Committee for Risk Assessment

RAC

Annex 1

Background Document

to the Opinion proposing harmonised classification and labelling at Community level of

Trisodium hexafluoroaluminate (Cryolite), natural and synthetic

ECHA/RAC/CLH-O-0000001052-90-02/A1
ECHA/RAC/CLH-O-0000001051-92-03/A1

Trisodium hexafluoroaluminate, synthetic

EC Number: 237-410-6

CAS Number: 13775-53-6

Trisodium hexafluoroaluminate, natural

EC Number: 239-148-8

CAS Number: 15096-52-3

Adopted

25 May 2010

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PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: **Trisodium hexafluoroaluminate, synthetic**

EC Number: **237-410-6**

CAS number: **13775-53-6**

Registration number (s):

Purity: 95 % (85 – 97 %)

Impurities: diiron trioxide (CAS no. 1309-37-1): ≤ 0.1%

quartz (CAS no. 14808-60-7): < 0.25%

aluminium fluoride (CAS-no. 7784-18-1): 5 – 10 %

aluminium oxide (CAS-no. 1344-28-1), lithium fluoride (CAS-no. 7789-24-4), magnesium fluoride (CAS-no. 7783-40-6), calcium fluoride (CAS-no. 7789-75-5): each ≤ 5 %

Substance Name: **Trisodium hexafluoroaluminate, natural**

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 Regulation EC 1272/2008 criteria:

The Risk Assessment Committee has concluded that the proposed additional classification of cryolite as Eye Irrit. 2 – H319 and Repr. 2 – H361d is not appropriate, whereas the proposed declassification of cryolite as Acute Tox. 4 – H302 is. Deleting the latter from the existing harmonised classification would give:

Acute Tox. 4	H332	Harmful if inhaled
STOT RE 1	H372	Causes damage to organs through prolonged or repeated exposure
Aquatic Chronic 2	H411	Toxic to aquatic life with long lasting effects

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

The Risk Assessment Committee has concluded that the proposed additional classification of cryolite as Xi;R36 and Repr. Cat. 3 (R63) is not appropriate, whereas the proposed declassification of cryolite as Xn;R22 is. Deleting the latter from the existing harmonised classification would give:

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

Proposed labelling based on Regulation EC 1272/2008:

GHS07, GHS08, GHS09, Dgr, H332, H372, H411

Proposed labelling based on Directive 67/548/EEC:

T; N

R: 20-48/23/25-51/53

S: (1/2-)22-37-45-61

Proposed specific concentration limits (if any): None

Proposed notes (if any): None

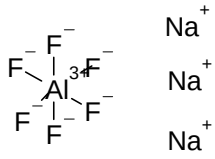
JUSTIFICATION

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:	13775-53-6 for synthetic trisodium hexafluoroaluminate 15096-52-3 for natural trisodium hexafluoroaluminate
IUPAC Name:	Trisodium hexafluoroaluminate

1.2 Composition of the substance

Chemical Name:	Trisodium hexafluoroaluminate
EC Number:	237-410-6 for synthetic trisodium hexafluoroaluminate 239-148-8 for natural trisodium hexafluoroaluminate
CAS Number:	13775-53-6 for synthetic trisodium hexafluoroaluminate 15096-52-3 for natural trisodium hexafluoroaluminate
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 exactly the same characteristics as CAS number 13775-53-6.

1.3 Physico-chemical properties

In tables 1.1 and 1.2 the physico-chemical properties of natural and synthetic cryolite are listed. These data were provided by the German Competent Authority and have not been evaluated by the Risk Assessment Committee.

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	4.1	clear or white to yellowish, sometimes reddish or black solid monoclinic cube-like crystals	Roholm (1937a,b)
VII, 7.2	Melting/freezing point	4.2	1027 °C	Solvay (1997)
VII, 7.3	Boiling point	4.3	No data	
VII, 7.4	Relative density	4.4	2.95 at 20 °C	Solvay (1997)
VII, 7.5	Vapour pressure	4.6	2.5 hPa at 1027 °C	Solvay (1997)
VII, 7.6	Surface tension	4.10	not determined (inorganic complex salt)	
VII, 7.7	Water solubility	4.8	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
VII, 7.8	Partition coefficient n-octanol/water (log value)	4.7	not applicable (inorganic complex salt)	
VII, 7.9	Flash point	4.11	not conducted (solid)	
VII, 7.10	Flammability	4.13	not determined (inorganic complex salt)	
VII, 7.11	Explosive properties	4.14	not determined (inorganic complex salt)	

VII, 7.12	Self-ignition temperature		not determined (inorganic complex salt)	
VII, 7.13	Oxidising properties	4.15	not determined (inorganic complex salt)	
VII, 7.14	Granulometry	4.5	No data	
IX, 7.15	Stability in organic solvents and identity of relevant degradation products	4.17	No data	
IX, 7.16	Dissociation constant	4.21	No data	
IX, 7.17	Viscosity	4.22	No data	
	Auto flammability	4.12	not determined (inorganic complex salt)	
	Reactivity towards container material	4.18	No data	
	Thermal stability	4.19	No data	

[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 1.2 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	4.1	white crystalline solid	
VII, 7.2	Melting/freezing point	4.2	1000 - 1009 °C	Sweetman (1944) [1)]
VII, 7.3	Boiling point	4.3	No data	
VII, 7.4	Relative density	4.4	2.9 - 2.96 at 20 °C	Weast (1987) [1)]
VII, 7.5	Vapour pressure	4.6	2.53 hPa at 1009 °C	Ullmann (1988) [1)]
VII, 7.6	Surface tension	4.10	not determined (inorganic complex salt)	
VII, 7.7	Water solubility	4.8	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)	4.7	not applicable (inorganic complex salt)	
VII, 7.9	Flash point	4.11	not conducted (solid)	
VII, 7.10	Flammability	4.13	not determined (inorganic complex salt)	
VII, 7.11	Explosive properties	4.14	not determined (inorganic complex salt)	

VII, 7.12	Self-ignition temperature		not determined (inorganic complex salt)	
VII, 7.13	Oxidising properties	4.15	not determined (inorganic complex salt)	
VII, 7.14	Granulometry	4.5	No data	
IX, 7.15	Stability in organic solvents and identity of relevant degradation products	4.17	No data	
IX, 7.16	Dissociation constant	4.21	No data	
IX, 7.17	Viscosity	4.22	6.7 mPa.s at 1027 °C	Solvay (1997) [2)]
	Autoflammability	4.12	not determined (inorganic complex salt)	
	Reactivity towards container material	4.18	No data	
	Thermal stability	4.19	No data	

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

[2)] Data of a safety data sheet

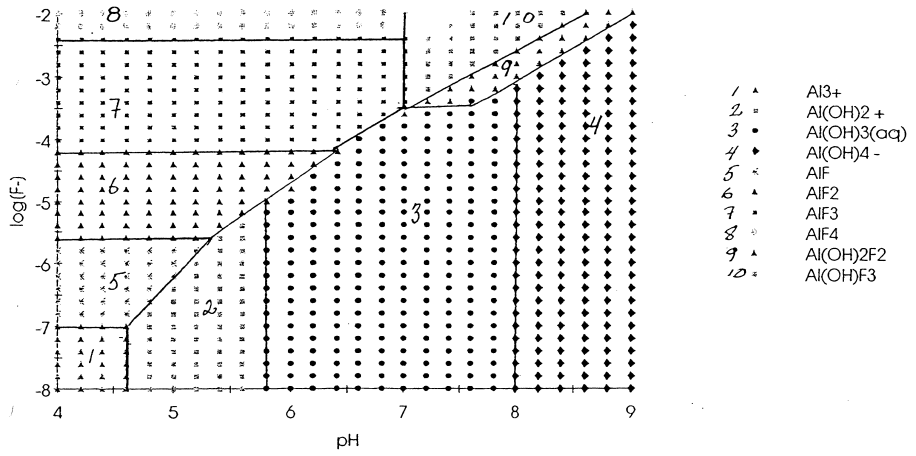


Figure 1.1 Predominance area diagram of the Al3+-F-.OH- system (Sjöberg, 2002)

2 MANUFACTURE AND USES

Not evaluated in this dossier.

3 CLASSIFICATION AND LABELLING

3.1 Classification in Annex VI of Regulation EC 1272/2008

Index number 009-016-00-2

According to CLP	According to 67/548/EEC
STOT RE 1, H372	T; R48/23/25
Acute Tox. 4, H332	Xn; R20/22
Acute Tox. 4, H302	
Aquatic Chronic 2, H411	N; R51-53

3.2 Self classification(s)

Not applicable.

4 ENVIRONMENTAL FATE PROPERTIES

Not evaluated in this dossier.

5 HUMAN HEALTH HAZARD ASSESSMENT

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

The following summary of toxicokinetic data relating to cryolite was taken from the classification proposal by the German Competent Authority. It is provided here without modification.

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). 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.

5.2 Acute toxicity

5.2.1 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).

5.2.2 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 or 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 (no further details provided).

5.2.3 Acute toxicity: dermal

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

5.2.4 Acute toxicity: other routes

No data available.

5.2.5 Summary and discussion of acute toxicity

In a well conducted and guideline-compliant rat inhalation study, a LC_{50} of 4.47 mg/l was derived. Hence, the existing harmonised classification of cryolite with R20, 'harmful by inhalation', is appropriate, as the LC_{50} is below the threshold value of 5 mg/l for R20. The corresponding classification according to CLP criteria is Acute Tox. 4, H332, as the thresholds are 1-5 mg/l for this category.

For assessment of dermal acute toxicity one rabbit study with a reported LD_{50} of >2100 mg/kg bw is available. No classification and labelling is required for acute dermal toxicity, since this LD50 is above the threshold value of 2000 mg/kg bw for both R21 and Acute Tox. 4, H312.

After oral administration to rats, an LD_{50} exceeding 5000 mg/kg was derived in several studies. In consequence, the existing harmonised classification with R22/Acute Tox. 4, H302 is not supported by the Risk Assessment Committee, since the LD_{50} is above the threshold value of 2000 mg/kg bw for both R22 and Acute Tox. 4, H302. During the public consultation, two MSCAs were in support of deleting R22/Acute Tox. 4, H302 from the existing Annex VI entry, whereas no information or comments opposing the proposal have been received.

5.3 Irritation

5.3.1 Skin

Not evaluated. No assessment of the skin irritating potential of cryolite has been made by the Risk Assessment Committee. No opinion has been developed regarding classification for skin irritation.

5.3.2 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 (no further details 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 101 study participants reported eye irritation a “few times monthly or more frequently, and 18 had eye irritation in relation to work”. The exact symptoms were not described. It is uncertain whether natural or synthetic

cryolite was produced. The authors speculate that “the symptoms were probably due to both the non-specific and corrosive effects of cryolite dust”.

5.3.3 Respiratory tract

Not evaluated. No assessment of the respiratory tract irritating potential of cryolite has been made by the Risk Assessment Committee. No opinion has been developed regarding classification for respiratory irritation.

5.3.4 Summary and discussion of eye irritation

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). 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 relation to work, but similar fractions of workers also self-reported skin irritation and irritation of mucous membranes of the mouth and pharynx. Although overall the data regarding eye irritation were considered not fully consistent, the German Compentent Authority proposed classification with R36/Eye irrit. 2, H319 because of the indication that eye contact with cryolite may have an irritating effect. The Risk Assessment Committee is of the opinion that the data are not sufficiently robust for classification. During the public consultation, two MSCAs were not supporting the German proposal whereas no information or comments supporting the proposal have been received.

5.4 Corrosivity

Not evaluated. No assessment of the corrosive potential of cryolite has been made by the Risk Assessment Committee. No opinion has been developed regarding classification for corrosivity.

5.5 Sensitisation

Not evaluated. No assessment of the sensitisation potential of cryolite has been made by the Risk Assessment Committee. No opinion has been developed regarding classification for sensitisation.

5.6 Repeated dose toxicity

The following summaries of repeated dose toxicity data relating to cryolite were taken from the classification proposal by the German Competent Authority. They have been provided here without modification, to facilitate an understanding of the general toxicity of cryolite to laboratory animals and humans, as far as this may be of relevance to the opinion in relation to "Reproductive toxicity”. It is to be noted that the repeated dose toxicity data themselves have not been evaluated by the Risk

Assessment Committee, nor has an opinion been offered on the existing harmonised classification of cryolite with T; R48/23/25 or STOT RE 1, H372.

5.6.1 Summary and discussion of repeated dose toxicity – animal data

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

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

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

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

As observed in inhalation studies, fluoride accumulation in bone (and teeth) did also occur after repeated oral administration to rats and dogs at all dose levels. The NOAEL for this effect could not be determined in any of these studies. After an exposure period of 90 days fluoride accumulation was determined in male and female Crl:CD(SD)BR rats from the lowest dose tested (50 ppm, corresponding to about 3.8 mg/kg bw/d in males and 4.5 mg/kg bw/d in females) onwards (Weltman, 1985 cited by Federal Register, 1996; EPA 1996, MRID 00158000); and in dogs from

500 ppm (corresponding to about 17 mg/kg bw/d) upwards, respectively (Hagen and Strouse, 1986 cited by Federal Register, 1996; EPA 1996, MRID 00157999). Data on clinical and histopathologic examinations of teeth were not routinely reported in repeated dose studies. Where evaluated, indicators of dental fluorosis as enamel striations, changes in coloration and physical properties of the teeth have been noted in albino rats giving cryolite in diet and drinking water at 0.58 mg/kg for 14 weeks [(University of Illinois, 3/29/39) cited from CalEPA (1995)] or higher in Sprague-Dawley (CD) rats after treatment for a period of four weeks at ≥250 ppm, representing ≥25 mg/kg bw/d (cited by Federal Register, 1996; EPA, 1996, MRID 00128109). This is in line with very early observations on bleached incisors at 1 mg/kg bw/d published by Roholm (1937a,b). Toxic effects on the 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 5.1 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 stippling, 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

5.6.2 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.

5.7 Mutagenicity

Not evaluated. No assessment of the mutagenic potential of cryolite has been made by the Risk Assessment Committee. No opinion has been developed regarding classification for mutagenicity.

5.8 Carcinogenicity

Not evaluated. No assessment of the carcinogenic potential of cryolite has been made by the Risk Assessment Committee. No opinion has been developed regarding classification for carcinogenicity.

5.9 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, were not available.

5.9.1 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. 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 apparently resulted from dose levels without any significant systemic toxicity (aside from dental fluorosis). These effects may thus be indicative for a specific toxic potential of cryolite adverse to (postnatal) development.

5.9.2 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 $\underline{\geq}$ 3000 mg cryolite/kg bw/day can be derived. Besides whitening of the teeth of the dams, no other compound-related systemically toxic effect (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 $\geq$ 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.

5.9.3 Human data

Limited human data is available. It is known that fluoride may cause dental fluorosis in humans via disruption of tooth mineralization (dental fluorosis)(WHO, 2002). 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). An increased frequency of dental fluorosis was identified in children of cryolite workers due to the indirect exposure to fluoride (Grandjean, 1983).

5.9.4 Other relevant information

No data available.

5.9.5 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.

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 in two independent studies. However, these skeletal anomalies were induced and observed at dose levels that also resulted in maternal mortality. 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 organ findings (paleness of liver and kidney, and enlarged heart) 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 can be derived from the two-generation reproduction study with rats.

Based on the data available, the German Competent Authority proposed to classify cryolite as Repr.Cat 3; R63. They considered the 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 indicative for a specific toxic potential of cryolite adverse to development. Is was noted that the postnatal effects were observed at dose levels without any significant systemically toxic effects in parental animals or in the lactating dams, but also that the primary data cannot be assessed and that there remains some uncertainties on the full toxicological significance of the developmental effects observed in the pups and the dental fluorosis observed in the dams.

In the public consultation, one comment in support and one comment opposing the proposal to classify cryolite for developmental toxicity have been received from MSCAs. The Risk Assessment Committee therefore considered the following.

The database contains five developmental toxicity studies and one 2-generation study, and they are all very poorly reported. Regarding the five developmental toxicity studies, they either report:

- no effects (three gavage studies in mice, rats, and rabbits, respectively), or
- "bent ribs/limb bones" in two gavage studies in mice where severe maternal toxicity was observed (probably some 10% maternal mortality at the dose of 300 mg/kg/day, where these variations/abnormalities were observed).

The Risk Assessment Committee is of the view that the maternal mortality in the two "positive" mouse studies is too high to allow any meaningful conclusions on developmental toxicity to be drawn from these studies (CLP Regulation, Annex I §3.7.2.4.4 "*Maternal mortality greater than 10 % is considered excessive and the data for that dose level shall not normally be considered for further evaluation.*"). Overall, there is then no support for classification from the developmental toxicity studies.

There is then also one 2-generation reproductive toxicity study where rats were fed cryolite via the diet, but it should be noted that the study is only available as a 17-lines summary. Aside from dental fluorosis no other parental effects were reported. In the progeny, no malformations were observed, but the summary reports on pale livers and kidneys, enlarged hearts, and decreased pup weights at the top dose (1800 ppm, approximately 150 mg/kg bw/day in the females).

The liver and kidney are target organs for cryolite in other repeated dose toxicity studies, so the reported paleness at the time of weaning could be substance-related (and possibly be caused by a haematological effect). However, it impossible to evaluate how adverse these effects are considering that no further information is given in the available summary, and it is consequently difficult to use this information (on paleness) in relation to the classification criteria.

The only quantitative data reported is a decreased pup weight at the highest dose (by 12-18% in F1, and by 11-26% in F2). The significant decreases are observed at days 7-21 in F1 and at days 4-21 in F2, but details on whether the effect was increasing, decreasing or stable over those days were not reported. The effect on the pup weight could potentially be viewed as a result of repeated dose toxicity (for which the substance is already classified), albeit in young animals, but as this effect is reported already on day 4 in F2, it could also be a sign of developmental toxicity. The CLP criteria say that "*altered growth*" in offspring is a reason to classify (CLP Regulation, Annex I §3.7.1.4), but note that "*small reductions in foetal/pup body weights*" need not to be considered (CLP Regulation, Annex I §3.7.2.4.3). The decreases observed in F1 (12-18%) obviously did not affect the animals possibility to reproduce, as no effects on the subsequent reproduction of F1-animals was reported. The decrease in F2 pup weight was bigger (11-26%), but as the F2-animals are not allowed to reach adulthood, the reversibility and degree of adversity can not be judged. The decreased pup weights, especially in F2 (11-26%), could be a reason for classification.

It is acknowledged that dental fluorosis (hypoplasia and hypomineralisation of dental enamel and dentine) has been observed in the very past in children of female cryolite workers (Roholm 1937). Although the reference is old, the fact that children up to 6-8 years of age are sensitive to dental fluorosis caused by environmental exposure to fluoride, supports that cryolite can cause dental fluorosis in children. As this adverse effect of cryolite only can arise in developing children, it could be discussed in relation to developmental toxicity. However, to our recollection other fluorides have not been classified in the EU for developmental toxicity on the basis of dental fluorosis.

In summary, it is believed that the decreased pup weights in both generations of the 2-generation study in rats fed cryolite via the diet is the only sign of developmental toxicity in animal studies that can be assessed in relation to the classification criteria. In relation to Cat. 2 (CLP), it is a borderline case with regard to whether the 11-26% decrease in pup growth is sufficient for classification.

In support of classification, it is noted that there is no reporting of maternal toxicity in the study and the effect was consistent between the generations. Arguments against classification are that no reporting of maternal toxicity in such a short summary does not necessarily mean that aside from dental fluorosis there was indeed no other maternal toxicity, and that the decreased pup weight was not adverse enough to affect the reproduction in F1.

Although being a borderline case, the Risk Assessment Committee does not support classification for reproductive toxicity, Cat 2 (CLP) (or Repro Cat. 3 (R63)), because the evidence for developmental toxicity is too limited and the quality of the reporting too poor to warrant classification.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Not evaluated in this dossier.

7 ENVIRONMENTAL HAZARD ASSESSMENT

Not evaluated in this dossier.

JUSTIFICATION THAT ACTION IS REQUIRED ON A COMMUNITY-WIDE BASIS

Justification as provided by the German Competent Authority

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.

Note: Justification not evaluated by the Risk Assessment Committee.

OTHER INFORMATION

Cryolite has also been risk assessed in the EU, and the draft risk assessment reports on natural and synthetic cryolite are available at the Ex-ECB webpage.

EU Draft Risk Assessment Report on trisodium hexafluoroaluminate (cryolite), CAS#: 13775-53-6, EINECS#: 237-410-6 and CAS#: 15096-52-3, EINECS#: 239-148-8. (2008).
http://ecb.jrc.ec.europa.eu/documents/Existing-Chemicals/RISK_ASSESSMENT/REPORT/cryolitereport309A.pdf

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