Annex VI Report

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: Trisodium hexafluoroaluminate

EC Number: 239-148-8

CAS Number: 15096-52-3

Submitted by: Germany

Version: September 2009

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PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: **Trisodium hexafluoroaluminate**

EC Number: **239-148-8**

CAS number: 15096-52-3

Registration number (s):

Purity: 75 to 95 %.

Impurities:

The principal impurity of natural cryolite is siderite (15 to 20 %). Quartz occurs in quantities of < 5 %. Other impurities are galena, zincblende, pyrite, chalcopyrite and fluorine minerals in small quantitites (Roholm, 1937a,b).

Proposed classification based on Directive 67/548/EEC criteria:

T	Toxic	
	R48/23/25	Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed
Xn	Harmful	
	R20	Harmful by inhalation
Xi	Irritating	
	R36	Irritating to eyes
Repr.Cat.3; R63		Possible risks of harms to the unborn child

No change to the current classification for the environment with N R 51/53 in Annex VI, Table 3.2 of Regulation (EC) 1272/2008 is proposed.

Proposed classification based on GHS criteria:

Acute Tox. 4 *H332*

Eye Irrit.2 *H319*

STOT Rep.1 *H372*

Repr. 2 *H361d*

No change to the current classification for the environment with H 411 in Annex VI, Table 3.1 of Regulation (EC) 1272/2008 is proposed

Proposed labelling:

Proposed specific concentration limits (if any):

Proposed notes (if any):

JUSTIFICATION

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Chemical Name: Trisodium hexafluoroaluminate

EC Name: Trisodium hexafluoroaluminate

CAS Number: 15096-52-3

IUPAC Name: Trisodium hexafluoroaluminate

1.2 Composition of the substance

Chemical Name: Trisodium hexafluoroaluminate

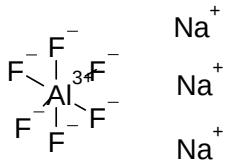
EC Number: 239-148-8

CAS Number: 15096-52-3

IUPAC Name: Trisodium hexafluoroaluminate

Molecular Formula: AlF_6Na_3

Structural formula:



Molecular Weight: 209.97 g/mol

Typical concentration (% w/w): 75 to 95 % (natural), > 95 % (synthetic)

Concentration range (% w/w): 75 – 95 % (natural), 85 – 97 % (synthetic)

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.

1.3 Physico-chemical properties

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

Table 1.1: Summary of physico- chemical properties of natural cryolite:

REACH ref Annex, §	**Property**	**IUCLID section**	**Value**	**Reference**
VII, 7.1	Physical state at 20°C and 101.3 kPa	3.1	clear or white to yellowish, sometimes reddish or black solid monoclinic cube-like crystals	Roholm (1937a,b)
VII, 7.2	Melting/freezing point	3.2	1027 °C	Solvay (1997)
VII, 7.3	Boiling point	3.3	no information available	
VII, 7.4	Relative density	3.4	2.95 at 20 °C	Solvay (1997)
VII, 7.5	Vapour pressure	3.6	2.5 hPa at 1027 °C	Solvay (1997)
VII, 7.6	Surface tension	3.10	not determined (inorganic complex salt)	
VII, 7.7	Water solubility	3.8	0.41 g/l at 25 °C (pH unknown) 0.9 g/l at 20 °C (pH 4 – 7) [1)] ca. 400-500 mg/l at 20 °C (pH 8) ca. 100-200 mg/l at 20 °C (pH 8.5) ca. 20-40 mg/l at 20 °C (pH 10) 144 mg/l at 20 °C (pH 7.7-7.9)	Rethmann (1996) Sjöberg (2002) [2)] Sjöberg (2002) [2)] Sjöberg (2002) [2)] Sjöberg (2002) [2)] IWL (1998) 2); after 24 h stirring; test medium of Daphnia ecotoxicity test (see section 3.2.1.1.2)
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7	not applicable (inorganic complex salt)	
VII, 7.9	Flash point	3.11	not conducted (solid)	
VII, 7.10	Flammability	3.13	not determined (inorganic complex salt)	
VII, 7.11	Explosive properties	3.14	not determined (inorganic complex salt)	

VII, 7.12	Self-ignition temperature			
VII, 7.13	Oxidising properties	3.15	not determined (inorganic complex salt)	
VII, 7.14	Granulometry	3.5		
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	3.17		
XI, 7.16	Dissociation constant	3.21		
XI, 7.17,	Viscosity	3.22		
	Auto flammability	3.12	not determined (inorganic complex salt)	
	Reactivity towards container material	3.18		
	Thermal stability	3.19		

[1)] Water solubility is not specified for natural or synthetic cryolite.

[2)] 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. 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 Sjödin results from loading "molecule-by-molecule". 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

Table 2: Summary of physico- chemical properties for synthetic cryolite

REACH ref Annex, §	Property	IUCLID section	Value	Reference
VII, 7.1	Physical state at 20°C and 101.3 kPa	3.1	white crystalline solid	
VII, 7.2	Melting/freezing point	3.2	1000 - 1009 °C	Sweetman (1944) [1)]
VII, 7.3	Boiling point	3.3	no information available	
VII, 7.4	Relative density	3.4	2.9 - 2.96 at 20 °C	Weast (1987) [1)]
VII, 7.5	Vapour pressure	3.6	2.53 hPa at 1009 °C	Ullmann (1988) [1)]
VII, 7.6	Surface tension	3.10	not determined (inorganic complex salt)	
VII, 7.7	Water solubility	3.8	0.39 g/l at 25 °C (pH unknown) 0.9 g/l at 20 °C (pH 4 – 7) (see table 1 for other values)	Roholm (1937a) Sjöberg (2002)
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7	not applicable (inorganic complex salt)	
VII, 7.9	Flash point	3.11	not conducted (solid)	
VII, 7.10	Flammability	3.13	not determined (inorganic complex salt)	
VII, 7.11	Explosive properties	3.14	not determined (inorganic complex salt)	

VII, 7.12	Self-ignition temperature		not determined (inorganic complex salt)	
VII, 7.13	Oxidising properties	3.15	not determined (inorganic complex salt)	
VII, 7.14	Granulometry	3.5		
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	3.17		
XI, 7.16	Dissociation constant	3.21		
XI, 7.17,	Viscosity	3.22	6.7 mPa.s at 1027 °C	Solvay (1997) [2)]
	Autoflammability	3.12	not determined (inorganic complex salt)	
	Reactivity towards container material	3.18		
	Thermal stability	3.19		
	[enter other property or delete row]			

[1)] No test method is available (literature value)

[2)] Data of a safety data sheet

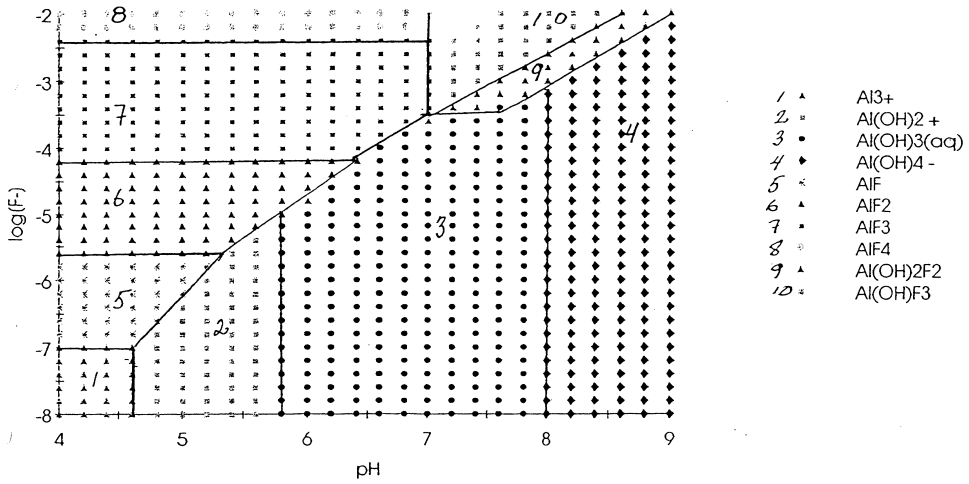


Figure 1.1 Predominance area diagram of the Al3+-F-.OH- system (Sjöberg, 2002)

1.4 Manufacture and uses

1.5 Manufacture

1.6 Identified uses

1.7 Uses advised against

2 CLASSIFICATION AND LABELLING

2.1 Classification in Annex I of Directive 67/548/EEC

Classification according to Annex I of Directive 67/548/EEC (Index number: 009-016-00-2)

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

Xn; R20/22: Harmful by inhalation and if swallowed

N; R51-53: Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment

2.2 Self classification(s)

This should include the classification, the labelling and the specific concentrations limits. The reason and justification for no classification should be reported here.
It should be stated whether the classification is made according to Directive 67/548/EEC criteria or according to GHS criteria

3 ENVIRONMENTAL FATE PROPERTIES

3.1 Degradation

3.1.1 Stability

Corresponds to IUCLID 4.1

3.1.2 Biodegradation

3.1.2.1 Biodegradation estimation

3.1.2.2 Screening tests

3.1.2.3 Simulation tests

3.1.3 Summary and discussion of persistence

3.2 Environmental distribution

3.2.1 Adsorption/desorption

Corresponds to IUCLID 4.4.1

3.2.2 Volatilisation

Corresponds to IUCLID 4.4.2

3.2.3 Distribution modelling

3.3 Bioaccumulation

3.3.1 Aquatic bioaccumulation

3.3.1.1 Bioaccumulation estimation

3.3.1.2 Measured bioaccumulation data

3.3.2 Terrestrial bioaccumulation

3.3.3 Summary and discussion of bioaccumulation

3.4 Secondary poisoning

3.5 Assessment of the potential for secondary poisoning

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

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), 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.

5.1.1 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 5.6.1.2.) 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.

5.1.2 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

5.1.3 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 5.1**. 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 (1949) 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 5.1**. 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 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, 1949
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, 1949
NaF, solution, 2 weeks	19.4	3.76	50.26	96.24	45.98	Largent and Heyroth, 1949
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, 1949
Cryolite, solution, 5 weeks	25.4	6.89	58.83	92.94	34.11	Largent and Heyroth, 1949
Cryolite, solid, 3 weeks	36.4	34.45	35.82	65.54	29.75	Largent and Heyroth, 1949
Cryolite, solid, 3 weeks, intake every 3rd day	12.4	32.5	44.52	67.50	22.98	Largent and Heyroth, 1949
Cryolite, solid, 4 weeks, intake every 2nd day	6.41	37.91	40.72	62.09	21.37	Largent and Heyroth, 1949

1) amount absorbed = total intake - faecal excretion

2) amount retained = amount absorbed - urinary excretion

*) no statement whether applied as solid or in solution

5.1.4 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.

5.1.5 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, 1949). 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 et al., 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 inhalation 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 et al., 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.

4.2 Acute toxicity

4.2.1 Acute toxicity: 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).

4.2.2 Acute toxicity: 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).

4.2.3 Acute toxicity: 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).

4.2.4 Acute toxicity: other routes

4.2.5 Summary and discussion 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, which demonstrated lower LD_{50} (IARC, 1982; Whitford, 1990, as referenced in WHO, 2002), indicating a lower bioavailability for cryolite. In consequence, existing classification with R 22 is not supported.

4.3 Irritation

4.3.1 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 5.5.1.

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.

4.3.2 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

Although several epidemiological studies on effects of natural or sythetic cryolith in humans are available eye irritation was virtually never included in the investigations. Only the study of Friis et al. (1989) considered eye irritation in the questionnaire and 21 out of 102 study participants reported eye irritation a “few times monthly or more frequently, and 18 had eye irritation in relation to work”. It is uncertain whether natural or synthetic cryolite was processed.

4.3.3 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 5.2.2.

In two 2-week range finding inhalation toxicity studies (repeated dose toxicity studies, for details, refer to section 5.6.1.2), also signs indicative for repiratory tract irritation were observed. After repeated exposure to 470 mg/m³ (6 hours/day) in the first study, granulomatous-type bronchiolites and pneumonitis were not indicative for sensory irritation (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 including alveolar fibrosis 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.

4.3.4 Summary and discussion 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 LC50 was performed (for details, refer to 5.2.2 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 5.6.1.2). 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 eye irritant by US EPA. In a study with cryolite workers about 20 % reported eye irritation in contact with work. . Overall, the data regarding eye irritation are not fully consistent. However there is an indication that eye contact with cryolite may have an irritating effect. Therefor classification with R36 is proposed.

Results obtained from rat inhalation studies do not require classification as a respiratory irritant. The nature of effects induced by irritant properties of the substances and observed in acute inhalation studies do not correspond to acute, reversible sensory irritation. The mortalities and significant inflammatory/fibrotic lung lesions observed were covered by classification as harmful via inhalation (R20). Similarly, granulomatous inflammatory lung lesions and hyperplasia of local lymph nodes from repeated inhalation are covered by R48/23.

4.4 Corrosivity

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

4.5 Sensitisation

4.5.1 Skin

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.

4.5.2 Respiratory system

no data available.

4.5.3 Summary and discussion 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.

4.6 Repeated dose toxicity

4.6.1 Studies in animals

5.6.1.1 Repeated dose toxicity: oral

Studies in animals

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. 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 (each) 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 be determined 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).

4.6.1.2 Repeated dose toxicity: inhalation

14-day studies (rat)

Two 2-week range-finding inhalation toxicity studies (in conformance with requirements of the standard repeated dose toxicity testing protocols) in rats are 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 large bronchioles, bronchiolar-alveolar junctions 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 $\pm$ 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 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).

4.6.1.3 Repeated dose toxicity: dermal

The only information available is a summary report on a repeated dose dermal toxicity study with synthetic cryolite (CAS-No. 15096-52-3) (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; therefore no final evaluation can be made.

A 21-day subacute dermal toxicity study in rabbits is reported which is innacceptable 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).

4.6.1.4 Other relevant 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 publications 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:

Table 4.2 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

4.6.1.5 Summary and discussion of repeated dose toxicity

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 (see Table 5.6.1.5). 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 haematopoietic system 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). Bone marrow suppression was indicated by myelofibrosis in the bone marrow in conjunction with (compensatory) extramedullarly hematopoiesis in the liver and spleen, decreases were noted in red cell count, haemoglobin, haematocrit, MCV, MCH, MCHC, and platelets. Increased incidences of specific alterations of red blood cell morphology (anisokaryocytes, microcytes, macrocytes, target cells, hypochromic cells, nucleated red cells, basophilic strippling, and Howell-Jolly bodies) indicated disturbances of erythropoiesis. 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 the 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.

From animal studies, the main toxic effects of cryolite are summarised in the following table (for key to symbols, see end of the table):

Table 4.3 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/m^3; + extra group receiving 5.7 mg/m^3 sodium fluoride No histopathology on bones and teeth	4.6 mg/m^3 (m/f): (↑) inorganic fluoride concentration in urine, bones, and teeth (↑) Aluminium concentration in the urine ↑* lung weight (abs) tracheobronch/mediast lymph nodes: accumulation of laden macrophages ≥1.04 mg/m^3 (m/f): lung: alveolitis with trace interstitial thickening (fibrosis) of alveolar duct walls 0.21 mg/m^3 (f): (↑) Aluminium concentration in the urine NOAEC: 4.6 mg/m^3 for systemic effects NOAEC: 0.21 mg/m^3 for local effects (lung)	BG Chemie, unpublished report 1997
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

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) 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
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

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**
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
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	0.58 mg/kg bw/d: 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)	≥500ppm (m/f): fluoride accumulation in the bone 50000 ppm (m/f): ↓ 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

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**
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)	3000 ppm: ↑ incidence of emesis, vomiting, white and yellow froth (m/f); ↓ specific gravity of the urine (f); ↑ nucleated red cells (m) ≥3000 ppm: renal lesions (m/f) regeneration of the tubular epithelium, interstitial fibrosis, tubular dilation, interstitial infiltration with lymphocytes (2m/2f) 10000 ppm: ↓ 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) 30000 ppm: ↑ 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

4.6.2 Human data

4.6.2.2 Epidemiological data

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 showed a brownish film on their 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 and Juric, 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 – Evaluation on adverse health effects from WHO report

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.

4.6.2.2 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 these industrial settings were also exposed to a number of other known harmful substances. Most occupational exposure was due to inhalation of cryolite dust. The toxic effects of cryolite are related to its content of fluoride. Thus, an evaluation of cryolite-induced toxicity in humans should include what is generally known about the adverse effects of fluorides, especially resulting from prolonged exposure.

An impairment of lung function was not associated 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, and the occurrence of pneumoconiosis was particlularly 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 can lead to brittle bones and a higher frequency of fractures; a concurrent calcification of the tendons can be painful and restricts 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.

4.6.3 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). The current classification of cryolite is confirmed based on the hazard identification and dose-response data from experimental animal testing. 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 ≥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/m³ (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/m³ 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 the 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). 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.

4.7 Mutagenicity

4.7.1 In vitro data

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 4.4 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

4.7.2 In vivo data

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 µm 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 4.5 **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

4.7.3 Human data

4.7.4 Other relevant information

4.7.5 Summary and discussion 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.

4.8 Carcinogenicity

4.8.1 Carcinogenicity: oral

In vivo studies

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.

4.8.2 Carcinogenicity: inhalation

No data available.

4.8.3 Carcinogenicity: dermal

No data available.

4.8.4 Carcinogenicity: human data

In vivo studies

Mortality and cancer morbidity at high occupational exposure to fluoride 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, high 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 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, 1937a,b; 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., 1992).

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, 1937a,b; 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.

4.8.5 Other relevant information

4.8.6 Summary and discussion 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. Histopathology findings from an one-year toxicity study in dogs fed with synthetic cryolite gave no hint on 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 (EC, 2001; 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 no 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) (extended for approximately one decade) revealed 119 cases of cancer in 425 male workers; 104 cases 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 confounding factor (Grandjean et al., 1992). 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 of 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.

4.9 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.

4.9.1 Effects on fertility

Two-generation reproduction (feeding) study rat

Schroeder (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 $\underline{\geq}$ 1800 ppm according to $\underline{\geq}$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. 5.6.1.1) 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. 5.6.1.2) 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.

4.9.2 Developmental toxicity

oral (gavage) rat

Harris 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 ≥ 3000 mg cryolite/kg bw/day can be derived. Besides whitening of the teeth of the dams, no other compound-related systemically toxic effect (no information on bone tisse examined is available) 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, 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. (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 range finding....."

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 (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 gain 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 (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 $\geq$ 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 (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 on fetuses at the higher dose levels were not possible due to excessive maternal toxicity in this study, 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.

4.9.3 Human data

No data available.

4.9.4 Other relevant information

4.9.5 Summary and discussion of reproductive toxicity

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.

4.10 Other effects

4.11 Derivation of DNEL(s) or other quantitative or qualitative measure for dose response

Not relevant for this type of dossier.

5 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

5.1 Explosivity

Including C&L

5.2 Flammability

Including C&L

5.3 Oxidising potential

Including C&L

6 ENVIRONMENTAL HAZARD ASSESSMENT

6.1 Aquatic compartment (including sediment)

6.1.1 Toxicity test results

6.1.1.1 Fish

Short-term toxicity to fish

Long-term toxicity to fish

6.1.1.2 Aquatic invertebrates

Short-term toxicity to aquatic invertebrates

Long-term toxicity to aquatic invertebrates

6.1.1.3 Algae and aquatic plants

6.1.1.4 Sediment organisms

6.1.1.5 Other aquatic organisms

6.1.2 Calculation of Predicted No Effect Concentration (PNEC)

Not relevant for this type of dossier.

6.2 Terrestrial compartment

6.2.1 Toxicity test results

6.2.1.1 Toxicity to soil macro organisms

6.2.1.2 Toxicity to terrestrial plants

6.2.1.3 Toxicity to soil micro-organisms

6.2.1.4 Toxicity to other terrestrial organisms

Toxicity to birds

Toxicity to other above ground organisms

6.2.2 Calculation of Predicted No Effect Concentration (PNEC_soil)

Not relevant for this type of dossier.

6.3 Atmospheric compartment

6.4 Microbiological activity in sewage treatment systems

6.4.1 Toxicity to aquatic micro-organisms

6.4.2 PNEC for sewage treatment plant

Not relevant for this type of dossier.

6.5 Calculation of Predicted No Effect Concentration for secondary poisoning (PNEC_oral)

Not relevant for this type of dossier.

6.6 Conclusion on the environmental classification and labelling

JUSTIFICATION THAT ACTION IS REQUIRED ON A COMMUNITY-WIDE BASIS

Cryolite fulfils the requirements according to article 36, 1 (d) regulation (EC) 1272/2008. The substance is proposed to be classified as Repr. Cat 3, R 63 (Repr. 2, H361d).

The current classification of cryolite regarding acute toxicity according to Annex VI, Part 3, (EC) 1272/2008 is R20/22 (Harmful by inhalation and if swallowed). Cryolite shows no relevant acute oral toxicity with LD50 values for rats > 5000 mg/kg bw and should be de-classified. The labelling with R22 is no longer justified and should be deleted in Annex VI. After inhalation of cryolite an acute LC_{50} of 4470 µg/l was estimated in rats. A classification as harmful and labelling with R20 remains appropriate. Therefore, the classification of cryolite regarding acute toxicity should be updated to "R20 (Harmful by inhalation)". As cryolite is currently listed in Annex VI the substance could only be de-classified by a community-wide harmonisation action.

Cryolite is also proposed to be classified as irritating to eyes, R 36 (Eye Irrit.2, H319). Whereas a poorly reported Draize eye test did not reveal eye irritation in rabbits, an EPA Chemical Fact Sheet reported "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 reported chemosis, redness and discharge reversible within 72 hours. In a study with cryolite workers about 20 % of the examined persons reported eye irritation in relation to work. Although the data are note fully consistent, the information on eye irritation indicates that cryolite may have a certain potential for eye irritation. 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 to dust containing cryolite. Therefore it is considered nessecary to harmonize the classification and communicate the eye irritating potenial of cryolite to the public.

There is also a potential exposure of humans via the environment although site and user specific exposure information is not available at present. According to the risk assessment report of cryolite prepared under the Existing Substances Regulation, downstream uses other than aluminium smelters cause releases and local concentrations in the environment and hence represent a local exposure situation for man via environment. Therefore harmonized classification and labelling of eye irritation and acute inhalative toxicity is justified for cryolite.

OTHER INFORMATION

It is suggested to include here information on any consultation which took place during the development of the dossier. This could indicate who was consulted and by what means, what comments (if any) were received and how these were dealt with. The data sources (e.g registration dossiers, other published sources) used for the dossier could also be indicated here.

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ANNEX

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