABS: ABSOLUTE; LOAEL: LOWEST OBSERVED ADVERSE EFFECT LEVEL; NOAEL: NO OBSERVED ADVERSE EFFECT LEVEL

In vitro studies

No data available.

4.1.2.6.2 Studies in humans

There are a number of epidemiological studies of working populations exposed to cryolite dust, which consisted of a fluoride content of 54%. Occupational cryolite exposure was reported from the mining and processing of natural cryolite, manufacture of synthetic cryolite and aluminium production. However, workers in this industrial setting were also exposed to a number of other known harmful substances.

Mining and processing of cryolite

Effects on bones

High and prolonged uptake of cryolite dust led to skeletal fluorosis, which is characterized by osteosclerosis (increased mineralization of the bones). This was first described in 1932 as a new occupational disease in cryolite workers in Copenhagen, Denmark. In roentgenographic examinations of 78 male workers engaged in the crushing and refining of cryolite, changes in the bones of varying degree and extent were found in 30 workers. The employees worked for varying periods of time in the presence of cryolite. The bones, especially the spongy, were enormously altered both in structure and outline. The bone density was increased, subperiosteal bone tissue was formed, and ligaments were calcified. In the final stage the condition is known as ‘crippling fluorosis’, which is a fairly well defined entity characterized by calcification of broad ligaments running along the spinal column, exostosis and hypercalcification of bones (osteosclerosis), leading to “pocker back”, painful joints and progressive disability. These abnormalities were found to be roughly proportionate to the duration of employment in this work. No such bone changes were observed in 21 examined workers exposed to fluorine fumes in glass, enamel, and sulfuric acid industries (Møller and Gudjonsson, 1932).

Shortly afterwards, skeletal effects were studied in detail in a group of 68 Copenhagen cryolite workers by Roholm (1937a,b). The workers (47 men and 21 women) had been exposed to high levels of dust, which contained 97% cryolite, 1-2% quartz, and 1.5-2.0% other components: siderite ($FeCO_3$) and varying quantities of other minerals including ZnS, PbS, $CuFeS_2$, FeS_2. Dust measurements in the grinding room showed total dust levels between 32 and 48 mg/m^3, with peak contents reaching values as up to 994 mg/m^3. The grain size in the dust was very small. More than 50% of the dust particles were <5 µm in diameter. Mortality was not increased in the cryolite workers. Bone changes developed only in workers with long-term, continual exposure to dust. Workers reported few non-specific clinical symptoms: moderate functional dyspnoe, lack of appetite, nausea, vomiting and constipation. At clinical examination one characteristic sign was found: a palpable, irregular thickening of subcutaneous edges of the clavicle, tibia, or ulna. Upon examination by x-ray radiography, 57 workers were found to have a characteristic type of osteosclerosis affecting primary the vertebral column, pelvis and ribs. In pronounced cases, exostosis and osteophyte formation, increased thickness of long bones, and ligament calcification were seen. In the course of this investigation, three stages of the condition were identified: ‘slight’ (stage 1: changes only just radiographically discernible), ‘moderate’ (stage 2: marked fluorosis with periostal deposits and incipient displacement of bone marrow), and ‘extensive’ (stage 3: severe calcification of the ligaments). Some relationships between time of exposure (period of continuous employment) and the onset of symptoms of chronic fluoride poisoning as shown by x-ray photographs were established. From the statistics obtained it was demonstrated that the average period of employment without discernible bone changes was 8 years. After an average of 9.3 years, changes corresponding to stage 1 were discernible; after 9.7 years the condition entered to the second stage; and a period of employment of an average of 21.7 years was required before the condition reached the third stage. The degree of fluorosis varied from individual to individual and the shortest period of employment for each of the three different stages of progression was: 2 years and 5 months for the first stage, 4 years and 10 months for the second stage, and 11 years and 2 months for the third stage. No calcium deposits were noted in the organs, and serum calcium content was not or slightly increased. Haematology revealed slight reduction of erythrocyte counts, simultaneously with an increase of the average MCH, moderate relative reduction of the leukocyte counts, moderate relative increase of the lymphocyte counts, considerable increase of neutrophil granulocytes and occurrence of a small number of metamyelocytes. The blood changes were more prominent in workers with marked osteosclerosis. At autopsy of two cryolite workers employed for 24 and 9 years, respectively, no abnormal findings, which were attributed with certainty to cryolite exposure, with exception of skeletal changes were observed. The weight of the bones examined was roughly three times the normal in the first case, and twice in the second case. The bone elasticity was decreased and the bone surfaces were chalky-white and displayed widespread periosteal deposits and calcification of ligaments. The fluoride content in the bones was very high and varied from 3.1 to 9.9 mg fluoride/g ash in one case and from7.6 to 13.1 mg/g ash in the other case (fluoride bone contents from individuals without fluoride exposure were between 0.48 and 2.1 mg fluoride/g ash). From this it follows that the osseous system of the two cryolite workers contained about 90 g and about 50 g fluoride, respectively. This corresponds to a content of up to 60 times the normal fluoride content. Increased fluoride contents were also determined in the kidneys of the two cryolite workers (2.3 and 2.4 mg fluoride/100 g tissue in exposed individuals; 1.1 mg fluoride/100 g tissue in non-exposed controls) and lung (79.2 and 10.8 mg fluoride/100 g dry weight tissue in the two cryolite workers; 0.73 mg fluoride/100 g dry weight tissue in control. The average fluoride absorption of cryolite workers (8 hour working day) was calculated to be 14-70 mg (of which maximal 4.6-23 mg were absorbed systemically) for a 70 kg weighed adult man. With an average half-life of 8 years for skeletal fluoride and a relative retention in the skeleton of 50% of the absorbed fluoride, a daily absorption of about 35 mg of fluoride, i.e., 0.5 mg/kg bw can calculated for these two workers. It was concluded that years are required for the development of demonstrable fluorosis in cryolite workers. The cases of skeletal fluorosis were caused by continuous daily exposure to 20 to 80 mg of fluorides (or more) for at least 4 years, and in cases of crippling fluorosis for 10 to 20 years.

Re-examinations of cryolite workers from Danish cryolite plant with formerly diagnosed skeletal fluorosis showed that the condition was reversible. When former workers were examined many years after their retirement from the cryolite factory indications were found that the skeletal fluorosis was less pronounced than expected in retired cryolite workers. This suggested that the osteosclerosis might be reversible. Despite long-term exposures, only 9 of 32 retired cryolite workers had skeletal fluorosis (Roholm, 1937a,b).

The frequency of cases of skeletal fluorosis in a cryolite factory in Copenhagen has decreased with improved industrial hygiene. Due to changed production methods since 1961, e.g. separation of cryolite by flotation, lower dust exposures occurred and thereafter no new cases have been diagnosed in Copenhagen (Grandjean, 1982).

Skeletal fluorosis as a result of long-term exposures to fluorides was also described in another study on workers of a cryolite refining plant in Copenhagen written in Danish with an abstract in English. Subsequent follow up studies have shown decreasing prevalence rates and a significant reversibility after cessation of exposure (Grandjean, 1983).

The reversibility of skeletal fluorosis in Danish cryolite workers was examined in a subsequent study. All traced Danish cryolite workers with acquired skeletal fluorosis after exposure to an average fluoride concentration of 28 mg/m^3 (measured in 1955) and later of 2.5 mg/m^3 (measured in 1961) at the certain work processes were included in this study. From the 17 cases of skeletal fluorosis identified among long term exposed cryolite workers in 1957 and 1967, four of these patients were alive 8 to 15 years after exposure had ended. A similar picture emerged in all four cases: extensive fading of the sclerosis of trabecular bone in ribs, vertebral bodies, and pelvis, whereas cortical bone thickening and calcification of muscle insertions and ligaments remained virtually unchanged. The fluoride excretion was increased in three cases with the shortest exposure free period. Results of the re-examination of workers with formerly diagnosed skeletal fluorosis showed that fluoride is not irreversibly bound to bone and that skeletal fluorosis may be reversible to some degree in a manner that is dependent upon the extent of bone remodelling (Grandjean and Thomsen, 1983).

Continued excessive fluoride excretion was documented in former cryolite workers with known skeletal fluorosis. Following long-term heavy cryolite exposure, the urinary excretion of fluoride was greatly increased (2.41-43.41 mg/l urine, average 16.05 mg/l urine) in 24 examined cryolite workers when compared with 0.30-1.60 mg/l urine (average 0.92 mg/l urine) in 30 random chosen hospital patients without cryolite exposure. Continued excessive fluoride excretion for several years was documented in former cryolite workers with known skeletal fluorosis. The fluoride concentration in the urine was still increased in 6 male cryolite workers several years after retirement. There was 0.92-7.42 mg fluorine/l urine, average about 5.60 mg/l (Brun et al., 1941). Thus, the continued metabolism in bone tissue and excretion of retained fluoride could lead to an improvement of the condition.

Long-term exposure to high exposure concentrations of cryolite may lead to dental effects, disruption of tooth mineralization (dental fluorosis). Dental fluorosis is a hypoplasia and hypomineralization of the dental enamel and dentine, which in humans may occur during dental development. Examination of children of female cryolite workers, who were employed at the Danish cryolite factory before or during pregnancy or started to work there soon after the birth showed anomalies of the permanent teeth diagnosed as mottled teeth. There were changes in the enamel: diffuse, chalky-white colour, and brownish pigmentation, mostly on the surface exposed to light, in patches and bands (Roholm, 1937a,b). One worker employed for 15 years in a fluorspar processing facility producing hydrofluoric acid, sodium fluoride and cryolite for showed a brownish film on the teeth, which was not removable by scraping (Peperkorn and Kähling, 1944). An increased frequency of dental fluorosis was identified in children of cryolite workers due to the indirect exposure to fluoride (Grandjean, 1983).

Effects on the respiratory system

Examination of the respiratory system revealed no local irritating effects on the mucous membranes. Pulmonary emphysema was observed in 11 workers (8 men, 3 women), and signs of pulmonary fibrosis in 34 workers (28 men, 6 women). The author discussed these observed lung changes as possibly attributable to exposure to quartz dust. Pneumoconiosis was not diagnosed by radiological examinations or autopsy (Roholm, 1937a,b).

Re-examination of x-ray photographic pictures from 1953, 1957 and 1966 of 24 Danish cryolite workers with skeletal fluorosis revealed no evidence of pneumoconiosis (Grandjean et al., 1984).

Routine measurements of dust concentrations in the refinery at the Danish cryolite plant in 1981 and 1982 showed that the threshold limit value for quartz and fluoride content of the dust was exceeded by a factor of 6. In 1984 the fluoride content in the dust was exceeded by a factor of 4. At a cross-sectional health study of 101 cryolite workers, aged between 21 and 67 (mean 41 years), using pulmonary function tests and a questionnaire no significant correlation between work-related exposure and pulmonary function was found. The occurrence of dyspnoea and chronic bronchitis in 22 workers was dependent on individual smoking habits. There was a significant association between chronic bronchitis and both high incidences of smoking and current smoking. X-ray examination of four workers employed in the plant for periods between 26 and 43 years showed no indications of pneumoconiosis (Fries et al., 1989).

Synthetic cryolite

Skeletal effects similar to those observed in workers employed in mining and processing of natural cryolite were also observed in workers exposed to synthetic cryolite.

After clinical and radiological investigation of 47 workers employed in a fluorspar processing facility producing hydrofluoric acid, sodium fluoride and cryolite for an average of 25 years, severe effects on the bones characteristic for skeletal fluorosis could be observed in 34 workers (72.3%). The workers were mix-exposed to different exposure concentrations of gaseous fluorides and cryolite dust in this plant. All examined workers complained of backache, stiff gait, tiredness and weakness, and functional dyspnoe. Gastrointestinal complaints were not reported. The workers were in good general condition. There were no indications of occupational diseases of the heart, lung, liver or spleen. Haematology and urinalysis were without abnormal findings with exception of a slight increase in red blood cell counts. Depending on the duration of employment, the workers developed, in the first stage after an average of 12 years (3 to 17 years), a somewhat less dense bone structure, starting from the pelvis and the lumbar spine. The individual trabeculae of the spongy substance were condensed, thickened and blurred and the edge contours were fuzzy. In 11 workers with an average duration of employment of 18 years (7 to 27 years), the spongy substance exhibited a honeycomb-like appearance with considerably condensed and broadened trabeculae. Bone marking was blurred and showed homogenous shadows. There were periosteal overgrowths and depositions, tendon insertions displayed incipient calcification and the tubular bones were thickened and broadened, their marrow cavities narrowed. At the most severe stage of bone changes, which was seen in 7 workers after an average of 22 years (15 to 32 years) of employment, the bones were radiologically opaque and there was marked periosteal overgrowth, which particularly affected the antebrachial and crural bones, the vertebrae and the ribs, and very marked calcification of the tendons and ligaments, especially in the region of the vertebral column. A brownish film on the teeth, which was removable by scraping, was also observed (Peperkorn and Kähling, 1944).

In a fluorspar processing facility in India producing freezing gas, HF acid, synthetic cryolite, NaF, and other fluoride-based compounds as the final products, a study was performed to identify the nature and magnitude of the problem of industrial fluorosis and to prepare baseline information. In this study 438 male workers were interrogated and examined clinically. 85% of them were between 25-50 years of age and more than 70% had been employed for more than 9 years in the period from 1965 to 1977 at the same department. Spot urine samples from 226 workers were analysed for fluoride levels, and 106 randomly selected workers were x-rayed (right forearms). The level of fluoride in the drinking water of the factory (working place) and the nearby city and surrounding villages (residence of workers) was less than 1 ppm. Health complaints have been described in 34% of the workers. The most common health complaints were backache (14.1%) and pains in arms and legs (12.1%). Dental changes such as chalky white teeth, pitting and mottling were present in 9.6% of the workers. Radiological changes suggestive of fluorosis such as increased bone density, thickening of cortex, irregular bone margin, calcification of interosseous membranes etc. were noted in 21.8% of the workers. Fluoride levels of spot urine samples collected during working hours showed the effect of cumulative exposure as well as immediate exposure in working environment. The overall mean urinary fluoride level was 1.96 ppm. In 46% of the examined workers, the urinary fluoride level was higher than 1.5 ppm, and in 11.9% higher than 4.5 ppm. There was a correlation between bone and dental findings and the urinary fluoride excretion and the level of exposure, but there was no clear correlation between findings and the duration of exposure or socio-economic status of the employees, respectively (Desai et al., 1983).

To identify the relationship between environmental exposure to fluoride compounds and urinary fluorine excretion, workers in a cryolite-producing plant in Japan were examined for a period of 6 years from 1977 until 1982. 68 workers were exposed to a mixture of gaseous and particulate fluorides at different workplaces. Average exposure levels of hydrogen fluoride were 0.09-0.49 ppm (0.9-4.9 mg/m^3), and mineral dust levels were 0.05-0.6 mg/m^3 during the observation period. The major component identified in the air was hydrofluoric acid. Medical examinations and fluorine analysis were carried out in three groups of workers according to the process of cryolite production together with environmental monitoring of fluoride dust levels. Both airborne fluoride concentrations and urinary fluorine concentrations of workers were monitored twice a year. Medical examinations included checking of objective or subjective symptoms; measurement of urinary fluorine, red blood cell counts and haemoglobin concentrations; hepatic function test (GOT, acidic phosphatase); measurements of serum protein and serum Ca; and chest radiograph. No abnormal findings were noted in the workers at all examinations. Urinary fluoride excretion varied between approximately 0.25 and 4 mg/l, reflecting the different exposure situation. It was found that the airborne fluoride levels correlated with the excretion of group averages of urinary fluorine levels and the urinary fluorine levels of the recovery, respectively. However, individual fluoride excretion was frequently influenced by the dietary habits of Japanese workers (Baba et al., 1985).

Manufacturing of aluminium

There are a number of health surveys of workers occupationally exposed to cryolite, particularly those employed in the aluminium smelting industry for different times. Aluminium is produced by electrolysis of alumina dissolved in molten cryolite. During the electrolytic process both particulate and gaseous fluorides are released by virtue of the high temperature of the molten bath. The particulate fluoride is cryolite-like in composition while the gas in primarily hydrogen fluoride. Additionally, workers were exposed to numerous other gaseous and particulate compounds at the workplace. Health complaints described in workers employed at aluminium plants were effects on the respiratory system and were effects in bones and joints – skeletal fluorosis.

Effects on the respiratory system

The fate of inhaled fluoride particles depends on their size and solubility. Considerable amounts of sparingly soluble fluorides have been found to accumulate in the lungs of cryolite workers (Roholm, 1937a,b). The rapid development of aluminium production has led to increasing problems associated with chronic fluoride intoxication. Workers employed in the aluminium production were more afflicted with asthma or respiratory disorders, which were ascribed, in particular, to the exposure to dust, sulphur dioxide and hydrogen fluoride. However, it was not possible to attribute the respiratory disorders solely to the exposure to fluorides per se owing to the complex mixed-exposure situation encountered in aluminium production. An increased incidence of bronchial asthma and eosinophilia was reported from workers in Norway and Hungary.

In two early publications written in Norwegian with an abstract in German, results of clinical, laboratory and x-ray examinations of workers from cryolite/aluminium industry in Norway were reported. No radiological changes suggestive of fluorosis were observed in the bones of 56 examined workers exposed to dust containing amounts of fluoride-derivatives from the alumina-oven up to 25%. Bronchial asthma with relative eosinophilia was found in three workers among the 89 pot workers (Hjort, 1938). In another plant examinations of 200 workers exposed to dusts containing fluoride compounds showed increased incidences of acute pulmonary symptoms such as bronchitis, dyspnoea and bronchial asthma. Haematology of 32 workers revealed increases in eosinophiles and lymphocyte counts. A correlation between occurrence of asthma and eosinophilia was noted. No signs of acute toxicity due to exposure to cryolite were observed, and x-ray examinations of 26 workers (working in the plant for 11-27 years) did not show changes indicative of fluorosis (Evang, 1938).

In a further study among workers from an aluminium smelter in Norway, increased cases of bronchitis-asthma were registered in workers which were exposed to dust, gas and fumes containing fluorine as aluminium fluoride and cryolite for an average exposure time of three years. Analysis of the fluorine content of the air in the pot rooms showed a total quantity of fluorine between 1-2 mg/m³ air. This concentration may be causative for bronchial asthma. At higher concentrations increased cases of asthma and serious dermatitis were reported. The coincidence between high fluorine concentration in the pot room atmosphere and asthma and dermatitis indicates a fluorine compound as allergen developed by high temperature (Midttun, 1960).

Industrial hygiene examinations including clinical and radiological studies were performed among approximately 1000 workers employed in a bauxite mine, in aluminium factories and foundries in Hungary. Workers had been exposed to high concentrations of dust and gas containing fluoride. However, no results from dust measurements were available. Lung changes were observed in 3.5% of the workers exposed to bauxite dust, in 4.9% of the aluminium workers, and in 6.3% of the workers in the foundries exposed to aluminium or cryolite dust, respectively. Radiologically, two types of lung changes could be differentiated:

in the first form there were unilateral or bilateral fine strandlike shadows and some pale foci; in the second type the foci were closer together and confluent within the denser areas. No progression was noted during two years of observation. Severe lung changes described as being due to inhalation of metallic aluminium were not observed during the examinations (Geher, 1955).

Effects on bones

Health surveys of pot room workers of two aluminium facilities with different location and different exposure concentrations of gaseous and particulate fluorides were performed to evaluate the effects of inhalation and ingestion of fluorides. The purpose of these studies was twofold. One was to ascertain the incidence of fluorosis, its effect on health of workers exposed to relatively high concentrations of fluorides over a period of years in a plant operating years ago with no environmental controls other than good general ventilation. The other was to detect any possible fluorosis and any deviation in health of workers exposed to modest concentration of fluorides over a period of years in an aluminium plant with facilities for collecting and treating the effluence. The Niagara Falls Works was one of the early aluminium reduction plants. A survey of pot room workers was done in 1945-1946 prior to termination of the unit. All 107 male pot room workers with an average age of 51.9 years (range 27 to 65 years) were exposed to high fluoride concentrations (2.4 to 6.0 mg/m^3 for average 8h/d, with 36-50% contents of gaseous fluoride) for 2 to 40 years with an average of 19.1 years. As controls, 108 employees at the same plant, not exposed to fluorides with an average age of 50.7 years with a range of from 22 to 70 years were examined. Medical examination of the pot room workers revealed no great difference compared to non exposed employees except for slight to moderate limitation of motion of the dorsolumbar spine in 22 of 107 workers. The x-ray examinations revealed an increased occurrence of skeletal fluorosis seen as demonstrable change in the density of bones in the pot room workers. 76 workers of this group showed demonstrable increased density of one or more bony structures. The degree of increase in bone density was slight in 58.3%, moderate in 5.1%, and marked in 33.0% of the workers. The workers with marked fluorosis of the spine showed rather restricted movements of the spine. Some of them, in addition, revealed calcification of spinous and pelvic ligaments and exostosis. The average urine concentration was 8.7-9.8 ppm fluoride which is tenfold increased as compared to non-exposed controls (0.7 ppm). There was no evidence of prneumoconiosis among the pot room workers. In the Massena Operations survey, 231 pot room employees were initially examined. Five and seven years after the initial examination, 66 of these workers were re-examined. The average age of those examined was 46 years with a range of 21 to 64 years. The fluoride exposure in this plant (as long as 40 years) was quite modest compared to the first plant. Because of the local nature of the contamination, the mobility of the workers, the exposure was monitored regularly by urinary fluoride analysis. The urinary fluoride concentrations were 2.7-4.0 ppm at the first survey in 1960, and 2.1-4.6 ppm in 1970. After 72 hr absence from work, concentrations in 1970 averaged 1.5 ppm. To serve as controls, 152 men employed in the same plant not exposed to fluorides with an average age of 48.8 years with a range of 31 to 64 years were examined. The average urinary fluoride concentrations after 5 working days were 0.8 ppm in the control-group. The incidence of upper respiratory infections as determined by history in the pot room workers (24.2%) was higher than in the control group (19.1%), but the difference was statistically not significant. Furthermore, the roentgenograms taken during the survey showed no evidence of prneumoconiosis among the pot room workers. The exposure to fluorides had no apparent effect on the gastrointestinal, genitourinary, haematological and nervous systems.

No skeletal fluorosis was seen in the 231 men exposed to fluorides in the pot room. The health status of the pot room workers was equivalent to that of controls in other respects. In summary, the results of the health study of the Niagara Falls Works demonstrated that a large percentage (96% of 79 employees x-rayed) chronically exposed to high amounts of fluoride developed a varying degree of skeletal fluorosis but without physical impairment or overt clinical signs of disease that can be ascribed to fluorides. The survey at Massena Operations showed that workers exposed to a modest concentration of fluorine compounds (2.1-4.6 ppm urinary fluoride concentration) over long periods (up to 40 years) developed neither osteosclerosis nor symptoms that could be attributed to fluoride absorption (Kaltreiter et al., 1972).

Forty-three male pot room workers employed in aluminium plants, with a mean age of 62 years exposed to 0.5-2.3 mg fluoride/m^3 air were examined in comparison to 18 controls of similar age, sex and physical activity but without exposure to fluorides. The assessment consisted of personal history with emphasis on occupational and osteoarticular history, laboratory studies focusing on bone metabolism including serum and urine fluoride concentration, bone radiographs, mineralometry, and bone biopsy for conventional histology, microradiography, bone fluoride content and morphometric studies. Environmental monitoring was conducted and was reported by Sutter (1973). In the group of pot room workers osteoarticular changes occurred more frequently than in controls. Workers reported on joint paints and restriction of motion. Clinical laboratory examinations revealed tendency for low blood and urine calcium values and increased excretion of fluorides in the urine (mean: 2.45 mg/24h, range 1.2 to 5.2 mg/24h; control: mean: 0.61 mg/24h, range: 0.38-1.11 mg/24h). Lowered urinary fluoride concentrations were determined among workers with chronic exposure who were subsequently employed at a workplace with a lower fluoride exposure concentration. Their plasma fluoride levels reflected their bone fluoride concentrations (based upon iliac crest biopsies) for long periods (2-3 years) after the industrial fluoride exposure had stopped. At x-ray examinations an increased frequency of ossification of ligaments, tendons and muscular attachments was observed in the pot room workers. Examinations of bone biopsy preparations showed with increasing bone fluoride content mottled appearance of periosteocytic lacunae and enlargement of periosteocytic lacunar surface, excessive cortical porosity and hypermineralized periosteal bone tissue (Boillat et al., 1979).

In an aluminium smelter in Canada 2066 employees were studied. The subjects were divided into groups by fluoride exposure: 570 persons who spent at least 50% of their working time in the pot room were labelled “high-exposure” and 332 who spent less than 50% of working time in the pot room were labelled “medium exposure”. A group of 284 workers (e.g. welders) was labelled “mixed-exposure”. There was also an unexposed internal control group consisting of 880 office workers and an external control group of 372 railroad workers. Observations included data from haematology (haemoglobin, haematocrit, white cell count) and clinical biochemistry (total bilirubin, alkaline phosphatase, sASAT, total protein, BUN, creatinine, Ca^{2+} and phosphate). Airborne fluorides were measured with personal monitors. For each group exposure to particulate and gaseous fluoride and urinary fluoride excretion were determined. The levels of exposure (average total airborne fluoride/ gaseous fluoride/ particulate fluoride in mg/m^3) in each group were: control: 0.053/0.015/0.038; potroom (high): 0.48/0.20/0.28; potroom (medium): 0.12/0.057/0.062; miscellaneous: 0.46/0.054/0.41. Fluoride concentrations measured in urine of the control group (total airborne fluorides 0.053 mg/m^3) were 1.2 mg/l before a shift work and 1.3 mg/l after a shift work (mean values); 1.9 mg/l (before) and 2.7 mg/l (after) in the high-exposure group (total airborne fluorides 0.48 mg/m^3); 1.4 mg/l (before) and 1.8 mg/l (after) in the medium-exposure group (total airborne fluorides 0.12 mg/m^3); and 1.5 mg/l (before) and 1.8 mg/l (after) in the mixed exposure group (total airborne fluorides 0.46 mg/m^3). Levels of fluoride in urine were correlated to exposures. Hips were x-rayed in a subgroup of 136 workers in the high-exposure group, 41 in the medium-exposure group who had been employed in the pot room for more than 10 years, and 33 unexposed workers (internal controls). The x-ray photographs showed slight indications of increased skeletal density in a few of those who had been exposed for more than 10 years. However, there was some disagreement among the radiologists as to how the x-ray photographs should be interpreted. The authors concluded that there were no definite cases of skeletal fluorosis among the pot room workers who were exposed to about 0.48 mg fluoride/m^3 (0.2 mg/m^3 for gaseous F^- and 0.28 mg/m^3 for fluoride dust) for at least 50% of their time at work (about 10 years) at an aluminium smelter. There were no differences between the groups with regard to occurrence of back and joint problems. Blood tests showed no indications of renal, hepatic or haematopoietic effects. Therefore, it is concluded that no overt signs of skeletal fluoris or renal, hepatic or haematopoietic effects were observed in workers exposed to 0.48 mg (total) fluoride/m3 for up to ten years (Chan-Yeung et al., 1983).

Clinical and radiological investigations performed on 2258 aluminium refinery workers in Poland exposed to fluoride for an average of 17.6 years showed several symptoms and clinical findings which were characteristic of fluoride toxicity in bones and joints. Workers were exposed to workplace concentrations exceeding the exposure limit (monitoring showed fluoride concentration in the air up to 4 times higher than the Polish threshold limit of 0.5 mg HF/m^3) in various parts of the plant. Changes in bone and joints were examined in three groups: (1) exposed for up to 5 years (135 cases), (2) exposed from 6 - 32 years (1463 cases), and (3) retired workers (660 cases). A 20.2% incidence of fluorosis was found. But only 5.12% with stage OI (initial fluourosis); and stages I to III according Roholms' classification as definite fluorosis with 1.05 % with stage I (slight), 0.05% with stage II (moderate) and none with stage III (extensive). The prevalence of skeletal changes was positively correlated to the 'index of exposure-years'. More pronounced changes were documented in older workers (Czerwinski et al., 1988).

Effects of fluorine (fluorides) on the locomotor system in workers employed in an aluminium reduction plant were analysed in a further study. Two groups of 328 workers (each group spent 5 to 12 years in the pot room and casting unit, respectively) were followed up during a twelve-year period. Up to the fifth year of follow-up there was no difference in the frequency of bone and joint complaints between the workers in the pot room and those in the casting unit. Workers of both groups showed chronic locomotor impairments seen as lumbo-sacral syndrome, inflammation of the extensor carpi tendons and rotatory shoulder tendons. Osteosclerosis and abundant trabeculation occurred in four pot room workers, remaining at a yearly rate of four cases in the following years. In the tenth year of follow up all the signs of osteofluorosis were present in 28 pot room workers (Sikic, 1985).

Occupational exposure to other fluorides

Marked bone changes were reported from a man employed for eighteen years in a fertilizer factory where he had handled finely ground rock phosphate. This rock contained, on average, 4% of fluorine. At x-ray examination an increase in bone density without alteration of normal bone structure was noted (Bishop, 1936).

Clinical and laboratory studies were conducted to assess the health of a group of 74 workers in a phosphate fertilizer manufacturing plant exposed to average concentrations of 2.81 mg/m^3

(range between 0.5 and 8.32 mg/m^3) fluorides in the form of dusts and gases as compared with a group of 67 workers equivalent in age, race, and living standards without industrial exposure to fluorides. The years of employment with fluoride exposure ranged from 4.5 to 29.9 years with an average of 14.1 years. 17 of 74 (23%) fluoride-exposed workers (average fluoride concentration: 3.38 mg fluoride/m^3) showed an increased bone density. The average urinary fluoride excretion in these workers was 5.18 mg/l (with a range of 2.2 - 8.9 mg/l). No gastrointestinal, respiratory, or other possible toxic effects were reported except for an increased incidence of albuminuria (degree not given) without obvious kidney lesions. Dental examinations showed no evidence of fluorosis. At an average air concentration of 2.65 mg/m^3 fluoride and an average urinary fluoride excretion of 4.53 mg fluoride/l no changes in bone density were noted (Derryberry et al., 1963).

Fluorides - adverse effects on human health

A number of epidemiological investigations on the relationship between the consumption of fluoridated drinking-water and other fluor-containing substances on human health have been reviewed by the WHO (2002). Effects on the teeth and skeleton may be observed at exposures below those associated with the development of other organ or tissue specific adverse health effects. Effects on the bone (e.g., skeletal fluorosis and fracture) are considered the most relevant outcomes when assessing the adverse effects of long-term exposure of humans to fluoride. The occurrence of endemic skeletal fluorosis has been well documented in case reports and surveys of individuals residing in certain areas of the world (e.g., India, China, northern, eastern, central and southern Africa), where the intake of fluoride may be exceptionally high. This is a result of significant consumption of drinking-water containing substantial amounts of naturally occurring fluoride, the indoor burning of fluoride-rich coal for heating and cooking, the preparation of foodstuffs in water containing increased fluoride and/or the consumption of specific foodstuffs naturally rich in fluoride. Large numbers of individuals residing in India and China are afflicted with skeletal fluorosis, which in some cases may be severely crippling. Two studies permit an evaluation of fracture risk across a range of fluoride intakes. In one study, the relative risks of all fractures and of hip fracture were elevated in groups drinking water with $\geq$1.45 mg fluoride/litre (total intake $\geq$6.5 mg/day); this difference reached statistical significance for the group drinking water containing $\geq$4.32 mg fluoride/litre (total intake 14 mg/day). In the other study, an increased incidence of fractures was observed in one age group of women exposed to fluoride in drinking-water in a non-dose-dependent manner. Based on studies from China and India it was concluded, that skeletal fluorosis and an increased risk of bone fractures occur at total intakes of 14 mg fluoride/day and evidence suggestive of an increased risk of bone effects at total intakes above about 6 mg fluoride/day.

Fluoride has both beneficial and detrimental effects on tooth enamel. The prevalence of dental caries is inversely related to the concentration of fluoride in drinking-water. The prevalence of dental fluorosis is highly associated with the concentration of fluoride, with a positive dose-response relationship. Dental fluorosis (hypoplasia/hypomineralisation of dental enamel and dentine) represents a further sensitive effect related to fluoride treatment. Dental fluorosis is a condition that results from the intake of excess levels of fluoride during the period of tooth development, usually from birth to approximately 6–8 years of age. Fluoride causes dental fluorosis by damaging the enamel-forming cells (ameloblasts). The damage to these cells results in mineralization disorder of the teeth, whereby the porosity of the sub-surface enamel is increased. In areas of the world in which endemic fluorosis of the skeleton and/or teeth has been well documented, levels of fluoride in drinking-water supplies range from 3 to more than 20 mg/litre. In areas in which drinking-water is fluoridated (i.e., fluoride is intentionally added for the prevention of dental caries), the concentration of fluoride in drinking-water generally ranges from 0.7 to 1.2 mg/litre.

4.1.2.6.3 Summary of repeated dose toxicity

4.1.2.6.3.1 Summary of animal toxicity data after repeated exposure to cryolite

The data on repeated dose toxicity in experimental animals with cryolite included studies from three routes of administration, i.e. inhalative, dermal and oral administration. The studies with inhalative and oral route of exposure were accepted for the requirements of the Regulation 793/93/EEC according to the Annex VIIA, 92/32/EEC and the methods of the Annex V, 67/548/EEC, respectively. There were no studies in conformance with requirements of the standard repeated dose toxicity testing protocols with dermal exposure to cryolite.

The toxic profile of predominantly respirable cryolite dust is dominated by its systemic toxicity characterized by distinct toxic effects on the skeletal system (bone fluorosis) and by local toxic effects on the lungs. The severity and incidence of the observed effects appeared to be dose-related and time-related. These effects are considered to be severe health effects. Fluoride has been identified as the main component of toxicological concern in cryolite and synthetic cryolite. Furthermore, cryolite has frequently been noted to cause dose-dependent dental fluorosis upon repeated administration in studies in rodents, the teeth of which grow continually in contrast to human teeth. In general, the health effects of fluoride include dental and skeletal fluorosis in experimental animals after inhalative and oral exposure.

In rats, repeated exposure (snout-only exposure) to ≥1.04 mg/m^3 (0.00104 mg/l) cryolite for 90 days caused lung lesions in males and females. A NOAEC of 4.6 mg/m^3 cryolite for systemic effects and of 0.21 mg/m^3 for local toxic effects on the respiratory tract was identified in a well-conducted standard 90-day repeated dose inhalation study (BG Chemie, unpublished report, 1997). Long-term inhalation exposure (up to 5 months) of rats to synthetic cryolite at concentrations of ≥1 mg/m^3 displayed severe enamel hyperplasia and increased brittleness, and a loss of normal tooth coloration. In bone tissue an increased lysis of osteocytes, a formation of an abnormally structured osseous tissue and a reduced and irregular calcification of the osteoid tissues, with a tendency towards a granular precipitation of the calcium salts were observed. Alveolitis, focal bleeding, and lymphoid hyperplasia in the tracheobronchial lymph nodes were seen in the lungs. In addition, cryolite dust induced distinct toxic effects on the liver, stomach, kidney and brain. Furthermore, a number of enzymes were inhibited by cryolite; and moreover effects of the ascorbate metabolism and reversible inhibition of phagocytic activity of leukocytes were reported. Repeated inhalation of 0.5 mg/m^3 cryolite for 5 months induced no systemic toxic effects in bones, teeth and lungs, and no local effects on the respiratory tract, respectively. Therefore, the NOAEC for systemic effects was set at 0.5 mg/m^3 (Plotko et al., 1973). In addition, there was reversibility of the decreased phagocytic activity of leukocytes (Egorova and Sadilova, 1971).

There are a number of feeding studies in rats and dogs with cryolite (CAS-No. 15096-52-3). Repeated oral administration of cryolite to rats in their feed resulted in stomach lesion while in dogs subchronic and chronic dietary administration of cryolite led to haematological alterations, even anaemia, and kidney effects, but only at high dose levels or after long-term treatment.

As observed in inhalation studies, fluoride accumulation in bone (and teeth) did also occur after repeated oral administration to rats and dogs at all dose levels. The NOAEL for this effect could not be determined in any of these studies. After an exposure period of 90 days fluoride accumulation was determined in male and female Crl:CD(SD)BR rats from the lowest dose tested (50 ppm, corresponding to about 3.8 mg/kg bw/d in males and 4.5 mg/kg bw/d in females) onwards (Weltman, 1985 cited by Federal Register, 1996; EPA 1996, MRID 00158000); and in dogs from 500 ppm (corresponding to about 17 mg/kg bw/d) upwards, respectively (Hagen and Strouse, 1986 cited by Federal Register, 1996; EPA 1996, MRID 00157999). Data on clinical and histopathologic examinations of teeth were not routinely reported in repeated dose studies. Where evaluated, indicators of dental fluorosis as enamel striations, changes in coloration and physical properties of the teeth have been noted in albino rats giving cryolite in diet and drinking water at 0.58 mg/kg for 14 weeks [(University of Illinois, 3/29/39) cited from CalEPA (1995)] or higher in Sprague-Dawley (CD) rats after treatment for a period of four weeks at ≥250 ppm, representing ≥25 mg/kg bw/d (cited by Federal Register, 1996; EPA, 1996, MRID 00128109). This is in line with very early observations on bleached incisors at 1 mg/kg bw/d published by Roholm (1937a,b). Toxic effects on the blood were observed in rats and dogs after subchronic dietary administration of a high dose of 50000 ppm cryolite (corresponding to about 4172.3 mg/kg bw/d in male rats and 4748.1 mg/kg bw/d in female rats; and 1692 mg/kg bw/d in dogs, respectively). In a one-year chronic study in dogs, effects on the blood characterized by an increased incidence of immature (nucleated) red blood cells in the peripheral blood were observed in males at 3000 ppm cryolite (corresponding to about 95 mg/kg bw/d). Serious haematotoxic effects were noted in both males and females given ≥10000 ppm cryolite (corresponding to about ≥366 mg/kg bw/d in males and ≥387 mg/kg bw/d in females). In the presence of myelofibrosis in the bone marrow in conjunction with extramedullarly hematopoiesis in the liver and spleen, decreases were noted in red cell count, haemoglobin, haematocrit, MCV, MCH, MCHC, and platelets. There was an increased incidence of specific alterations of red blood cell morphology (anisokaryocytes, microcytes, macrocytes, target cells, hypochromic cells, nucleated red cells, basophilic strippling, and Howell-Jolly bodies). Kidney lesions with regeneration of the tubular epithelium, interstitial fibrosis, tubular dilation, interstitial infiltration with lymphocytes, dilation of Bowman's space were observed in dogs after chronic administration of cryolite at levels ≥3000 ppm (corresponding to about ≥95 mg/kg bw/d in males and ≥105 mg/kg bw/d in females) in the feed (Tompkins, 1992 cited by Federal Register, 1996; EPA 1996, MRID 42575101).

Local effects on the digestive tract were reported from a subchronic study in rats. Lesions in the stomach, including epidermal hyperplasia and hyperkeratosis/acanthosis in the non-glandular portion of the stomach, and submucosal inflammation in the glandular portion, were observed in animals of both sexes given ≥5000 ppm, representing ≥399.2 mg/kg bw/d in males and ≥455.9 mg/kg bw/d in females, for a period of 90 days. The gastrointestinal lesions were probably caused by hydrofluoric acid (hydrogen fluoride), which can be released from ingested cryolite in the stomach (Weltman, 1985 cited by Federal Register, 1996; EPA 1996, MRID 00158000).

Dental fluorosis (hypoplasia/hypomineralisation of dental enamel and dentine) represents a most sensitive adverse effect related to cryolite treatment. Dental effects were observed in rodent studies following chronic whole body exposure to concentrations of ≥1 mg/m^3 cryolite. The lowest dose where indications on dental fluorosis were seen was reported in the study of

University of Illinois, which was primarily designed for toxicokinetic purposes and was not conducted according to standard study designs on repeated dose toxicity. Changes in dental enamel described as striations in tooth enamel were observed after giving cryolite in diet and drinking water to rats at 0.58 mg/kg for 14 weeks [(University of Illinois, 3/29/39) cited from CalEPA (1995) (031 071325)] and after long-term intake of ≥1 mg/kg bw/d cryolite. The affected teeth exhibited loss of normal tooth coloration (bleaching on the incisors and later yellowish-brown mottling) and enamel defects (Plotko et al., 1973; DeEds and Thomas, 1934; Marcovich et al., 1937; Roholm, 1937a,b; Smyth and Smyth, 1932).

Overall, prolonged inhalation of cryolite dusts causes adverse health effects on the respiratory tract. By inhalation and by oral uptake continous cryolite exposure induces dose- and time-related systemic toxic effects. The major target organs are the skeleton system (bones and teeth), liver, kidney, stomach and haematopoietic system.

4.1.2.6.3.2 Summary of human toxicity data

Occupational cryolite exposure was reported from the mining and processing of natural cryolite, manufacture of synthetic cryolite and aluminium production. However, workers in this industrial setting were also exposed to a number of other known harmful substances. Most occupational exposure was due to inhalation of dust. The toxic effects of cryolite are related to its content of fluoride. Thus, an evaluation of cryolite-induced toxicity in humans also has to include what is generally known about the adverse effects of fluorides, especially resulting from prolonged exposure.

An impairment of lung function was not correlated with exposure to cryolite dust and no association was found between chronic bronchitis and exposure to cryolite, respectively. An increased occurrence of respiratory problems and effects on lung function, sometimes with asthma, were reported in several workplace studies of aluminium-fluoride production and in aluminium smelters (Evang, 1938; Midttun, 1960; Geher, 1955). However, repeated x-ray examinations carried out in workers from the same cryolite factory at a later time yielded no indications of pathological lung changes, with pneumoconiosis, in particular, being excluded. Since there was simultaneous exposure to several other substances including oven gases, the role of fluoride compounds in the reported health effects cannot be determined with certainty. Although there were demonstrated correlations between fluoride in air and in urine, simultaneous exposure to other respiratory irritants may have caused or contributed to the health problems.

Skeletal fluorosis in conjunction with joint pain and limited movements of the joints is considered the most relevant adverse effect following long-term occupational exposure to cryolite dust with a fluoride content of 54%. High and prolonged uptake of fluoride led to skeletal fluorosis, which is characterized by osteosclerosis (increased mineralization of the bones). The underlying cause of the disease referred to as fluorosis is the incorporation of fluoride into the bone tissue. Fluoride displaces the hydroxyl ions of the hydroxyapatite present in bone, thus forming fluoroapatite, and additionally stimulates the formation of new bone. As a rule, the vertebral column, pelvis and ribs are affected, but in severe cases the entire skeletal system may be affected. Skeletal fluorosis is characterised by a thickening and blurring of the normal, trabecular bone structure, the more pronounced cases exhibited exostoses and osteophyte formation and a thickening of the bones of the extremities in conjunction with a narrowing of the medullary cavity and the most severe cases showing ligament calcification. The severity of the effects associated with skeletal fluorosis is related to the amount of fluoride incorporated into bone. Osteosclerosis itself is seldom a problem, but it can lead to brittle bones and a higher frequency of fractures, and a concurrent calcification of the tendons can be painful and restrict movement. The association between skeletal fluorosis and work-related intake of fluoride via inhalation of cryolite dust for several years was investigated in cryolite workers in Copenhagen. Workers developing osteofluorosis had been exposed for many years (before 1961) to dust levels of approximately 30-40 mg/m^3 with peak levels of up to 994 mg/m^3. Workers with mild osteosclerosis had been employed for an average of 9.3 years; pronounced cases had been employed for an average of 21.1 years (Roholm, 1937a,b). However, not all cryolite workers developed fluorosis. A number of factors, such as age, nutritional status, renal function and calcium intake, in addition to the extent and duration of exposure, can influence the amount of fluoride deposited in bone and, consequently, the development of skeletal fluorosis (Baba et al., 1985). Cases of skeletal fluorosis have been caused by continuous daily intake of 20 - 80 mg of fluorides (Roholm, 1937a,b; Grandjean, 1982). Skeletal fluorosis seems to develop slowly and is - at least partly - reversible after fluoride exposure had stopped (Roholm, 1937a,b; Grandjean, 1982; Grandjean and Thomsen, 1983). Eight to fifteen years after exposure had ended, extensive fading of the sclerosis of trabecular bone in ribs, vertebral bodies, and pelvis was detected. However, cortical bone thickening and calcification of muscle insertions and ligaments remained virtually unchanged (Grandjean and Thomsen, 1983). The majority of pot room workers in the aluminium industry exposed to relatively high concentrations of fluoride (2.4 to 6.0 mg/m^3 for average 8h/d, with 36-50% content gaseous fluoride) developed some degree of skeletal fluorosis after ten years of exposure. Those with more than 15 years of such exposure may develop moderate to severe osteosclerosis with limitation of mobility of the dorsolumbar spine. No cases of skeletal fluorosis were seen in aluminium smelter workers with 10 to 43 years of fluoride exposure and urine fluoride concentrations of 2.1 - 4.6 ppm (Kaltreiter et al., 1972). In another aluminium plant, pot room workers with a mean age of 62 years exposed to 0.5-2.3 mg fluoride/m^3 in air showed fluorosis when compared to controls of similar age, sex and physiological activity but no exposure to fluoride (Boillat et al., 1979). Somewhat elevated skeletal density was found in 17 of 74 persons with an average exposure to 3.38 mg fluoride/m^3 and an average employment time of 14.1 years in the phosphate industry. At average air concentration of 2.65 mg/m^3 fluoride and an average urinary fluoride excretion of 4.53 mg/l no changes in bone density were noted (Derryberry et al., 1963). No definite cases of skeletal fluorosis were reported among the 570 pot room workers at an aluminium smelter in Canada who were exposed to about 0.48 mg fluoride/m^3 for at least 50% of their time at work for more than 10 years. In addition, no observed differences among the groups with regard to occurrence of back and joint problems were noted (Chan-Yueng et al., 1983). In a more recent study in which skeletal changes in 2258 workers employed at an aluminium plant in Poland were assessed (clinically and radiologically), the occurrence of fluorosis (multiple joint pain, initial ossification, osteosclerosis) was reported to increase with increasing duration of employment (Czerwinski et al., 1988). The occurrence of these skeletal changes was related not to quantitative data on the concentration of airborne fluoride per se, but to a qualitative "exposure index," calculated on the basis of the years of employment and the extent to which the concentration of fluoride in the air in different areas of the plant exceeded the highest permitted Polish limit level of 0.5 mg hydrogen fluoride/m^3. The prevalence of skeletal fluorosis increased according to this "index of exposure-years," and more severe effects were observed in older workers.

Dental fluorosis with an increased frequency was observed in children of Danish cryolite workers due to indirect exposure to fluoride (Roholm, 1937a,b; Grandjean, 1983).

No data regarding repeated dermal exposure to cryolite in humans were located in the literature.

In conclusion, the most serious health effect is the skeletal accumulation of fluoride from long-term excessive occupational exposure to fluoride and its effect on non-neoplastic bone disease — specifically, skeletal fluorosis and bone fractures.

4.1.2.6.3.3 No-observed-adverse-effect-level/concentration (NOAEL/NOAEC)

Animal data

Inhalation

With the purpose to derive a suitable NOAEC for systemic effects as basis for the risk assessment calculation, a NOAEC was derived in rats both from a 90-day study (BG Chemie, unpublished report, 1997) and from a 5-month inhalation study (Plotko et al., 1973). Both studies addressed the same adverse effect from which different NOAECs could be derived. Dental and bone effects were only examined in the 5-month study of Plotko et al. (1973). Local effects on the respiratory tract were characterised as alveolitis, thickening/fibrosis of alveolar walls, focal bleeding, and hyperplasia/accumulation of laden macrophages in the tracheobronchial lymph nodes (Plotko et al., 1973). Effects observed in the respiratory tract were similar to those reported by BG Cemie, unpublished report (1994a). The lowest $\text{NOAEC}_{\text{local}}$ of 0.21 mg/m^3 (6h/d, 5d/week) for local toxic effects on the respiratory tract in male and female Sprague Dawley (CD) rats was derived from a 90-day study (BG Chemie, unpublished report, 1997). It was stated that this 90-day rat study gives also most reliable data on the effect level for systemic toxicity. The method used showed the highest equivalency to the OECD TG 413. In the 90-day study a NOAEC for systemic effects was set at 4.6 mg/m^3 cryolite. In the 5-month rat study a NOAEC for toxic effects on bones, teeth and for local effects on the respiratory tract was established at 0.5 mg/m^3 (6h/d, 6d/week). At ≥ 1 mg/m^3 there were dystrophic lesions on the bones and teeth, and also adverse effects on the respiratory tract, stomach, kidney, liver, and brain. Typical lesions in bone tissue were osteolysis and osteodystrophia with formation of abnormal osseous tissue and decalcification. Examination of the teeth showed severe enamel hyperplasia and increased brttleness, and a loss of normal tooth colouration. Although the test procedure described differs in some respect from the test guideline (no data on sex and rat strain, histopathology only in 6 animals), this study was accepted, because it was comparable to a guideline study, was well-documented and meets basic scientific principles. Main findings of this study showed good consistency with other experimental data, published summaries and abstracts and also with data in humans. Therefore results of this study appeared useful for hazard identification and risk assessment. Therefore, this study was also considered relevant to establish the NOAEC or LOAEC. In conclusion, the lowest systemic NOAEC derived from the 5-month rat study of 0.5 mg/m^3 (6h/d, 6d/week) and the lowest local NOAEC derived from the 90-day inhalation study with Sprague Dawley (CD) rats of 0.21 mg/m^3 (6h/d, 5d/week) should be used for risk characterization.

5-months inhalation study/rat

$\text{NOAEC}_{\text{sys}}$: 0.5 mg/m^3, 6 h/d, 5 d/week (Plotko et al., 1973)

$\text{NOAEC}_{\text{local}}$: 0.21 mg/m^3, 6 h/d, 5 d/week (BG Chemie, unpublished report, 1997)

Oral administration

Data on oral animal toxicity studies in conformance with requirements of the standard repeated dose toxicity testing protocols were presented only in summary form for cryolite, CAS No. 15096-52-3 (EPA 1996). Up to now complete study reports are not available; therefore no final evaluation can be made. Fluoride accumulation was the critical adverse effect in several feeding studies in rats and dogs. Fluoride was accumulated at all dose levels of cryolite tested in rats and dogs for different duration of exposure. It was not possible to identify the NOAEL for this effect in any of the repeated oral dose studies. After a repeated administration of cryolite for 90 days fluoride accumulation was observed in rats from the lowest dose tested of 50 ppm (3.8 mg/kg bw/d in males, 4.5 mg/kg bw/d in females) upward, and in dogs from 500 ppm (17 mg/kg bw/d) upward, respectively (EPA 1996). The lowest dose tested (50 ppm, 3.8/4.5 mg/kg bw/d) in male/female Crl:CD(SD)BR rats feeded for 90 days represents the LOAEL for fluoride accumulation (EPA 1996). In repeated dose toxicity studies data on clinical and histopathologic examinations of teeth were not routinely reported. Indicators of dental fluorosis as enamel striations, changes in colouration and physical properties of the teeth have been noted in albino rats receiving cryolite at 0.58 mg/kg bw/d for 14 weeks [(University of Illinois, 3/29/39) cited from CalEPA (1995)] and in a 28-day feeding study in Sprague-Dawley rats. Mottling of tooth enamel was seen in rats given the lowest dose of 250 ppm (25 mg/kg bw/d in males and females) (cited by Federal Register, 1996; EPA, 1996, MRID 00128109). This was in accordance with observations from earlier chronic toxicity studies which, however, were not performed according to the current standard methods on repeated dose toxicity tests. Changes in the teeth were noted at a low dose level of ≥1 mg/kg bw/d. Prolonged dosing with 5 mg/kg bw/d resulted in development of abnormally structured osseous tissue and renal effects. First symptoms of disturbance of general condition such as slight inhibition of growth and behaviour were observed at about 15 mg/kg bw/d (Roholm 1937a,b). It might be argued that dental fluorosis in rats has no significance for adult humans. Dental effects were observable in adult rats due to the life-long growth of their teeth. In humans, fluoride intoxication causing dental lesions is only relevant during the period of tooth development in pregnancy and childhood. But, as teeth are part of the skeletal system, dental lesions are considered as a marker for bone fluorosis. In most studies cryolite related bone lesions are not identified due to inadequate or missing examinations. Where teeth and bones were investigated simultaneously in the same study on cryolite, toxic effects were seen at booth sites (e.g. Plotko et al., 1973). The lowest dose where indications on dental fluorosis were observed was reported in the study of University of Illinois, which was primarily designed for toxicokinetic purposes and was not conducted according to standard study designs on repeated dose toxicity. Although a full study report is not available, the rapporteur believes that data evaluated by CalEPA are reliable.

The following $\text{NOAEL}_{\text{sys}}$/$\text{LOAEL}_{\text{sys}}$ for cryolite were reported for effects other than fluoride accumulation: in dogs, there were decreases in food consumption, body weight, body weight gain and red blood cells, haemoglobin, haematocrit, MCV and MCH at 50000 ppm (corresponding to about 1692 mg/kg bw/d). Results of a chronic study (12-month study) with dogs have shown that cryolite induced toxic effects on the kidneys at ≥3000 ppm (corresponding to about ≥95 mg/kg bw/d in males and ≥105 mg/kg bw/d in females) and on the blood at dose levels of ≥10000 ppm (corresponding to about ≥366 mg/kg bw/d in males and ≥387 mg/kg bw/d in females) (EPA 1996).

Dental fluorosis (hypoplasia/hypomineralisation of dental enamel and dentine) represents a most sensitive adverse effect related to cryolite treatment. Changes in dental enamel described as striations in tooth enamel were observed after giving cryolite in diet and drinking water to rats at 0.58 mg/kg bw/d for 14 weeks [(University of Illinois, 3/29/39) cited from CalEPA (1995) (031 071325)]. Therefore, the lowest oral LOAEL of 0.58 mg/kg bw/d for changes in dental enamel derived from a 14-day study in rats was selected for the risk characterisation.

14-week feeding (diet and drinking water) study/ albino rat

LOAEL$_{sys}$ 13 ppm (0.58 mg/kg bw/d)

For local effects of cryolite on the digestive tract a NOAEL$_{local}$ of 50 ppm (corresponding to about 3.8 mg/kg bw/d in males, and 4.5 mg/kg bw/d in females) could be derived from the 90-day feeding study in rats. Lesions in the stomach, including epidermal hyperplasia and hyperkeratosis/acanthosis in the nonglandular portion of the stomach, and submucosal inflammation in the glandular portion, were observed in Crl:CD(SD)BR rats at ≥5000 ppm (corresponding to about ≥399.2 mg/kg bw/d in males and ≥455.9 mg/kg bw/d in females) after a 90 day administration in the diet (EPA 1996). The gastrointestinal lesions were probably caused by hydrofluoric acid (hydrogen fluoride), which can be released from ingested cryolite in the stomach (Weltman, 1985 cited by Federal Register, 1996; EPA 1996, MRID 00158000). The lowest observed adverse effect level for local effects of 50 ppm (3.8 mg/kg bw/d in males, 4.5 mg/kg bw/d in females) derived from the 90-day feeding study in rats was selected for the risk characterisation.

90-day feeding study/Crl:CD(SD)BR rat

NOAEL$_{local}$ 50 ppm (3.8 mg/kg bw/d in males, 4.5 mg/kg bw/d in females)

Human data

Local toxic effects on the respiratory tract after repeated exposure to cryolite dust were not reported in the literature. From several epidemiological studies no association between impairment of lung function and exposure to cryolite was observed, and in addition, no association was found between chronic bronchitis and exposure to cryolite dust (Roholm, 1937a,b; Evang, 1938; Grandjean et al., 1984; Fries et al., 1989).

Prolonged (i.e. several years) occupational inhalative exposure to cryolite dust may cause skeletal fluorosis. In Danish cryolite workers cases of skeletal fluorosis were caused by continuous daily exposure to 20 - 80 mg of fluorides, or more, for at least 4 years, and in cases of crippling fluorosis for 10 to 20 years (Roholm, 1937a,b). Subsequent examinations in Danish cryolite workers showed skeletal fluorosis after exposure to an average fluoride concentration of 28 mg/m^3 (measured in 1955) and later of 2.5 mg/m^3 (measured in 1961) (Grandjean and Thomsen, 1983). A further study showed development of skeletal fluorosis at intakes of approximately 310-1250 µg fluoride/kg bw/d in adults weighing 64 kg (Grandjean, 1982). Radiological changes such as increased bone density, thickening of cortex, irregular bone margin, calcification of interosseous membranes etc. suggestive of fluorosis were noted in 21.8% of the workers employed in a fluorspar processing facility in India. The overall mean urinary fluoride level was 1.96 ppm. In 11.9% of the examined workers, the urinary fluoride level was higher than 4.5 ppm, and in 46% higher than 1.5 ppm, respectively (Desai et al., 1983). No abnormal findings on a series of medical examinations including chest radiography were noted in workers of a cryolite-producing plant in Japan exposed to average exposure levels of 0.09 - .49 ppm (0.9-4.9 mg/m^3) hydrogen fluoride, and of 0.05-0.6 mg/m^3 mineral dust levels during the observation period (Baba et al., 1985). All 107 male pot room workers with an average age of 51.9 years (range: 27 to 65 years) exposed to high fluoride concentrations (2.4 to 6.0 mg/m^3 for average 8h/d, with 36 - 50% content gaseous fluoride) for 2 to 40 years with an average of 19.1 years revealed an increased occurrence of skeletal fluorosis seen as demonstrable change in the density of bones. 76 of this group showed demonstrable increased density of one or more bony structures. Workers exposed to a modest concentration of fluorine compounds, measured as urinary fluoride excretion, of 2.7 - 4.0 ppm (1960), and of 2.1-4.6 ppm (1970) over long periods (up to 40 years) developed neither osteosclerosis nor symptoms that can be attributed to fluoride absorption (Kaltreiter et al., 1972). Aluminium refinery workers in Poland exposed to fluoride concentration in the air at the work place up to 4 times higher than the Polish threshold limit of 0.5 mg hydrogen fluoride/m^3 for an average of 17.6 years showed several symptoms and clinical findings which were characteristic of fluoride toxicity in bones and joints. More pronounced changes were documented in older workers (Czerwinski et al., 1988). In a study in phosphate fertilizer manufacturing plant an increased bone density was seen in 17 of 74 workers exposed to an average concentration of 3.38 mg fluoride/m^3 in the form of dusts and gases over a period ranging from 4.5 to 29.9 years with an average of 14.1 years. At an average air concentration of 2.65 mg fluoride/m^3 and an average urinary fluoride excretion of 4.53 mg fluoride/l no changes in bone density were noted (Derryberry et al., 1963). No definite cases of skeletal fluorosis occurred among the 570 pot room workers at an aluminium smelter in Canada who were exposed to about 0.48 mg fluoride/m^3 for at least 50% of their time at work for more than 10 years. There were no observed differences among the groups with regard to occurrence of back and joint problems (Chan-Yeung et al., 1983).

Taken from the above mentioned studies, no cases of osteosclerosis have been found in studies at workplaces with fluoride concentrations below 2.65 mg/m^3 and urine fluoride below 4.5 mg/l (Derryberry et al., 1963). No definite signs of skeletal fluorosis were reported from pot room workers employed in an aluminium smelter exposed to 0.48 mg fluoride/m^3 and therefore this is considered the NOAEC$_{sys}$ for skeletal fluorosis in humans (Chan-Yeung et al., 1983). Although significant effects have not been demonstrated in humans, WHO has concluded that there is some increase in risk of skeletal fluorosis with an intake (mostly in food and drink) of over 6 mg fluoride/day. Significant effects are seen at a total intake of 14 mg fluoride/day (WHO 2002). Using a dose of 6 mg fluoride/day as basis, and assuming 100% uptake and inhalation of 10 m^3 air per workday and 5 workdays/week, an air level of 0.8 mg fluoride/m^3 would yield this daily dose. If this calculation is made for the dose of 14 mg fluoride/day, the resulting air content would be 2.0 mg fluoride/m^3.

Overall, the critical effect of long-term exposure to inorganic fluorides is the effect on the bones. Calculations from the WHO, which are based on intake in food and drink, indicate that skeletal effects appear at an air condition of 0.8 to 2.0 mg fluoride/m^3 for an 8-hour workday. In an epidemiological study, no definite indications of skeletal effects were seen in aluminium smelter workers with long-term occupational exposure to 0.48 mg fluoride/m^3 (Chan-Yeung et al., 1983).

NOAEC$_{sys}$ 0.48 mg fluoride/m^3 for skeletal fluorosis in humans (Chan-Yeung et al., 1983)

Classification

Currently, cryolite is classified as toxic and labelled with T, Toxic, R48/23/25 (Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed). On the basis of the data submitted, the current classification of cryolite is confirmed. The corroboration for classification is based on the hazard identification determined on tests with experimental animals. The toxic profile of cryolite is dominated by its systemic as well as local toxicity. The critical effects, which are considered to be serious health effects, after prolonged inhalation or oral route of exposure, are distinct toxic effects on the bones and teeth. Local effects after subchronic exposure to predominantly respirable cryolite dust led to lung lesions while repeated oral administration of cryolite to rats in their feed resulted in stomach lesions.

Lung toxicity occurred at the low concentration of 1.04 mg/m^3 cryolite or more (6 hours/d, 5 d/week) in a 90-day inhalation study in rats (BG Chemie, unpublished report, 1997). At the same concentration range of $\geq$1 mg/m^3 cryolite (6 hours/d, 6d/week) toxic effects on the bones and teeth were observed in rats after whole body exposure for a period of 5 months (Plotko et al., 1973). These identified concentrations are far below the cut-off value for attributing R48/20 (0.25 mg/l) in a 90-day inhalation study in rats. The observed critical effect concentrations presented in experimental animals are comparable in magnitude to the effect dose concentrations described in man occupationally exposed to cryolite dust. In male pot room workers employed in aluminium plants skeletal fluorosis was observed at average fluoride concentrations of 2.4 to 6.0 mg/m^3 (for average 8h/d, with 36 - 50% content gaseous fluoride) (Kaltreiter et al., 1972). Increased bone density was noted in workers of a phosphate fertilizer manufacturing plant exposed at concentrations of about 3.38 mg fluoride/m^3 in the form of dusts and gases over a period ranging from 4.5 to 29.9 years with an average of 14.1 years (Derryberry et al., 1963).

Critical effect following repeated dietary exposure to cryolite in experimental animals was fluoride accumulation and its effect on non-neoplastic bone disease - skeletal fluorosis - observed in rats (males/females) from the lowest dose tested of 3.8/4.5 mg/kg bw/d upward and in dogs from 17 mg/kg bw/d, respectively (90-day studies, EPA 1996). Dental fluorosis (hypoplasia/hypomineralisation of dental enamel and dentine) represents a most sensitive adverse effect related to cryolite treatment. Changes in dental enamel described as striations in tooth enamel were observed after giving cryolite in diet and drinking water to rats at 0.58 mg/kg bw/d for 14 weeks [(University of Illinois, 3/29/39) cited from CalEPA (1995) (031 071325)]. Toxic effects on the bones and teeth in rats were also reported in early repeated dose toxicity studies. Findings on the teeth were noted at 1 mg/kg bw/d, and development of abnormally structured osseous tissue and renal effects at 5 mg/kg bw/d (Roholm, 1937a,b). These identified dose levels are far below the cut-off value for attributing R48/22 (50 mg/kg bw/d) in a 90-day study in rats. Comparable effect dose levels were also described in man. In occupationally exposed workers 20-80 mg of fluoride per day caused skeletal effects (Roholm, 1937 a,b). Long-term intake of fluoride in water and foodstuffs is the primary causative factor for endemic skeletal fluorosis in humans. Very high intakes have been observed in areas world-wide in which the environment is rich in fluoride and where groundwater high in fluoride is consumed by humans. There is clear evidence from India and China that significant skeletal effects are seen at a total intake of 14 mg fluoride/day, equivalent to about 0.2 mg/kg bw/d calculated on an assumed body weight of 70 kg person (WHO 2002).

Thus, classification and labelling with T, Toxic, R48/23/25 (Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed) is confirmed.

4.1.2.7 Mutagenicity

4.1.2.7.1 Studies in vitro

Synthetic cryolite was negative in a gene mutation assay with Salmonella typhimurium tester strains TA1535, TA1537, TA98 and TA100 with and without S-9 mix obtained from Aroclor-induced rat livers (Bayer AG, 1988). Doses ranging from 20 to 12500 µg/plate were tested without toxic effects. The test was conducted in line with the OECD guideline. The purity of the test substance was >95 % (impurities: 3.2 % Al_2O_3, 0.25 % SiO_2, 0.027 % P_2O_5).

Negative Salmonella gene mutation tests with cryolite were also described by Stankowski (1991; cited by EPA, 1996; doses ranging from 167 to 10 000 µg/plate) and by CalEPA (1995; also described by BG-Chemie, 2005; doses ranging from 50 to 5000 µg/plate). Reports and details on these studies are not available.

According to EPA (1996) cryolite was negative in two mammalian cell genotoxicity assays:

- an in vitro chromosomal aberration test in human lymphocytes with and without S-9 mix for doses of 100, 500 and 1000 µg/ml (San Sebastian, 1991a)
- an UDS test in vitro, i.e. a test for induction of DNA excision repair in primary rat hepatocytes, for doses up to 50 µg/ml (San Sebastian, 1991b).

Detailed data on these investigations are not available.

Table 4.2 In vitro genotoxicity tests with cryolite

Test system	Concentration range		Result	Toxicity	Remarks	Reference
	with S-9 mix	without S-9 mix				
Bacterial gene mutation test	20 - 12500 µg/plate	20 - 12500 µg/plate	negative	no toxicity		Bayer AG, 1988
Bacterial gene mutation test	167 - 10000 µg/plate	167 - 10000 µg/plate	negative	no data	cited in EPA (1996), no detailed data	Stankowski, 1991
Bacterial gene mutation test	50 - 5000 µg/plate	50 - 5000 µg/plate	negative	No toxicity	Also cited in BG Chemie (2005)	Unpublished report described in CalEPA (1995)
chromosomal aberration test with human lymphocytes	100 - 1000 µg/ml	100 - 1000 µg/ml	negative	no data	cited in EPA (1996), no detailed data	San Sebastian, 1991b
UDS test with primary rat hepatocytes		up to 50 µg/ml	negative	no data	cited in EPA (1996), no detailed data	San Sebastian, 1991b

4.1.2.7.2 Studies in vivo

In an in vivo bone marrow chromosomal aberration test, male and female Crl:CD BR Sprague-Dawley rats were exposed by snout-only inhalation to 2130 mg/m^3 cryolite (synthetic, purity 98.9 %) for 6 hours (Huntingdon Life Science Ltd, 1997a). Results were negative for male (Bayer AG, 1997b) and female (Bayer AG, 1998) animals. Mass median aerodynamic diameter of the particle atmosphere was 5.7 µg with 59 % of the particles being <7 µm. Bone marrow cells were sampled after recovery periods of 16, 24 and 48 hours. No clinical signs or mortalities were induced and there was no inhibition of mitotic activities of the target cells. All experimental parts were run in compliance with GLP and according to the OECD guidelines.

Furthermore, inhalation exposure to 4.6 mg/m^3 cryolite (synthetic, purity 98.9 %) for 13 weeks was negative in a bone marrow chromosomal aberration test with male Crl:CD BR Sprague-Dawley rats; there was no effect on mitotic activity (Bayer AG 1997a). This cytogenetic test was run within the 13-week study described in 4.1.2.6. (Huntingdon Life Science Ltd., 1997b).

According to Voroshilin et al. (1973) cryolite (no specification of the test substance) gave a positive response after 5 months inhalation exposure of rats to 3 mg/m^3. However, this finding is not reliable due to severe methodological insufficiencies, e.g. small number of cells analysed, lack of positive control group, unclear number of animals per group.

Table 4.3 In vivo genotoxicity tests with cryolite

Test system	Doses	Exposure regimen	Sampling times	Result	Remarks	Reference
chromosomal aberration test on rat bone marrow	2130 mg/m^3	6 h snout-only inhalation	after 16, 24, 48 h recovery	negative	no local cytotoxicity, no general toxic effects	Bayer AG, 1997b; Bayer AG, 1998; Huntingdon Life Science Ltd, 1997a
chromosomal aberration test on rat bone marrow	4.6 mg/m^3	13 weeks snout-only inhalation		negative	no local cytotoxicity	Bayer AG 1997a; Huntingdon Life Science Ltd., 1997b
chromosomal aberration test on rat bone marrow	0.5 - 1.0 - 3.0 mg/m^3	5 months inhalation		positive	not reliable due to severe methodological insufficiencies	Voroshilin et al., 1973

4.1.2.7.3 Summary of mutagenicity

Cryolite does not induce gene mutations in a bacterial in vitro system. In vitro tests on induction of chromosomal aberrations (human lymphocytes) and unscheduled DNA synthesis (rat hepatocytes) are reported to be negative, but cannot be adequately assessed because of the lack of full reports.

In vivo, cryolite was negative in rat bone marrow chromosomal aberration tests after acute and repeated inhalation exposure.

There is no evidence for mutagenicity of cryolite. Cryolite should not be classified as a mutagen.

4.1.2.8 Carcinogenicity

4.1.2.8.1 Studies in animals

In vivo studies

Carcinogenicity studies with cryolite are not available. Therefore, in order to assess all available information on the carcinogenic potential of cryolite, data on neoplastic findings from animal studies with prolonged exposure were used. Fluoride has been identified as the moiety of toxicological concern in natural and synthetic cryolite. Cryolite, consisting of a fluoride content of approximately 54%, serves as a source of fluoride and is essentially metabolized as free fluoride, especially under acidic conditions. Released in aqueous solution, the fluoride is deposited primarily in teeth and bone. To complete the database, studies with fluorides other than cryolite were included.

Inhalation

No data available.

Dermal

No data available.

Oral

There is a one-year chronic feeding toxicity study in dogs with synthetic cryolite (CAS-No. 15096-52-3). The study results were presented in summary form (cited by Federal Register, 1996, and by EPA, 1996). Up to now a complete study report is not available; therefore no final evaluation can be made. Cryolite (purity: 97.3-97.4%) was tested in Beagle dogs (4/sex/group) at dose levels of 0, 3000, 10000, and 30000 ppm, representing 0, 95, 366 and 1137 mg/kg bw/d in males and 0, 105, 387, and 1139 mg/kg bw/d in females for 12 months. Histopathology gave no indications of substance-induced neoplastic effects in this study.

Carcinogenicity studies with fluorides different from cryolite

Four carcinogenicity studies with sodium fluoride (NaF, CAS-No. 7681-49-4) are available. There are two carcinogenicity studies, one in the rat and one in the mouse, with NaF conducted by the National Toxicology Program (NTP). Special attention was given to cancer of the skeletal system, since fluoride accumulates in calcified tissue. The sodium fluoride concentrations selected for the 2-year studies in both rats and mice were 0, 25, 100 or 175 ppm. Fluoride was administered in drinking water to groups of F344/N rats and B6C3F1 mice. Groups of 100 rats and mice of each sex received 0 or 175 ppm sodium fluoride and groups of 70 rats and mice of each sex received 25 or 100 ppm sodium fluoride in deionized drinking water ad libitum for up to 103 weeks. An additional group of 50 animals of each sex and species was included to provide paired (age-matched) controls. These animals received deionized drinking water (NTP 1990).

The daily amounts of sodium fluoride ingested by rats were 0, 1.3, 5.2, and 8.6 mg/kg bw/d in males and 0, 1.3, 5.5, and 9.5 mg/kg bw/d in females. All dose groups showed dose-dependent dental fluorosis. The incidence of osteosclerosis in the long bones of female rats treated with 175 ppm was significantly increased compared to controls. Osteosarcoma of the vertebrae was only observed in one male in the 100 ppm group and in the vertebrae or the humerus of three males in the 175 ppm group. In addition, an extraskeletal osteosarcoma in the subcutis of the flank was noted in a further male treated with 175 ppm. There were no statistically significant increases in incidences of osteosarcoma relative to the controls (0/80 and 0/50). However, the incidences of osteosarcoma exhibited a statistically significant dose-response trend. Based on the occurrence of a small number of osteosarcomas in dosed animals, there was equivocal evidence of carcinogenic activity of sodium fluoride in male F344/N rats. There was no evidence of carcinogenic activity of sodium fluoride in female F344/N rats.

The daily amounts of sodium fluoride ingested by mice were 0, 2.4, 9.6, and 16.7 mg/kg bw/d in males and 0, 2.8, 11.3, and 18.8 mg/kg bw/d in females. No significant compound-related adverse effects upon survival and body weight gain compared to controls were noted. There was no evidence of carcinogenic activity of sodium fluoride in B6C3F1 mice.

In combined toxicity/carcinogenicity studies, Sprague-Dawley rats [Crl:CD(SD)BR] and Crl:CD-1 (ICR)BR mice were fed a diet containing NaF (>99% pure) for up to 99/97 weeks (Maurer et al. 1990; 1993).

Rats received NaF at a dose of 0, 4.0, 10, and 25 mg/kg bw/d (equal to 0, 1.81, 4.52 and 11.24 mg F^-/kg bw/d, respectively). Each treatment group consisted of 70 rats of each sex. Through the (low-fluoride) diet the animals received 0.16 mg F^-/kg bw/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-related increased in all groups. Dental fractures and malocclusions were enhanced at 10 and 25 mg/kg bw/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 bw/d and above. In the females this effect was less pronounced. Relative and absolute stomach weight was significantly increased at 10 mg/kg bw/d and above. Mononuclear cell infiltration of the glandular epithelium of the stomach was dose-related increased from 4 mg/kg bw/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 bw 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).

In mice NaF was given at a dose of 0, 4.0, 10, and 25 mg /kg bw/d (equal to 0, 1.79, 4.43 and 11.17 mg F^-/kg bw/d, respectively) in the diet for up to 97 weeks. Through the (low-fluoride) diet the animals received 0.45 mg F^-/kg bw/d. Each treatment group consisted of 60 mice of each sex. Observations included clinical status, body and organ weights (extensive) and histopathology (extensive). Dose related changes in teeth were found at 4 mg/kg bw/d 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, and hyperostosis) were observed at 10 mg/kg bw/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 bw/d. Soft tissue lesions, though looked for were 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).

In vitro studies

No data available.

4.1.2.8.2 Studies in humans

In vivo studies

Mortality and cancer morbidity after heavy occupational fluoride exposure were evaluated in workers of a cryolite plant in Copenhagen. A cohort of 431 male workers employed for at least six months between 1924 and 1961 was selected for examination. During this period, heavy fluoride exposure resulted in at least 74 cases of skeletal fluorosis. On the basis of the death certificates, all deaths up until 1 July 1981 were coded according to the official Danish classification system. During 1941-1981, 206 men died, while only 149.3 deaths for the general male population in Denmark were expected from national mortality statistics. The follow-up study showed an increased incidence of mortality from cancer of the respiratory system. Cancer morbidity data for the period from 1943-1977 showed 78 cases of malignant neoplasms in the cryolite workers compared to 53.2 cases expected for Denmark as a whole and 67.9 for Copenhagen. The excess was almost entirely due to an excess number of respiratory cancers. There were 29 cases with tumours: 4 of the larynx and 24 primary of the lung as compared with 11.8 cases expected for Denmark and 17.2 cases expected for Copenhagen. There were 8 cases of urinary bladder cancer as compared with 5.7 cases expected for the Copenhagen residents. Cancer morbidity showed no apparent correlation with duration of employment or time from first exposure. Although increases in lung cancer were observed in several studies, it is not possible to attribute these increases to fluoride exposure per se due to concomitant exposure to other substances, such as quartz, siderite and small amounts of metal sulfides. In summary, no indication of any carcinogenic effect related to cryolite exposure was noted from this epidemiological study of former cryolite workers (Grandjean et al., 1985).

The cancer mortality rates during 1941-1961 among Danish cryolite workers were reanalysed by Burk (1985). The numbers of deaths in cryolite workers were analysed exclusively in relation to the general Danish population. In this cohort of 425 male cryolite workers in Copenhagen a markedly increased figure for total mortality (SMD/100000 workers: 334), overall cancer mortality (SMD/100000 workers: 94.7), an excess rate of respiratory cancer mortality (SMD/100000 workers: 91.8) and violent deaths (suicides and accidents) in cryolite workers (SMD/100000 workers: 85.3) were identified, but no cardiovascular diseases, respectively. For respiratory cancer the increased risk was 2.37.

The follow-up of a cohort of 425 men and 97 women employed for at least 6 months in the period from 1924-1961 at the Copenhagen cryolite processing plant has been extended by approximately one decade for cancer mortality and incidence, respectively, compared with their previous analysis. There were elevated incidences of lung and larynx cancer (42 observed versus 29.9 expected cases) and bladder cancer (17 observed versus 9.2 expected cases). The average daily fluoride absorption in cryolite workers was estimated from two datasets. In the first dataset it was reported that the workers had been exposed to cryolite dust to average levels of 30-40 mg/m^3 (estimated to be equivalent to daily absorption of 14-70 mg fluoride by an adult weighing 70 kg) and traces of quartz (Roholm, 1937a,b). In the second dataset a daily absorption of about 35 mg of fluoride, i.e. 0.5 mg/kg bw/d was calculated. The second dataset came from analyses of bone tissue from two deceased cryolite workers employed for 9 and 24 years, in which 3.1-9.9 mg fluoride/g ash and 7.6-13.1 mg fluoride/g ash were analysed, and a fluoride content of about 90 g and 50 g for the skeletal system was calculated (Roholm, 1937a,b). Although no data are available, exposures may have been somewhat lower after 1945. A total of 300 deaths occurred, while 223 deaths were expected from national mortality rates. A total of 119 cancer cases occurred in these workers, from

Copenhagen, 103.7 cases were expected. Cancers of lungs (n = 35, standard incidence ratio, SIR = 1.35), larynx (n = 5, SIR = 2.29) and urinary bladder (n = 17, SIR = 1.84) were significantly increased. Although no stable association with the duration of the employment was apparent, a latency period of at least 10 years was apparent. Also, the cancer incidence was higher in men who had been hired at a young age. The pattern of low cardiovascular mortality and increased morbidity of cancer in the larynx, lungs and urinary bladder would suggest that this industrial cohort was exposed to an occupational carcinogen. Furthermore, the authors discussed smoking as confounding factor for the elevation of cancer of the lung and larynx in this cohort, but not for the increase in bladder cancer alone, respectively. They assumed that heavy occupational exposure to fluorides could cause an increased carcinogenic risk. However, the cohort members were mixed-exposed to other compounds at the workplace (especially quartz as the major contaminant, usually about 1-5%, siderite and small amounts of metal sulfides) (Roholm, 1937; Grandjean, 1982; Grandjean et al., 1985; Fries et al., 1989). Thus, no definite cancer risk in male cryolite workers could be derived from the fluoride exposure. The second analysis of the cause of death and cancer mortality among Danish cryolite workers also included 97 women. In the female workers, 28 cancer cases were observed, compared with an expected number of 29.2 for the female population of the Copenhagen area (SIR 0.96). Primary cancer of the lungs (two cases, SIR = 1.11) and cancer of the bladder (two cases, SIR = 2.18) did not show any significant excess above the numbers expected. However, the observed cancer incidences were too low for a differentiated analysis (Grandjean et al., 1992a,b).

A number of epidemiological studies reported an increased incidence of lung and bladder cancer and elevated mortality due to various forms of cancer, especially lung and bladder cancer but also tumours in stomach, oesophagus, pancreas, the lymphatic-haematopoietic system, prostate and brain, from occupationally fluoride-exposed workers employed in the aluminium smelting industry (WHO 2002). However, it was not possible to attribute these increases to fluoride exposure alone due to concomitant exposure to other substances, especially aromatic hydrocarbons (Gibbs and Horowitz, 1979; Milham, 1979).

Since the workers occupationally exposed to fluoride were additionally exposed to several other compounds, such as quartz, siderite and small amounts of metal sulfides reported for the workers in the cryolite processing factory in Copenhagen (Roholm, 1937; Grandjean, 1982; Grandjean et al., 1985; Fries et al., 1989); to radon for the fluorspar miners (de Villiers and Windish, 1964), and to polyaromatic hydrocarbons for the aluminium workers (Gibbs and Horowitz, 1979; Milham, 1979), respectively, an increased cancer risk may not directly be related to fluoride exposure.

In vitro studies

No data available.

4.1.2.8.3 Summary of carcinogenicity

The available data are insufficient to demonstrate a carcinogenic effect of cryolite in experimental animals. Cryolite has not been tested for carcinogenicity in experimental animals. In one-year chronic feeding toxicity study in dogs with synthetic cryolite results of histopathology gave no information of neoplastic effects (cited by Federal Register, 1996, and by EPA, 1996). Studies with sodium fluoride (NaF) may provide insight in the carcinogenicity of cryolite, especially for systemic tumours. With NaF four animal studies have been performed, two in which NaF was supplied in the drinking water to rats and mice, and two in which NaF was administered via the diet, again in rats and mice. In the two-year rat drinking water study , evidence of bone cancer was found in three male rats treated with 175 ppm (corresponding to about 8.6 mg/kg bw/d) NaF (NTP 1990). The results were judged to show equivocal evidence of cancer in male rats of one strain. There was no evidence of carcinogenic activity in female rats. The rat diet study was negative, despite clear indications of fluoride intoxication (Maurer et al., 1990). The two-year mouse drinking water study, in which male and female mice receiving NaF at concentrations of up to 18 mg/kg bw/d, was negative (NTP 1990). The mouse diet study might be confounded by the presence of a retrovirus which according to the author's opinion 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. The same data base from NaF was used in the EU risk assessment of hydrogen fluoride (HF, CAS No. 7664-39-3, 1st priority list) for evaluation of the carcinogenicity because carcinogenicity studies with HF are not available. From these studies with NaF in rats and mice it was concluded for HF that "the available data are sufficient to suggest that fluoride is not a carcinogenic substance in animals."

There are limited data from humans that may indicate a carcinogenic risk from exposure to cryolite. Excess cancer risk has been identified in workers exposed to fluorides, including fluoride-spar and aluminium production workers (Grandjean, 1982). In a Danish cohort study of 425 male cryolite workers an excess rate of respiratory cancer, violent deaths, pulmonary and other kinds of death, but not cardiovascular diseases were identified. An increased risk of 2.37 of respiratory cancer was identified (Burk, 1985). The follow-up of the Danish cohort (1924-1961) has been extended for approximately one decade. Of the 425 male workers, 119 developed cancers, 104 were expected. The incidence of respiratory and urinary cancers was particularly high in men who were younger than 35 years at first employment. Smoking was discussed as a confounding factor (Grandjean et al., 1992a,b). The excess cancer risk identified in workers exposed to fluorides, including fluoride-spar and aluminium production workers, may be due to other factors than fluoride exposure. The miners were also exposed to radon, the workers in the cryolite processing factory to quartz, siderite and small amounts of metal sulfides and the aluminium workers to polyaromatic hydrocarbons, respectively. Thus, it is difficult to relate the excess cancer incidence directly to fluorides.

In conclusion, from carcinogenicity studies with NaF in rats and mice it is concluded that cryolite is not considered to be carcinogenic in animals. No conclusion can be drawn as to the carcinogenicity of cryolite in humans, because in the studies available, humans were exposed to other substances as well.

4.1.2.9 Toxicity for reproduction

Several reproductive toxicity studies with cryolite are reported in EPA (1996), CalEPA (1995), the Federal Register (1996) as well as in BG Chemie (2005). The original study reports on the below indicated investigations, however, are not available to the rapporteur.

4.1.2.9.1 Effects on fertility

Studies in animals

Two-generation reproduction (feeding) study rat

Schroeder, R. (1994) cited from EPA (1996)

> "In a two-generation reproduction study, Sprague-Dawley rats (30 per group) were administered cryolite (96 %) in the diet at dose levels of 0, 200, 600, or 1800 ppm (representing 0, 14, 42, and 128 mg/kg/day for males and 0, 16, 49, and 149 mg/kg/day for females, respectively, during premating). Compound-related systemic toxicity was observed in a dose related manner among both sexes and generations at all dose levels as evidenced by clinical signs of dental fluorosis. Whitening of the upper and/or lower incisors was observed in most treated animals of both generations. Bevelled anterior edge of the lower incisor was observed in 67 % of animals from both generations at 1800 ppm. Mottled appearance of lower incisor was noted at dose levels ≥ 600 ppm in 6%-40% of F_1 animals; however, this sign was not dose related. The NOEL was not determined. The LOEL for systemic toxicity was 200 ppm (15 mg/kg/day) based on dental fluorosis.
>
> Reproductive toxicity was observed at 1800 ppm as evidenced by significantly decreased pup body weights during lactation days 7, 14, and 21 (82%-88% of control in F_1 offspring) and days 4, 7, 14, and 21 (74%-89%) of control in F_2 offspring). Gross findings were also observed in pups at 1800 ppm by the time of weaning. They were manifested as pale kidneys, pale livers and enlarged hearts and were considered to be compound related. No effects were observed on parental reproductive performance...(MRID 43387501)."

From the report of this study a NOAEL/fertility of ≥ 1800 ppm according to ≥ 128 mg cryolite/kg bw/day can be derived and should be taken forward for quantitative risk assessment. Besides dental fluorosis and teeth whitening, no other compound-related systemically toxic effects could be revealed from this study with daily dosages of up to and including 128 mg cryolite/kg bw.

Based on the observation of decreased pup body weights during the preweaning period at 1800 ppm also a NOAEL/developmental toxicity of 600 ppm according to 42 mg cryolite/kg bw/day can be derived from the report of the study.

Effects on postnatal growth evidenced by significantly decreased pup body weights during lactation as well as pathologic gross findings in several organs of the pups resulted from dose levels without any significant systemic toxicity. These effects are thus considered indicative for a specific toxic potential of cryolite adverse to (postnatal) development.

Further, several studies with repeat oral administration of cryolite are available in the data base (c.f. 4.1.2.6) during which organs of the reproductive system should have been evaluated as a standard for organ weights and for organ histopathology. The full reports of these studies, however, are not available to the rapporteur. Therefore, these studies can not be further exploited.

During a study with repeat inhalatory administration of cryolite (OECD TG 413, c.f. 4.1.2.6) on Sprague-Dawley rats also organs of the reproductive system had been evaluated. No substance-related effects were observed on testes and epididymides organ weights and no histopathological changes were observed in testis, epididymidis, uterus, cervix and ovaries after 13 weeks of exposure up to and including concentrations of 4.6 mg/m^3.

Studies in humans

No data available.

4.1.2.9.2 Developmental toxicity

Studies in animals

oral (gavage) rat

Harris, S. et al. (1983) cited from EPA (1996)

> "Cryolite was tested by gavage in a developmental toxicity study in Sprague-Dawley derived fBR Simonsen albino rats (30/group) at dose levels of 0, 750, 1500 or 3000 mg/kg/day during gestation days 6-15 inclusive. At 3000 mg/kg/day, well above the limit dose, the only observation was whitening of the teeth of dams. The NOEL for maternal toxicity is 3000 mg/kg/day. The LOEL is greater than 3000 mg/kg/day. The NOEL for developmental toxicity is 3000 mg/kg/day. The LOEL is greater than 3000 mg/kg/day (MRID 00128112)."

From the report of the study a NOAEL/maternal toxicity and a NOAEL/developmental toxicity for rats of $\geq$ 3000 mg cryolite/kg bw/day can be derived. Besides whitening of the teeth of the dams, no other compound-related systemically toxic effect was revealed from this study with daily dosages of up to and including 3000 mg cryolite/kg bw.

In addition, adverse effects on rat postnatal developmental had been observed at maternal dose levels of 149 mg/kg/day during the two-generation feeding study (Schroeder, R. 1994) in terms of significantly decreased pup body weights during lactation in both the F_1 offspring and the F_2 offspring. Additionally, at necropsy compound related findings were observed in several organs (kidney, liver, heart) in the pups by the time of weaning, whereas for the dams no clinical signs except dental fluorosis had been observed during this study.

oral (gavage) mouse

Nemec, M.D. (1991b) cited from CalEPA (1995)

> "Dose levels of 0, 10, 30, 100, 300, and 1000 mg/kg/day were administered on p.c. days 6-15 to 8 Crl:CD-1* (ICR)BR mice/group. No clear developmental nor maternal toxicity was identified at any dose. Pregnancy rates were very low (2 groups with as few as 3 pregnant dams/group: not treatment-related), hence this pilot study was of limited utility for rangefinding......"

Since it appears from the reporting that this study is of very poor validity, the study is not further taken into consideration for any hazard assessment purposes.

Nemec, M.D. (1992b) cited from CalEPA (1995)

> "Kryocide, purity of 97.3%, was administered via gavage at concentrations of 0 (0.5% Methylcellulose), 100, 300 or 1000 mg/kg/day to 30 mated Crl:CD-1* (ICR) BR

> mice/group during gestation days 6 through 15. Maternal toxicity NOEL = 100 mg/kg/day. Mortality was 40% and 10% for high and mid dose groups, respectively, with occasional necropsy reporting of "red stomach contents" or "reddened adrenals". Food consumption and body weight gains were reduced at 1000 mg/kg/day. Survival was too low at 1000 mg/kg/day to meaningfully assess treatment effects on fetuses, however a small increase in incidences of cleft palate and a single incident of open eyelid contributed toward a general increase in malformations in this group. There were no definitive developmental effects at or below 300 mg/kg/day, however a single incident of the variation "bent ribs" was considered an equivocal indication of a treatment effect, so that 100 mg/kg/day is the developmental NOEL.....”

The reporting of the study reveals severe maternal toxicity in terms of mortality and signs of toxicity in the gastrointestinal tract and at the adrenals and reduced body weight gain induced at dosages of ≥ 300 mg cryolite/kg bw/day leading to derivation of a NOAEL/maternal toxicity of 100 mg cryolite/kg bw/day.

Based on the observation of a single incident of a skeletal anomaly (bent ribs) at the dose level of 300 mg cryolite/kg bw/day also a NOAEL/developmental toxicity of 100 mg cryolite/kg bw/day can be derived from the report of the study.

Nemec, M.D. (1991a) cited from EPA (1996)

> “Cryolite (97.3%) was tested by gavage in a developmental toxicity study in female CD-1 mice (25/group) at dose levels of 0, 30, 100 or 300 mg/kg/day. There was increased mortality at 300 mg/kg/day. The glandular portion of the stomach was red beginning at 100 mg/kg/day. In addition, females in the 300 mg/kg/day group exhibited dark red contents of the stomach. The NOEL for maternal toxicity is 30 mg/kg/day and the LOEL is 100 mg/kg/day based on the occurrence of dark red contents of the stomach. Fetuses at 300 mg/kg/day exhibited bent ribs and bent limb bones. The NOEL for developmental toxicity is 100 mg/kg/day. The LOEL is 300 mg/kg/day based on an increase in bent ribs and bent limbs (MRID 42297902).”

The reporting of the study reveals severe maternal toxicity in terms of mortality and signs of toxicity in the gastrointestinal tract induced at dosages of ≥ 100 mg cryolite/kg bw/day leading to derivation of a NOAEL/maternal toxicity of 30 mg cryolite/kg bw/day.

Based on the observation of skeletal anomalies at the dose level of 300 mg cryolite/kg bw/day also a NOAEL/developmental toxicity of 100 mg cryolite/kg bw/day can be derived from the report of the study.

oral (gavage) rabbit

Nemec, M. (1992a) cited from EPA (1996)

> “Cryolite (97.3%) was tested by gavage in a range-finding developmental toxicity study in female New Zealand White rabbits (5/group) at dose levels of 0, 10, 30, 100, 300 or 1000 mg/kg/day. Mortality was increased in the 30, 100, 300 and 1000 mg/kg/day groups. Toxic signs including decreased defecation, decreased urination, soft stool and black coloured faeces were increased in the treated groups when compared to controls. Food consumption was decreased in all treated groups. Most animals studied in the 30, 100, 300 and 1000 mg/kg/group exhibited dark red areas, dark red contents and/or reddened mucosa of the stomach. The NOEL for maternal toxicity is 10 mg/kg/day and the LOEL is 30 mg/kg/day based on an increased

> incidence of soft stool and dark coloured faeces and decreased defecation and urination. The NOEL for developmental toxicity is 30 mg/kg/day. The LOEL could not be assessed due to excessive toxicity at dose levels of 30 mg/kg/day (MRID 42297901)."

The reporting of the study reveals severe maternal toxicity in terms of mortality, signs of toxicity in the gastrointestinal tract and clinical signs of toxicity induced already at dosages of 30 mg cryolite/kg bw/day leading to derivation of a NOAEL/maternal toxicity of 10 mg cryolite/kg bw/day. Whereas reasonable evaluations in the fetuses from this study at the higher dose levels were not possible due to excessive maternal toxicity, obviously no effects in the progeny were observed at maternal doses of 30 mg cryolite/kg bw/day. Therefore a NOAEL/developmental toxicity of 30 mg cryolite/kg bw/day is derived from the report of the study.

<u>Studies in humans</u>

No data available.

4.1.2.9.3 Summary of toxicity for reproduction

Cryolite was investigated for reproductive toxicity in rats with the oral (dietary) route of administration in a two-generation study. From the results of the study there are currently no indications for any specific potential of cryolite adverse to fertility. Besides dental fluorosis (LOAEL: 15 mg/kg/d) and teeth whitening effects, a NOAEL/systemic toxicity and a NOAEL/fertility of $\geq$ 128 mg cryolite/kg bw/day can be derived from the study and should be taken forward for quantitative risk assessment. From studies with repeat inhalatory administration in rats there was no indication for any impairment of organs of the reproductive system at concentrations of up to and including 4.6 mg/m^3(NOAEC/reproductive organ toxicity).

Cryolite was investigated for prenatal developmental toxicity in rats, mice and rabbits with the oral (gavage) route of administration. With regard to maternal toxicity after oral (gavage) administration, pregnant rabbits as well as pregnant mice, both exhibiting maternal mortality, revealed to be clearly more sensitive to cryolite than pregnant rats. While from the study with rats and with rabbits there were no indications for prenatal developmental toxicity, in the studies with mice skeletal anomalies in terms of bent ribs and bent limb bones were reported repeatedly from two independent studies. These skeletal anomalies were induced and observed at dose levels that also resulted in maternal toxicity. Further, growth retardation in postnatal development was observed during the two-generation study with rats, evidenced by significantly reduced offspring body weight gain during the preweaning period in the highest tested dose group as well as compound related pathological organ findings in several pup organs at the time of weaning. Overall it appears from the available studies, that postnatal growth retardation as well as pup organ changes were the most sensitive developmental effects to be induced. Thus, for developmental toxicity a NOAEL of 42 mg cryolite/kg bw/day derived from the two-generation reproduction study with rats should be taken forward for quantitative risk assessment.

Postnatal growth retardation and pup organ changes as observed during the two-generation reproduction study in rats as well as the induction of anomalies in the skeletal system as observed in the studies in mice is considered indicative for a specific toxic potential of cryolite adverse to development. Although the postnatal effects were observed at dose levels without any significant systemically toxic effects in parental animals or in the lactating dams, the primary data cannot be assessed and there remain some uncertainties on the full toxicological significance of the developmental effects observed in the pups and the dental fluorosis observed in the dams. Therefore it is proposed to classify cryolite as Repr.Cat 3; R63

4.1.3 Risk characterisation [6]

4.1.3.1 General aspects

Toxicokinetics

In animals and humans, cryolite can be absorbed after oral application. Dependent on the way, how cryolite was applied (e.g. as a solid substance or in solution), up to 93 % fluoride from cryolite was absorbed in humans. Therefore a 95 % oral absorption can be taken for risk characterisation.

In animals and humans, cryolite can be absorbed after inhalative exposure as could be seen from acute inhalative studies in rats and from cryolite exposed workers, in which serum and urinary fluoride had been quantified. The extent of inhalative absorption can be assumed to be dependent on the size of the cryolite particles. In occupationally cryolite exposed workers (crushing, separation and grinding of dry cryolite, particle size has not been determined; it might be possible that during crushing non-respirable particles have been formed in addition to respireable particles), based on maximal achievable values, up to 31 % of the inhaled amount of fluoride was excreted via urine. Based on the assumption, that intake might have been higher if only fine ground cryolite had been applied and because it is known from oral studies, that comparable quantities of fluoride from cryolite that are excreted via urine, may be retained in the body, a default value of 100 % inhalative absorption is taken for risk characterisation.

Data on dermal uptake of cryolite are not available. Based on the low solubility and the type of compound (inorganic salt) and based on the fact, that systemic effects could not be observed after dermal administration of cryolite, dermal absorption of cryolite can be assumed to be quite low. Cryolite is insoluble in organic solvents and thus will not easily pass the lipophilic stratum corneum of the skin. Factors that may promote oral uptake of fluoride like the slightly alkaline environment in the small intestine and the presence of ions like Ca, Ba, Mg and Fe that can form soluble chelate with cryolite are absent for the dermal route. Furthermore, salts are usually poorly absorbed via the dermal route. Therefore, a value of 10 % dermal absorption is taken for risk characterisation.

Acute toxicity, irritation/corrosivity, sensitisation

In well conducted and guideline-compliant rat inhalation study, an LC50 of 4470 µg/l was derived. Hence, classification of cryolite with R 20, 'harmful by inhalation', is appropriate. For assessment of dermal acute toxicity only a rabbit screening assay is available, suggesting an LD50 of >2100 mg/kg. After oral administration in rats, an LD50 exceeding 5000 mg/kg was concluded in several studies. Clinical signs were consistent with other oral fluoride studies

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[6] Conclusion (i) There is a need for further information and/or testing.
Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

(WHO, 1984), which demonstrated lower LD50s (IARC, 1982; Whitford, 1990, as referenced in WHO/ IPCS 2002), indicating a lower bioavailability for cryolite. In consequence, existing classification with R 22 is not supported.

On the basis of the available data it can be concluded that cryolite does not have skin irritating properties. Scarce data on eye irritation indicate a low potential of cryolite to induce eye irritation, but due to a low quality of available data, a final assessment is difficult. In a well-conducted acute rat inhalation study using cryolite aerosol in a 4-hours whole body exposure in the range of the LC50 (for details, refer to 4.1.2.2.1 inhalation). Since no effects were reported for the eyes, these negative findings support the conclusion, that cryolite is not a strong eye irritant. Overall, a data gap remains that may require additional testing. Inhalation studies demonstrated an irritative potential of the substance on the airways, which do not warrant classification as respiratory irritant.

Data from skin and eye irritation studies do not indicate any corrosive potential of cryolite.

In a Magnusson Kligman Test with guinea pigs, no skin sensitisation was observed. Human data and data on respiratory tract sensitisation are not available. In conclusion, no classification is proposed.

Repeated dose toxicity

In experimental animals, the toxic profile of cryolite is dominated by its systemic and local toxicity. The critical effects, which are considered to be serious health effects, after prolonged inhalation or oral route of exposure, are characterized by distinct toxic effects on the bones. Local effects after subchronic exposure to predominantly respirable cryolite dust led to lung lesions while repeated oral administration of cryolite to rats in their feed resulted in stomach lesions. Fluoride has been identified as the main component of toxicological concern in natural cryolite and synthetic cryolite for systemic and local effects. Furthermore, cryolite has frequently been noted to cause dose-dependent dental fluorosis upon repeated administration to rodents, the teeth of which grow continually in contrast to human teeth.

Repeated exposure by inhalation to ≥1.04 mg/m^3 (6h/d, 6d/week) cryolite for 90 days caused lung lesions in male and female rats. After chronic inhalation of ≥1 mg/m^3 (6h/d, 6d/week) cryolite for up to 5 months dystrophic lesions in the bones and teeth, and adverse effects in the respiratory tract, stomach, kidney, liver, and brain were noted in both male and female rats. The lowest NOAEC for systemic effects of 0.5 mg/m^3 (6h/d, 6d/week) was derived from the 5-month rat study. The lowest concentration of 0.21 mg/m^3 (6h/d, 5d/week) cryolite from a 90-day inhalation study with Sprague Dawley (CD) rats (BG Chemie 1997) is considered as NOAEC for local effects on the respiratory tract and should be taken forward to quatitative risk characterisation.

Dental effects were observed in rodent studies following chronic whole body exposure to concentrations of ≥1 mg/m^3 cryolite. The affected teeth exhibited loss of normal tooth coloration (bleaching of the incisors and later yellowish-brown mottling) and enamel defects.

There were no studies in conformance with requirements of the standard repeated dose toxicity testing protocols for dermal exposure to cryolite.

Data of animal toxicity studies by oral route in conformance with requirements of the standard repeated dose toxicity testing protocols were presented only in summary form for synthetic cryolite, CAS No. 15096-52-3. Up to now, complete study reports are not available; therefore no final evaluation can be made. There are several studies addressing the same effects. Repeated oral administration of cryolite to rats in their feed resulted in stomach lesions, while in dogs subchronic and chronic dietary administration of cryolite led to haematological alterations, even anaemia, and kidney effects, but only at high dose levels or after long-term treatment [blood: rat, 90-day study at 50000 ppm (corresponding to about 4172.3 mg/kg bw/d in males and 4748.1 mg/kg bw/d in females, and dog, 12-month study at ≥10000 ppm (corresponding to about ≥366 mg/kg bw/d in males and ≥387 mg/kg bw/d in females), respectively); kidney: dog, 12-month study at ≥3000 ppm (corresponding to about ≥95 mg/kg bw/d in males and ≥105 mg/kg bw/d in females)]. Critical effect following repeated dietary exposure to cryolite in experimental animals was fluoride accumulation in bones. Fluoride accumulation in bones has been found in rats and dogs at all dose levels tested after subchronic or chronic administration in the diet. Therefore, the NOAEL for this effect could not be determined in any of these studies. After treatment for 90 days, fluoride accumulation in bones was found in male and female Crl:CD(SD)BR rats from the lowest dose tested of 50 ppm (corresponding to about 3.8 mg/kg bw/d in males, 4.5 mg/kg bw/d in females) upwards and in dogs from 500 ppm (corresponding to about 17 mg/kg bw/d), respectively. Indicators of dental fluorosis as enamel striations, discoloration and changed physical properties of the teeth have been noted in rats receiving 0.58 mg/kg bw/d for 14 weeks or higher in Sprague-Dawley (CD) rats after treatment with ≥250 ppm, representing ≥25 mg/kg bw/d for a period of four weeks. This is in line with very early observations on toxic effects on the bones and teeth (bleached incisors) at 1 mg/kg bw/d, and development of abnormally structured osseous tissue and renal effects at 5 mg/kg bw/d. The lowest oral LOAEL of 0.58 mg/kg bw/d for changes in dental enamel derived from 14-day study in rats was selected for the risk characterisation (CalEPA 1995).

In humans the main route of exposure to cryolite is by inhalation. Occupational cryolite exposure was reported from the mining and processing of natural cryolite, manufacture of synthetic cryolite and aluminium production. Several epidemiological studies were available describing adverse effects following inhalation to cryolite and indicated that prolonged (i.e. several years) and repeated occupational exposure to cryolite dust may lead to skeletal fluorosis, characterised by harder and more brittle bones, and increased x-ray opacity. In light cases of skeletal fluorosis, the bone changes are often associated with non-specific joint and muscle pains. A continuous daily exposure to 20 - 80 mg fluorides or more for at least 4 years appeared to be sufficient to cause skeletal fluorosis in humans, and in cases of crippling fluorosis, exposure for 10 to 20 years was required. In subsequent studies skeletal fluorosis was observed after exposure to an average fluoride concentration of 28 mg/m^3 and of 2.5 mg/m^3. Radiological changes such as increased bone density were diagnosed in workers employed in a fluorspar processing facility in India for more than 9 years with an overall mean urinary fluoride level of 1.96 ppm. In male pot room workers employed in aluminium plants skeletal fluorosis was observed at average fluoride concentrations of 2.4 to 6.0 mg/m^3 (for average 8h/d, with 36-50% content gaseous fluoride). Increased bone density was noted in workers of a phosphate fertilizer manufacturing plant exposed at concentrations of about 3.38 mg/m^3 fluorides in the form of dusts and gases over a period ranged from 4.5 to 29.9 years with an average of 14.1 years.

No abnormal findings on a series of medical examinations including chest radiography were noted in workers of a cryolite-producing plant in Japan exposed to average exposure levels of 0.09-0.49 ppm (0.9-4.9 mg/m^3) hydrogen fluoride, and of 0.05-0.6 mg/m^3 mineral dust levels during the observation period from 1977-1982. In workers of a phosphate fertilizer manufacturing plant no bone density changes were noted at an average air concentration of 2.65 mg fluoride/m^3 and an average urinary fluoride excretion of 4.53 mg fluoride/l exposed of an average of 14.1 years. Prolonged exposure to about 0.48 mg fluoride/m^3 for at least 50%

of their time at work for more than 10 years yielded no definite cases of skeletal fluorosis among the 570 pot room workers at an aluminium smelter in Canada.

Impairment of lung function was not correlated with exposure to cryolite and no association was found between chronic bronchitis and exposure to cryolite dust.

No data concerning repeated dermal exposure to cryolite in humans were located in the literature.

WHO has concluded that there is some increase in risk of skeletal effects with an intake in food and drink higher than 6 mg fluoride/day. Significant effects are seen at a total intake of 14 mg fluoride/day (WHO 2002). Calculations from the WHO data indicate that skeletal effects appear at an air concentration of 0.8 to 2.0 mg fluoride/m^3 for an 8-hour workday.

Mutagenicity

Cryolite does not induce gene mutations in a bacterial in vitro system. In vitro tests on induction of chromosomal aberrations (human lymphocytes) and unscheduled DNA synthesis (rat hepatocytes) are reported to be negative, but cannot be adequately assessed because of the lack of full reports.

In vivo cryolite was negative in rat bone marrow chromosomal aberration tests after acute and repeated inhalation exposure.

Carcinogenicity

There are limited data either from humans or animals that may indicate a carcinogenic risk from exposure to cryolite. Cryolite has not been tested for carcinogenicity in experimental animals. No informations of neoplastic effects were reported from a one-year study with Beagle dogs, in which cryolite was given at dietary concentrations of up to 30000 ppm, corresponding to about 1137 mg/kg bw/d in males and 1139 mg/kg bw/d in females, for a period of 12 months. From carcinogenicity studies with sodium fluoride (NaF) in rats and mice it is concluded that fluoride is not considered to be carcinogenic in animals. The carcinogenic potential of NaF has been studied in F344 rats and B6C3F1 mice in the context of the U.S. National Toxicology Program (NTP 1990) and in two combined toxicity/carcinogenicity diet studies in which Sprague-Dawley rats and in CD-1 mice were tested (Maurer et al., 1990; Maurer et al., 1993). The results of the two-year drinking water studies were judged to show equivocal evidence of carcinogenic activity of sodium fluoride in male F344/N rats. No evidence in female F344/N rats and in male and female B6C3F1 mice was found. The rat diet study was negative, despite clear indications of fluoride intoxication (Maurer et al., 1990). The mouse diet study might be confounded by the presence of a retrovirus which according to the author’s opinion may have (co)-induced the growth of benign osteomas thus thwarting the interpretation of the study. In the diet studies bone fluoride levels were higher than in the drinking water studies, while in the diet studies no indications for osteosarcomas were obtained. The same data base from NaF was used in the EU risk assessment of hydrogen fluoride (HF, CAS No. 7664-39-3, 1st priority list) for evaluation of the carcinogenicity because carcinogenicity studies with HF are not available. From these studies with NaF in rats and mice it was concluded for HF that “the available data are sufficient to suggest that fluoride is not a carcinogenic substance in animals."

Elevated cancer morbidity was observed in workers exposed to fluorides in the cryolite industry and also in the aluminium industry. In a Danish cohort study of male cryolite workers an increased risk of 2.37 of respiratory cancer was identified. In a follow-up of the Danish cohort a high incidence of respiratory and urinary cancers were noted in men less than

35 years old at first employment. Smoking was discussed as a confounding factor. However, the excess cancer risk identified in workers exposed to fluorides, including fluoride-spar and aluminium production workers, may be due to other factors than fluoride exposure. Since the workers occupationally exposed to fluoride were supplementary exposed to several other compounds, such as quartz, siderite and small amounts of metal sulfides reported for the workers in the cryolite processing factory in Copenhagen; to radon for the fluorspar miners, and to polyaromatic hydrocarbons for the aluminium workers, respectively, an excess cancer risk may not be related directly to fluoride exposure.

On the basis of carcinogenicity studies with NaF in rats and mice it is concluded that cryolite is not considered to be carcinogenic in animals. No conclusion can be drawn as to the carcinogenicity of cryolite in humans, because in the studies available, humans were exposed to other substances as well.

Toxicity for reproduction

No data on studies in humans available.

From the results of a two-generation study with rats with the oral (dietary) route of administration there are currently no indications for any specific toxic potential of cryolite adverse to fertility up to and including the highest tested dose level of 128 mg/kg bw/d.

From the results of studies investigating prenatal developmental toxicity in mice with the oral (gavage) route of administration there are indications for disturbances of the skeletal system. Effects adverse to development were further identified from the two-generation study with rats evidenced from postnatal growth retardation and pup necropsy findings at dose levels according to 128 mg/kg bw/day without any significant maternal toxicity. On the basis of the information that is available to the rapporteur cryolite is proposed to be classified and labelled as Repr.Cat3; R63.

Table 4.4 Toxicological hazard identification
No/Low Observed Adverse Effect Concentrations/Levels to be taken forward to quantitative risk assessment in bold letters

trisodium hexafluoroaluminate, CAS-No.: 13775-53-6	**Inhalation**	**Dermal**	**Oral**
Acute toxicity	LC_{50} (rat) = 4470 µg/l R20 - harmful by inhalation	LD_{50} (rabbit) > 2100 mg/kg (screening assay)	LD_{50} (rat) > 5000 mg/kg
Irritation / corrosivity	skin: no skin irritating properties in a guinea pig maximisation test eye: no adequate data for thorough assessment respiratory tract: no well-conducted inhalation study		
Sensitization	skin: no skin sensitisation in guinea pigs respiratory tract: no data		
Repeated dose toxicity (local)	to lung lesions at ≥1.04 mg/m^3 (6h/d, 6d/week, 90-day inhalation study) (NOAEC of 0.21 mg/m³, 6h/d, 5 d/week, 90-day inhalation study, Sprague-Dawley CD rat) R48/23 confirmed		stomach lesions at ≥5000 ppm, corresponding to about ≥399.2 mg/kg bw/d in males and ≥455.9 mg/kg bw/d in females; 90-day feeding study, Crl:CD(SD)BR rat (**NOAEL of 50 ppm** equivalent to about 3.8 mg/kg bw/d in males and 4.5 mg/kg bw/d in females; 90 day feeding study, Crl:CD(SD)BR rat)
Repeated dose toxicity (systemic)	concern for man due to toxic effects on the bones and teeth, and on the liver, stomach, kidney and brain at ≥1 mg/m^3 (6h/d, 6d/week, 5-months study, rat) (**NOAEC of 0.5 mg/m³**, 6h/d, 5 d/week, 5-months inhalation study, rat) Concern for man due skeletal fluorosis NOAEC of 0.48 mg fluoride/m^3 R48/23 confirmed		concern for man due to fluoride accumulation in bone at ≥50 ppm, equivalent to about 3.8 mg/kg bw/d in males and 4.5 mg/kg bw/d in females; 90-day feeding study, Crl:CD(SD)BR rat; ≥500 ppm, equivalent to about 17 mg/kg bw/d in males and females, 90-day feeding study, Beagle dog concern for man due to dental lesions/dental fluorosis (hypoplasia/hypomineralisation of dental enamel and dentine) at 0.58 mg/kg bw/d, 14-day study, rats (**LOAEL of 0.58mg/kg bw/d** for dental fluorosis (teeth effects); 14-week feeding study, rat) There is clear evidence from India and China that significant skeletal effects are seen at a total intake of 14 mg fluoride/day. Equivalent to about 0.2 mg/kg bw/d calculated on an assumed body weight of 70 kg person (WHO 2002) R48/25 confirmed

Mutagenicity	no evidence for mutagenicity from in vitro and in vivo studies		
Carcinogenicity	no data	no data	No carcinogenic effects up to 30000 ppm, equivalent to about 1137 mg/kg bw/d in males and 1139 mg/kg bw/d in females, 12-month feeding study, Beagle dog; from four carcinogenicity studies with NaF in rats and mice it is concluded that cryolite is not considered to be carcinogenic in animals; no conclusion can be drawn as to the carcinogenicity of cryolite in humans, because in the studies available, humans were exposed to other substances as well.
Fertility impairment	no data **NOAEC ≥ 4.6 mg/m³** (reproductive organ effects)	no data	no specific effects adverse to fertility up to the highest dose level tested LOAEL (dental effects) 15 mg/kg bw/d NOAEL (systemic tox.) ≥ 128 mg/kg bw/d **NOAEL (fertility) ≥ 128 mg/kg bw/d**
Developmental toxicity	no data	no data	postnatal growth retardation and organ impairment LOAEL (dental effects) 15 mg/kg bw/d NOAEL (systemic tox.) ≥ 128 mg/kg bw/d **NOAEL (dev. tox.) 42 mg/kg bw/d**

4.1.3.2 Workers

Introductory remarks

Occupational exposure to cryolite may occur during production and further processing and use of the substance. This risk assessment is based upon the occupational exposure assessment (chapter 4.1.1.2) and the toxicological profile of cryolite (chapter 4.1.2). The threshold levels identified in the hazard assessment are taken forward to characterise the risks at the workplace and give indication for concern according to the MOS approach as outlined in the TGD (Human Health Risk Characterisation, Final Draft).

Systemic availability for different routes of exposure

For cryolite information on absorption mainly comes from fluoride determination (F^-) in excrements (animal or human studies) after oral application. Very little is known on the absorption and bioavailability of the aluminium-containing moiety. On the background of the fluoride data the oral absorption in humans is assumed to be 95 % based on the study of Largent and Heyroth (Largent and Heyroth, 1948). For animals, 85 % oral absorption is taken for risk characterisation in animals (rats) based on the study of Wright and Thompson (1978). Inhalation data are rare but give indication that also after inhalation of cryolite dust a considerable amount of F^- may be absorbed. For inhalation a default value of 100 % absorption is taken forward to worker risk assessment. For dermal absorption no data are available. A value of 10% for dermal absorption of cryolite is assumed, because cryolite is insoluble in organic solvents and thus will not easily pass the lipophilic stratum corneum of the skin. Furthermore, salts are usually poorly absorbed via the dermal route. In all cases it has to be recognised, that the information on absorption only applies to the F^- content of the cryolite molecule.

Occupational exposure and internal body burden

In table 4.5 the exposure levels of table 4.1 which concern cryolite are summarised and the route-specific internal body burdens of F^- are identified. To this end the F^--content in cryolite of 54% is taken into account in combination with the route-specific percentages for absorption (100 % for inhalation and 10 % for dermal exposure). For combined exposure the internal budy burdens of F^- by inhalation and dermal contact are summed up to give a total internal body burden.

Table 4.5 Occupational exposure levels(cryolite) and internal body burden (F^-)

Exposure scenario	Inhalation shift average	Dermal contact shift average		Internal body burden of F□ of workers after repeated exposure(1)		
				Inhalation(2)	Dermal(3)	Combined
	mg/m^3	mg/pers/day	mg/kg/day	mg/kg/day		
1. Production of synthetic cryolite dust	5	42	0.6	0.38	0.03	0.41
Production of synthetic cryolite granules	1	42	0.6	0.08	0.03	0.11
2. Aluminium industry	2	84	1.2	015	0.07	0.22
3. Use in other industries	10	3000	43	0.8	2.3	3.1
4. Abrasives, grinding discs EASE(4)	1	252	3.6	0.08	0.2	0.28
Abrasives, grinding discs analogous data(5)	0.1	252	3.6	0.008	0.2	0.208

(1) taking into accout the F^- content of cryolite of 54%
(2) based on the assumption of 100% inhalative absorption; breathing volume of 10 m^3 per shift
(3) based on the assumption of 10% systemic availability of fluoride after dermal contact
(4) without LEV
(5) with LEV

MOS Approach

The MOS approach for human risk characterisation is described in detail in the TGD (Human Health Risk Characterisation, Final Draft). The following paragraphs contain a short introduction to aspects relevant in case of cryolite. The basic principle of the MOS approach is a comparison of scenario-specific MOS values (the relationship between the experimental NOAEL respectively the adjusted starting point and the exposure level) with a reference MOS (product of various assessment factors).

MOS calculation and the adequate starting point

Basically, MOS values are calculated as quotient of a relevant NOAEL from experimental animal testing or human studies and actual workplace exposure levels. In specific situations, the MOS approach requires converting the original NOAEL into an adequate starting point or corrected NOAEL previously to MOS calculation in order to be directly comparable to the exposure assessment. If the route of application in animal or human studies is different from the actual occupational exposure, the dose units of the experimental data are converted to the dose unit of the exposure data. Additionally, possible differences in bioavailability between routes, as well as possible differences in bioavailability between animals and humans are accounted for in the calculation of the corrected NOAEL. If necessary in occupational risk assessment, the starting point for inhalation risk assessment also includes a correction for the difference between the standard respiratory volume of a person at rest (6.7 m^3) and the respiratory volume of workers under light activity (10 m^3).

MOS values are calculated for different routes of exposure and for different toxicological endpoints. In occupational risk assessment inhalation and dermal contact generally resemble the relevant exposure routes. In addition, for assessment of combined risks the simultaneous exposure by inhalation and dermal contact needs to be considered. For cryolite the adequate NOAEL in this case is given by the respective internal level of fluoride which is expressed as well in mg F^-/person as in mg F^-/kg. This is easily comparable to the data on occupational and non-occupational fluoride uptake, which also are given as internal values (internal body burden). Inhalation exposure and dermal exposure to cryolite may contribute differently to the internal body burden of fluoride. With respect to the possible outcome of an assessment for combined risks, interest focuses on scenarios with conclusion ii at both exposure routes. Based on theoretical considerations, combined exposure will not increase the most critical route-specific risk component more than twice.

Reference MOS

The MOS values calculated have to be compared with a reference MOS. The reference MOS results an overall assessment factor from the multiplication of the different specific factors for a certain risk situation. The Technical Guidance Document emphasis the different aspects which are involved in these considerations, especially the extrapolation of experimental data to the human situation. For several aspects default assessment factors are recommended. It is important to point out that any relevant substance-specific data and information may overrule the defined default values.

Interspecies extrapolation as one central element is based on allometric scaling (factor 4 for rats, factor 7 for mice, and factor 2 for rabbits). For remaining interspecies differences the TGD proposes an additional factor of 2.5. Another element is adjustment for intraspecies differences. For workers, a default factor of 5 is recommended, based on an evaluation of empirical data by Schneider et al. (2004). It is anticipated that a default factor of 5 will be sufficient to protect the major part of the worker population (about 95%). For cryolite these default assessment factors are indicated for some endpoints only, because in most cases reliable human data are available which are preferred as direct basis for the assessment.

It is usually expected that the experimental NOAEL will decrease with increasing duration of application. Furthermore, other and more serious adverse effects may appear with prolonged exposure duration. This may result in the necessity to perform a duration adjustment of data using default factors. For cryolite however, data on health effects after chronic exposure are available which are sufficient for the assessment. There is no need for a numerical correction.

The TGD describes two further adjustment factors (uncertainty in route-to-route extrapolation and dose-response relationship including severity of effect) which in specific cases may be different from one. For cryolite there are uncertainties from route-to-route extrapolation and from dose-response relationship especially for the endpoint carcinogenicity. However, the problem is not dealt with additional assessment factors but reference is made to repeated dose toxicity and the respective risk characterisation.

Comparison of MOS and reference MOS

The different scenario- and endpoint-specific MOS values are compared with the respective reference MOS. MOS values clearly above the reference MOS do not lead to concern, whereas MOS values that are clearly below the reference MOS give reason for concern. There are also risk-related aspects which cannot be covered quantitatively by assessment factors. These additional aspects are considered qualitatively when performing the risk assessment and have adequate influence on the finding of the conclusions. Especially in case of borderline scenarios these aspects might be decisive.

Critical Exposure Levels

In a parallel procedure, which gives identical but more direct results, the adjusted toxicological starting point is directly divided by the reference MOS. As a result, an exposure level (in mg/m³ or mg/kg/d) is identified, which may serve as a direct trigger for decisions when compared with the occupational exposure levels. In the context of this risk assessment report this trigger value is called “critical exposure level”. Concern will be expressed for scenarios with occupational exposure levels higher than the relevant “critical exposure level”.

4.1.3.2.1 Acute toxicity

From acute inhalation studies in animals with cryolite dust there is indication for severe local effects in the respiratory tract, leading to mortality at high air concentrations. These effects will be evaluated in chapter 4.1.3.2.3, irritation and corrosivity, in combination with the results of the short-term inhalation studies. These also give evidence of significant local irritation properties of cryolite and allow for a quantitative analysis. For the evaluation of acute toxicity in this chapter the local effects in the acute inhalation study therefore are not used.

From the oral and the dermal application route there is no indication for adverse systemic effects of cryolite after short-term exposure up to limit doses. In a guideline-compliant rat inhalation study, a LC50 of 4,470 mg/m^3 was derived. No mortality and no clinical sings were observed at 1,330 mg/m^3 . The highest occupational exposure value is described in scenario 3 with 10 mg/m^3. Compared to the value of 1,330 mg/m^3, where no severe effects are described, the margin of safety is judged to be sufficient. This is confirmed by data from workers with high exposure to cryolite and by the different long-term studies, which did not give evidence of acute symptoms except those of local irritation.

In summary there is no indication that significant systemic effects might be caused by short-term exposure to cryolite at the workplace, there is no concern for workers from this aspect.

Conclusion: ii

Table 4.6 Occupational risk assessment for acute toxicity

	Inhalation				Dermal				Combined			
	Exposure	NOAEL	MOS	Conclusion	Exposure	NOAEL	MOS	Conclusion	Exposure	NOAEL	MOS	Conclusion
Production												
Subscenario 1												
Subscenario 2												
Subscenario 3												
Subscenario 4												
Subscenario 5												
Formulation												
Subscenario 1												
Uses												
Subscenario 1												
Subscenario 2												
Subscenario 3												

[click here to insert table note or Table X.X continued overleaf or delete if not appropriate]

4.1.3.2.2 Irritation and corrosivity

Skin

There is no standard skin irritation test available. In a well-conducted skin sensitisation study (GPMT) no dermal reactions at all have been obtained. From literature data cryolite is said to be not irritating to skin. There are no reports on skin effects from the different studies on workers. In summary there is no concern for dermal irritation at the workplace.

Conclusion: ii

Eyes

Information on eye irritation indicates that cryolite may have a certain potential for eye irritation, but due to the low quality of the available data a final assessment is not possible. A precautionary classification with R36 is proposed.

Due to that insufficient data base for C&L decisions conclusion (i) on hold applies.

Conclusion: i (on hold)

Respiratory tract

From human examinations no local effects on the respiratory tract were described. Also in the rat LC_{50}-study no clinical signs of respiratory tract irritation were observed at 1,330 mg/m³. However, in animal studies with longer duration (14-day inhalation study with 5.1, 14, 60, 130, 470 mg/m^3 of particulate test substance) various inflammatory lesions were observed which concerned the alveolar parenchyma, the bronchiolar –alveolar junctions and the lumen of the large bronchioles slight bronchiolar hyperplasia. Also after chronic inhalation of Cryolite, rats showed lung changes.

With respect to short-term single exposure up to 10 mg/m³ (highest exposure value, resulting from scenario 3), severe airway damage is not anticipated and no concern is expressed. For the assessment of local effects after repeated contact see the chapter below.

Conclusion: ii

4.1.3.2.3 Sensitisation

Skin

In a fully guideline-compliant Magnusson Kligman Test a skin sensitising potential of cryolite could not be demonstrated. Also monitoring data at the workplace do not indicate specific skin reactions of workers to cryolite. There is no concern with respect to skin sensitisation of cryolite.

Conclusion: ii

Respiratory tract

No information on the sensitising potential of the substance at the respiratory tract is available. For the time being a valid study to investigate respiratory sensitisation in experimental animals cannot be recommended. Some cases of bronchial asthma have been observed at workplaces with mixed exposure to several chemicals, which however, did not give notice of a specific sensitising potential of cryolite. These effects are dealt with in chapter 4.1.3.2.2, irritation and corrosivity, respiratory tract. On the background of these data cryolite is not suspected to be a potent respiratory sensitiser in humans. There is no concern with respect to respiratory sensitisation at the workplace.

Conclusion: ii

4.1.3.2.4 Repeated dose toxicity

Local effects

Inhalation exposure

For prolonged inhalation exposure of workers to cryolite, data on possible health effects are available from different sources such as mining and processing of natural cryolite, production of syntethic cryolite and manufacturing of aluminium. There has been no indication for cryolite specific chronic respiratory effects in humans although specific examinations have been made (x-ray photography, pulmonary function tests, questionaires concerning incidences of acute pulmonary symptoms). Exposure in some cases has been rather high and long-lasting, causing severe skeletal fluorosis.

In a well-conducted 90-day inhalation study rats were exposed snout-only to particulate aerosols of cryolite in the concentration of 0, 0.21, 1.04, and 4.6 mg/m^3. Alveolitis with interstitial thickening of alveolar duct walls and increased collagen in alveolar ducts occurred in the high dose group. At the intermediate dose of Cryolite, a proportion of rats had interstitial thickening of the alveolar duct walls. These effects might indicate of the start of a fibrotic process in the lung. At the low dose (0.21 mg/m^3) no effect was observed.

For the risk assessment this NOAEC of 0.21 mg/m^3 is used as starting point concerning effects of cryolite after repeated inhalation.

For the identification of the reference MOS the following aspects are taken into account: The human data give no indication for cryolite specific chronic respiratory effects. Therefore, the NOAEC gives a very precautious value for the evaluation of this endpoint. On that background it does not seem indicated to apply any additional assessment factors like inter- or intraspecies extrapolation or duration adjustment. On the other hand the NOAEC, based on a 90-day study, might make a <u>duration factor of about 2 necessary</u>, because a progression of effects in the lungs (thickening of alveolar ducts and increased collagen) cannot excluded. In summary for the reference MOS a value of about 2 is proposed; the critical exposure level calculates then to 0.1 mg/m^3 (0.2 mg/m^3 / 2).

Table 4.7. shows, that all scenarios exceed the critical exposure level thus giving reason for concern.

Conclusion: iii

Table 4.7 Irritation and Corrosivity, respiratory tract

	Inhalation		
Starting point for MOS calculation	0.2 mg/m^3		
Reference MOS	2		
Critical exposure level	0.1 mg/m^3		
	Exposure (mg/m^3)	MOS	Conclusion
1. Production of synthetic cryolite dust	5	0.04	iii
Production of synthetic cryolite granules	1	0.2	iii
2. Aluminium industry	2	01	iii
3. Use in other industries	10	0.02	iii
4. Abrasives, grinding discs EASE	1	0.2	iii
Abrasives, grinding discs analogous data	0.1	2	iii borderline

Dermal contact

No data are available concerning local effects after repeated dermal contact with cryolite. The acute skin tests did not show local irritating or sensitizing properties. From epidemiological data no observations on skin reactions from workers have been reported. In summary local effects by prolonged skin contact of workers are not expected. There is no reason for concern.

Conclusion: ii

Systemic effects

Repeated dose studies in mice and rats with oral and inhalation application demonstrated that prolonged exposure to cryolite causes accumulation of fluoride in teeth and bones with striations of the teeth and development of abnormally structured osseous tissues. From a well-conducted 90-day inhalation study in rats the systemic NOAEC is identified as 0.21 mg cryolite/m^3. With oral application fluoride accumulation in bone and teeth was observed in rats from the lowest dose tested upwards. The respective LOAEL is 50 ppm, corresponding to 3.8 mg cryolite/kg/day for male and 4.5 mg cryolite/kg/day for female rats. In a 5-month rat study a NOAEC for toxic effects on bones, teeth and for local effects on the respiratory tract was established at 0.5 mg/m^3 (6h/d, 6d/week). At ≥1 mg/m^3 there were dystrophic lesions on the bones and teeth, and also adverse effects on the respiratory tract, stomach, kidney, liver, and brain.

From prolonged occupational inhalative exposure to cryolite dust it is known that cryolite may cause skeletal fluorosis in humans which is characterized by increased mineralisation of the bones and is identified in x-ray examinations by e.g. increased bone density, narrowing of the medullary cavity and ligament calcification. Joint pain and limited movement of the joints belong to the clinical symtoms. In severe cases skeletal crippling might occur with progressive disability. Also osteosclerosis can lead to brittle bones and a higher frequency of fractures. The underlying cause of the disease is the incorporation of fluoride into the bone tissue.

The human NOAEC for inhalation is derived in this report from a study in aluminium smelter workers with long-term occupational exposure and is given as 0.48 mg F^-/m^3 (see chapter 4.1.2.6.3.2 summary of human toxicity data). Taking into account an occupational respiratory volume of 10 m^3 in 8 hours and the fact that oral and inhalation absorption of cryolite are in a comparable range and relatively high (95% and 90% for oral and inhalation absorption, respectively), this value corresponds to an oral dose of about 5 mg F^- per person caused by cryolite. This may be compared to the evaluation of drinking-water data from China and India by the WHO (EHC 2002). The data give indication for an increased risk of effects on the skeleton at total fluoride intakes above about 6 mg F^-/person/day.

There is also concern with respect to dental fluorosis, which might occur as consequence of elevated fluoride levels in children under the age of 8 years (COT Statement 2003). Oriented to that, recommendation for intake of fluoride in the general population is given as 0.05 mg F^- /kg/day which is about two times below the level for skeletal fluorosis. However, for occupational risk assessment effects in children are not decisive.

The mechanism of cryolite toxicity in humans is comparable to that seen in animals. Quantitatively, however, animals appear to be more sensitive than humans. The inhalation NOAEC in rats is two times below the respective NOAEC in humans, if the NOAEC of 0.5

mg/m^3 from the 5-months rat study is used, not taking into account differences in exposure, assessment factors for species extrapolation or variability. Doing a MOS calculation the corresponding critical exposure level would result in a value of 0.02 mg/m^3 (0.5 / 25 with 2.5 for interspecies differences, 5 for intraspecies differences and 2 for duration adjustment) Oral data are difficult to compare because a NOAEL in animals has not been identified. Risk assessment at the workplace will be based on the F^- levels in humans which are identified as no effect levels with respect to skeletal fluorosis. From two completely different data sources two very similar values have been obtained (see above). It is recognised that the NOAEC from the animal data would lead to a more cautious assessment which, however, is not assumed to be representative for humans.

Inhalation exposure

Using directly the human NOAEC of 0.48 mg F^-/m^3 for workers as starting point for risk assessment and taking into account the F^- content of cryolite of 54 % reveals a critical air concentration for cryolite at the workplace of 0.89 mg cryolite/m^3 (0.48 mg F^- x 100/54 cryolite/ F^-). As alternative, risk assessment could be based on the reference value for fluoride of 6 mg F^-/person/day. Doing so, it should be taken into account that fluoride intake by food and drinking water in Europe is assumed to be about 1 mg F^-/person/day. Additional intake of fluoride by workplace conditions should therefore not exceed 5 mg F^- /person/day. Under this presumption the critical air concentration of cryolite would be 1.03 mg cryolite/m^3 for workers inhaling 10 m^3 per shift and taking into account the F^- content of cryolite and assuming 90 % absorption by inhalation (5 mg F^- x 100/54 cryolite/F^- / 0.9 / 10 m^3).

The German MAK-value for fluoride has recently been set to 1 mg F^-/m^3 (DFG 2005). It is recognised that application to cryolite would reveal an air concentration of 1.9 mg cryolite/m^3 (1 mg F^- /m^3 x 100/54 cryolite/F^-).

The human NOAEC of fluoride for workers of 0.48 mg F^- which corresponds to about 0.89 mg cryolite/m^3, and the reference value for fluoride from the WHO which corresponds to about 1.03 mg cryolite/m^3 are quite similar. In this report for risk assessment at the workplace a value of 1 mg cryolite/m^3 is used as critical exposure level. Additional assessment factors for worker risk assessment are not deemed necessary. The reference MOS is 1. Borderline scenarios are included in the concern range taking into account that no specific precautionary elements have been included in inhalation risk assessment.

As can be seen from table 4.8 air concentrations of cryolite in the aluminium industry and during use in other industries clearly exceed the critical exposure level thus giving reason for concern. During production of synthetic cryolite exposure may occur against dust or granules, the latter one giving lower air concentrations. In both cases however there is reason for concern. The same holds true for grinding activities. By two methodical approaches a spectrum for the exposure data is given, which results at the upper end in a borderline scenario. These risks should not be neglected.

In summary concern is to be expressed for all scenarios (1 – 4). For grinding activities under certain conditions risks can be excluded.

Conclusion: iii

Dermal contact

No specific data are available to assess the systemic toxicity of cryolite after repeated dermal contact. For a first approximation also the maximum additional fluoride intake of 5 mg F^-/person or 0.07 mg F^-/kg is used as reference (see inhalation exposure). Taking into account the F^- content of cryolite and assuming 10 % skin absorption results in an exposure level for workers of 92 mg cryolite/person/day (5 mg F^- x 100/54 cryolite/F^- / 0.1) or 1.3 mg cryolite/kg/day as starting point for risk assessment. Since additional assessment factors for worker risk assessment are not deemed necessary this value similarly resembles the critical dermal exposure level. The reference MOS is 1.

According to table 4.8 for production of cryolite (scenario 1) and the use of cryolite in the aluminium industry (scenario 2) the dermal exposure is low enough to be out of the concern range. However with a MOS of 1.1 in scenario 2 it is still very close. For the other scenarios a MOS below 1 gives clear indication for concern. It should be kept in mind though, that the uncertainty of the assessment is high because for dermal absorption of the dusty material a value of 10 % is assumed without data. As way forward, robust information on dermal absorption of fluoride from solid cryolite could significantly improve the risk assessment.

Conclusion: iii

Combined exposure

For all exposure scenarios of cryolite, there is concern for one or both routes of exposure and thus for combined exposure as well. A special case is production of synthetic cryolite using granules because inhalation and dermal exposure are each associated with borderline results. In combination, however, this leads to clear indication of concern. For quantitative data see table 4.8.

Conclusion: iii

Table 4.8 Repeated dose toxicity, systemic effects

	Inhalation(1)			Dermal(1)			Combined(2)		
Starting point for MOS calculation	1 mg/m^3			1.3 mg cryolite/ kg/day			0.07 mg F$^-$/kg/day		
Reference MOS	1			1			1		
Critical exposure level	1 mg/m^3			1.3 mg/kg/day			0.07 mg F$^-$/kg/day		
	Exposure (mg/m^3)	MOS	Conclusion	Exposure (mg/person/d)	MOS	Conclusion	Internal body burden (mg/person/d)	MOS	Conclusion
1. Production of synthetic cryolite dust	5	0.2	iii	0.6	2.2	ii	0.38	0.2	iii(3)
Production of synthetic cryolite granules	1	1	border -line iii	0.6	2.2	ii	0.1	0.7	iii(3)
2. Aluminium industry	2	0.5	iii	1.2	1.1	ii	0.22	032	iii(3)
3. Use in other industries	10	0.1	iii	43	0.03	iii	3.0	0.02	iii(3)
4. Abrasives, grinding discs EASE	1	1	border -line iii	3.6	0.4	iii	0.27	0.26	iii(3)
Abrasives, grinding discs analogous data	0.1	10	ii	3.6	0.4	iii	0.207	0.3	iii(3)

(1) external exposure values for croylite are used for the assessment

(2) internal fluoride levels are used for the assessment

(3) conclusion iii already results from inhalative and/or dermal exposure

Table 4.9 Occupational risk assessment for repeated dose toxicity

	Inhalation				**Dermal**				**Combined**			
	Exposure	**NOAEL**	**MOS**	**Conclusion**	**Exposure**	**NOAEL**	**MOS**	**Conclusion**	**Exposure**	**NOAEL**	**MOS**	**Conclusion**
Production												
Subscenario 1												
Subscenario 2												
Subscenario 3												
Subscenario 4												
Subscenario 5												
Formulation												
Subscenario 1												
Uses												
Subscenario 1												
Subscenario 2												
Subscenario 3												

[click here to insert table note or Table X.X continued overleaf or delete if not appropriate]

4.1.3.2.5 Mutagenicity

Cryolite does not induce gene mutations in a bacterial in vitro system. In vitro tests on induction of chromosomal aberrations (human lymphocytes) and unscheduled DNA synthesis (rat hepatocytes) are reported to be negative, but cannot be adequately assessed because of the lack of full reports. In vivo cryolite was negative in rat bone marrow chromosomal aberration tests after acute and repeated inhalation exposure.

In summary there is no reason for concern with respect to mutagenicity

Conclusion: ii

4.1.3.2.6 Carcinogenicity

In order that carcinogenicity studies with cryolite are not available and fluoride has been identified as the moity of toxicological concern, studies with fluorides other than cryolite are included for the risk assessment.

Four carcinogenicity studies with sodium fluoride (two diet studies and two drinking water studies, see chapter 4.1.2.8.1) are available. From these studies with NaF in rats and mice it was concluded that “the available data are sufficient to suggest that fluoride is not a carcinogenic substance in animals." (EU risk assessment of hydrogen fluoride).

Since the results with the oral studies with NaF give no indications that fluoride has a carcinogenic potential in animals, and taking into account that cryolite is not mutagenic there is no reason for concern for workers with regard to carcinogenicity of cryolite.

Conclusion: ii

4.1.3.2.7 Toxicity for reproduction

Effects on fertility

Cryolite was investigated for reproductive toxicity in a two-generation study in rats with dietary administration in the range of 15 to 150 mg/kg/day. Dental fluorosis as indication for fluoride accumulation occurred at all dose levels. The results of this study do not direct towards a specific potential of cryolite to cause adverse effect to fertility. During a study with repeated inhalation of cryolite in rats also organs of the reproductive system have been evaluated. No substance-related effects on these organs were observed up to an air concentration of 4.6 mg/m^3. Fluoride concentrations in bones and tooth samples, however, were increased at that dose.

In summary there is no indication for fertility risks caused by cryolite, a quantitative assessment is not deemed necessary, there is no concern for workers from this aspect.

Conclusion: ii

Developmental toxicity

Cryolite was investigted for prenatal developmental toxicity in rats, mice and rabbits with the oral route of administration. While from the studies with rats and with rabbits there was no prenatal developmental toxicity, some indications for bent ribs and bent limb bones were reported from the mice study. These anomalies were only reported at dose levels showing severe maternal toxicity. Thus the effects are not considered to be indicative for a substance specific teratogenic potential of cryolite. During the two-generation study with rats, administering 0, 14, 42, 128 mg cryolite/kg/day in the diet, growth retardation in postnatal development was observed. Because this effect ocurred without any significant sign for systemic toxicity it is considered indicative for a specific toxic potential of cryolite adverse to postnatal development. The respective NOAEL in the diet study was 42 mg cryolite/kg/day. This value is taken forward for risk assessment. Data for other routes or human data are not available.

Inhalation exposure

Inhalation risk assessment will be based on the oral NOAEL of 42 mg cryolite/kg/day from the two-generation rat study. Taken forward to workers (bodyweight 70 kg) and taking into account oral absorption of 85% for animals and 100% inhalation absorption this value corresponds to an air concentration at the workplace of 250 mg cryolite /m^3 (42 mg/kg/day x 70 kg x 0.85/1 / 10 m^3), assuming a respiratory volume of 10 m^3 for workers in 8 hours shift. The air concentration resembles the corrected NOAEC and gives the starting point for inhalation risk assessment.

The following adjustment factors are applied for the identification of the reference MOS: (1) the allometric scaling factor for the rat is 4; (2) a default factor of 2.5 accounts for additional interspecies differences; (3) for intraspecies differences (workers) the default factor is 5. This gives a reference MOS of 50 (4 x 2.5 x 5). An adjustment for study duration is not deemed necessary. The critical inhalation exposure level at the workplace is identified as 5 mg cryolite /m^3 (250/50).

As can be seen from table 4.10 there is one inhalation scenario at risk (scenario 3: use in other industries). It has to be kept in mind though, that under the aspect of systemic toxicity the critical air concentration for repeated inhalation of cryolite is 1 mg/m^3. If this would be kept, developmental risks would also be diminished.

Conclusion: iii

Dermal contact

Also dermal risk assessment is based on the NOAEL from the two-generation diet study in rats. Taking into account oral (85%) and dermal (10 %) absorption a value of 357 mg cryolite /kg/day (42 mg cryolite/kg/day x 0.85 / 0.1) is used as starting point for the dermal route.

The following adjustment factors are applied for the identification of the reference MOS: (1) the allometric scaling factor for the rat is 4; (2) a default factor of 2.5 accounts for additional interspecies differences; (3) for intraspecies differences (workers) the default factor is 5. This gives a reference MOS of 50 (4 x 2.5 x 5). An adjustment for study duration is not deemed necessary. The critical dermal exposure level at the workplace is identified as 7.1 mg cryolite/kg/day (357/50).

As can be seen from table 4.10 there is one dermal scenario at risk (scenario 3: use in other industries). It has to be kept in mind though, that under the aspect of systemic toxicity the critical exposure level for repeated dermal contact with cryolite is 1.3 mg/kg/day (92 mg/person/day / 70 kg/person). If this would be kept, developmental risks would also be diminished.

Conclusion: iii

Combined exposure

For risk assessment of combined exposure the internal level of fluoride corresponding to the oral NOAEL is calculated as 19.3 mg F^- /kg/day (42 mg cryolite/kg/day x 0.85 x 0.54), taking into account the oral absorption percentage and the fluoride content of cryolite. This is used as starting point for combined risk assessment.

Similar adjustment factors as above for dermal and inhalation exposure are applied giving a reference MOS of 50. The critical internal fluoride level results as 0.39 mg F^-/kg/day (19.3/50) with respect to developmental toxicity.

In comparison to inhalation and dermal risk assessment one additional scenario is identified to be of concern because of combined exposure at both routes. However, from repeated dose toxicity the reference dose for fluoride uptake at the workplace is derived as 0.07 mg F^-/kg/day or 5 mg F^-/person/day. If this would be kept, developmental risks would also be diminished.

Conclusion: iii

Table 4.10 Developmental toxicity, postnatal effects

	Inhalation(1)			Dermal(1)			Combined(2)		
Starting point for MOS calculation	250 mg cryolite/m^3			357 mg cryolite/kg/day (external value)			19.3 mg F^-/kg/day (internal value)		
Reference MOS	50			50			50		
Critical exposure level	5 mg cryolite/m^3			7.1 mg cryolite/kg/day			0.39 mg F^-/kg/day		
	Exposure (mg/m^3)	MOS	Conclusion	Exposure (mg/ kg /d)	MOS	Conclusion	Internal body burden (mg/kg/d)	MOS	Conclusion
1. Production of synthetic cryolite dust	5	50	ii	0.6	595	ii	0.38	51	ii
Production of synthetic cryolite granules	1	250	ii	0.6	595	ii	0.1	193	ii
2. Aluminium industry	2	125	ii	1.2	298	ii	0.22	88	ii
3. Use in other industries	10	25	iii	43	8.3	iii	3.0	6.4	iii(3)
4. Abrasives, grinding discs EASE	1	250	ii	3.6	99	ii	0.27	72	iii
Abrasives, grinding discs analogous data	0.1	2500	ii	3.6	111	ii	0.207	93	ii

(1) external exposure values for croylite are used for the assessment
(2) internal fluoride levels are used for the assessment
(3) conclusion iii already results from inhalative and/or dermal exposure

4.1.3.2.8 Summary of risk characterisation for workers

As result of occupational risk assessment for cryolite, concern is expressed and risk reduction measures have to be initiated. The most important adverse health effects for which protection is needed are local irritation in the airways induced by repeated exposure and fluorosis caused by increased systemic fluor levels as result of repeated exposure to cryolite. Table 4.11

summarizes the toxicological endpoints of concern. Besides the ones already mentioned there is also some concern with respect to developmental toxicity. In this case the combination of inhalation and dermal exposure results in concern for one scenario which is not at risk in the route-specific assessments (see table 4.10). For acute toxicity, respiratory irritation, skin irritation, respiratory sensitisation, mutagenicity and fertility no concern is expressed. Due to insufficient data base for eye irritation conclusion i (on hold) is expressed.

Table 4.11 Endpoint-specific overall conclusions for the occupational risk assessment of cryolite

Toxicological endpoints		concern
Acute toxicity	inhalation	ii
	dermal	ii
	combined	ii
Irritation/ Corrosivity	dermal	ii
	eye	i (on hold)
	acute respiratory tract	ii
Sensitisation	skin	ii
	respiratory	ii
Repeated dose toxicity	local, inhalation	iii
	local, dermal	ii
	systemic, inhalation	iii
	systemic, dermal	iii
	systemic, combined	iii(1)
Mutagenicity		ii
Carcinogenicity	inhalation	ii
	dermal	ii
	combined	ii
Fertility impairment	inhalation	ii
	dermal	ii
	combined	ii
Developmental toxicity	inhalation	iii
	dermal	iii
	combined	iii

(1) conclusion iii already results from dermal exposure and/or inhalation, therefore no specific concern for the combined exposure scenario is indicated

Risk estimation is based either upon epidemiological studies of certain working populations exposed to cryolite or on long-term inhalation studies with cryolite dust (rats). For oral absorption of fluoride a value of 95 % is used and for the inhalation route 90% is taken, both on the background of experimental data. For dermal absorption a value of 10% is assumed to be reasonable, however, reliable data are not available.

Tables 4.12. (inhalation) and 4.13 (dermal contact) intend to visualize the risk profile of cryolite. According to the arrangement of the tables high risks occur on the left side, low risks on the right side of the table-matrix.

With respect to local effects in the airways after repeated inhalation exposure levels to cryolite dust should be controlled to values in the range of 0.1 mg/m^3 (critical exposure level for local effects after repeated exposure). In doing so, inhalation risks from other endpoints, especially adverse effects by fluorosis after long-term exposure (critical exposure level: 1 mg/m^3), as well as risks by developmental toxicity (critical exposure level: 6.2 mg/m^3) are similarly and effectively be mitigated too.

Special attention should be given to skin contact. From the risk assessment there is indication that repeated dermal exposure at the workplace to cryolite dust might contribute to critical elevated systemic fluoride levels. This could lead to fluorosis and also an elevated cancer risk cannot fully be ruled out. If it causes severe problems to controll the dermal exposure situation at the workplace to a level below 1.3 mg/kg/day or 92 mg/person/day (critical exposure level for fluorosis), a suitable dermal absorption study could give an additional option to refine the dermal risk estimation and might be taken into consideration.

To prevent adverse health effects by fluorosis according to the WHO (EHC 2002) a total daily uptake of 6 mg F^-/person should not be exceeded. In this respect cryolite exposure at the workplace is only one factor among others which might contribute to systemic fluoride accumulation. To control the different sources for elevated systemic fluoride levels a more general approach is needed which includes fluoride uptake by working conditions as well as fluoride exposure of the general public by other sources too. This however is no subject of this report.

Table 4.12 Ranking of health risks for workers (inhalation)

Exposure scenario	Exposure level in mg/m³	Repeated dose toxicity, local effects	Repeated dose toxicity, systemic effects: fluorosis, carcinogenicity	Developmental effects
		Critical exposure level in mg/m^3		
		0.1	1	5
3. Use in other industries	10	iii	iii	iii
1. Production of synthetic cryolite dust	5	iii	iii	
2. Aluminium industry	2	iii	iii	
1. Production of synthetic cryolite granules	1	iii	borderline iii	
4. Abrasives, grinding discs EASE	1	iii	borderline iii	
Abrasives, grinding discs analogous data	0.1	borderline iii		

(1) blank fields: conclusion ii

Table 4.13 Ranking of health risks for workers (dermal contact)(1)

Exposure scenario	Exposure level in mg/kg/day	Repeated dose toxicity, systemic effects: fluorosis,	Developmental toxicity
		Critical exposure level in mg/kg/day	
		1.3	7.1
3. Use in other industries	43	iii	iii
4. Abrasives, grinding discs EASE, analogous data	3.6	iii	ii
2. Aluminium industry	1.2	ii	ii
1. Production of synthetic cryolite dust, granules	0.6	ii	ii

(1)

Table 4.14 Overview of the conclusions with respect to occupational risk characterisation

		Acute toxicity		Local toxicity after single or repeated exposure			Sensiti sation	Repeated dose toxicity Systemic			Muta genicity	Carcino genicity	Reproduc tive toxicity
		Dermal	Inhalation	Dermal	Inhalation	Eye		Dermal	Inhalation	Combined			
Production													
Subscenario 1	MOS												
	Concl.												
Subscenario 2	MOS												
	Concl.												
Subscenario 3	MOS												
	Concl.												
Subscenario 4	MOS												
	Concl.												
Subscenario 5	MOS												
	Concl.												
Formulation													
Subscenario 1	MOS												
	Concl.												
Uses													
Subscenario 1	MOS												
	Concl.												
Subscenario 2	MOS												
	Concl.												
Subscenario 3	MOS												
	Concl.												

4.1.3.3 Consumers

Exposure of consumers to cryolite occurs via inhalation through use of glazes in pottery. For the use of powdery cryolite the modelled data by EASE estimation without local exhaust ventilation was selected with considering a duration of 1 hour an inhalation exposure of 6.25 mg/m^3 (see chapter 4.1.1.2.3 for details)

The bioavailibility is estimated as 100 % after inhalation.

4.1.3.3.1 Acute toxicity

Human data on the acute toxicity of cryolite are not available.

Inhalation

In a well conducted and guideline-compliant rat inhalation study, a LC50 of 4470 mg/m3 was derived. Therefore, a classification as harmful and labelling with R20 is appropriate. Taken into account the exposure value of 6.25 mg/m3 derived from a worst case scenario (chapter 4.1.1.3) the margin of safety is judged to be sufficient.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Irritation and corrosivity

Skin

Standard skin irritation tests on cryolite are not available. The reported consumer exposure sources did not covered dermal scenarios. Therefore there is no concern for consumers.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Eye

Information on eye irritation indicates that cryolite may have a certain potential for eye irritation. Due to insufficient data quality a final assessment is not possible. Since eye protection measures of consumers does not exist there is concern for eye effects. Due to that insufficient data base for C&L decisions conclusion (i) on hold applies.

Conclusion (i) on hold There is a need for further information and/or testing.

Respiratory tract

Chronic as well acute toxicity studies showed that there are no severe effects regarding respiratory irritation mediated by cryolite. Human data are lacking. Therefore classifcation and labelling is not necessary that leads to no concern for consumers.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.3.2 Sensitisation

Skin

A skin sensitisation potential of cryolite could not be demonstrated in a fully guideline-compliant Magnusson Kligman Test. Therefore there is no concern for consumers regarding skin sensitisation.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Respiratory tract

Regarding the sensitising potential of cryolite at the respiratory tract no information is available. Therefore there is no concern for consumers regarding respiratory sensitisation.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.3.3 Repeated dose toxicity

Since the relevant consumer exposure scenarios are characterized by inhalation of cryolite dermal and oral repeated dose toxicity was not further calculated.

Inhalation

The human NOAEC for inhalation is derived from a study in aluminium smelter with long-term occupational exposure and is given as 0.48 mg fluoride/m^3 for skeletal fluorosis. Animal data showed dystrophic lesions in bones and teeth and adverse effects in the respiratory tract, stomach, kidney, liver and brain in a 5-month inhalation study in male and female rats with a systemic NOAEC of 0.5 mg/m^3 that should be used for risk characterisation.

For the decision on the appropriateness of MOS, the following aspects have been considered and taken into account

-overall confidence in the data base:

The data taken into account for performing the risk characterisation have been evaluated with regard to their reliability, relvance and completeness according to section 3.2 of the TGD

-uncertainty arising from the variability in the experimental data:

The data on toxicity after inhalation exposure is sufficient to allow the identification of an effect level for risk characterisation. There are no reason to assume a special extent of uncertainty which has to be taken into account.

intra- and interspecies variation:

Available data do not allow a conclusion on the intraspecies or interspecies variability of the toxicokinetic or toxicodynamic characteristics of cryolite under consideration.

The nature and severity of the effect:

The observed adverse effects in animals and humans are regard as serious. The systemic health effects are the basis for the classification as toxic, R48/23/25.

- dose-response relationship:

There is no reason to assume a special concern

The human population to which the information on exposure applies: following the exposure pattern there is no reason to assume a special risk for children, elderly, or pregnant women

-other factors:

There are no other factors known that might require a particular margin of safety.

MOS for the inhalation exposure scenario,systemic effects

Repeated exposure by inhalation of cryolite for 90 days caused lung lesions in male and female rats. After chronic inhalation of cryolite for up to 5 months dystrophic lesions in the bones and teeth, and adverse effects in the respiratory tract, stomach, kidney, liver, and brain were noted in both male and female rats. The NOAEC for systemic effects was set at 0.5 mg/^{3} of cryolite and selected for risk characterisation.

The margin of safety between

exposure level of	6.25 mg/m^3

and the

inhalative NOAEC of	0.5 mg/m^3

is judged to be not sufficient.

MOS calculation for local effects is not necessary since uncertainties exist whether the lung lesions detected in animal studies are relevant for humans.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Mutagenicity

Cryolite was tested in a bacterial in vitro system and in mammalian cellular in vitro systems with negative results. In in vivo rat bone marrow chromocomal aberration tests cryolite showed negative test results after acute and repeated inhalation exposure. Therefore there is no concern for consumers.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.3.4 Carcinogenicity

Data on the carcinogenic potential of cryolite from human experience and animal studies are available. There are limited data from humans that indicate a carcinogenic risk from exposure to cryolite. The excess cancer risk identified in workers exposed to fluorides, including fluoride-spar and aluminium production workers, may be due to other factors than fluoride exposure. In summary, it is difficult to relate the excess cancer incidence directly to fluorides. The available data in experimental animals are insufficient to demonstrate a carcinogenic effect of cryolite. Studies in dogs, rats and mice had been performed with synthetic cryolite and the analog sodium fluoride (NTP studies). Due to negative and equivocal test results with synthetic cryolite and sodium fluoride there is no concern for carcinogenicity. The RAR on HF (EC, 2001) concluded that fluoride is not a carcinogenic substance.Therefore the handling of cryolite regarding carcinogenicity is safe for consumers.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.3.5 Toxicity for reproduction

Effects on fertility

There is no indication for fertility risks caused by cryolite, therefore there is no concern for consumers. A quantitative risk characterisation is not necessary.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Developmental toxicity

Cryolite was investigated for prenatal developmental toxicity in rats, mice and rabbits with the oral route of administration. During the two-generation study with rats, administering 0, 14, 42, 128 mg cryolite/kg bw/day in the diet, growth retardation in postnatal development was observed. Because this effect occured without any significant sign for systemic toxicity it is considered indicative for a specific toxic potential of cryolite adverse to postnatal development. The respective NOAEL in the diet study was 42 mg cryolite/kg bw/day. This value is taken for risk characterisation and used for MOS calculation.

For the decision on the appropriateness of MOS, the following aspects have been considered and taken into account.

-overall confidence in the database:

The data taken into account for performing the risk characterisation have been evaluated with regard to their reliability, relevance and completeness according to section 3.2 of the TGD. Most of the animal data are citations from the secondary literature. The orginal data are not available. Due to the developmental effects described the proposal to classify cryolite as Repr. Cat 3, R63 is justified.

-uncertainty arising from the variability in the experimental data:

There are no reasons to assume a special extent of uncertainty

-intra- and interspecies variation:

Available data do not allow a conclusion on the intraspecies or interspecies variability of the toxicokinetic or toxicodynamic characteristics of cryolite under consideration.

The nature and severity of the effect:

The observed adverse effects in animals are regard as serious. The systemic health effects are the basis for the proposal of classification as repr. Cat. 3, R63.

- dose-response relationship:

There is no reason to assume a special concern

The human population to which the information on exposure applies:

following the exposure pattern there is no reason to assume a special risk for children, elderly, or pregnant women

-other factors:

There are no other factors known that might require a particular margin of safety.

MOS for the inhalation exposure scenario, local effects

Inhalation risk assessment will be based on the oral NOAEL of 42 mg cryolite/kg bw/day from the two-generation rat study. Taken forward to consumers (bodyweight 70 kg) and taking into acount oral (95%) and inhalation (90%) absorption this value corresponds to an air concentration for consumers of 3736 mg/m^3 (42 mg/kg bw/day x 0.95/0.9/0.83 m^3), assuming a respiratory volume of 0.83 for consumers in 1 hour shift. The air concentration resembles the corrected NOAEC.

The margin of safety between the

exposure level of 6.25 mg/m^3

and the

inhalative NOAEC of 3736 mg/m^3

is judged to be sufficient.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.3.6 Summary of risk characterisation for consumers

Concern is expressed and risk reduction measures should be intiated for consumer use in pottery. Inhalative repeated dose treatment of cryolite can induced fluorosis at relatively low doses. Regarding acute toxicity, skin irritation , sensitisation, mutagenicity, carcinogenicity and reproductive toxcicty no concern is expressed. Due to insufficient data base for eye irritation conclusion (i) on hold is appropriate.

4.1.3.4 Humans exposed via the environment

There is a need providing exposure information that has been included into the present draft Article 10(2)-Regulation. It is therefore not possible to provide at present realistic worst case exposure estimates for man via the environment. Conclusion (i) is drawn in analogy with the environmental assessment (see chapter 4.1.1.4).

4.1.3.4.1 Exposure via air

4.1.3.4.2 Exposure via food and water

[click here to insert text]

4.1.3.4.3 Summary of risk characterisation for exposure via the environment

[consider overview summary table with MOSs and conclusions]

4.1.3.5 Combined exposure

[click here to insert text; consider whether appropriate to conduct such an assessment, in particular when considering a consumer exposure of a similar order of magnitude to an environmental exposure]

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

4.2.1 Exposure assessment

[click here to insert text]

4.2.1.1 Workers

[click here to insert text]

4.2.1.2 Consumers

[click here to insert text]

4.2.1.3 Humans exposed via the environment

[click here to insert text]

4.2.2 Effects assessment: Hazard identification

[click here to insert text]

4.2.2.1 Explosivity

Cryolite is not explosive.

4.2.2.2 Flammability

Cryolite is not flammable.

4.2.2.3 Oxidizing potential

Due to its chemical structure, cryolite is not expected to possess any oxidising properties.

4.2.3 Risk characterisation

[click here to insert text]

4.2.3.1 Workers

not applicable
conclusion: ii

4.2.3.2 Consumers

[click here to insert text]

4.2.3.3 Humans exposed via the environment

[click here to insert text]

5 RESULTS [7]

5.1 INTRODUCTION

5.2 ENVIRONMENT

General

Conclusion (i) There is a need for further information and/or testing.

Information on downstream user industries (other than aluminium smelters), use volumes, life-cycle steps, emissions, pollution abatement techniques and processes should be provided to replace the generic exposure assessment with a more specific evaluation.

Furthermore, information on waste management and emissions from waste management step of all downstream uses should be provided. Especially aluminium smelters produce considerable amounts of cryolite waste. The amount of this waste, its management and potential emissions should be clarified.

Aquatic compartment (including sediment)

Conclusion (i) There is a need for further information and/or testing.

Conclusion (i) applies to production sites 2,3,4 and downstream uses other than the aluminium industry. Long term toxicity tests with fish, Daphnia and algae are needed for the refinement of PNECsurface water. A microbial inhibition test is needed with higher test concentration than in the available study.

Conclusion (i) applies also to all downstream user sites regarding waste management.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to production sites 3 and 5 for dissolved fluorides to aquatic environment (HF/F -approach). It also applies to aluminium smelter sites for the releases of fluorides to aquatic environment (HF/F -approach).

Terrestrial compartment

Conclusion (i) There is a need for further information and/or testing.

This conclusion applies to production sites 3, 4 and 5 and downstream user sites other than aluminium smelters. The sites should provide information on the amount of particulate cryolite emissions to air (*particulate cryolite approach*).

---

[7] Conclusion (i) There is a need for further information and/or testing.
Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

This conclusion applies for aluminium smelters and production site 2 regarding their emissions of particulate cryolite (*particulate cryolite approach*).

Atmosphere

Conclusion (i) There is a need for further information and/or testing.

Conclusion (i) applies to:

- Production sites 3, 4 and 5 should provide information on particulate cryolite emissions to air (*particulate cryolite approach*).
- all downstream uses, except aluminium smelters (see "General") (*HF/F approach and particulate cryolite approach*). It is expected, that also the PECregional for HF can be refined after specific information on these downstream uses becomes available.
- all downstream user sites regarding waste management (see "General") (*HF/F approach and particulate cryolite approach*).

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

This conclusion cover the production sites 2 and 4 as they contribute to the local ambient concentrations less than the regional background concentration of HF (*HF/F-approach*).

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iii) applies to the production sites 3 and 5 (*HF/F approach*).

Secondary poisoning

The conclusions for the atmosphere cover also the conclusions for the indirect exposure via the food chain.

5.3 HUMAN HEALTH

5.3.1 Human health (toxicity)

5.3.1.1 Workers

Conclusion (i on hold) There is a need for further information and/or testing.

Conclusion (i on hold) applies for eye irritation due to insufficient data base.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iii) applies to repeated dose toxicity (local and systemic effects), and developmental toxicity. On the background of local effects in the airways air concentrations of cryolite dust at the workplace should be controlled to a level in the range of 0.1 mg/m^3 (critical exposure level for local effects after repeated exposure). In doing so also inhalation risks from other endpoints, especially systemic effects by fluorosis as result of repeated exposure and developmental toxicity are similarly and effectively mitigated.

Special attention should be given to skin contact. With respect to fluorosis and taking into account carcinogenicity the dermal exposure at the workplace should not exceed 92 mg/person/day (1.3 mg/kg/day). If this is difficult to ensure with risk management tools, dermal risk estimation might be refined by an additional suitable dermal absorption study.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already

For the other toxicological endpoints the risk orientated conclusions result in no concern with the consequence that risk reduction measures are of low priority.

5.3.1.2 Consumers

Conclusion (i) on hold There is a need for further information and/or testing.

Conclusion (i) on hold applies due to insufficient data base for C&L decision.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iii) applies to repeated dose toxicity and eye irritation. Concern is expressed and risk reduction measures should be intiated for consumer use in pottery. Inhalative repeated dose treatment of cryolite can induced fluorosis at relatively low doses. Since eye protection measures of consumers does not exist there is concern for eye effects.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

This conclusion applies to all the other toxicological endpoints i.e. acute toxicity, irritation other than eye irritation, sensitisation, mutagenicity, carcinogenicity and reproductive toxcicty.

5.3.1.3 Humans exposed via the environment

Conclusion (i) There is a need for further information and/or testing.

5.3.1.4 Combined exposure

[keep only appropriate conclusion(s)]

Conclusion (i) There is a need for further information and/or testing.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion () applies to [click here to insert text in accordance with conclusion(s)]

5.3.2 Human health (risks from physico-chemical properties)

[keep only appropriate conclusion(s)]

Conclusion (i) There is a need for further information and/or testing.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion () applies to [click here to insert text in accordance with conclusion(s)]

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ABBREVIATIONS

[update the list to correspond to the substance RAR]

ADI	Acceptable Daily Intake
AF	Assessment Factor
ASTM	American Society for Testing and Materials
ATP	Adaptation to Technical Progress
AUC	Area Under The Curve
B	Bioaccumulation
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BCF	Bioconcentration Factor
BMC	Benchmark Concentration
BMD	Benchmark Dose
BMF	Biomagnification Factor
bw	body weight / *Bw*, *b.w.*
C	Corrosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
CA	Chromosome Aberration
CA	Competent Authority
CAS	Chemical Abstract Services
CEC	Commission of the European Communities
CEN	European Standards Organisation / European Committee for Normalisation
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
CSTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment (DG SANCO)
CT_{50}	Clearance Time, elimination or depuration expressed as half-life
d.wt	dry weight / dw
dfi	daily food intake
DG	Directorate General
DIN	Deutsche Industrie Norm (German norm)
DNA	DeoxyriboNucleic Acid
DOC	Dissolved Organic Carbon
DT50	Degradation half-life or period required for 50 percent dissipation / degradation
DT90	Period required for 50 percent dissipation / degradation
E	Explosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties [Model]

EbC50	Effect Concentration measured as 50% reduction in biomass growth in algae tests
EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
EDC	Endocrine Disrupting Chemical
EEC	European Economic Communities
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency (USA)
ErC50	Effect Concentration measured as 50% reduction in growth rate in algae tests
ESD	Emission Scenario Document
EU	European Union
EUSES	European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment]
F(+)	(Highly) flammable (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
FAO	Food and Agriculture Organisation of the United Nations
FELS	Fish Early Life Stage
GLP	Good Laboratory Practice
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)
HELCOM	Helsinki Commission -Baltic Marine Environment Protection Commission
HPLC	High Pressure Liquid Chromatography
HPVC	High Production Volume Chemical (> 1000 t/a)
IARC	International Agency for Research on Cancer
IC	Industrial Category
IC50	median Immobilisation Concentration or median Inhibitory Concentration
ILO	International Labour Organisation
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database (existing substances)
IUPAC	International Union for Pure and Applied Chemistry
JEFCA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
Koc	organic carbon normalised distribution coefficient

Kow	octanol/water partition coefficient
Kp	solids-water partition coefficient
L(E)C50	median Lethal (Effect) Concentration
LAEL	Lowest Adverse Effect Level
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOED	Lowest Observed Effect Dose
LOEL	Lowest Observed Effect Level
MAC	Maximum Allowable Concentration
MATC	Maximum Acceptable Toxic Concentration
MC	Main Category
MITI	Ministry of International Trade and Industry, Japan
MOE	Margin of Exposure
MOS	Margin of Safety
MW	Molecular Weight
N	Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC
NAEL	No Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program (USA)
O	Oxidizing (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OJ	Official Journal
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic
P	Persistent
PBT	Persistent, Bioaccumulative and Toxic
PBPK	Physiologically Based PharmacoKinetic modelling
PBTK	Physiologically Based ToxicoKinetic modelling
PEC	Predicted Environmental Concentration

pH	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
PNEC	Predicted No Effect Concentration
POP	Persistent Organic Pollutant
PPE	Personal Protective Equipment
QSAR	(Quantitative) Structure-Activity Relationship
R phrases	Risk phrases according to Annex III of Directive 67/548/EEC
RAR	Risk Assessment Report
RC	Risk Characterisation
RfC	Reference Concentration
RfD	Reference Dose
RNA	RiboNucleic Acid
RPE	Respiratory Protective Equipment
RWC	Reasonable Worst Case
S phrases	Safety phrases according to Annex III of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SBR	Standardised birth ratio
SCE	Sister Chromatic Exchange
SDS	Safety Data Sheet
SETAC	Society of Environmental Toxicology And Chemistry
SNIF	Summary Notification Interchange Format (new substances)
SSD	Species Sensitivity Distribution
STP	Sewage Treatment Plant
T(+)	(Very) Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
TDI	Tolerable Daily Intake
TG	Test Guideline
TGD	Technical Guidance Document
TNsG	Technical Notes for Guidance (for Biocides)
TNO	The Netherlands Organisation for Applied Scientific Research
UC	Use Category
UDS	Unscheduled DNA Synthesis
UN	United Nations
UNEP	United Nations Environment Programme
US EPA	Environmental Protection Agency, USA
UV	Ultraviolet Region of Spectrum
UVCB	Unknown or Variable composition, Complex reaction products of Biological material

vB	very Bioaccumulative
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
v/v	volume per volume ratio
w/w	weight per weight ratio
WHO	World Health Organization
WWTP	Waste Water Treatment Plant
Xn	Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
Xi	Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)

Appendix A

Estimation of the concentration of particulate cryolite in air and deposition around aluminium smelters using OPS-Pro 4.1
It is noted, that the calculation examples below do not represent any specific case of the present RAR –version.

Program settings

Note: the emission data was from the year 2002
Source size: 500 m * 500 m
Source height: 25 m ± 0 m
Weather conditions: NL average for the year 2002
    climatological area : The Netherlands (region 0)
    type of statistics : normal statistics
    climatological period: 020101 - 030101 year period
Surface roughness (z0) data used: Regionally differentiated z0 values determined by OPS (not relevant for local assessment)
Grid cell size: 50 m *50 m
Particle size: "coarse" class used for calculations as defined in the program (see below).

	"Coarse"	"Medium"	"Fine"
Class 1 <0.95 µm	42 %	53 %	70 %
Class 2 0.95 – 4 µm	33 %	28 %	20 %
Class 3 4 – 10 µm	14.5 %	11.5 %	5.5 %
Class 4 10 – 20 µm	5.9 %	4.2 %	2.5 %
Class 5 > 20 µm	4.6 %	3.3 %	2 %

Calculation of Clocal,air

The Clocal,air was calculated as the average of the values in the non-coloured cells (see the OPS-Pro 4.1 output grid below). This corresponds to an area which reaches from the edge of the source to 100 m distance from the edge of the source. Red cells cover the area of the source.

The calculation procedure used two OPS-Pro program runs:

- a run where the average concentration in air (O) for the whole area (14*14 grid = 196 cells = m+n) was calculated
- a run where the average concentration in air (B) for the source area (10*10 grid = 100 cells = n) was calculated

The average of the 100 m broad edges (A) of the whole area was calculated with the following equation:

$$A = \frac{(n+m) * O - n * B}{m}$$

This procedure was used because OPS-Pro 4.1 gives as output the avearages of the whole receptor area of a specific run.

```
Project  : cryol. Clocalair, in 100 mdistance, max, 50 %, coarse
 Substance: cryolite
 Date/time: 14-01-2007; 11:47:49
 ============================ OPS-4.1.15  22 Mar 2005 ============================
 concentration distribution of cryolite: ( 1.E+00 ug/m3)

 137 165 193 244 308 361 404 425 429 428 388 352 319 280

 156 162 193 246 316 397 469 486 460 424 380 350 317 324

 176 184 186 253 322 385 401 424 409 419 378 318 363 366

 198 209 235 295 329 381 412 427 400 383 374 393 405 411

 227 241 257 334 318 361 419 433 387 349 388 451 464 459

 237 267 325 356 365 336 418 413 348 399 424 449 526 489

 245 290 340 380 407 421 353 351 433 441 436 441 561 492

 242 281 326 370 402 405 349 368 449 432 433 440 547 474

 229 249 306 344 344 324 411 429 356 405 429 449 474 432

 213 217 244 301 297 353 400 408 379 346 383 420 395 376

 182 185 197 246 305 346 380 386 385 353 342 320 317 315

 159 161 153 196 253 322 352 357 369 350 284 239 259 258

 139 138 161 190 227 278 320 337 315 282 252 229 211 216

 120 138 160 189 228 254 271 277 274 262 235 215 195 180
 grid cell dimension  :  0.050 km
 number of grid points:  14x14
 top left coordinates :   -0.325,    0.325 km
 average cryolite concentration         : 0.328E+03 ug/m3
```

Calculation of the average deposition around the source

The deposition around the source was calculated as the average of the values in the cells of the non-coloured area (see the OPS-Pro 4.1 output extract below). This area corresponds to an area which reaches from the edge of the source to the 1000 m distance from the edge of the source. Red cells cover the area of the source.

The calculation procedure used two OPS-Pro program runs:

- a run where the average deposition (*O*) for the whole area (50*50 grid = 2500 = m+n) was calculated
- a run where the average deposition in air (*B*) for the source area (10*10 grid = 100 = n) was calculated

The average of the 1000 m broad edges (*A*) of the whole area was calculated with the previous equation.

Project : cryol. deposition in 1000 m dist. min, 50 %, coarse
total deposition distribution (as cryolite): (1.E-04 g/m2/y)

56	58	61	65	70	73	78	82	88	95	100	107	114	121	128	135	142	149	155	161	161	167	172	176	180	183	186	186	186	186	184	181	176	172	168	162	156	150	143	136	131	125	119	114	108	104	99	94	92	88
58	59	62	66	69	75	80	84	90	98	103	110	118	126	134	141	149	157	166	173	178	179	184	189	194	196	199	199	199	198	196	194	187	183	176	170	163	156	149	141	136	129	122	117	111	106	101	98	94	91
61	62	63	66	70	74	82	86	93	98	106	114	122	131	140	148	157	168	176	183	192	191	199	203	208	211	214	214	214	212	210	206	200	194	186	178	170	162	154	146	139	133	125	120	113	108	105	101	97	94
64	66	66	67	71	75	80	88	93	100	109	118	127	136	146	156	166	177	186	197	207	209	215	222	227	230	230	231	230	228	225	221	215	205	196	188	179	169	160	152	143	135	129	121	116	112	109	104	102	101
67	69	70	70	73	76	81	90	95	103	112	122	132	143	153	164	175	188	198	210	224	224	233	241	246	249	251	252	250	247	243	237	230	219	209	198	187	177	167	157	148	139	133	125	122	119	112	110	108	106
70	72	73	75	76	82	83	88	98	106	113	124	135	146	161	173	185	200	214	225	237	244	254	262	268	271	273	273	271	267	263	255	245	232	221	209	195	184	172	162	153	144	136	130	136	122	118	116	113	110
74	76	78	79	81	83	137	91	96	107	117	128	140	153	166	182	196	213	229	241	256	274	275	285	292	298	299	298	295	289	284	274	261	246	233	218	205	192	180	169	158	150	143	182	133	128	125	123	119	116
78	80	82	84	86	87	90	145	101	107	119	130	143	160	174	193	208	227	246	263	280	300	302	313	321	327	328	327	322	315	309	296	279	262	247	230	215	199	186	175	167	162	194	146	139	137	132	128	124	120
82	85	87	89	91	94	96	101	153	169	120	136	149	164	184	201	222	244	263	287	308	328	332	347	356	362	363	361	354	348	338	317	300	279	259	243	224	209	196	186	224	207	165	153	148	143	138	135	130	126
87	90	91	95	98	101	103	107	168	162	179	137	154	170	191	210	235	260	285	309	336	358	370	384	397	404	405	400	391	382	365	343	320	296	273	254	235	220	213	241	222	228	170	163	157	151	145	140	136	131
90	94	97	101	105	107	111	114	120	178	172	191	209	182	201	225	252	281	309	337	369	395	411	431	445	453	453	446	434	422	399	372	345	318	292	269	251	286	259	240	246	191	179	172	165	159	152	146	141	135
95	99	103	107	112	115	121	124	130	137	190	185	205	233	217	239	268	299	332	370	408	439	464	487	502	509	507	501	489	470	439	402	370	339	312	294	322	282	263	265	218	199	189	181	174	167	160	152	146	140
99	104	109	114	119	124	130	134	141	146	209	203	198	223	254	265	289	322	364	402	447	490	535	551	572	580	577	562	548	516	480	442	402	368	348	354	313	284	289	294	223	210	199	191	182	175	167	158	151	144
104	109	114	121	127	133	140	147	153	159	170	231	221	214	253	279	335	355	398	442	501	552	606	634	659	667	661	640	620	578	528	484	443	426	393	355	308	318	327	254	236	222	222	211	201	193	183	175	156	149
109	114	120	127	134	143	149	158	168	176	185	201	250	248	234	278	322	368	446	492	557	628	688	733	764	777	767	737	707	646	591	545	515	455	393	339	358	358	295	268	251	237	223	211	200	190	180	171	161	153
113	119	126	134	142	152	161	172	181	190	205	219	243	273	270	259	310	374	439	567	637	719	796	867	912	926	909	872	806	743	682	617	528	436	373	392	396	346	308	286	267	251	236	222	208	198	186	176	165	156
117	125	132	141	150	160	171	183	197	209	226	242	262	302	310	302	288	361	443	527	743	824	926	1019	1083	1099	1070	1016	928	871	737	616	506	408	434	452	418	360	330	305	284	266	248	231	216	204	192	181	170	159
121	129	139	148	159	170	183	197	212	228	248	267	289	320	348	354	350	326	414	528	654	968	1079	1207	1303	1326	1283	1202	1107	875	723	570	451	501	516	506	429	386	353	326	301	280	260	241	224	209	197	185	173	162
124	133	143	153	166	179	194	210	225	246	269	293	323	355	402	407	417	402	367	497	644	849	1241	1405	1570	1598	1524	1381	1064	838	665	496	562	595	594	519	459	415	377	347	317	292	270	249	231	215	202	186	174	163
129	138	148	160	171	186	201	220	242	264	289	320	350	389	437	510	479	492	477	432	620	862	1157	1484	1886	1885	1567	1327	1042	779	566	653	695	699	637	551	492	445	402	365	332	304	279	257	237	220	205	190	178	166
132	141	152	164	179	194	212	233	252	279	309	345	382	429	483	557	662	583	593	586	531	842	1256	1606	1701	1744	1585	1383	957	644	767	822	835	808	683	593	528	472	423	381	342	311	285	262	241	224	208	192	179	167
134	144	155	168	183	200	218	241	266	295	329	362	407	462	530	614	709	852	735	774	792	736	1030	1466	1698	1720	1448	1074	787	956	1004	1009	1013	847	731	630	555	489	436	392	353	319	289	265	242	226	208	192	178	166
135	145	157	170	186	203	223	247	273	306	342	386	440	502	584	662	782	915	1085	966	1068	1002	724	1201	1697	1703	1210	739	1062	1367	1285	1264	1100	903	772	663	578	509	449	399	354	320	288	263	240	223	207	189	176	165
135	146	158	171	187	205	226	250	278	312	350	397	454	523	612	712	842	989	1164	1135	1362	1319	1157	727	1621	1564	730	1214	1449	1575	1550	1354	1142	950	797	672	582	510	446	397	353	317	287	261	237	220	203	188	174	163
135	146	158	172	187	206	227	251	280	314	353	401	460	531	623	728	860	1014	1218	1408	1441	1516	1561	1549	733	727	1582	1685	1692	1681	1704	1371	1140	943	796	669	575	502	439	390	347	312	283	256	232	215	199	183	170	158
13	14	15	17	18	20	22	24	27	31	35	39	45	52	61	71	84	989	119	134	136	146	154	147	699	738	160	167	166	166	163	131	108	90	76	64	55	48	42	37	33	30	27	24	22	21	19	17	16	15

5	5	7	1	7	5	5	9	7	1	0	7	6	5	0	0	1		2	8	1	6	7	9			9	2	9	4	1	2	4	5	3	2	8	7	6	8	5	1	3	7	8	1	5	9	6	5
133	144	155	169	184	202	221	245	272	304	341	386	438	502	580	669	785	894	1039	1041	1231	1231	1063	671	1475	1547	715	1186	1400	1500	1351	1164	990	824	702	599	525	459	406	360	319	290	262	237	220	203	187	172	160	149
132	142	153	166	181	198	216	239	263	293	325	366	414	461	527	587	689	792	907	833	895	853	636	1065	1534	1550	1125	689	981	1138	1031	1022	865	728	624	545	479	426	380	336	304	273	249	226	210	194	179	167	155	144
130	139	150	163	176	191	214	235	254	277	304	329	368	413	465	530	606	708	638	636	612	566	862	1194	1472	1464	1293	917	643	700	739	738	750	632	543	481	419	376	337	308	281	257	235	214	198	184	172	158	149	139
127	141	152	161	175	188	202	221	236	258	282	308	335	373	414	469	544	507	491	463	398	586	836	1185	1366	1341	1276	974	625	422	500	529	547	550	469	418	374	335	307	277	255	235	219	200	186	175	162	151	140	133
127	136	144	155	164	176	189	206	222	237	258	280	303	330	366	420	416	413	381	329	450	593	760	937	1143	1144	957	770	608	449	333	391	423	426	410	359	323	295	273	249	228	215	198	184	173	162	154	142	134	125
121	129	138	146	155	167	179	192	203	218	236	251	274	297	331	349	347	321	284	369	461	576	785	867	917	909	849	784	581	459	366	285	327	353	358	322	290	266	244	227	210	196	188	176	165	153	143	136	128	120
117	123	131	139	147	156	165	177	189	199	214	227	242	266	290	294	281	254	314	385	459	619	661	715	744	736	696	641	599	454	380	307	253	287	299	295	259	237	221	207	193	183	174	163	153	145	138	131	122	115
112	117	123	130	137	144	152	162	172	180	193	204	218	253	252	238	227	275	326	379	484	513	563	594	608	603	582	539	492	459	372	319	269	225	243	254	244	214	198	187	175	168	161	151	143	136	130	123	117	112
106	111	116	122	128	135	142	150	156	162	173	183	202	217	214	204	237	279	319	376	402	440	478	499	505	505	492	454	423	382	356	313	272	230	202	216	219	198	178	169	159	154	149	141	134	128	122	117	112	107
101	105	110	114	120	125	129	135	143	148	155	167	197	194	183	212	241	269	299	320	349	377	405	420	425	425	417	388	365	335	305	284	263	234	204	180	196	196	164	152	146	142	135	129	126	120	115	111	106	102
95	99	103	107	111	114	119	124	128	132	142	181	172	167	192	211	237	242	260	281	306	329	349	359	366	365	358	335	317	296	271	248	229	221	204	185	162	170	179	140	132	128	125	119	115	112	108	104	101	97
89	93	96	100	103	105	109	111	116	121	160	156	154	171	190	190	199	214	233	251	270	290	302	311	317	317	310	300	279	261	243	225	206	190	179	184	163	149	154	159	121	117	112	110	106	105	101	98	95	91
84	86	89	92	95	96	100	102	106	113	144	142	155	174	159	167	180	194	209	225	241	256	266	274	278	278	273	265	244	234	220	204	189	173	160	150	169	148	138	142	114	108	103	102	98	97	94	92	88	86
78	80	83	85	88	88	91	93	98	135	131	144	157	134	142	154	166	178	190	202	214	225	234	241	245	245	241	233	215	210	199	186	174	161	149	138	129	151	137	126	132	99	95	93	91	90	88	85	83	81
74	76	77	79	81	83	84	86	126	122	134	112	116	124	133	142	153	163	173	182	194	202	210	215	218	218	214	209	194	189	180	170	160	149	139	130	121	114	108	128	118	123	88	86	85	83	81	79	79	77
69	71	72	72	74	76	77	82	115	125	97	102	109	116	125	133	142	150	158	167	176	182	188	193	195	195	193	188	175	170	165	156	149	140	132	124	115	108	101	95	120	111	84	79	79	77	75	75	74	72
64	66	67	68	70	70	73	108	82	86	91	96	103	110	117	124	131	138	144	151	160	167	172	176	177	177	176	172	166	154	151	145	139	132	124	117	110	103	96	91	85	82	105	75	73	72	71	70	69	67
61	62	63	63	64	66	102	73	77	81	86	92	97	103	109	116	122	127	132	138	146	152	156	159	160	160	159	156	151	141	139	134	128	122	116	110	104	98	93	87	82	77	74	99	69	67	66	66	65	64
56	57	58	59	60	66	66	69	73	78	82	87	92	97	103	107	112	117	123	129	134	139	142	145	146	146	145	142	139	130	127	123	119	114	109	104	99	94	89	84	80	75	70	67	68	63	62	61	61	60
54	54	55	55	59	59	64	67	70	75	79	83	87	92	96	100	104	108	112	118	124	128	131	133	133	133	133	131	128	121	117	114	111	107	103	98	94	90	86	81	77	73	69	65	63	61	58	58	58	57
51	51	51	54	55	59	62	65	68	71	75	79	83	86	90	94	97	101	104	112	115	118	120	122	123	123	122	120	118	112	108	106	103	100	96	93	89	86	82	78	74	70	67	63	60	59	56	55	55	54
47	48	50	51	55	57	60	63	66	69	72	75	78	82	85	88	91	94	98	103	107	109	111	113	113	113	113	112	110	107	101	99	96	94	91	88	85	82	78	75	72	69	65	63	59	56	55	53	51	51
45	47	47	51	53	55	58	60	63	66	69	72	74	77	80	82	85	88	92	96	99	101	103	104	105	105	104	103	102	100	94	92	90	88	86	83	81	78	75	72	69	67	64	61	58	55	53	52	50	49
44	44	47	50	52	54	56	58	61	63	66	68	71	73	75	78	80	82	86	90	92	94	95	96	97	97	97	96	95	93	89	86	85	83	81	79	76	74	72	69	67	64	62	59	57	54	52	49	49	47

grid cell dimension : 0.050 km
number of grid points: 50x50
top left coordinates : -1.225, 1.225 km
average deposition : 0.294E-01 g/m2/y
total deposition : 0.583E-02 g/s

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The report provides the comprehensive risk assessment of the substance Trisodium hexa fluoroaluminate. It has been prepared by Germany 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.

The environmental risk assessment concludes that there is a risk for the atmosphere due to the manufacturing of the substance. Further information is needed to come to definitive conclusions for the aquatic compartment, terrestrial compartment and the atmosphere regarding production and downstream uses.

The human health assessment concludes that there is concern for Workers and Consumers. For man via environment, further information and/or testing is needed.