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TOXICOLOGICAL EVALUATIONS

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TOXICOLOGICAL EVALUATION

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Cryolite

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Cryolite

Cryolite (sodium aluminium fluoride) has been approved as an insecticide in the United States of America since 1957. In the context of a reregistration process, the United States Environmental Protection Agency (EPA) and the California Environmental Protection Agency (CalEPA) published results from numerous studies relevant to the assessment of the toxicological potential of cryolite. The original reports for the toxicity studies which were assessed for validity by EPA or CalEPA are not available to BG Chemie. Hence, the present TOXICOLOGICAL EVALUATION cites such results from the relevant EPA Reregistration Eligibility Decision (RED) Cryolite (1996) or, as appropriate, the CalEPA Summary of toxicology data (1986–1995) with reference to these secondary sources (EPA, 1996; CalEPA, 1995).

1 Summary and assessment

It is known from older animal studies that cryolite can be absorbed via the gastrointestinal tract. Studies in the rat have demonstrated absorption following dietary administration to be approximately 10 to 85%. A portion of the fluoride absorbed is excreted in the urine. Relevant quantities are incorporated into the bone and dental tissues where fluoride displaces the hydroxyl groups of hydroxyapatite, thus forming fluorapatite. Studies in volunteers and workers employed in the cryolite industry have demonstrated that cryolite can be absorbed via both the gastrointestinal tract and the respiratory tract. With average occupational exposure to dust ranging from 0.16 to 21.2 mg/m³ and the major part of the dust consisting of cryolite with a fluoride content of 54%, average pre-shift fluoride concentration levels in the serum and urine of cryolite workers were 4.2 and 250 µmol/l, respectively, while post-shift levels were 19 and 410 µmol/l, respectively. After a one-week period without exposure, fluoride levels in the serum and the morning urine were 1.1 and 89 µmol/l. Serum fluoride concentrations and urinary fluoride excretion showed a statistically significant correlation with the level of exposure whereas urinary fluoride concentration did not. The average fluoride half-life in serum determined in the workers was 5.6 hours (with individual values varying between 3.3 and 6.9 hours). Fluoride clearance was 53.2 ml/minute (ranging from 40.5 to 76.5 ml/minute) with urinary flow

averaging 1.37 ml/minute (ranging from 0.89 to 2.21 ml/minute). Average aluminium concentrations in the serum and the urine were 1.2 and 2.4 µmol/l, respectively, after a work-free period of one week and 0.9 and 4.7 µmol/l, respectively, after several days' work but exhibited no clear correlation with the level of exposure. On a molar basis, urinary excretion of fluoride was almost 100 times higher than that of aluminium. Following oral administration of cryolite, human subjects eliminated the entire amount of ingested fluorine of approx. 10 mg/day (inclusive of dietary fluoride intake). Approximately 30% was eliminated in the faeces and, in accord with temperature and humidity, 29.8 to 61.7% and 15.6 to 33.3% in urine and perspiration, respectively. When fluoride (in the form of cryolite) was administered in food to a male subject at dose levels ranging from 6.41 to 36.4 mg/day in a study of several weeks' duration, 23 to 37.8% of the ingested fluoride underwent faecal excretion in a dose-independent manner. Of the fluoride that was not excreted in the faeces, 52 to 65.9% was eliminated in the urine, again in a dose-independent manner.

Cryolite is of low toxicity following acute oral, inhalation and dermal administration (LD_{50} rat oral > 2500 and > 5000 mg/kg body weight; LC_{50} rat 4470 mg/m³ after 4-hour exposure and > 2060 < 5030 mg/m³ after unspecified duration of exposure; and LD_{50} rabbit dermal 2100 mg/kg body weight). Depressed general condition, salivation, ruffled fur and laboured respiration have been reported as clinical signs of toxicity following oral administration of cryolite at dose levels of up to 5000 mg/kg body weight, with terminal necropsy yielding no abnormal findings. Exposure of rats to high levels of cryolite dust (up to 4340 mg/m³) evokes reactions including partial closing of the eyes, abnormal respiration, lethargy, piloerection, hunched posture and depressed body weight gain. Necropsy of the decedents and terminal survivors reveals increased lung weights and, histopathologically, alveolar lesions at and above 1330 mg/m³ and lung congestion and prominent goblet cells in the bronchioles at and above 2830 mg/m³. Findings noted upon exposure to 4340 mg/m³ include subpleural foci in the survivors while bronchiolar epithelial changes, centrilobular hepatocyte necrosis and sinusoidal congestion of the liver are seen only in the decedents.

Cryolite is not irritating to the skin and eye of the rabbit. The technical-grade chemical has been evaluated as causing moderate irritation to the eye.

In the closed-patch test, technical-grade cryolite has not been found to cause skin sensitisation in the guinea pig.

In summary, subchronic oral administration of cryolite to rats in their feed results in pathological stomach lesions while subchronic exposure to predominantly respirable cryolite dust leads to lung lesions. In the dog, subchronic and chronic dietary administration of cryolite has been noted to cause haematological alterations, even anaemia, and kidney lesions, but only at high dose levels or after a long duration of treatment. Bone, plasma and urine fluoride concentrations, where determined, have been found in rats and dogs to be increased at all dose levels after subchronic or chronic administration. Furthermore, the presence of basophilic granules in the incisors (dental fluorosis) has been noted in male rats. In particular, subchronic oral administration of cryolite to Charles River Crl:CD(SD)BR rats at levels of and above 5000 ppm in the feed (corresponding to approx. 399.2 and 455.9 mg/kg body weight/day in males and females, respectively, as administered in a study investigating dose levels of 50, 5000 and 50000 ppm) resulted in stomach lesions, including epidermal hyperplasia and hyperkeratosis/acanthosis in the non-glandular portion of the stomach, and submucosal lymphoid foci, erosions/ulcerations, mucosal atrophy and chronic submucosal inflammation in the glandular portion. Following administration of 50000 ppm in feed (corresponding to approx. 4172.3 and 4758.1 mg/kg body weight in males and females, respectively) both sexes exhibited reduced body weight and decreases in haemoglobin, haematocrit and total protein, while only males showed reduced albumin and inorganic phosphate levels. High dose-recovery groups placed under observation for 4 weeks indicated substantial recovery from the stomach lesions, and haematology and clinical chemistry changes were completely reversible. Not taking into account the dose-related accumulation of fluoride in bone, the *no observed effect level* (NOEL) for subchronic dietary administration of cryolite in that study was 50 ppm, corresponding to daily doses of 3.8 and 4.5 mg/kg body weight in male and female rats, respectively. However, the next dose level was as high as 5000 ppm in feed (corresponding to approx. 399.2 and 455.9 mg/kg body weight/day in males and females, respectively). The gastrointestinal lesions were probably caused by hydrofluoric acid (hydrogen fluoride), which can be released from ingested cryolite in the stomach. In a one-year chronic study in dogs, administration of 3000 ppm cryolite in the feed (corresponding to approx. 95 and 57 mg/kg body weight/day in males and females, respectively) resulted in an increased incidence of immature (nucleated) red blood cells in the peripheral blood and in decreases in serum calcium and total protein in males and serum albu-

min in females. Serious haematology changes in the dog were observed as signs of anaemia at dietary cryolite dose levels ≥ 10000 ppm (corresponding to approx. 366 and 209 mg/kg body weight/day in males and females, respectively). In the presence of myelofibrosis in the bone marrow in conjunction with extramedullary haematopoiesis in the liver and spleen and megakaryocytosis in the spleen, decreases were noted in red blood cell count, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC) and platelets, and there were increased incidences of various types of abnormal red cells. Females had increased leukocytes, primarily segmented neutrophils and eosinophils. Following subchronic administration over a period of 90 days, haematology changes in the dog (decreases in red blood cell counts, haemoglobin, haematocrit and MCV and MCH) were observed only in the top dose group given 50000 ppm in the feed (corresponding to approx. 1692 mg/kg body weight/day), at which dose level food consumption, body weight and body weight gain were also reduced. Kidney changes with regeneration of the tubular epithelium, interstitial fibrosis, interstitial infiltration with lymphocytes, tubular dilatation and/or dilation of Bowman's space in the renal corpuscles and a decrease in specific gravity of the urine (in females only) were observed in the dog after chronic administration of cryolite at levels ≥ 3000 ppm in the feed. Subchronic administration of up to 50000 ppm in diet is not associated with kidney changes in the dog. Not taking into account the dose-related accumulation of fluoride in urine, plasma and bone, the *no observed effect level* (NOEL) for subchronic administration to dogs was established as 10000 ppm in feed (corresponding to 368 mg/kg body weight/day). For chronic (one-year) administration, the *no observed effect level* (NOEL) in the dog is < 3000 ppm in feed (corresponding to approx. 95 and 57 mg/kg body weight/day in males and females, respectively). Following subchronic exposure of Crl:CD®BR Sprague-Dawley rats to predominantly respirable aerosol containing particulate cryolite at 5.0 mg/m³ (analysed concentration: 4.6 mg/m³), substance-related findings were confined to the respiratory tract. Animals had increased lung weights and alveolitis with thickening of alveolar duct walls. Some animals from the top concentration group additionally had perivascular inflammatory infiltration around the alveolar ducts extending into the bronchioles. In addition, macrophage aggregation was noted around the alveolar ducts and there were brown pigment-containing macrophages around the alveolar ducts and in the tracheobronchial and medias-

tinal lymph nodes. The investigators referred to the changes, which were fully or partially reversible in a recovery group observed for 13 weeks, as being typical of a non-specific reaction to a particulate with irritant properties and clearance of the deposited material via the lung macrophage/lung node route. At the end of the exposure period, fluoride concentrations in bone, teeth and urine were increased in the top dose group exposed to cryolite at 4.6 mg/m³. Aluminium concentrations in the urine were concentration-independently increased in all exposure groups. After the 13-week recovery period, fluoride and aluminium concentrations in the urine and fluoride concentrations in the teeth were similar to control levels again, whereas the elevated fluoride concentration in bone remained practically unchanged throughout the recovery period. The *no observed effect level* (NOEL) for subchronic inhalation of cryolite was 0.21 mg/m³. 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. Dental fluorosis is a hypoplasia and hypomineralisation of the dental enamel and dentine, which in humans occurs following chronic intake of fluorine doses > 2 mg/day during dental development. Incorporation of excessive fluoride results in poor enamel formation. The dentition is of a chalky-white basic colour, and the affected teeth exhibit white spots and decalcification and later, yellowish-brown mottling in severe cases. In many parts of the world, drinking water is artificially fluoridated in order to promote mild incorporation of fluoride into the dental enamel as this leads to resistance to dental caries, with a concentration of 1 mg/l being considered the optimum level. EPA has evaluated the dental changes frequently observed in rodent studies as cosmetic effects rather than toxicologically relevant findings (see also EPA, 1996; IPCS, 1997).

Cryolite possesses no genotoxic potential. The genotoxic potential of cryolite has been investigated in vitro both with and without metabolic activation (S-9 mix from Aroclor 1254-induced rat liver) in Salmonella/microsome assays using *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538, in the chromosome aberration test in human lymphocytes and in the UDS test in primary rat hepatocytes. In vivo, chromosome aberration tests have been carried out in the Crl:CD®BR Sprague-Dawley rat upon acute and subchronic inhalation exposure. The results of an older study, according to which cryolite induced clastogenic effects in bone marrow cells from albino rats after subchronic inhalation exposure, have not

been confirmed by a recent subchronic chromosome aberration study conducted in the Crl:CD®BR Sprague-Dawley rat in accordance with the current guidelines for testing.

Cryolite has been investigated in compliance with current standards in teratogenicity/embryotoxicity studies conducted in the Sprague-Dawley rat with oral doses of up to 3000 mg/kg body weight/day and in the Crl:CD-1 (ICR)BR mouse with oral doses of up to 1000 mg/kg body weight/day as well as in a two-generation study in the Sprague-Dawley rat with oral doses of up to 1800 ppm in the diet (corresponding to approx. 128 and 148 mg/kg body weight/day in males and females, respectively). There are no indications so far that the chemical possesses reproductive toxic, teratogenic, embryotoxic or foetotoxic potential. Foetal findings in the form of retardation phenomena (bent ribs and limb bones and, in the two-generation study, reduced body weight gain in the offspring as well as pale kidneys and livers and enlarged hearts at necropsy of the pups) have been noted only at dose levels associated with parental toxicity.

Long-term human exposure to high levels of cryolite dust results in typical sclerotic changes of the skeleton in conjunction with joint pain and limited movement of the joints. 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 exhibiting 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. There are IPCS (International Programme on Chemical Safety) estimates that skeletal fluorosis occurs from threshold concentration levels > 2.5 mg total fluoride/m³ or urinary fluoride excretion > 9 mg/l. It is assumed by EPA and IARC (International Agency for Research on Cancer) that skeletal fluorosis does not occur when daily fluoride intake is < 20 mg (approx. 0.29 mg/kg body weight) or fluoride concentrations in the morning urine are < 4 mg/l. Cryolite workers in Copenhagen who developed osteofluorosis had been exposed for many years before 1961 to dust levels of approx. 30 to 40 mg/m³ with peak levels of up to 994 mg/m³. The

cryolite content of the largely respirable dust (50% of particles having a diameter < 5 µm) was approx. 97%. The remainder of the dust consisted of quartz and other accompanying minerals of natural cryolite. According to calculations, systemic absorption of fluoride by workers in such an exposure situation is in the range from 35 to 80 mg per day. Skeletal fluorosis is slowly reversible, the half-life of the fluoride incorporated in the bone matrix being assumed to be 8 years. The reports on the occupational exposure studies in cryolite workers give no data on extent to which there was an increase in the number of bone fractures. It appears unlikely that cryolite possesses marked pulmonary toxicity. Although some Danish cryolite workers were found to have pulmonary changes in terms of emphysema or not very severe fibrosis in 1936/1937, repeated x-ray examinations carried out in workers from the same cryolite factory at a later time yielded no indications of pathological lung changes, with pneumoconiosis, in particular, being excluded. More recent studies of pulmonary function in workers employed at that plant gave no indications that pulmonary function was impaired due to the exposure situation in the workplace where the threshold limit values which in the 1980s applied for quartz and dust and for fluorine were repeatedly exceeded by factors of 6 and 4, respectively. Particularly after heavy dust exposure, approx. one third of the workers repeatedly complained of gastrointestinal symptoms (nausea, vomiting, diarrhoea and epigastric pain) and irritation of the eyes, mouth, pharynx and skin. It is thought that the complaints were caused by an unspecific effect of dust and the release of hydrofluoric acid from cryolite in the gastrointestinal tract. The carcinogenic potential of cryolite in humans was also investigated in the workers from the Danish cryolite plant. The cohort comprised 425 men who had been employed at the plant for at least 6 months between 1 January 1924 and 1 July 1961. The cryolite workers were compared with the general population of Denmark and the population of Copenhagen with regard to the number of deaths occurring during the 1941–1989 period and the number of cancer cases occurring during the 1943–1987 period. Among the cryolite workers there were 300 deaths during the period under investigation as compared with 223.3 deaths expected for the general population of Denmark (SMR 1.34 (95% confidence interval 1.20 to 1.50)). Of the 300 deaths, 82 were due to any type of cancer with an expected 55.8 deaths (SMR 1.47 (1.17 to 1.82)), 112 were due to cardiovascular diseases with an expected 104.6 deaths (SMR 1.07 (0.88 to 1.29)), 8 were due to cirrhosis of the liver with an expected 2.2 deaths (SMR 3.62 (1.56 to 7.13))

and 30 were due to violence (suicides or accidents) with an expected 15 deaths (SMR 2.00 (1.35 to 2.85)). Of the fatal primary cancers, a large proportion was situated in the lungs and the larynx (no incidence data given). Compared with the population of Copenhagen, the overall cancer incidence was slightly increased in the cryolite workers (119 observed cases, 103.6 expected cases, SIR 1.15 (0.95 to 1.37)). Among the cryolite workers there were 42 observed cases of respiratory cancers as compared with 29.9 expected cases (SIR 1.40 (1.01 to 1.90)), of which 35 were primary lung cancer cases as compared with 25.9 expected cases (SIR 1.35 (0.94 to 1.88)) and 5 were cases of laryngeal cancer as compared with 2.1 expected cases (SIR 2.29 (0.77 to 5.56)). There were also 17 observed cases of urinary bladder cancer compared with 9.2 expected cases (SIR 1.84 (1.08 to 2.96)). Cancers of the lung and urinary bladder were observed more frequently in workers who were younger than 35 years of age at the onset of exposure. The value of the study is greatly limited by the fact that no data are available on the smoking habits of the workers. The investigators worked under the general assumption that the smoking habits of the cryolite workers were comparable with those of the general population of Copenhagen. However, they also pointed out that the SIR for cancers at sites particularly affected in smokers (lips, tongue, buccal cavity, pharynx and oesophagus) was 2.29 (1.05 to 4.36) and thus showed an increase. There was no clear relationship between the incidence of organ-specific cancers and the length of exposure. Most cancers occurred 10 to 19 years after the onset of exposure, and all cohort members had a potential follow-up of at least 27 years. Discussing their results, the study investigators concluded that the increases in lung cancer morbidity and, in particular, bladder cancer morbidity could not be ascribed to an increased rate of tobacco smoking alone. They hypothesised that the workers had possibly absorbed a carcinogen via the lungs and excreted it via the urinary tract. Among 97 female employees at the cryolite plant there were 28 cases of cancer as compared with 29.2 cases expected for the female population of Copenhagen (SIR 0.96). No differentiated analysis of cancer morbidity was carried out for this subcohort.

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (“MAK-Kommission”) has listed cryolite in the “Yellow Pages” of the List of MAK and BAT Values 2004 in order that a MAK value be established for the chemical.

2 Name of substance

2.1	Usual name	Cryolite
2.2	IUPAC name	Trisodium hexafluoroaluminate
2.3	CAS No.	15096-52-3 13775-53-6
2.4	EINECS No.	239-148-8

3 Synonyms, common and trade names

Aluminate (3-), hexafluoro-, trisodium
Aluminium sodium fluoride
Aluminiumtrinatriumhexafluorid
Aluminium trisodium fluoride
Cryolit
Cryolith
Eisstein
Greenland spar
Ice spar
Icestone
Koyoside
Kryocide®
Kryolith
Kryoside
Natriumaluminiumfluorid
Natriumhexafluoroaluminat
Prokil®
Sodium aluminofluoride
Sodium aluminum fluoride
Sodium fluoroaluminate
Sodium hexafluoroaluminate
Trinatriumhexafluoroaluminat
Trisodiumhexafluoroaluminat
Villiaumite

4 Structural and molecular formulae

4.1	Structural formula	$3Na^{+}[AlF_6]^{3-}$ and also 3 NaF • AlF_3
4.2	Molecular formula	Na_3AlF_6

5 Physical and chemical properties

5.1	Molecular mass, g/mol	209.95
5.2	Melting point, °C	960–027 (synthetic cryolite) (EPA, 1996) > 1000 (Bayer, 1999) 1009–1012 (Falbe and Regitz, 1997) 1009 (Wechsberg et al., 1976) 1009 (natural cryolite) (EPA, 1996) ca. 1010 (natural cryolite) (Frank et al., 2000) 1027 (Solvay Fluor und Derivate GmbH, 1996) ca. 1035 (Bayer, 1987)
5.3	Boiling point, °C	No information available
5.4	Vapour pressure, hPa	2.53 (at 1009 °C) (Wechsberg et al., 1976) 2.5 (at 1027 °C) (Solvay Fluor und Derivate GmbH, 1996)
5.5	Density, g/cm³	2.8 (Bayer, 1987) 2.95 (at 20 °C) (Solvay Fluor und Derivate GmbH, 1996) 2.96 (at 20 °C) (Bayer, 1999) 2.97 (Falbe and Regitz, 1997)
5.6	Solubility in water	400–1200 (at 25 °C) (EPA, 1996) 0.41 g/l (at 25 °C) (Bayer, 1999) 0.42 g/l (at 25 °C) (Wechsberg et al., 1976) 1.35 g/l (at 100 °C) (Solvay Fluor und Derivate GmbH, 1996; Wechsberg et al., 1976) Hydrolysis at pH values of 5, 7 and 9 results in liberation of fluoride anions at respective levels of 15.5%, 36.8% and 43.3% (CalEPA, 1995)

5.7	Solubility in organic solvents	Insoluble in alcohol	(EPA, 1996)
5.8	Solubility in fat	No information available	
5.9	pH value	6 (at 0.42 g/l and 20 °C) (Solvay Fluor und Derivate GmbH, 1996) 8–10 (1-percent suspension) (Bayer, 1987)	
5.10	Conversion factor	1 ml/m³ (ppm) ≙ 8.7 mg/m³ 1 mg/m³ ≙ 0.12 ml/m³ (ppm) (at 1013 hPa and 25 °C)	

6 Uses

The main application of cryolite is as a fluxing agent for electrolytic aluminium production. The chemical is further used as a protective and refining salt in the melting of light metals; as a filler in abrasive pastes and resin-bonded abrasives for metal treatment; as a flux and opacifying agent in the production of enamel, ceramics, glazing frits and glass; as a component of electrically conducting ceramics; as a component of fluxing agents in the production of soldering agents; as a component of welding rod coatings and welding powders in the production of welding agents; for fireworks in pyrotechnics; as a catalyst and, in the United States of America, as an insecticide (EPA, 1996; Frank et al., 2000; Falbe and Regitz, 1997; Solvay Fluor und Derivate GmbH, 2000; Wechsberg et al., 1976).

7 Experimental results

7.1 Toxicokinetics and metabolism

Male albino rats were administered cryolite in their feed over a period of 7 days, during which time the excretion of fluoride was determined in the faeces and urine. Over the 7-day period, the 6 animals exposed each had a mean intake of 8.7 mg fluoride, 15% of which was excreted in the faeces. Of the fluoride absorbed, only 35.7% was excreted in the urine over the 7-day period. The fluoride concentrations measured in the kidney and femur correlated with the quantities of fluoride absorbed. Comparative studies

with sodium fluoride yielded similar results (no further details; Wright and Thompson, 1978).

In another study, two rats were administered, by gavage, a single oral dose of fluoride at 690 mg/kg body weight in the form of natural cryolite. Fluoride excretion in the faeces and the urine was measured over a period of 4 days before administration and 7 days following administration. The fractions of the administered fluoride dose excreted in the faeces within the first 24 hours following administration were found to be 68 and 82%, followed by another 19 and 9% over the subsequent 24 hours. At day 5 after dosing, fluoride excretion in the faeces was back to baseline values. An increase in urinary fluoride excretion was seen only during the first two days following administration, during which time respective fractions of 0.12 and 0.25% of the administered fluoride dose were excreted in the urine. Analysis of blood samples obtained from groups of 4 rats at 24 hours after oral administration of 16 g natural cryolite/kg body weight or 10 g synthetically prepared cryolite/kg body weight revealed fluoride levels of 0.65 and 1 mg/kg, respectively. Analogous studies were conducted in groups of two rabbits treated with natural cryolite at dose levels of 3 or 9 g/kg body weight. The concentration of fluoride was determined in the blood, faeces and urine for 4 days before and up to 16 days after administration. Most of the administered fluoride was excreted within the first 4 days after administration. Overall, the fluoride levels found in the faeces and the urine remained elevated during the entire observation periods of 13 and 16 days. There was no correlation between blood fluoride levels and fluoride excretion in the urine. The finding that excretion was considerably slower in the rabbit than in the rat was attributed by the investigator to the difference in length of the intestinal tracts in the two species (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 approx. 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 0.14 to 1.4 mg/day (mean value 0.91 mg/day) and faecal 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 230 mg/kg) and 2010 mg/kg (control 380 mg/kg), respectively. The fluoride levels in the lungs, 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).

7.2 Acute and subacute toxicity

Acute toxicity

The acute toxicity data for cryolite are summarised in Table 1 below. Cryolite is of low toxicity following acute oral, inhalation and dermal administration (LD_{50} rat oral > 2500 and > 5000 mg/kg body weight; LC_{50} rat 4470 mg/m³ after 4-hour exposure and > 2060 < 5030 mg/m³ after unspecified duration of exposure; and LD_{50} rabbit dermal 2100 mg/kg body weight). Clinical signs of toxicity following oral administration included depressed general condition, salivation, ruffled fur and laboured respiration. Terminal necropsy was without abnormal findings. When rats were exposed to levels of up to 4340 mg/m³ of predominantly respirable cryolite dust, their reactions included partial closing of the eyes, abnormal respiration, lethargy, piloerection and hunched posture. Body weight was adversely affected at and above 2830 mg/m³. Necropsy of the decedents and terminal survivors revealed increased lung weights and, histopathologically, alveolar lesions at and above the lowest test concentration of 1330 mg/m³ and lung congestion and prominent goblet cells in the bronchioles at and above 2830 mg/m³. Findings noted after exposure to the highest test concentration of 4340 mg/m³ included subpleural foci in the survivors while bronchiolar epithelial changes, centrilobular hepatocyte necrosis and sinusoidal congestion of the liver were seen only in the decedents (Bayer, 1972, 1987; Bomhard, 1996; Elars Bioresearch Laboratories and Westpath Laboratories, 1981; EPA, 1996; Hazleton, 1983 a; HRC, 1993).

Beginning of Table 1

Table 1. Acute toxicity studies of cryolite						
Species, strain, sex[1]	Route	Dose (mg/kg body weight or mg/m³)	Purity	Effect	Observation period	Reference
Rat, male	oral	2500, administered by gavage as an aqueous Cremophor formulation; dose range tested: 100–2500 mg/kg body weight	n. d.	mortality: 0/15; ≥ 250 mg/kg body weight: depressed general condition and laboured breathing up to 5 days after administration	14 days	Bayer, 1972
Rat, Wistar (Bor:WISW (SPF Cpb)), male, female	oral	5000, administered by gavage as a suspension in peanut oil	n. d.	mortality: 0/10; 15 minutes to 8 hours after administration: slight salivation and ruffled fur; terminal necropsy revealed no abnormalities	14 days	Bayer, 1987; Bomhard, 1996
The test was carried out in accordance with Directive 84/449/EEC.						
Rat	oral	> 5000	technical grade	LD_{50}	n. d.	Hazleton, 1983 a; EPA, 1996
Rat, Sprague-Dawley, male, female	inhalation	4470 ± 0.85, 4-hour whole-body exposure, concentrations tested: 1330, 2830 and 4340 mg/m³; respective fractions of respirable particles ≤ 6 µm in diameter were 77.8, 67.9 and 78% of the administered dust	synthetic cryolite containing small quantities of aluminium fluoride (AlF_3), powder	LC_{50}; during exposure: partial closing of the eyes, accumulation of test material on the fur; after exposure: abnormal respiration, lethargy, brown crusty staining around the snout and jaws, piloerection, hunched posture, reductions in body weight in the top dose group, reversible reductions in body weight or body weight gain and temporary reduction in food consumption up to 2830 mg/m³; necropsy: from 1330 mg/m³: increased lung weights and alveolar lesions as revealed by histopathology; from 2830 mg/m³: lung congestion and prominent goblet cells in the bronchioles; at 4340 mg/m³: subpleural foci in the survivors, and bronchiolar epithelial changes, centrilobular hepatocyte necrosis and sinusoidal congestion of the liver in the decedents only	21 days	HRC, 1993
The study was conducted in compliance with the relevant EPA, EEC and OECD guidelines.						

Table 1. Acute toxicity studies of cryolite						
Species, strain, sex[1]	Route	Dose (mg/kg body weight or mg/m³)	Purity	Effect	Observation period	Reference
Rat	inhalation	> 2060 < 5030	technical grade	LC_{50} (no further details)	n. d.	Elars Bioresearch Laboratories and Westpath Laboratories, 1981; EPA, 1996
Rabbit	dermal	2100	technical grade	LD_{50}	n. d.	Elars Bioresearch Laboratories and Westpath Laboratories, 1981; EPA, 1996

[1] where specified
n. d. no data

End of Table 1

The acute toxicity data from older exploratory studies, which are no longer relevant to the assessment of the toxicological potential of cryolite due to what by modern standards are serious inadequacies (e.g. only 1 or 2 animals were tested per dose, only one dose was tested, inadequate documentation), are summarised in Table 2 in the appendix.

Subacute toxicity

In a dermal toxicity study, cryolite (96% pure) was applied to the skin of 5 New Zealand rabbits/sex and dose at dose levels of 0 (control), 25, 250 or 1000 mg/kg body weight for 6 hours/day on 5 days/week over a period of 3 weeks. Oral exposure to the test substance was not prevented; the animals were observed licking their fur during the study. EPA evaluated the study as inadequately conducted and attributed the observed signs of toxicity to ingestion of the test substance. In the top dose group, 3 out of 5 males and 1 out of 5 females died intercurrently. The animals exhibited marked decreases in body weight and hypoactivity, anaemia and changes in several clinical chemistry parameters (no precise details). In the intermediate dose group, which was treated with cryolite at 250 mg/kg body weight, body weight decrease was seen only on day 5 and was reversible. A *no observed effect level* (NOEL) was not determined (no further details; Battele Columbus Division, 1989; EPA, 1996).

There are further studies on the systemic effects of multiple administration of cryolite. However, they must be considered exploratory because only single parameters were measured, no more than 1 or 2 animals were used per dose, documentation was inadequate, the test substance was not precisely specified and/or no controls were included. The results of these studies are compiled in Table 3 in the appendix.

7.3 Skin and mucous membrane effects

Cryolite had no irritating effect on the rabbit ear. Application of cryolite to the inner surface of the ears of 2 rabbits/group for 8 or 24 hours caused no skin lesions. The observation period was 7 days (Bayer, 1972).

Cryolite also proved not to be irritating to the rabbit eye. Each of 2 rabbits received an instillation of approx. 50 mg of cryolite into one eye. Conjunctivae, scleras and corneas were without remarkable findings throughout the one-week observation period (Bayer, 1972).

Technical-grade cryolite was evaluated as moderately irritating to the eye and not irritating to the skin (no further details; Ralston Purina, 1981; EPA, 1996).

7.4 Sensitisation

In the closed-patch test, technical-grade cryolite was not been found to cause skin sensitisation in the guinea pig (no further details; Hazleton, 1983 b; EPA, 1996).

7.5 Subchronic and chronic toxicity

In a 3-month feeding study, cryolite (96% pure) was administered to groups of 50 male and 50 female Charles River Crl:CD(SD)BR rats/dose in the diet at levels of 0 (control), 50, 5000 or 50000 ppm. These levels corresponded to daily doses of 0 (control), 3.8, 399.2 and 4172.3 mg/kg body weight in males and 0 (control), 4.5, 455.9 and 4758.1 mg/kg body weight in females. Bone fluoride analyses were carried out in 10 animals/sex and dose. Out of 50 animals/sex and dose, 10/sex and dose served as recovery groups which were placed under observation for 4 weeks. In the top dose group both sexes exhibited reduced body weight and decreases in haemo-

globin, haematocrit and total protein, while only males showed reduced albumin and inorganic phosphate levels. Gross stomach lesions were noted in both sexes in the intermediate and top dose groups. Necropsy revealed thickened stomach walls with light, dark, red and/or raised focal areas and dark gastric contents. Histopathological examination revealed epidermal hyperplasia and hyperkeratosis/acanthosis of the non-glandular areas of the stomach and submucosal lymphoid foci, erosion/ulcerations, mucosal atrophy and chronic submucosal inflammation of the glandular areas of the stomach. Bone fluoride concentrations were elevated in all dose groups, with levels reaching a plateau over the dose range of 5000 to 50000 ppm. Basophilic granules in the incisors were noted in males. High-dose recovery groups indicated substantial recovery from the stomach lesions, and haematology and clinical chemistry changes were completely reversible. Bone fluoride concentrations were not determined in the recovery groups. Not taking into account the accumulation of fluoride in bone, the *no observed effect level* (NOEL) for cryolite was given as 50 ppm in feed, corresponding to daily doses of 3.8 and 4.5 mg/kg body weight in male and female rats, respectively (Hazleton, 1985; CalEPA, 1995; EPA, 1996).

Groups of 6 male and 6 female dogs were administered cryolite (97.3%) in the diet at concentration levels of 0 (control), 500, 10000 or 50000 ppm over a period of 3 months. According to the investigators, the animals' daily cryolite intake was 0 (control), 17, 368 or 1692 mg/kg body weight. The top dose group additionally included one male and one female for interim necropsy at 45 days and one male and one female for observation over a recovery period of 28 days. In the top dose group, there was decreased food consumption, body weight, body weight gain and red blood cell count, haemoglobin, haematocrit, mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH). Plasma, urine and bone fluoride concentrations exhibited dose-related increases which recovered partially during the observation period. Not taking into account the accumulation of fluoride in plasma, urine and bone, the *no observed effect level* (NOEL) was given as 10000 ppm in feed (corresponding to 368 mg/kg body weight/day; no further details; WIL Research Laboratories, 1986; CalEPA, 1995; EPA, 1996).

A one-year chronic feeding study was conducted in 4 beagle dogs/sex/dose which received cryolite (97.3 to 97.4% pure) in the feed at dose levels of 0 (control), 3000, 10000 or 30000 ppm. On average, males and females had daily dietary cryolite intakes of 0 (control), 95, 366 and 1137 mg/kg bo-

dy weight and 0 (control), 57, 209 and 615 mg/kg body weight, respectively. The incidence of emesis shortly after eating was increased in all dose groups. One male and one female from the low dose group and most animals from the intermediate and high dose groups exhibited kidney changes (regeneration of the tubular epithelium, interstitial fibrosis, interstitial infiltration with lymphocytes, tubular dilatation and/or dilation of Bowman's space in the renal corpuscles). The females also showed a decrease in specific gravity of the urine. The males of the 3000 ppm dose group had nucleated red cells in the peripheral blood. At and above 10000 ppm cryolite in the feed the following serious haematology changes were observed as signs of anaemia. Decreases were noted in red blood cell count, haemoglobin, haematocrit, MCV (mean corpuscular volume), MCH (mean corpuscular haemoglobin), MCHC (mean corpuscular haemoglobin concentration) and platelets, and there were increased incidences of abnormal red cells (anisokaryocytes, microcytes, macrocytes, target cells, hypochromic cells, nucleated red cells, basophilic stippling and Howell-Jolly bodies). Females had increased leukocytes, primarily segmented neutrophils and eosinophils. Myelofibrosis in the bone marrow was found in conjunction with extramedullary haematopoiesis in the liver and spleen and megakaryocytosis in the spleen. Serum calcium and total protein levels were decreased in males, and serum albumin levels were reduced in females. At 30000 ppm dietary cryolite, body weight gain was increased and blood sodium was decreased in males. Both males and females exhibited increased lactate dehydrogenase activity. A *no observed effect level* (NOEL) was not established because toxicologically relevant changes were induced in the kidney and blood even at the lowest dose level of 3000 ppm (equivalent to 95 and 57 mg/kg body weight/day in males and females, respectively; no further details; WIL Research Laboratories, 1992 a; CalEPA, 1995; EPA, 1996).

The toxic effects of subacute inhalation exposure to cryolite (98.9% pure) as compared with sodium fluoride (100.8% pure) were investigated in Crl:CD®BR Sprague-Dawley rats in a study conducted in accordance with OECD guideline No. 413. Groups of 10 males and 5 females per concentration level were exposed (snout-only) to cryolite at 0 (controls), 0.2, 1 or 5 mg/m³ or to sodium fluoride at 6 mg/m³ for 6 hours/day on 5 days/week for 13 consecutive weeks. In order to assess the reversibility of the effects of cryolite and sodium fluoride, additional groups of 10 males and 10 females were similarly exposed to substance-free air (control), cryolite at 5 mg/m³

or sodium fluoride at 6 mg/m³ for 13 weeks and subsequently placed under observation for 13 weeks. The analysed concentration levels were 0 (controls), 0.21, 1.04 and 4.6 mg/m³ for cryolite and 5.7 mg/m³ for sodium fluoride. The particulate aerosols employed in the study contained 86 to 89% respirable particles with diameters < 7 µm. Clinical signs, body weight gain, food and water consumption, ophthalmological examinations and haematology and clinical chemistry investigations did not reveal any changes related to cryolite or sodium fluoride treatment. The top concentration group treated with cryolite at 4.6 mg/m³ showed increased lung weights. Alveolitis with thickening of alveolar duct walls was noted in 8 out of 20 animals from the top concentration group and 8 out of 20 animals from the intermediate concentration group, and some animals from the top concentration group additionally had perivascular inflammatory infiltration around the alveolar ducts extending into the bronchioles. The majority of animals from the top concentration group exhibited macrophage aggregation around the alveolar ducts and brown pigment-containing macrophages around the alveolar ducts and in the tracheobronchial and mediastinal lymph nodes. Histological and macroscopic examination of cryolite-treated animals revealed no further changes. In the recovery group treated with cryolite at 4.6 mg/m³ and placed under observation for 13 weeks after exposure, lung weights in males were slightly increased and pigment-containing alveolar macrophages were noted in 8/19 animals, while the alveolitis was fully reversible. The investigators referred to the lung changes seen in cryolite-treated animals as being typical of a non-specific reaction to a particulate with irritant properties and clearance of the deposited material via the lung macrophage/lung node route. Following exposure to sodium fluoride at 5.7 mg/m³, 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. The group exposed to sodium fluoride was without pathological findings at the end of the recovery period. The investigators suggested that the differences in localisation of the respiratory tract lesions caused by the two chemicals were related to the markedly higher solubility of sodium fluoride as compared with cryolite, which reached the lower part of the respiratory system as a particulate. Upon subchronic inhalation exposure to both cryolite at 4.6 mg/m³ and sodium fluoride at 5.7 mg/m³, fluoride concentrations in bone and urine were markedly increased and fluoride concentration in teeth was slightly increased. Whereas fluoride concentrations in

the urine and teeth returned to the control range again after the 13-week recovery period, the concentration of fluoride in bone was practically unchanged compared with the levels seen at the end of exposure. Upon exposure to cryolite, aluminium concentrations in the urine were concentration-independently increased in females of all exposure groups and increased in males of the two higher concentration groups. Aluminium concentrations were in the control range again after the 13-week recovery period. The *no observed effect level* (NOEL) for cryolite was 0.21 mg/m³ (HLS, 1997 a).

The concentrations used in the subchronic inhalation study described above (HLS, 1997 a) were selected on the basis of two range-finding studies. Groups of 5 animals/sex and concentration underwent whole-body exposure to analysed cryolite concentrations of 0 (controls), 5.1, 13.6, 60, 130 or 470 mg/m³ (nominal concentrations of 0 (controls), 5, 15, 50, 150 or 500 mg/m³) for 6 hours/day on 5 days/week for 2 weeks. The following concentration-dependent effects were noted. At and above the lowest test concentration of 5.1 mg/m³, there were inflammatory changes in the alveolar parenchyma with enlarged tracheobronchial and mediastinal lymph nodes and prominent macrophages, sometimes pigmented. From 13.6 mg/m³, lung weights were increased. At 50 mg/m³ and above, histopathological changes also involved the terminal bronchioles, larger bronchioles and the larynx. Macroscopic examination revealed pale mottled and oedematous lungs, the lungs failing to collapse. Neutrophil numbers were increased. From 150 mg/m³, blood protein levels were reduced, and at 500 mg/m³ clinical signs (half-closed eyelids) and increased red blood cell numbers were seen (HRC, 1994 a, b).

There are further studies on the systemic effects of multiple administration of cryolite. However, they must be considered exploratory because only single parameters were measured, documentation was inadequate, the test substance was not precisely specified and/or no controls were included. The results of these studies are compiled in Table 3 in the appendix.

7.6 Genotoxicity

7.6.1 In vitro

In the Salmonella/microsome assay, cryolite was not mutagenic. In a standard plate incorporation test carried out both in the absence and presence

of metabolic activation (S-9 mix from Aroclor 1254-induced rat liver), *Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 were incubated with cryolite at 20, 100, 500, 2500 or 12500 µg/plate. Water served as the solvent. Cryolite was not bacteriotoxic nor did it induce any increase in revertant counts up to 12500 µg/plate, the highest test concentration required by OECD and EC guidelines. Tests employing the positive controls sodium azide, nitrofurantoin, 4-nitro-1,2-phenylenediamine and 2-aminoanthracene gave the expected results (BASF, 1988).

A further Salmonella/microsome assay, in which cryolite (97.6% pure) concentrations of 0 (the vehicle DMSO serving as the negative control), 0.05, 0.15, 0.50 and 5.0 mg/plate were tested on *Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1538, also yielded no indication that the chemical possesses mutagenic potential. The assay was carried out in 3 plates per concentration and strain in the absence and presence of metabolic activation (S-9 mix from Aroclor 1254-induced rat liver). Cryolite was not bacteriotoxic up to the highest test concentration of 5 mg/plate nor did it give rise to any increase in revertant counts (no further details; Microbiological Associates, 1981 a; CalEPA, 1995).

In the absence of further details, it has been reported that a Salmonella/microsome assay which was carried out as a plate incorporation test (Ames test) with cryolite levels of 167, 500, 1670, 5000, 7500 and 10000 µg/plate yielded a negative result both with and without metabolic activation (Pharmakon Research, 1991 a; EPA, 1996).

An in-vitro chromosome aberration test was carried out using mitogen (PHA) stimulated human lymphocytes which were incubated with cryolite (97.3% pure) at 0 (untreated), 0 (solvent control), 100, 500 or 1000 µg/ml with and without metabolic activation (S-9 mix from Aroclor 1254-induced rat liver). The result of this test was also negative. Two whole-blood cultures were evaluated per concentration and stage of the cell cycle (G_0/G_1, S and G_2, positive controls were evaluated at the S phase only; no further details; Pharmakon Research, 1991 b; CalEPA, 1995; EPA, 1996).

A UDS test in primary hepatocytes from Fischer-344 rats was carried out with cryolite (97.3% pure) at concentration levels of 0 (control), 1, 5, 10, 50, 100, 125, 250, 500 or 1000 µg/ml. The test provided no indication that cryolite possesses any DNA-damaging potential. A total of 105 cells/culture

from 3 cultures/concentration were scored up to the 50 µg/ml level. Concentration levels ≥ 100 µg/ml were cytotoxic (no further details; Pharmakon Research, 1991 c; CalEPA, 1995; EPA, 1996).

7.6.2 In vivo

Synthetic cryolite (98.9% pure) produced no clastogenic effect in an in-vivo chromosome aberration test which was carried out following single inhalation exposure of male and female Crl:CD®BR Sprague-Dawley rats. The test was carried out in accordance with OECD, EC and EPA guidelines. Groups of 6 animals/concentration and sampling time underwent 6-hour (snout-only) exposure to 2130 mg/m³ (a nominal concentration of 2500 mg/m³). The mean diameter of dust particles was 5.7 µm, with 59% of the particulate being < 7 µm in diameter and hence respirable. The animals were killed 16, 24 or 48 hours after the end of exposure, 2 hours after they were treated with colchicine by intraperitoneal injection of 4 mg/kg body weight in order to arrest dividing cells at metaphase. The negative control group, which underwent 6-hour exposure to air, and the positive control, which was treated with cyclophosphamide at 25 mg/kg body weight by intraperitoneal injection, were terminated 24 hours after exposure. From each animal, 1000 bone marrow cells were scored for mitotic index determination and 100 metaphases were examined with respect to structural chromosome aberrations. Cryolite treatment did not give rise to any increase in the incidence of structural chromosome aberrations when compared with the negative control. Analysis of chromosome aberrations was performed both including and excluding gaps and exchanges. As expected, the positive control cyclophosphamide induced chromosome aberrations (Bayer, 1997 a, 1998; HLS, 1997 b).

Cryolite was also devoid of clastogenic effect following subchronic inhalation exposure of male Crl:CD®BR Sprague-Dawley rats. A satellite group of 6 males in a subchronic toxicity study (HLS, 1997 a; see Section 7.5) underwent (snout-only) exposure to cryolite at 5 mg/m³. The animals were sacrificed 24 hours after the last exposure and the bone marrow was harvested from the femurs. The remaining details of study conduct and data analysis corresponded to the procedures used in the acute chromosome aberration test described above (Bayer, 1997 a, 1998; HLS, 1997 b). The incidence of structural chromosome aberrations in bone marrow cells from

cryolite-exposed animals was not increased relative to the negative control. A further group, which was treated with sodium fluoride at 6 mg/m³, also showed no increase in chromosome aberration rate. The cyclophosphamide-treated positive control displayed the expected clastogenic changes (Bayer, 1997 b; HLS, 1997 a).

In a cytogenetic study classified as unacceptable by CalEPA because it was conducted in males only and lacked historical control data, cryolite (96% pure) was administered to groups of 5 male rodents (no precise details) by oral gavage at dose levels of 0 (control), 0.6, 1.8 or 6 g/kg body weight on 5 consecutive days. The animals were sacrificed 4 hours after the last dosing, the mitotic indices were determined and 50 metaphases/animal were examined for chromosome aberrations. No adverse effects on chromosomes were noted. The positive control was treated with TEM (presumably triethylenemelamine; no further details; Microbiological Associates, 1981 b; CalEPA, 1995).

In an older cytogenetic study, 4 to 7 male albino rats/dose inhaled cryolite concentrations of 0 (control), 0.5, 1 or 3 mg/m³ or mixtures of 0.5 mg cryolite/m³ and 0.05 or 0.35 mg hydrogen fluoride/m³ for 6 hours/day on 6 days/week over a period of 5 months. Per rat, 240 to 511 bone marrow cells were examined for chromosome aberrations. The groups treated with cryolite at 3 mg/m³ or a mixture containing cryolite at 0.5 mg/m³ and hydrogen fluoride at 0.35 mg/m³ showed statistically significant increases to 6.5 and 5.9%, respectively, in the incidence of damaged chromosomes as compared with 1.4% in the control, with aberrations of the chromatid type prevailing (5.68 and 5.09%, respectively, as compared with 1.24% in the control; Voroshilin et al., 1973). The investigators provided no exact details regarding the types of chromosome aberrations detected and the manner in which they were included in data analysis. It was merely stated that chromosome aberrations were analysed in terms of chromosome and chromatid aberrations and hyperdiploid cells. Therefore it is not possible to judge whether gaps were included in data analysis.

Voroshilin et al. (1973) also conducted a study in male albino mice which inhaled cryolite concentrations of 0 (control), 0.1 or 0.5 mg/m³ or a mixture of 0.25 mg cryolite/m³ and 0.05 mg hydrogen fluoride/m³ for 6 hours/day on 6 days/week over a period of 2 months prior to assessment of cytogenetic effects on the testicular cells. From each of 7 mice/group, 700 meiotic testi-

cular cells were examined without significant findings (no further details; Voroshilin et al., 1973).

7.7 Carcinogenicity

Cryolite has not been investigated in any carcinogenicity studies to date.

However, the carcinogenic potential of sodium fluoride has been studied in the F344/N rat and the B6C3F1 mouse in the context of the U.S. National Toxicology Program (NTP). Animals received drinking water containing sodium fluoride levels of 0 (untreated control), 0 (paired control), 25, 100 or 175 ppm for 2 years. This corresponded to daily dose levels, as expressed in mg/kg body weight, of 1.3, 5.2 and 8.6 in male rats, 1.3, 5.5 and 9.5 in female rats, 2.4, 9.6 and 16.7 in male mice and 2.8, 11.3 and 18.8 in female mice. All dose groups of both rats and mice had dose-dependent dental fluorosis, and the 175 ppm female rats also had osteosclerosis of the long bones. Sodium fluoride was not carcinogenic (no evidence) in the female rat and the male and female mouse. One out of 50 male rats in the intermediate dose group had osteosarcoma of the vertebrae and 3 out of 80 male rats in the high dose group had osteosarcoma of the vertebrae or the humerus. In addition, one male from the top dose group had an extraskeletal osteosarcoma in the subcutis of the flank. The osteosarcoma incidences were not statistically significant relative to the controls (0/80 and 0/50), but exhibited a statistically significant dose-response trend. Evaluating the carcinogenic potential of sodium fluoride in the male rat, the investigators concluded that there was “equivocal evidence of carcinogenic activity” (NTP, 1990).

7.8 Reproductive toxicity

In a teratogenicity study conducted in the Sprague-Dawley rat, cryolite was devoid of reproductive toxicity up to 3000 mg/kg body weight, the highest dose level investigated. Groups of 30 females/dose were treated with cryolite by oral gavage at dose levels of 0 (control), 750, 1500 or 3000 mg/kg body weight/day on gestation days 6 to 15 inclusive. The only treatment-related change noted was whitening of the teeth of dams from the top dose group. The *no observed effect level* (NOEL) for the developmental and maternal toxicity of cryolite was given as 3000 mg/kg body weight/day (no further details; Science Applications, 1983; CalEPA, 1995; EPA, 1996).

In a teratogenicity study conducted in the Crl:CD-1 (ICR)BR mouse, groups of 25 pregnant mice were administered cryolite (97.3% pure) by oral gavage at daily dosages of 0 (controls), 30, 100 or 300 mg/kg body weight from day 6 to day 15 of gestation. There was increased maternal mortality in the 300 mg dose group; the dams' glandular portion and contents of the stomach were red. The glandular portion of the stomach was also red in dams from the dose group treated with 100 mg/kg body weight. Foetuses from the top dose group exhibited retardation phenomena in the form bent ribs and limb bones. The respective *no observed effect levels* (NOELs) for maternal toxicity and developmental toxicity were given as 30 and 100 mg/kg body weight/day (no further details; WIL Research Laboratories, 1991; CalEPA, 1995; EPA, 1996).

The findings from the mouse teratogenicity study described above (WIL Research Laboratories, 1991; CalEPA, 1995; EPA, 1996) were confirmed by a subsequent study in which groups of 30 Crl:CD-1 (ICR)BR mice received treatment with cryolite (97.3% pure) by oral gavage at 0 (control), 100, 300 or 1000 mg/kg body weight/day on gestation days 6 to 15 inclusive. Maternal mortality was 40% and 10% for the high and intermediate dose groups, respectively with necropsy reporting of red stomach contents and/or red stomachs. In the top dose group, body weight gains and food consumption were reduced. Survival was too low in the top dose group to permit meaningful assessment of the foetal findings, according to the authors; however, it was stated that there was a small increase in incidences of cleft palate and a single incident of open eyelid in one foetus. In the mid dose group, one foetus had bent ribs. These effects were evaluated as possibly related to treatment so that the *no observed effect level* (NOEL) for both maternal toxicity and developmental toxicity was 100 mg/kg body weight/day in this study (no further details; WIL Research Laboratories, 1992 b; CalEPA, 1995).

Considered unacceptable by EPA due to noncompliance with the requirements of the relevant guidelines, one range-finding study investigated the reproductive toxicity of cryolite (97.3% pure) in the New Zealand rabbit by treating groups of 5 rabbits at dose levels of 0 (control), 10, 30, 100, 300 or 1000 mg/kg body weight/day. At the lowest dose level of 10 mg/kg body weight and above, maternal food consumption was reduced. Dose levels $\geq$ 30 mg/kg body weight increased maternal mortality and resulted in reddened stomachs and red stomach contents. Defecation and urination were

decreased, and the stools were soft and very dark in colour. Details of the foetal findings were not reported in the available secondary source. The respective *no observed effect levels* (NOELs) for maternal toxicity and developmental toxicity were given as 10 and 30 mg/kg body weight/day (no further details; WIL Research Laboratories, 1992 c; EPA, 1996).

A two-generation study was carried out with cryolite in the Sprague-Dawley rat. Groups of 30 males and 30 females were administered cryolite of 96% purity in the diet at concentration levels of 0 (control), 200, 600 or 1800 ppm. During the pre-mating period, this represented daily dose levels of 0 (control), 14, 42 and 128 mg/kg body weight for males and 0 (control), 16, 49 and 149 mg/kg body weight for females. From the lowest dose tested, substance-related dental fluorosis was observed in a dose-dependent manner in the parental animals of both generations. Whitening of the incisors was noted, and from 600 ppm cryolite in the diet, incisors were mottled in 6 to 40% of F_1 animals. At the top dose level of 1800 ppm, incisors were observed to have bevelled edges in $\geq$ 67% of parental animals from both generations. In the top dose group, body weight gain decrements were seen in parental males. There were no treatment-related effects on the reproductive performance of parental males and females at dietary cryolite levels of up to 1800 ppm (approx. 128 and 149 mg/kg body weight/day, respectively). Effects in the offspring were confined to the top dose group, in which pup body weights during lactation were decreased to 74 to 89% of controls and necropsy at the time of weaning revealed pale livers, pale kidneys and enlarged hearts. The *no observed effect level* (NOEL) for reproductive toxicity in the offspring was given as 600 ppm cryolite in diet (approx. 45 mg/kg body weight/day). The respective *no observed effect levels* (NOELs) for parental toxicity including and excluding dental fluorosis were given as 200 and 600 ppm cryolite in diet (representing approx. 15 and 45 mg/kg body weight/day; no further details; Pharmaco LSR, 1994; CalEPA, 1995; EPA 1996).

7.9 Effects on the immune system

No information available.

7.10 Neurotoxicity

No information available.

7.11 Other effects

No information available.

8 Experience in humans

Metabolism and toxicokinetics

The metabolism and toxicokinetics of cryolite was investigated in 8 workers with at least 3 years' occupational exposure to the chemical during the refining of natural Greenland cryolite. After a one-week holiday, blood samples were obtained from the workers before and after shifts and urine samples were collected at intervals on each of 4 days. Throughout the working shifts, 7 workers wore portable pumps close to the breathing zone in order to collect dust from the breathing air for assessment of individual dust exposure at 4-hour intervals. None of the workers was a regular tea-drinker or exposed to any other known, nonoccupational fluoride source. Average dust exposures varied between 0.16 and 21.2 mg/m³ for the 4-hour periods, exceeding the threshold limit of 2.5 mg/m³ for occupational exposure at least once in all individuals except the foreman. The major part of the dust consisted of cryolite, with 54% of the cryolite being fluoride. The respective fluoride concentrations found in serum and urine increased from median values of 1.1 and 89 µmol/l on the morning after the holiday to 4.2 and 250 µmol/l on the morning of the 4th working day. The post-shift levels seen in the serum and urine on the third working day were 19 µmol/l and 410 µmol/l, respectively. Though values varied considerably, serum fluoride concentrations and urinary excretion of fluoride correlated in a statistically significant manner with the exposure levels. There was no statistically significant relationship between urinary fluoride concentration and the level of exposure. The average fluoride half-life in serum was 5.6 hours (with individual values varying between 3.3 and 6.9 hours). Fluoride clearance was 53.2 ml/minute (ranging from 40.5 to 76.5 ml/minute) with urinary flow averaging 1.37 ml/minute (ranging from 0.89 to 2.21 ml/minute) as determined during the work-free period between the shifts on day 3 and day 4 of observation. Subsequent to the holiday, the average pre-shift aluminium concentrations in the serum and urine were 1.2 and 2.4 µmol/l, respectively. After three working days, the respective pre-shift levels on the fourth working day were 0.9 and 4.7 µmol/l. There was no clear relationship be-

tween the aluminium concentrations in the urine and serum and the extent of dust exposure. However, the workers with the highest exposures also exhibited the highest concentrations. On a molar basis, urinary excretion of fluoride was almost 100 times higher than that of aluminium. During the week of work, the serum levels of calcium, magnesium and parathyroid hormone remained constant, whereas the concentration of phosphate increased from 1.26 mmol/l to 1.45 mmol/l (Grandjean et al., 1990).

In 1945, McClure et al. investigated the toxicokinetics of cryolite in humans under various conditions of temperature and relative humidity. They gave young men (aged 19 to 27 years, 2 to 4 subjects/experiment) fluoride at 3 mg/day in the form of dietary supplements of synthetic or natural cryolite on 5 consecutive days. Via their food and drinking water, the subjects ingested another 4.5 to 7.5 mg fluoride/day. The subjects spent 8 hours/day in a chamber with controlled environmental temperature (84 to 85 °F (approx. 29 °C) or 100 to 101 °F (approx. 39 °C)) and humidity (49 to 52% or 66 to 70%), during which time perspiration samples were collected. The urine and faeces were collected during the entire study period of 5 days. The subjects eliminated exactly the same quantities of fluorine as they had ingested. Approx. 30% was eliminated in the faeces and, in accord with temperature and humidity, 29.8 to 61.7% and 15.6 to 33.3% in urine and perspiration, respectively (McClure et al., 1945).

It has been reported that one male subject, who in several individual studies had average daily dietary intakes of 6.41, 6.61, 12.4, 18.4 or 36.4 mg fluoride in the form of cryolite over periods of 3 or 4 weeks, exhibited dose-independent excretion of 23 to 37.8% of the ingested fluoride in the faeces. The dose fraction not excreted in the faeces was considered absorbed. Of the amount absorbed, 52 to 65.9% appeared in the urine in a dose-independent manner (no further details; Largent and Heyroth, 1949; Machle and Largent, 1943).

Occupational exposure to cryolite

- **Processing of natural Greenland cryolite**

Workable, but now exhausted, deposits of natural cryolite have been known to exist only in Greenland. In 1932, Møller and Gudjonsson were the

first to describe skeletal changes later known as fluorosis (see Grandjean, 1982) which they discovered by chance when examining for silicosis Danish workers employed in the processing and purification of the cryolite. The majority of the workers who were thereupon examined comprehensively by Roholm (Roholm, 1936, 1937) complained of moderate functional dyspnoea, pains of a rheumatic nature, lack of appetite, nausea, vomiting and constipation. Upon examination by x-ray radiography, 57 of 68 workers (47 men and 21 women) were found to have a characteristic type of osteosclerosis affecting primarily the vertebral column, pelvis and ribs but in some cases also the entire skeletal system. The osteosclerosis was characterised by a thickening and blurring of the normal, trabecular structure, the more pronounced cases exhibiting 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. Mobility of the vertebral column was restricted depending upon the severity of the osteosclerosis and it was nearly completely absent in 4 out of 7 workers with extremely severe osteosclerosis. The organs contained no calcium deposits, and serum calcium content was not or only slightly increased. Urinary excretion of fluoride was greatly increased (2.41 to 43.41 mg/day or 16 mg/day on average in 24 workers exposed to cryolite, as compared with 0.30 to 1.6 mg/day (0.92 mg/day on average) in individuals without exposure; Brun et al., 1941). Further findings in the cryolite workers included pulmonary changes, which the author discussed as possibly attributable to exposure to quartz dust. Eleven workers had pulmonary emphysema whereas 34 workers had not very severe pulmonary fibrosis. The blood count displayed a slight leftward shift, which was most prominent in the workers with very marked fluorosis. Post-mortem examination of 2 workers with 24 years' and 9 years' employment at the factory, both of whom died of intercurrent diseases, yielded no abnormal findings which would have been attributable with certainty to cryolite exposure, apart from skeletal changes. Their bones weighed 2 to 3 times more than normal bones, bone elasticity was decreased and the bone surfaces were chalky-white and displayed widespread periosteal deposits and calcification of ligaments. Histologically, the osteosclerosis was characterised by an irregular organic matrix and varying, generally excessive calcium deposits. The calcium deposits consisted of precipitates in the form of coarse granules or lumps, frequently present in the medullary cavities and blood vessel-containing canals. The fluoride content of bone ash varied from 3.1 to 13.1‰,

while that of tooth ash was 2.5‰. Bone ash from individuals without fluoride exposure had fluoride levels of 0.48 to 2.1‰ while levels determined in their tooth ash were approx. 0.26‰ (0.19 to 0.30‰). Overall, the skeletal system contained 50 and 90 g of fluoride in the two workers, as compared with 1.5 to 6 g in individuals without exposure. In addition, the fluorine content was elevated in the lungs and kidneys. The workers had been exposed to high levels of dust while engaged in the cleaning, hand-sorting and grinding of natural cryolite, which contained 1 to 5% quartz, 15 to 20% siderite ($FeCO_3$) and varying quantities of other minerals (including ZnS, PbS, $CuFeS_2$, FeS_2). Dust levels averaged 30 to 40 mg/m³, with peak levels reaching values as high as 994 mg/m³. Approximately 97% of the dust consisted of cryolite and more than 50% of the dust particles were < 5 µm in diameter. The author estimated that the daily quantity of fluoride inhaled was 70 mg, of which 15 to 25 mg was absorbed systemically (elsewhere the author gave an estimate of 14 to 70 mg fluoride for a man weighing 70 kg; see also Grandjean et al., 1992 a). Bone changes developed only in workers with long-term, continual exposure to the dust. Changes that were only just radiographically discernible were seen after an employment period of no less than 2.4 years (9.3 years on average), marked fluorosis with periosteal deposits and incipient displacement of the bone marrow were observed after at least 4.8 years of employment (9.7 years on average) and severe calcification of the ligaments was noted after a duration of employment of no less than 11.2 years (21.1 years on average). Of 9 mine workers who had been seasonally employed in the opencast cryolite mine in Greenland for 1.3 to 8 years in total, 3 were found to have pulmonary fibrosis, or indications thereof, and one worker was found to have mild osteosclerosis as demonstrated by radiography. Findings in children indicated that fluorine is excreted in mother's milk. Three children were breastfed for 1 to 2.5 years by their mothers who worked in cryolite processing. The children's permanent teeth showed changes and were diagnosed as mottled teeth – opaque or chalky-white teeth with brown or black patches and bands. According to the IPCS (International Programme on Chemical Safety), fluoride concentrations in mother's milk and blood plasma are approximately the same and fluorine does not pass the placenta (IPCS, 1984, 1997). Examination of former workers many years after their retirement from the factory indicated that skeletal fluorosis may be slowly reversible. Mortality was not increased in the cryolite workers (Roholm, 1936, 1937).

Repeated follow-up examinations of workers from the Danish cryolite plant at which Roholm (1936, 1937) carried out his studies on fluoride toxicity yielded indications of the slow reversibility of skeletal fluorosis. Until 1961 the levels of airborne dust remained very high. The average dust levels reported by Roholm in 1936 and 1937 were 30 to 40 mg/m³. For 1955, the fluoride concentration was reported as 28 mg/m³, corresponding to approx. 40 mg/m³ in terms of cryolite. It was not until 1961, after the introduction of a floatation method for purification, that dust levels in the factory were reduced to 2.5 mg/m³. The workers' urinary fluoride excretion averaged 15 to 20 mg/l in 1941 while it was 7.6 mg/l on average in 1955. Up until 1957, there were 10 new cases of skeletal fluorosis at the factory, while three new cases occurred during the period from 1957 to 1967. In one worker, an improvement in the skeletal fluorosis was noted in 1967 as compared with the findings from 1957. A total of 17 workers exhibited skeletal fluorosis in 1957 and 1967. Of these individuals, 4 were still alive in 1982. Their bone changes were clearly reversible by 8 to 15 years after the end of exposure, whereas the calcification of muscle insertions and ligaments were not. Three of the 4 workers still had increased urinary fluoride concentrations. It was demonstrated that about 99% of the fluorine stored in the body is to be found in the bones and teeth. In bone, fluoride replaces the hydroxyl ions of hydroxyapatite, thus forming fluorapatite, and additionally stimulates the formation of new bone. The biological half-life of bone-incorporated fluoride is about 8 years, according to indirect calculations (Grandjean, 1982; Grandjean et al., 1984; Largent, 1961; IPCS, 1984, 1997).

A further, epidemiological study of the Danish workers who cleaned, crushed and sorted the natural cryolite mined in Greenland (see above; Roholm, 1936, 1937; Grandjean et al., 1984; Grandjean and Thomsen, 1983) addressed in greater detail the question as to the carcinogenic potential of cryolite. The cohort comprised 425 men who had been exposed to mineral cryolite for at least 6 months at the Copenhagen plant between 1 January 1924 and 1 July 1961 and who died no earlier than 1941. During this period, heavy exposure (30 to 40 mg dust/m³, or 28 mg fluoride/m³, see above) led to at least 74 cases of skeletal fluorosis. Roholm (1936, 1937) estimated the quantity of fluoride inhaled per day at approx. 70 mg (see above). Grandjean et al. (1985) give daily fluoride absorption as 40 to 80 mg. Based on the total quantities of fluoride determined by Roholm

(1936, 1937) in the bones of 2 deceased cryolite workers (see above), they later estimated daily fluoride absorption to be 35 mg (approx. 0.5 mg/kg body weight; Grandjean et al., 1992 a; see below). On the basis of the death certificates, all deaths up until 1 July 1981 were coded according to the official Danish classification system. Between 1941 and 1981, 206 men died as compared with an expected mortality rate of 149.3 for the general male population in Denmark. The standardised mortality ratio (SMR), i.e. the ratio of observed to expected deaths, and the lower and upper 95% confidence limits were calculated under the assumption of a Poisson distribution and given as 1.38 (1.19, 1.57). In particular, the number of violent deaths due to suicides and accidents (SMR 2.15 (1.42, 3.14)) and the number of deaths due to cancers (SMR 1.43 (1.07, 1.86)), especially respiratory carcinomas (not distinguished, SMR 2.37 (1.56, 3.45)), were increased as compared with the national average mortality. The rate of violent death among workers remained in excess when compared with the mortality rate for the male population of Copenhagen whereas mortality due to respiratory malignancies was only minimally increased when compared with the Copenhagen rates (no SMR data provided by the investigators). Cardiovascular mortality in the cohort was comparable with the national rate. The cancer morbidity data for the period from 1 January 1943 to 31 December 1977, as recorded by the official Danish Cancer Registry, revealed 78 cases of malignant neoplasms among the cryolite workers as compared with 53.2 cases expected for Denmark (standardised incidence ratio (SIR) 1.47 (1.16, 1.83)) and 67.9 cases expected for Copenhagen (SIR 1.15 (0.91, 1.43), statistically nonsignificant). Here too, cancers of the respiratory organs occupied first place with 29 cases (4 cases of cancer of the larynx and 24 cases of primary lung cancer) as compared with 11.8 cases expected for Denmark (SIR 2.5 (1.6, 3.5)) and 17.2 cases expected for Copenhagen (SIR 1.5 (1.0, 2.1), statistically nonsignificant). There were 8 cases of urinary bladder cancer as compared with 5.7 cases expected for the Copenhagen population (SIR 1.4 (0.6, 2.8)). There was no association between the incidence of cancers and the length of exposure or the time from onset of exposure. No exact information was available on smoking habits but they were assumed by the investigators to be similar to those in the control cohort from Copenhagen. In the discussion of their results, the investigators concluded that any major carcinogenic effect of cryolite exposure was very unlikely (Grandjean et al., 1985).

The mortality data collected by Grandjean et al., 1985 (see above) were reanalysed by Burk, 1985, who calculated not only standardised mortality ratios (SMR) but also standardised mortality differences (SMD, the difference between the numbers of observed and expected deaths extrapolated to 100000 workers). The investigator analysed the numbers of deaths in cryolite workers exclusively in relation to the general Danish population and also arrived at markedly increased figures for total mortality (SMD/100000 workers: 334), overall cancer mortality (SMD/100000 workers: 94.7), respiratory cancer mortality (SMD/100000 workers: 91.8) and mortality due to violence (suicides and accidents) in the cryolite workers (SMD/100000 workers: 85.3; Burk, 1985).

When Grandjean et al. (1992 a, b) carried out a further analysis of the group they had studied earlier on in 1985 (see above; Grandjean et al., 1985), they extended the follow-up periods for cancer mortality and incidence by 8.5 years (1941 to 1989) and 10 years (1943 to 1987), respectively, compared with their previous analysis. Among the cryolite workers there were 300 deaths as compared with 223.3 deaths expected for the general population of Denmark (SMR 1.34 (1.20 to 1.50)). Of the 300 deaths, 82 were due to any type of cancer with an expected 55.8 deaths (SMR 1.47 (1.17 to 1.82)), 112 were due to cardiovascular diseases with an expected 104.6 deaths (SMR 1.07 (0.88 to 1.29)), 8 were due to cirrhosis of the liver with an expected 2.2 deaths (SMR 3.62 (1.56 to 7.13)) and 30 were due to suicides or accidents with an expected 15 deaths (SMR 2.00 (1.35 to 2.85)). Of the fatal primary cancers, a large proportion was situated in the lungs and the larynx (no incidence data given). A more detailed analysis of cancer morbidity based on the Danish Cancer Registry in comparison with the population of Copenhagen revealed that the overall cancer incidence was slightly increased (119 observed cases, 103.6 expected cases, SIR 1.15 (0.95 to 1.37)). Among the cryolite workers there were 42 observed cases of respiratory cancers as compared with 29.9 expected cases (SIR 1.40 (1.01 to 1.90)), of which 35 were primary lung cancer cases as compared with 25.9 expected cases (SIR 1.35 (0.94 to 1.88)) and 5 were cases of laryngeal cancer as compared with 2.1 expected cases (SIR 2.29 (0.77 to 5.56)). There were also 17 observed cases of urinary bladder cancer compared with 9.2 expected cases (SIR 1.84 (1.08 to 2.96)). Compared with the results of the first study, the standardised incidence ratios for primary lung cancers and cancers of the larynx were slightly reduced

while the standardised incidence ratio for urinary bladder cancers was increased. Cancers of the lung and urinary bladder were more frequent in workers who were below the age of 35 years at the onset of exposure. As was the case with the first analysis of the cohort, no data were available on the smoking habits of the workers. The investigators pointed out, however, that the SIR for cancers at sites particularly affected in smokers (lips, tongue, buccal cavity, pharynx and oesophagus) was 2.29 (1.05 to 4.36) and thus showed an increase. The second analysis of the causes of death and cancer morbidity among Danish cryolite workers also included 97 women. However, the observed cancer incidences were too low for a differentiated analysis (28 observed cases of cancer as compared with 29.2 cases expected for the female population of Copenhagen (SIR 0.96)). The incidence of bone cancers was not increased among the cryolite workers. However, the cohort was too small to allow a statistically sound evaluation of any risks related to very rare cancer types, e.g. bone cancers. As in the first analysis, there was no clear relationship between the incidence of organ-specific cancers and the length of exposure. Most cancers occurred 10 to 19 years after the onset of exposure. All cohort members had a potential follow-up of at least 27 years. Discussing their results, the investigators concluded that the increases in lung cancer morbidity and, in particular, bladder cancer morbidity could not be ascribed to an increased rate of tobacco smoking alone. They hypothesised that the workers had possibly absorbed a carcinogen via the lungs and excreted it via the urinary tract, and recommended that further studies be carried out to investigate the carcinogenicity of fluoride to the urinary bladder (Grandjean et al., 1992 a, b).

Repeated radiological examination (in 1953, 1957 and 1966) of the Danish cryolite workers revealed no pathological lung changes in terms of silicosis/pneumoconiosis, according to Grandjean et al. (1984). After measurements carried out at the Danish cryolite plant in 1981 and 1982 showed that the threshold limit values for quartz and dust and for fluoride were repeatedly exceeded by factors of up to 6 and 4, respectively, pulmonary function test were carried out in 101 workers from the plant in 1988. In addition, the workers were asked about clinical symptoms and smoking habits. There was no notable impairment of pulmonary function due to occupational exposure. Pulmonary function and the occurrence of dyspnoea and chronic bronchitis were found, as expected, to depend on individual smoking habits. Examination by x-ray of 4 workers who had been em-

ployed at the plant for periods between 26 and 43 years yielded no indications of pneumoconiosis. About one third of the workers repeatedly complained of gastrointestinal symptoms (nausea, vomiting, diarrhoea and epigastric pain) and irritation of the eyes, mouth, pharynx and skin, particularly subsequent to heavy dust exposure. The investigators suggested that the complaints were caused by an unspecific effect of dust and the release of hydrofluoric acid from cryolite in the gastrointestinal tract (Friis et al., 1989).

- **Manufacture of synthetic cryolite**

Skeletal changes similar to those observed by Roholm (1936, 1937) in workers employed in the processing of natural cryolite were also noted by Peperkorn and Kähling in 1944 in workers employed at a production plant for inorganic fluorine compounds. A total of 47 workers were examined who were heavily exposed to synthetic cryolite, hydrofluoric acid, sodium fluoride and fluorspar (CaF_2), with the exposure to dust being particularly heavy (no measured data given). The workers complained of rheumatic symptoms, stiffness, exhaustion, weakness and functional dyspnoea. They had no gastrointestinal complaints such as those frequently observed in the group examined by Roholm (1936, 1937) and later in the group examined by Friis et al. (1989). The workers were in good general condition. There were no indications of occupational diseases of the heart, lung, liver or spleen. The urinalyses and blood counts were without abnormal findings with the exception of a slight increase in red blood cell counts. Out of the 40 workers who were exposed to fluorine compounds throughout the working day, 32 were found to have skeletal changes. Depending on the duration of employment, the workers developed, in a 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 markings were blurred and showed homogeneous 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 were marked periosteal overgrowths, 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 (Peperkorn and Kähling, 1944).

In India, an occupational exposure study was undertaken of 438 out of 496 workers who were employed in the manufacture of hydrogen fluoride from calcium fluoride as well as in the production of synthetic cryolite, sodium fluoride and other fluorine compounds from hydrogen fluoride. Of the examined workers, 70% had worked at the plant for more than 9 years in the period from 1965 to 1977. Urinary fluoride levels were only determined for 226 workers and only 106 workers were x-rayed. The mean urinary fluoride level was 1.96 ppm, with levels exceeding 4.5 ppm in 27 of the 226 (11.9%) workers examined. Out of the 438 workers, 34% had complaints, primarily concerning the spine and the knee and ankle joints, and 9.6% had typical dental defects. Of the 106 workers examined by x-ray, 21.8% were found to have slight osteofluorosis. Bone and dental findings correlated with urinary fluoride excretion and the level of exposure. There were no clear correlations between the findings and the duration of exposure or socio-economic status of the employees (Desai et al., 1983).

Between 1977 and 1982, 68 workers (as per 1982) employed at a Japanese production plant were exposed to phosphate rock containing 3 to 4% fluorides, cryolite, hydrofluoric acid, sodium aluminate and fluorosilicate. Twice a year, the workers received a thorough medical examination including chest x-ray and urinary fluoride level determination. Levels of airborne dust and fluoride were measured in parallel with the medical examinations regarding occupational exposure and were found on average to vary from 0.05 to 0.6 mg/m^3 and 0.09 to 0.49 ppm, respectively. The major component identified in the air was hydrofluoric acid. All workers were found to be without abnormal findings at all examinations. Urinary fluoride excretion varied between approx. 0.25 and 4 mg/l, reflecting the individual exposure situation. However, it was also greatly influenced by the workers' dietary habits in terms of food and, especially, beverage consumption, particularly the drinking of green or black tea containing relatively high fluoride concentrations (Baba et al., 1985).

- **Production of aluminium**

Workers employed in aluminium fused-salt electrolysis are exposed to numerous gaseous and particulate compounds. Frequently encountered substances include elemental aluminium, aluminium oxides, aluminium fluorides, carbon monoxide, sulphur dioxide, chlorine and hydrogen chloride, cryolite, fluorides, hydrogen fluoride, silicon compounds, nickel, chromium, vanadium and cyanides and mineral oil, coke, pitch, tar, petroleum and their distillation products. The use of Söderberg anodes, i.e. self-consuming carbon anodes which are formed in situ from coal, tar and pitch pastes and baked utilising the process heat of approx. 1000 °C, was associated with the emission of benzo[a]pyrene and other polycyclic aromatic hydrocarbons, in part in large quantities. The health risk to workers employed in the production of aluminium has been the subject of numerous epidemiological studies and has been evaluated by, *inter alia*, the International Programme on Chemical Safety (IPCS) and the International Agency for Research on Cancer (IARC) as part of the World Health Organization (IPCS, 1984, 1997; IARC, 1984, 1987). It was not possible to demonstrate any association between the prevalence of malignancies or cancer mortality and the exposure to fluorine compounds (IPCS, 1984, 1997). However, in connection with the use of Söderberg anodes, dependence was observed between the level and duration of exposure to tar volatiles (benzene-soluble compounds) or aromatic polycyclic hydrocarbons (benzo[a]pyrene) and mortality due to cancers (all malignancies, lung cancers and urinary bladder cancers; IARC, 1987; IPCS, 1997). Furthermore, workers were more frequently afflicted with asthma or respiratory disorders, which were ascribed, in particular, to the exposure to dust, sulphur dioxide and hydrogen fluoride. 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 (IARC, 1984; IPCS, 1997). Especially during the initial years of aluminium production, workers developed fluorosis or osteosclerosis, caused by the incorporation of fluoride into bone. Fluoride displaces the hydroxyl ions of the hydroxyapatite present in bone, thus forming fluorapatite, and additionally stimulates the formation of new bone. Osteosclerosis occurred when total fluoride exceeded threshold concentration levels of 2.5 mg/m³ or when urinary fluoride levels were in excess of 9 mg/l (IARC, 1984). It is considered unlikely that skeletal fluorosis develops if fluoride intake is ≤ 20 mg/day (approx. 0.29 mg/kg body

weight/day; EPA, 1996). It is assumed for persons with occupational exposure to fluorine compounds that the development of skeletal fluorosis can be excluded if fluoride concentrations in the morning urine are < 4 mg/l (IPCS, 1984).

9 Classifications and threshold limit values

No threshold limit values have been established so far for cryolite in particular. However, there exist threshold limit values for fluorides in general, the class of chemicals into which cryolite falls:

- MAK value (maximum allowable concentration at place of work) for fluorides (Germany): 2.5 mg/m³ (as fluorine; DFG, 2004).
- TLV for fluorides in general: 2.5 mg/m³, based on fluorine content (ACGIH, 1992).
- MAK value (Switzerland): fluorides including hydrogen fluoride: 1.8 ml/m³ (ppm), or 1.3 mg/m³, based on fluorine content (SUVA, 1984).

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (“MAK-Kommission”) has listed cryolite in the “Yellow Pages” of the List of MAK and BAT Values 2004 in order that a MAK value be established for the chemical (DFG, 2004).

Table 2. Exploratory acute toxicity studies of cryolite

Species, strain, sex[1]	Route	Dose (mg/kg body weight or mg/m³)	Purity, origin, state[1]	Effect	Observation period	Reference
Rat	oral	2000 (administered by gavage as a paste prepared with water; dose range tested: 200–2500 mg/kg body weight)	synthetic cryolite	not lethal (only one animal was tested per dose); no clinical signs of toxicity	n. d.	Sweetman and Bourne, 1944
Rat	oral	13500 (administered in feed over a period of 20 hours)	very finely ground synthetic cryolite	not lethal	n. d.	Marcovitch et al., 1937
Rat	oral	33600 (administered by gavage as a paste prepared with water; dose range tested: 25–33600 mg/kg body weight)	natural cryolite	not lethal (only one animal was tested per dose); no clinical signs of toxicity	n. d.	Sweetman and Bourne, 1944
Rat	oral	16000 (administered by gavage as a paste prepared with water; dose range tested: 3000–16000 mg/kg body weight)	natural cryolite	not lethal in the 1 to 4 animals tested per dose; maximum body weight loss was 5% and weight loss was reversible; no clinical signs of toxicity; necropsy revealed no abnormalities	21 days	Largent, 1948
Rat	oral	16000 (administered by gavage as a paste prepared with water)	synthetic cryolite	not lethal (4 animals tested); maximum body weight loss was 26% and weight loss was reversible; no clinical signs of toxicity; necropsy revealed no abnormalities	21 days	Largent, 1948
Rabbit	oral	1500–2000	synthetic cryolite	lowest lethal dose (no precise details)	n. d.	Français, 1935
Rabbit	oral	3000, 6000, 9000 or 12000 (administered by gavage as a paste prepared with water)	natural cryolite	mortality: 2/4, 1/2, 1/5 and 7/8, respectively; dose-independent body weight loss of up to 40%	21 days	Largent, 1948
Rabbit	oral	3000, 6000, 9000 or 12000 (administered by gavage as a paste prepared with water)	synthetic cryolite	mortality: 0/2, 0/2, 3/4 and 2/2, respectively	21 days	Largent, 1948
Guinea pig	oral	3000	synthetic cryolite	one-half of the exposed animals died	n. d.	Français, 1935
Dog	oral	5000	synthetic cryolite	tolerated by 50% of animals (no further details); vomiting	n. d.	Français, 1935
Sheep	oral	1000	synthetic cryolite	lowest toxic dose (no precise details)	n. d.	Français, 1935
Cat	oral	3000	synthetic cryolite	no findings	n. d.	Français, 1935
n. d.	n. d.	200*	n. d.	LD_{50}	n. d.	Lehman, 1951

* In view of the other data on the chemical's acute toxicity and its effects upon repeated administration, this value appears most unlikely as all the data are indicative of low toxicity.

[1] where specified

n. d. no data

Beginning of Table 3

Table 3. Effects of cryolite in exploratory repeated-dose studies				
Species, sex[1]	Route of administration, duration of treatment/regimen	Dose (mg/kg body weight or mg/m³)	Findings	Reference
Subacute oral administration				
Young albino rats, male	daily oral administration in feed for 9 days	ca. 3500 (1.9 g fluoride/kg body weight, admixed to the feed as natural cryolite)	lethal	Smith and Leverton, 1934
Rat	daily oral doses by gavage for 10 days or a total of 10 doses given thrice weekly	8000 (natural cryolite)	mortality: 0/2 in both cases; no adverse effect on body weight gain	Largent, 1948
Rat	daily oral doses by gavage for 10 days	8000 (synthetic cryolite)	mortality: 1/2; maximum body weight loss was 24%; weight loss was reversible in the survivor	Largent, 1948
Rat	oral gavage, a total of 10 doses given thrice weekly	8000 (synthetic cryolite)	mortality: 0/3; maximum body weight loss was 18%	Largent, 1948
Young rats	dietary administration for 4 to 5 weeks	125, 250 or 500 (0.25, 0.5 or 1.0% in feed as a fine powder)	markedly reduced body weight gain in all dose groups (no further details)	Møller and Gudjonsson, 1932
Rat, Sprague-Dawley, male, female, 5 rats per sex and dose	dietary administration, 28 days	ca. 0 (controls), 25, 50, 100, 200, 400, 1000, 2500 or 5000 (0, 250, 500, 1000, 2000, 4000, 10000, 25000 or 50000 ppm in the diet)	dose-dependent dental fluorosis; the teeth were whiter and the enamel became soft and granular	EPA, 1996
The cryolite tested was 97.5% pure.				
Dog, one per sex and dose	dietary administration, 28 days	0 (control), 500, 10000, 50000 or 60000 ppm in the diet	the 50000 ppm female lost weight and had reduced food and water consumption while the 60000 ppm female was comparable to the control; urine and plasma fluoride levels increased in a dose-dependent manner though the 50000 ppm female values exceeded the 60000 ppm female values	WIL Research Laboratories, 1985; CalEPA, 1995
The cryolite tested was 97.3% pure.				
Cat	oral, 9 administrations within a 3-month period	3000 (synthetic cryolite)	no findings	Français, 1935

Table 3. Effects of cryolite in exploratory repeated-dose studies				
Species, sex[1]	Route of administration, duration of treatment/regimen	Dose (mg/kg body weight or mg/m³)	Findings	Reference
Subchronic or chronic oral administration				
Young albino rats, male	daily dietary administration for 6 weeks	diet containing 0.00141 to 2.712% fluorine (admixed to the diet as natural cryolite)	dose-dependent changes in the tooth enamel in all dose groups; at and above 0.226% fluorine in the feed (according to the investigators approx. 250 mg fluorine/kg body weight (approx. 460 mg cryolite/kg body weight)): reduced growth rate and food consumption; 2.712% fluorine in the feed was lethal	Smith and Leverton, 1934
Rat	daily dietary administration for 5, 6, 8 or 10 weeks	4, 7 or 11 ppm in feed	dose-dependent accumulation of fluorine in the teeth (presumably no further parameter investigated)	Marcovitch et al., 1937
Rat, Wistar	oral administration in the drinking water for periods of presumably 15 weeks (no precise details)	10 mg fluoride/l water (added as cryolite)	slight depigmentation of the incisors; no adverse effect on body weight development; unclear liver, lung and kidney changes	Janecek et al., 1974
Overall, documentation of study conduct and findings was unclear and inaccurate; test animals presumably also had infectious diseases.				
Young rats	daily dietary administration for 16 weeks	6.3, 11.8, 21.8, 42.5, 78.9 or 158 mg fluorine/kg body weight/day, administered as cryolite	6.3 and 11.8 mg/kg body weight yielded no abnormal findings; 21.8 mg/kg body weight produced doubtful toxic effects and 42.5 mg/kg body weight and above caused marked dose-dependent toxic effects including reduced appetite, retardation in growth, poor general condition, reduced fecundity and typical dental changes; autopsy revealed liver and kidney degenerations (no precise details)	Smyth and Smyth, 1932
Young rats, male	repeated oral administration in the diet	0.0050% cryolite, or 24.3 ppm fluorine, in the diet	incipient dental changes	DeEds and Thomas, 1933-1934
Rat	dietary administration for up to 585 days	0.05 to 0.15% cryolite in the diet	diarrhoea, reduced food consumption, reduced body weight gain; the 0.15% group showed increased mortality, diffuse sclerosis, nephritis and increased length of superior incisors	Roholm, 1937
Rat, albino	oral administration in the diet or drinking water for 19 to 20 weeks	9.1 mg fluorine/kg or litre in the diet or drinking water, as cryolite	dental discoloration, increased concentration of fluorine in bone, teeth and tissues; administration in the drinking water was associated with impairment of appetite and depressed body weight gain and transient haematuria	Lawrenz et al., 1939

Table 3. Effects of cryolite in exploratory repeated-dose studies				
Species, sex[1]	Route of administration, duration of treatment/regimen	Dose (mg/kg body weight or mg/m³)	Findings	Reference
Dog (one animal)	dietary administration for 587 days	79.8 mg fluorine/kg body weight/day, administered in the feed as cryolite	poor general condition, reduced food consumption, body weight loss, increased water consumption, anaemia, nephritis, bone alterations, increased fluorine content in bones and teeth	Roholm, 1937
Pig (4 animals)	dietary administration for 168 days	15 mg fluorine/kg body weight/day, administered in the feed as cryolite	nephritis, changes of the teeth and bones, increased fluorine content in the bones	Roholm, 1937
Calf (one animal)	dietary administration for 295 days	60 mg fluorine/kg body weight/day, administered in the feed as cryolite	diarrhoea, retardation of growth, bone alterations, increased fluorine content in the bones	Roholm, 1937
Subchronic inhalation exposure				
Rat	inhalation, 6 hours/day for 5 months	cryolite at 0.5 mg/m³ together with hydrogen fluoride at 0.35 mg/m³	reversible decrease in phagocytic activity of leukocytes (no further details)	Egorova and Sadilova, 1971; EC, 2000
Rat, albino	inhalation, 6 hours/day, chronic exposure	0.5 to 3.1 mg/m³	no findings at 0.5 mg/m³; toxic at and above 1 mg/m³ (no precise details in the English abstract of a paper published in Russian)	Plotko et al., 1973
[1] where specified				

End of Table 3

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