EUROPEAN COMMISSION

Directorate-General for Health & Consumers

Scientific Committee on Health and Environmental Risks

SCHER

Critical review of any new evidence on the hazard profile, health effects, and human exposure to fluoride and the fluoridating agents of drinking water

Scientific Committees
on consumer safety
on emerging and newly identified health risks
on health and environmental risks

SCHER adopted this pre-consultation opinion at its 7th plenary on 18 May 2010

About the Scientific Committees

Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat. They are: the Scientific Committee on Consumer Safety (SCCS), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and are made up of external experts.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Evaluation Agency (EMEA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

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Opinions on risks related to pollutants in the environmental media and other biological and physical factors or changing physical conditions which may have a negative impact on health and the environment, for example in relation to air quality, waters, waste and soils, as well as on life cycle environmental assessment. It shall also address health and safety issues related to the toxicity and eco-toxicity of biocides.

It may also address questions relating to examination of the toxicity and eco-toxicity of chemical, biochemical and biological compounds whose use may have harmful consequences for human health and the environment. In addition, the Committee will address questions relating to methodological aspect of the assessment of health and environmental risks of chemicals, including mixtures of chemicals, as necessary for providing sound and consistent advice in its own areas of competence as well as in order to contribute to the relevant issues in close cooperation with other European agencies.

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ABSTRACT

Fluoride is not an essential element for human growth and development, and for most organisms in the environment.
Large variation in naturally occurring fluoride in drinking water is observed in EU Member States ranging from 0.1- ca. 6.0 mg/L. Hexafluorosilicic acid and hexafluorosilicates are the most commonly used agents in drinking water fluoridation. These compounds are rapidly and completely hydrolyzed to fluoride ion. No residual fluorosilicate intermediates have been reported. Thus the main relevant substance to be evaluated is the fluoride ion (F^-).
Systemic exposure to fluoride in drinking water is associated with an increased risk of dental and bone fluorosis in a dose-response manner without a detectable threshold. Limited evidence from epidemiological studies points towards adverse health effects following systemic fluoride consumption, e.g., carcinogenicity, developmental neurotoxicity and reproductive toxicity, but using a weight of evidence approach these observations cannot be substantiated.
The total exposure to fluoride was estimated for infants, children, and adults from all sources of fluoride, e.g., water based beverages, food, food supplements, and the use of toothpaste. Contribution from other sources is limited except for occupationally exposure to dust from fluoride containing minerals.
The tolerable upper intake level (UL), as established by EFSA, was only exceeded in the worst case scenario for adults and children > 15 years old at a daily consumption of 2800 ml drinking water and the level of fluoride > 3 mg/L, and for children (6-15 years) when consuming more than 1.5 L. For younger children (1-6 yrs) the UL was exceeded when consuming more than 1 L water at 0.8 mg fluoride/L assuming the worst case scenario. For infants up to 6 month receiving infant formula, the safe level as established by UK (DoH) was only exceeded if the water fluoride level was higher than 0.8 mg/L.
The cariostatic effect of topical fluoride application, e.g. fluoridated toothpaste, is to maintain a continuous level of fluoride in the oral cavity. Scientific evidence for the protective effect of topical fluoride application is strong, while the respective data for systemic application via drinking water is less convincing. No obvious advantage appears in favour of water fluoridation as compared with topical application of fluoride. An advantage in favour of water fluoridation is that caries prevention will reach disadvantaged children from the lower socioeconomic groups.
In several environmental scenarios it was found that fluoridation of drinking water did not add any risk to the organisms in the environment, and thus that the added risk of drinking water fluoridation to the environment has to be considered negligible.

Keywords: fluoride, drinking water, fluoridating agents, silicofluorides, (hydro)fluorosilicic acid, sodium silicofluoride, disodium hexafluorosilicate, hexafluorosilicic acid, dental fluorosis, tooth decays, environmental risk, aquatic organisms

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1. BACKGROUND

Fluoride is not considered to be essential for human growth and development but it is considered to be beneficial in the prevention of dental caries (tooth decay). As a result intentional fluoridation of drinking water and the development of fluoride containing oral care products (toothpastes and mouth rises), foods (fluoridated salts) and supplements (fluoride tablets) have been employed since the early 20th century in several parts of the world as a public health protective measure against tooth decay. Additional exposure to fluoride comes from naturally occurring water (tap and mineral), beverages, food and to a lesser extent from other environmental sources.

A body of scientific literature seems to suggest that fluoride intake may be associated with a number of adverse health effects. Dental fluorosis and effects on bones (increased fragility and skeletal fluorosis) are two well documented adverse effects of fluoride intake. Systemic effects following prolonged and high exposure to fluoride have also been reported and more recently effects on the thyroid, developing brain and other tissues, and an association with certain types of osteosarcoma (bone cancer) have been reported.

Individual and population exposures to fluoride vary considerably and depend on the high variability in the levels of fluoride found in tap (be it natural or the result of intentional fluoridation of drinking water) and mineral waters, and on individual dietary and oral hygiene habits and practices. The emerging picture from all risk assessments conducted on fluoride is that there exists a narrow margin between the recommended intakes for the prevention of dental caries and the upper limits of exposure. Invariably, all assessments to date call for continued monitoring of the exposure of humans to fluoride from all sources and an evaluation of new scientific developments on its hazard profile.

Exposure assessment was conducted in the most recent evaluations by the European Food Safety Authority (EFSA), setting Tolerable Upper Intake levels and related to concentration limits for fluoride in natural mineral waters (EFSA, 2005) and on calcium fluoride and sodium monofluorophosphate as a source of fluoride (EFSA, 2008) and the Commission Scientific Committee on Consumer Products (fluoride in dental care products (SCCP, 2009). A similar approach was taken by the United States National Academies of Science in its 2006 review of the United States Environmental Protection agency's water standards for fluoride.

There is a continuous controversy over the benefit of fluoride and, in particular, the practices of intentional water fluoridation in tooth decay prevention. This has led several countries to discontinue drinking water fluoridation and in some cases to expand it.

Besides questioning the practice of intentional water fluoridation itself as being unnecessary or superfluous in light of the high exposure to fluoride from other sources, opponents of water fluoridation, have pointed to reports showing that the health and environmental risks of the most commonly used fluoridating agents, silicofluorides (e.g. (hydro)fluorosilicic acid, sodium silicofluoride, disodium hexafluorosilicate or hexafluorosilicate or hexafluorosilicic acid) have not been properly assessed and suggest that these chemicals in drinking water may cause adverse effects to the health of humans and exert possible exacerbating effects on fluoride disposition in bone.

The debate over water fluoridation has prompted several questions from the European Parliament from Ireland and the United Kingdom where intentional water fluoridation is still practiced.

In order to obtain an updated advice on the issue, the Commission considers it necessary to seek the advice of its Scientific Committee on Health and Environmental Risks who should work in close collaboration with the Scientific Committee on Consumer Products (SCCP), EFSA's panel on dietetic products, nutrition and allergies (EFSA NDA) and EFSA's panel on contaminants in the food chain (EFSA CONTAM) who have previously delivered opinions on fluoride.

2. TERMS OF REFERENCE

The Scientific Committee on Health and Environmental Risks (SCHER) is requested to:

1. Taking into consideration the SCCP opinion of 20.09.05 on the safety of fluorine compounds in oral hygiene products, the EFSA NDA opinion of 22.2.05 on the Tolerable Upper Intake Level of Fluoride, and the EFSA CONTAM panel opinion of 22.06.05,

a. Critically review any information that is available in the public domain on the hazard profile and epidemiological evidence of adverse and/or beneficial health effects of fluoride. In particular the Committee should considerer evidence that has become available after 2005 but also evidence produced before and which was not considered by the SCCP and EFSA panels at the time.

b. Conduct an integrated exposure assessment for fluoride covering all known possible sources (both anthropogenic and natural). In doing so and in the case of uncertainties or in lack of actual exposure data, the SCHER is requested to conduct a sensitivity analysis that includes a range of possible exposure scenarios (e.g. sources, age group), and describe using appropriate quantitative or qualitative means the weight of the evidence behind each scenario, the uncertainties surrounding each scenario, and the probability of it occurring in real life.

c. On the basis of its answers above, the SCHER is also asked

c1 - To evaluate the evidence of the role of fluoride in tooth decay prevention and rank the various exposure situations as to their effectiveness in offering a potential tooth decay preventive action.

c2 - To pronounce itself as to whether there may be reasons for concern arising from the exposure of humans to fluoride and if so identify particular exposure scenarios that may give rise to concern in particular for any particular population subgroup.

d. Identify any additional investigative work that need to be done in order to fill data gaps in the hazard profile, the health effects and the exposure assessment of fluoride.

2. Assess the health and environmental risks that may be associated with the use of the most common drinking water fluoridation agents like silicofluorides (e.g. (hydro)fluorosilicic acid, sodium silicofluoride, disodium hexafluorosilicate or hexafluorosilicate or hexafluorosilicic acid) taking into account their hazard profiles, their mode of use in water fluoridation, their physical chemical behaviour when diluted in water, and the possible adverse effects they may have in exacerbating fluoride health effects as reported in some studies.

3. SCIENTIFIC RATIONALE

Fluoride, either naturally present or intentionally added to water, food, consumer and medical products, is considered beneficial to prevent dental caries (tooth decay). However, the cause of dental caries is multi-factorial. These include the microorganisms in dental plaque, sucrose, time, the individual's health status and level of oral hygiene which depends on socioeconomic and educational status.

Fluorides are ubiquitous in air, water and the lithosphere. Fluorine as an element is seventh in the order of frequency of occurrence, accounting for 0.06-0.09% of the earth's crust, e.g., cryolite (Na_3AlF_6). Cryolite, used for the production of aluminium, and rock phosphates used for the production of fertilizers, has fluoride contents up to 54%. Most of this fluoride is insoluble and not biologically available. Availability of fluoride from soil depends on the solubility of the compound, the acidity of the soil and the presence of water. Fluorine has been detected in the ash from the Icelandic volcano eruption, but EFSA (26/4-2010) has concluded that based upon available information, the potential risk posed by the fluoride for human and animal health through food and feed is not considered to be of concern in the EU.

All water contains fluoride. The concentration of fluoride in ground water in the EU is generally low, but there are large regional differences due to different geological conditions. Surface water usually has lower fluoride contents than ground water, most often below 0.5 mg/L, and sea water between 1.2 and 1.5 mg/L. There are no systematic data on the concentration of fluoride in natural drinking water in EU Member States, but rudimentary data show large variation between and within countries, e.g., Ireland <0.01-5.8 mg F/L, Finland 0.1-3.0, and Germany 0.1-1.1. The Council Directive 98/83/EC of 3 November 1998 on the quality of water for human consumption determines the maximum fluoride concentration of drinking water at 1.5 mg/L.

Bottled natural mineral water is increasingly being used as a major source of water for drinking. A large variation in the level of fluoride has been observed reaching up to 8 mg/L (EFSA, 2005). Commission Directive 2003/40/EC of 16 May 2003 establishing the list, concentration limits and labelling requirements for the constituents of natural mineral waters and the conditions for using ozone-enriched air for the treatment of natural mineral waters and spring waters, and requires that waters which contain more than 1.5 mg/L must be labelled as not suitable for the preparation of infant formula.

WHO has established a guidance value for naturally occurring fluoride in drinking water of 1.5 mg/L based upon a consumption of 2 L water/day, and recommended artificial fluoridation of water supplies to reach fluoride levels of 0.5-1.0 mg/L (WHO, 2006). In Europe only Ireland and selected regions in the UK currently fluoridate drinking water at and at concentrations from 0.8 –1.2 mg/L.

Fluoride intake from food is generally low, except when food is prepared with fluoridated water or salt. However, some brands of instant teas represent a significant source of fluoride intake. Vegetables and fruits, milk and milk products, bread and cereals contains between 0.02-0.29 mg/kg (EFSA, 2005). Recently, EFSA (2008, a,b) has approved CaF_2 and Na_2PO_3F as a source of fluoride in food supplements.

Dental products (toothpaste, mouthwashes and gels) contain fluoride at different concentrations up to 1500 mg/kg (1500 ppm). The mean annual usage of toothpaste in EU member states in 2008 was 251 ml (range 130-405 ml) per capita. The extent of systemically available fluoride from toothpaste depends on the percentage of toothpaste application swallowed, which is a concern for children.

Fluoride is widely distributed in the atmosphere, originating from the dust of fluoride containing soils, industry and mining activities, and the burning of coal. The fluoride

content in the air in non-industrialized areas has been found to be low and is not considered to contribute more than 0.01 mg/day to the total intake.

A tolerable upper intake level (UL) of 0.1 mg/kg BW/day for fluoride has been derived by the EFSA NDA panel (2005) based upon a prevalence of less than 5% of moderate dental fluorosis in children up to the age of 8 years as the critical endpoint as follows: 1.5 mg/day for children 1-3 years of age, 2.5 mg /day for children 4-8 years. For adults a UL of 0.12 mg/kg BW/day was based on a risk of bone fracture, which converts on a body weight basis into 7mg/day for populations 15 yrs and older, and 5 mg/day for children 9-14 years of age.

Tolerable upper intake levels for fluoride have not been established for infants. For infants up to 6 months old, the UK DoH (1994) concluded that 0.22 mg F/kg BW/day was safe.

Several pathologies have been linked to high level fluoride exposure but mostly based upon circumstantial evidence. Thus this opinion will focus on fluorosis of teeth and bones, osteosarcoma, neurotoxicity and reprotoxicity.

3.1. Dissociation of hexafluorosilicic acid in aqueous solution

Hexafluorosilicic acid and hexafluorosilicates are the most commonly used agents in drinking water fluoridation and it has been claimed that incomplete dissociation of these agents in drinking water may result in human exposure to these chemicals. The toxicology of these compounds is incompletely investigated. Recent studies have addressed the equilibrium of free fluoride ion and fluorosilicate species in aqueous solutions over a wide concentration and pH range. In the pH-range and at the concentrations of hexafluorosilicates/fluoride relevant for drinking water, hydrolysis of hexafluorosilicates to fluoride was rapid and the release of fluoride ion was essentially complete, and residual fluorosilicate intermediates were not observed by sensitive ^{19}F-NMR. Other hydrolysis products of hexafluorosilicate such as $Si(OH)_4$ are rapidly transformed to colloidal silica (Finney et al, 2008). $Si(OH)_4$ is present naturally in drinking water in large quantities and is not considered a risk. In summary, these observations suggest that human exposure to fluorosilicates due to the use of hexafluorosilicic acid or hexafluorosilicate for drinking water fluoridation, if any, is very low as fluorosilicates in water are rapidly hydrolyzed to fluoride, as illustrated in the equation:

$$H_2SiF_6(aq) + 6OH^-(aq) \Leftrightarrow 6F^-(aq) + Si(OH)_4(aq) + 2H_2O(l)$$

Studies on Na_2SiF_6 and H_2SiF_6, compounds used to fluoridate drinking water, show a pharmacokinetic profile for fluoride identical to that of NaF (Maguire et al. 2005, Whitford et al. 2008). It therefore seems unlikely that the rate and degree of absorption, fractional retention, balance and elimination of fluoride will be affected if these fluoride compounds are added artificially in low concentrations or the fluoride is naturally present in drinking water.

Hexafluorosilicic acids used as fluoridating agent may contain some impurities. A potential addition of toxic heavy metals to drinking water has been speculated to occur due to the presence of several heavy metals as low-concentration impurities in commercial hexafluorosilicic acid. However, based on the average concentrations of arsenic, mercury, lead and cadmium present in hexafluorosilicic acid (0.5 to 5.7 mg/L), only a very low additional exposure of the population to these metals can occur (expected drinking water concentrations between 3.0 and 16.2 ng/L). These calculated concentrations are at least 2 orders of magnitude below drinking water guideline values for these metals established by WHO and other organizations, and therefore are not regarded as additional health risks.

It has been claimed that fluoridated drinking water increases human exposure to lead due to solubilisation of lead from drinking water pipes by formation of highly soluble lead complexes. The claim was based on relationships of drinking water fluoridation and blood lead concentrations observed in a case study (Coplan et al, 2007).
Based on the available chemistry of fluoride in solution, the chemistry of lead and lead ions, and the concentrations of fluoride in tap water, it is highly unlikely that there would be an increased release of lead from pipes due to hexafluorosilicic acid. The added concentrations of hexafluorosilicic acid do not influence the pH of the tap water, and do not form soluble lead complexes at the low concentrations of hexafluorosilicic acid present in the gastrointestinal tract after consumption of fluoridated drinking water (Urbansky and Schock, 2000).

3.2. Physico-chemical properties

As indicated in section 3.1, the main substance of concerns is the fluoride ion (F^-) and therefore the identification and the physico-chemical properties of NaF given in Table 1 are considered applicable.

Table 1 - Main physico-chemical properties of sodium fluoride

Substance		sodium fluoride	
Elemental symbol		NaF	
Ionic form		Na^+, F^-	
CAS-number		7681-49-4	
EINECS-number		231-667-8	
Molecular weight	M	42 (Na: 23 F: 19)	g/mol
Melting point	MP	ca. 1000	ºC
Boiling point	BP	1700	ºC
Vapour pressure	VP	133	Pa at 1077 ºC
Vapour pressure at 25 ºC	VP	1.97E-5	Pa, conversion by EUSES
Water solubility	WS	40000	mg/L at 20 ºC
Water solubility at 25 ºC	WS	42900	mg/L, conversion by EUSES
Octanol-water partition	log K_{ow}	Not appropriate	-
Henry's Law constant	H	1.93E-8 (calculation by EUSES)	$Pa.m^3/mol$
Sorption capacity	K_d	0.0006 – 0.03 (estimation)	dm^3/kg (Bégin et al., 2003) (see 3.1)
Removal rate	R	1.39E-06 (default)	d^{-1} at 12 ºC
Bioconcentration factor	BCF	Not relevant	dm^3/kg_{wwt}

SCHER agreed to use these physico-chemical properties where relevant in this opinion.

3.3. Pharmacokinetics of fluoride ions

3.3.1. Oral uptake

In humans and animals ingested fluoride is effectively absorbed from the gastrointestinal tract and occurs as HF in the acidic environment of the stomach, while there is no proved absorption from the oral cavity. Peak plasma levels are typically seen within 30–60 minutes after ingestion. Ingestion of fluoride with food will delay the gastric emptying and the rate of fluoride absorption. Highly soluble fluoride compounds, such as NaF present in tablets, aqueous solutions and toothpaste are almost completely absorbed, whereas compounds with lower solubility, such as CaF_2, MgF_2, and AlF_3, are less well absorbed. Ingestion of fluoride with milk or a diet high in calcium will decrease fluoride absorption.

3.3.2. Dermal absorption

No experimental data on the extent of dermal absorption of fluoride from dilute aqueous solutions are available. As fluoride is an ion it is thus expected to have low membrane permeability and limited absorption through the skin from dilute aqueous solutions at near neutral pH (such as drinking water used for bathing and showering). This exposure pathway is unlikely to significantly contribute to fluoride body burden.

3.3.3. Inhalation

No systematic experimental data on the absorption of fluoride after inhalation is available. A few older occupational studies have shown uptake of fluoride in heavily exposed workers from fluoride-containing dusts, but it is unlikely that inhalation exposure will contribute significantly to the body burden of fluoride in the general population.

3.3.4. Fluoride distribution, metabolism and excretion

Once absorbed, fluoride is rapidly distributed throughout the body via the blood. The short term plasma - half life is normally in the range from 3 to 10 hours. Fluoride is distributed between the plasma and blood cells, with plasma levels being twice as high as blood cell levels. Plasma fluoride concentrations are not homeostatically regulated, but rise and fall according to the pattern of fluoride intake. In adults, plasma fluoride levels appear to be directly related to the daily exposure of fluoride. Mean plasma levels in individuals living in areas with a water fluoride concentration of 0.1 mg/L or less are normally 0.5 µmol/L, compared to a mean plasma fluoride level of 1.0 – 1.5 µmol/L in individuals living in areas with a water fluoride content of 1.0 mg/L. In addition to the level of chronic fluoride intake and recent intake, the level of plasma fluoride is influenced by the rates of bone accretion and dissolution, and by the renal clearance rate of fluoride. Renal excretion is the major route of fluoride removal from the body. The fluoride ion is filtered from the plasma by the glomerulus and then partially reabsorbed; there is no tubular secretion of fluoride. Renal clearance rates of fluoride in humans average at 50 mL/minute. A number of factors, including urinary pH, urinary flow, and glomerular filtration rate, can influence urinary fluoride excretion. There are no apparent age related differences in renal clearance rates (adjusted for body weight or surface area) between children and adults. However, in older adults (>65 years), a significant decline in renal clearance of fluoride has been reported consistent with the age-related decline in glomerular filtration rates.

Approximately 99% of the fluoride in the human body is found in bones and teeth. Fluoride is incorporated into tooth and bone by replacing the hydroxyl ion in hydroxyapatite to form fluorohydroxyapatite. The level of fluoride in bone is influenced by several factors including age, past and present fluoride intake and the rate of bone turnover. Fluoride is not irreversibly bound to bone and is mobilized from bone through bone remodelling.

Soft tissues do not accumulate fluoride, but a higher concentration has been reported for the kidney due to the partial re-absorption. The blood-brain barrier limits the diffusion of fluoride into the central nervous system, where the fluoride level is only about 20% that of plasma. Human studies have shown that fluoride is transferred across the placenta, and there is a direct relationship between fluoride levels in maternal and cord blood. In humans, fluoride is poorly transferred from plasma to milk. The fluoride concentration in human milk is in the range of 3.8 – 7.6 µg/L.

4. OPINION

4.1. Question 1-a

Critically review any information that is available in the public domain on the hazard profile and epidemiological evidence of adverse and/or beneficial health effects of fluoride.

4.1.1. Dental and skeletal fluorosis

4.1.1.1. Dental fluorosis

Clinically "mild" fluorosis appears as white opaque striations across the enamel surface. In more severe cases the porous areas increase in size and pitting occurs with secondary discoloration of the surface. For classification of fluorosis see appendix I. The severity and prevalence of dental fluorosis has been shown to be directly related to the fluoride concentration in drinking water, however it is the daily total fluoride intake over a prolonged period of time during the developmental phase of the teeth that results in fluorosis.

The pre-eruptive developments of the deciduous and permanent teeth are critical phases for dental fluorosis. Early ossification of the jaw and development of deciduous tooth buds occurs between 4-6 months *in uterus*. Mineralisation of the permanent tooth buds start at the time of birth and continues slowly for 12-14 years.

Numerous studies have demonstrated that exposure to fluoride levels during tooth development can result in dental fluorosis. Excess systemically absorbed fluoride may impair normal development of enamel in the pre-eruptive tooth. This will not be apparent until tooth eruption, which will be more than 4-5 years after exposure. The development and severity of fluorosis is highly dependent on the dose, duration, and timing of fluoride exposure (see appendix II).

Fluorosed enamel is composed of hypomineralized subsurface enamel covered by well-mineralized enamel. The exact mechanisms of dental fluorosis development have not been fully elucidated. It seems that fluoride systemically can affect the ameloblasts, particularly at high fluoride levels, while at lower fluoride levels, the ameloblasts may respond to topical effects of fluoride on the mineralizing matrix (Bronckers et al., 2009).

The EFSA NDA panel considered that an intake of <0.1 mg F/kg BW/day in children up to 8 years old corresponds to no significant occurrence of "moderate" forms of fluorosis in permanent teeth (EFSA, 2005). Figure 1 shows a plot of the Community Fluorosis Index versus the daily fluoride dose/kg bodyweight (Richard et al., 1967, Butler et al., 1985; Fejerskov et al., 1996). The plot shows a linear dose–response relationship and indicates that fluorosis may occur at very low fluoride intake from water.

Enamel fluorosis seen in areas with fluoridated water (0.7 – 1.2 mg/L F) has been attributed to early tooth brushing behaviours, and inappropriate high fluoride intake (Ellewood et al., 2008), i.e., use of infant formula prepared with fluoridated drinking water (Forsman, 1977). Similarly, enamel fluorosis may occur in non-fluoridated areas, in conjunction with the use of fluoride supplements and in combination with fluoridated toothpaste (Ismail and Hasson, 2008). Fluoridated toothpaste has been dominating the European toothpaste market (>90%) for more then 30 years. There is no compelling scientific evidence indicating an increase of fluorosis in young children in the EU countries where fluoridated toothpaste is the main fluoride source.

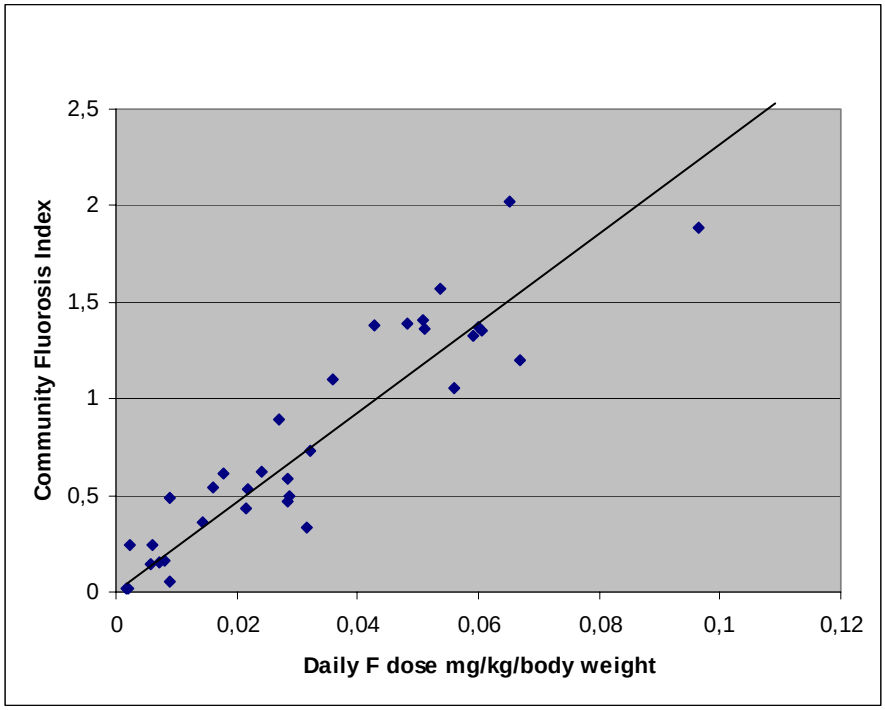

Figure 1 - Regression line between Dean's Community Fluorosis Index and daily fluoride dose from water per kg body weight.

4.1.1.2. Skeletal fluorosis

A number of mechanisms are involved in the toxicity of fluoride to bone. Fluoride ions are incorporated into bone substituting hydroxyl groups in the carbonate-apatite structure to produce fluorohydroxyapatite, thus altering the mineral structure of the bone. Unlike hydroxyl ions, fluoride ions reside in the plane of the calcium ions, resulting in a structure that is electrostatically more stable and structurally more compact. Because bone strength is thought to derive mainly from the interface between the collagen and the mineral (Catanese and Keavney, 1996), alteration in mineralization affects bone strength.

Skeletal fluorosis is a pathological condition, resulting from long term exposure to high levels of fluoride. Skeletal fluorosis, in some cases with severe crippling, has been reported in individuals residing in India, China and Africa, where the fluoride intake is exceptionally high e.g., high concentration of fluoride in drinking water, indoor burning of fluoride-rich coal resulting in a high indoor fluoride concentration It is difficult to estimate the dose-response relationship from studies on skeletal fluorosis as other factors such as nutritional status as well as climate influence water intake (IPCS, 2002).

4.1.1.3. Effect on bone strength and fractures

A large number of epidemiological studies has investigated the effect of fluoride intake on bone fractures. The amount of fluoride taken up by bone is inversely related to age. During the growth phase of the skeleton, a relatively high portion of ingested fluoride will be deposited in the skeleton: up to 90 % during the first year of life, which gradually decrease to 50 % in children > 15 years. There is no clear association of bone fracture with water fluoridation (McDonagh et al., 2000), however fluoride can weaken bone and increase the risk of bone fractures under certain conditions, and a water concentration ≥4 mg fluoride/L will increase the risk of bone fracture compared to 1 mg fluoride/L (US NRC 2006).

4.1.1.4. Conclusion

SCHER acknowledges that there is a risk for mild forms of dental fluorosis in children in EU countries with systemic fluoride exposure in a dose-dependent manner and a threshold cannot be detected. The occurrence of endemic skeletal fluorosis has not been reported in EU. SCHER agrees that there are insufficient data to evaluate the risk of bone fracture at the fluoride level seen in areas with fluoridated water.

4.1.2. Genotoxicity and Carcinogenicity

4.1.2.1. Genotoxicity studies

In general, fluoride is not mutagenic in prokaryotic cells, however sodium and potassium fluoride (500-700 mg/L) induced mutation at the thymidine kinase (Tk) locus in cultured cells at concentrations that were slightly cytotoxic and reduced growth rate. In contrast, fluoride did not increase the mutations frequency at the HGPRT locus (200-500 mg/L). Chromosomal aberrations, mostly breaks/deletions and gaps, following exposure to NaF has been investigated in many *in vitro* assays, but no significant increase in frequency was observed in human fibroblast at concentrations below 4.52 mg F/L and for CHO cells below 226 mg F/L.

Positive genotoxicity findings *in vivo* were only observed at doses that were highly toxic to animals, while lower doses were generally negative for genotoxicity. Chromosomal aberrations and micronuclei in bone marrow cells were observed in Swiss mice (up to 18 mg F/kg body weight), however no effects were observed in Swiss Webster following oral exposure for at least seven 7 generations compared to low fluoride exposure (EFSA,2005). Fluoride has only been reported to be positive in genotoxicity tests at high concentrations (> 10 mg/L), and this effect is most likely due to a general inhibition of protein synthesis and enzymes such as DNA polymerases.

There are conflicting reports on genotoxic effects in humans. An increase in SCE and micronuclei has been reported in peripheral lymphocytes from patients with skeletal fluorosis or residents in fluorosis-endemic areas in China and India, while no increased frequency of chromosomal aberrations or micronuclei were observed in osteoporosis patients receiving sodium fluoride treatment. The quality of the former studies is questionable.

4.1.2.2. Carcinogenicity studies

Carcinogenesis studies have been conducted by the US National Toxicology Program. Male rats (F344/N) receiving 0.2 (control), 0.8, 2.5 or 4.1 mg F/kg BW in drinking water developed osteosarcoma with a statistically significant dose-response trend. However, a pair wise comparison of the incidence in the high dose group versus the control was not statistically significant (p=0.099). No osteosarcoma was observed in female rats. Thus NTP concluded that there was "equivocal evidence of carcinogenic activity of NaF in male F344/N rats".

In male (SD) rats receiving up to 11.3 mg F/kg BW day, no osteosarcoma was observed, but only one fibroblastic sarcoma (1/70) at the highest dose, and no tumours in female rats.

In a bioassay in B6C3F1 mice, receiving up to 8.1 and 9.1 mg F/ kg BW day for male and females respectively, a total of three osteosarcomas occurred, but no osteosarcomas occurred in the medium or high-dose groups.

On the basis of the results from the most adequate long-term carcinogenicity studies, there is only equivocal evidence of carcinogenicity of fluoride in male rats and no evidence of carcinogenicity in mice (ATSDR 2003). No carcinogenicity studies have been conducted using (hydro)fluorosilicic acid, sodium silicofluoride, disodium hexafluorosilicate or hexafluorosilicate or hexafluorosilicic acid.

4.1.2.3. Epidemiological studies

Early epidemiological studies did not find a consistent relationship between mortality from all types of cancer and the consumption of fluoride-containing drinking water. Two recent studies from the US found a higher incidence of osteosarcoma, a rare form of cancer, among males under 20 living in fluoridated communities compared with non-fluoridated communities (Hoover, 1991; Cohn, 1992). However, two case control studies did not find an increase in osteosarcoma in young male consuming fluoridated drinking water (>0.7 mg/L) (Eyre et al., 2009 - review).

A recent case-control study found an association between fluoride exposure during childhood and the incidence of osteosarcoma among males, but not among females (Bassin, 2006). The study was conducted as a hospital based case-control study in 11 hospitals in the USA – the Harvard Fluoride Osteosarcoma Study- and limited to cases below the age of 20. Fluoride level in drinking water was the primary exposure of interest, and the estimated exposure was based upon source of drinking water (municipal, private well, bottled) and the subject's age(s) while at each address. The level of fluoride in drinking water was obtained from local, regional and national registries. For well water, water samples were analyzed in the laboratory, while a value of 0.1 mg /L was assumed for bottled water. As water consumption may vary based on climate, the fluoride exposure estimates were based on CDC recommendations for optimal target levels for the fluoride level in drinking water. The CDC target level for warmer climate was 0.7 mg/L and 1.2 mg/L for colder climate. The exposure estimate was expressed as the percent of climate specific target level in drinking water at each age, and grouped into >30%, 30-99% and >100 %. Information on the use of fluoride supplements and mouth rinses was also obtained, however it is of concern that the exposure assessment is based upon retrospectively collected data. The study consisted of 103 cases and 215 controls matched to the cases. A statistically significant increased risk was only observed for males exposed at the highest level >100% of the CDC optimal target level and when this exposure took place between the age of 6-8 year. This coincides with the mid-childhood growth spurt in boys. The increased risk remained after adjustment for e.g., socioeconomic factors, use of fluoride products. No increased risk was observed in females. The conclusion was based upon an intermediate evaluation and the authors recommend that further research is required to confirm or refute this observation.

4.1.2.4. Conclusion

SCHER agrees that some epidemiological studies seem to indicate a possible link between fluoride in drinking water and osteosarcoma, but the studies are equivocal. There is no evidence from animal studies to support the link, and thus fluoride cannot be classified as to its carcinogenicity.

4.1.3. Neurotoxcity

4.1.3.1. Animal studies

There are only limited data on the neurotoxicity of fluoride in experimental animals. One study in female rats exposed to high doses of fluoride (7.5 mg/kg/day for 6 weeks) resulted in alterations of spontaneous behaviour, and the authors noted that the observed effects were consistent with hyperactivity and cognitive deficits (ATSDR, 2003). In a recent study in female rats given doses up to 11.5 mg/kg/day for eight months, no significant difference among the groups in learning or performance of the operant tasks were observed. Tissue fluoride concentrations, including seven different brain regions, were directly related to the levels of exposure (Whitford et al., 2009). The authors concluded that ingestions at high level, 230 times higher than those experienced by humans consuming fluoridated water, had no significant effect on appetitive-based learning in female rats.

Some animal studies have suggested a potential for thyroid effects following fluoride exposure. However, the available information is inconsistent and no effects on the

thyroid were observed in long term studies with fluoride in rats. Furthermore, fluoride does not interfere with iodine uptake into the thyroid.

4.1.3.2. Human Studies

There are limited data on neurotoxicity of fluoride in humans. It has been demonstrated that degenerative changes in the central nervous system, impairment of brain function, and abnormal development in children are caused by impaired thyroid function. Increases in serum thyroxine levels without significant changes in T_3 or thyroid stimulating hormone levels were observed in residents of regions in India and China, with high level of fluoride in drinking water, but these data are inconclusive due to the absence of adequate control for confounding factors. Thus, fluoride is not considered to be an endocrine disruptor (ATSDR, 2003).

A series of studies on developmental effects of fluoride were carried out mostly in China. They consistently show an inverse relationship between fluoride concentration in drinking water and IQ in children. Most papers compared mean IQs of schoolchildren from communities exposed to different levels of fluoride, either from drinking water or from coal burning used as a domestic fuel. All these papers are of a rather simplistic methodological design, with no - or at best little - control for confounders, e.g., iodine or lead intake, nutritional status, housing condition, parent's education level or income.

Tang et al. (2008) published a meta-analysis of 16 studies carried out in China, between 1998 and 2008, evaluating the influence of fluoride levels on the IQ of children. The authors conclude that children living in an area with high incidence of fluorosis and high ambient air fluoride levels have five times higher odds of developing a low IQ than those who live in a low fluorosis area. However, the paper is methodologically unsatisfactory.

Wang et al. (2007) carried out a study on the intelligence and fluoride exposure in 720 children between 8 and 12 years from a homogenous rural population Shanxi province, China. Subjects were drawn from control (fluoride concentration in drinking water 0.5 mg/L, n = 196), high-fluoride (8.3 mg/L), low arsenic (n = 253), medium arsenic (n = 91), and high arsenic (n = 180) groups. The IQ scores in the high-fluoride group were significantly reduced as compared to the control group, independently of arsenic exposure. The influence of socio-economic and genetic factors cannot completely be ruled out, but is expected to be minimal.

In a cross-sectional design, Rocha-Amador et al. (2007) studied the link between fluoride in drinking water and IQ in children from 3 rural communities in Mexico, with different levels of fluoride (0.8 mg/L; 5.3 mg/L; 9.4 mg/L; in this latter setting, children were supplied with bottled water) and arsenic in drinking water. Children IQ was assessed blind as regards fluoride or arsenic levels in drinking water. Socio-economic status was calculated according to an index including household flooring material, crowding, potable water availability, drainage, and father's education. Additional information about type of water used for cooking (taps or bottled), health conditions, etc., were obtained by questionnaire. An inverse association was observed between fluoride in drinking water and IQ after adjusting for relevant confounding variables, including arsenic.

4.1.3.3. Conclusion

Available human studies do not allow concluding firmly that fluoride intake hampers children's neurodevelopment. A systematic evaluation of the human studies does not suggest a potential thyroid effect at realistic exposures to fluoride. The absence of thyroid effects in rodents after long-term fluoride administration and the much higher sensitivity of rodents to changes in thyroid related endocrinology as compared with humans do not support a role for fluoride induced thyroid perturbations in humans. Limited animal data cannot support the link between fluoride exposure and neurotoxicity, noted in the epidemiological studies, at relevant non-toxic doses. SCHER agrees that there is not enough evidence to conclude that fluoride in drinking water may impair IQ.

4.1.4. Reproductive and developmental effects

4.1.4.1. Animal studies

Most of the animal studies on the reproductive effects of fluoride exposure deal with the male reproductive system of mice and rats. They consistently show an effect on spermatogenesis or male fertility. Sodium fluoride administered in drinking water at 2, 4, and 6 mg/L for 6 months to male rats adversely affected their fertility and reproductive system (Gupta et al., 2007). In addition, in male Wistar rats fed 5 mg/kg/day for 8 weeks, the percentage of fluoride-treated spermatozoa capable of undergoing the acrosome reaction was decreased relative to control spermatozoa (34 vs. 55%), and the percentage of fluoride-treated spermatozoa capable of oocyte fertilization was significantly lower than in the control group (13 vs. 71%). It was suggested that sub-chronic exposure to fluoride causes oxidative stress damage and loss of mitochondrial trans-membrane potential, resulting in reduced male fertility (Izquierdo-Vega et al., 2008). However, the fluoride doses used in these studies were high and cause general toxicity, e.g., reduced weight gain. Therefore, the effects reported are likely to be secondary to the general toxicity.

Multi-generation studies in mice did not demonstrate reproductive toxicity at doses up to 50 mg F/kg BW. When mice were administered > 5.2 mg fluoride/kg BW/day on days 6-15 after mating no sign of pregnancy and implantation was observed. Sperm mobility and viability were reduced in both mice and rats after 30 days of 4.5 and 9.0 mg F/kg BW weight/day (ATSDR, 2003).

Serum testosterone increased in rats after drinking water with a fluoride content of 45 and 90 mg/L for two weeks. Thereafter the level decreased and was not different from the controls after 6 weeks. No effect was observed in rats receiving up to 90.4 mg fluoride/L for 14 weeks on several reproductive parameters.

4.1.4.2. Human studies

The NHS review on Public Water Fluoridation (2000) did not find any evidence of reproductive toxicity in humans due to fluoride. Since then, no new evidence seems to be available apart from abstracts without methodological details.

Male reproduction

There is slight evidence that high level occupational exposure to fluoride affect male reproductive hormone levels. A significant increase in FSH ($P < 0.05$) and a reduction of inhibin-B, free testosterone, and prolactin in serum ($P < 0.05$), as well as decreased sensitivity in the FSH response to inhibin-B ($P < 0.05$) was found when the high-exposure group was compared with a low-exposure group. Significant partial correlation was observed between urinary fluoride and serum concentrations of inhibin-B ($P < 0.028$). No abnormalities were found in the semen parameters in either the high- or low-fluoride exposure groups (Ortiz-Perez et al., 2003). The alteration in the reproductive hormone levels after occupational fluoride exposure is not very relevant for drinking water exposure.

4.1.4.3. Conclusion

There is no new evidence from human studies indicating that fluoride in drinking water influences male and female reproductive capacity. Few studies on human populations have suggested that fluoride might be associated with alterations in reproductive hormones, fertility, but their design limitations make them of little value for risk evaluation. Experimental animal studies are of limited quality and no reproductive toxicity was observed in a multi-generation study. SCHER concludes that a low level of fluoride exposure does not influence the reproductive capacity.

4.2. Question 1-b

Conduct an integrated exposure assessment for fluoride covering all known possible sources (both anthropogenic and natural).

Exposure to fluoride occurs orally, by inhalation and by dermal uptake, the former being the major route. Oral fluoride exposure is mainly by ingestion of water, water-based beverages, food (including fluoridated salt and food supplements) and swallowed dental hygienic products. Much of the fluoride in the dental product is spat out or retained in the oral cavity in the biofilm of the enamel surface of the tooth.

Inhalation of fluoride present in ambient air within Europe is limited and does not contribute more than 0.01 mg/day to the total intake, except in occupational settings, e.g. aluminium workers, where intake can be several milligrams. Fluoride might be a component of urban and ambient air pollution, especially in coal mining and coal burning communities, but information on the level of fluoride is limited and is restricted to industrial areas. Thus inhalation exposure of fluoride is not considered important.

4.2.1. Exposure to fluoride from food and water-based beverages

There is no adequate new EU data on fluoride in food. EFSA considered the German background exposure to fluoride from food based upon intake of milk, meat, fish, eggs, cereals, vegetables, potatoes and fruits still to be valid. The exposure corresponds for young and older children, and adults to 0.042, 0.114 and 0.120 mg/day, respectively (EFSA NDA, 2005). Exposure to fluoride from fruit juice, soft drinks, mineral water for younger and older children was considered to be 0.011 and 0.065 mg F/day respectively. The current assessment of the exposure to fluoride from drinking water is based on the EFSA concise database compiling the results of consumption surveys across European countries. However, this database is only for adult exposure. The mean consumption of water-based beverages, namely tap water, bottled water, soft drinks and stimulants ranges from about 400 ml to about 1950 ml with a median value of 1321 ml/day/person. These figures are consistent with the default value for water consumption used by WHO (2000 ml/day). The value for total consumption of liquids across European countries ranges from about 700 mL/day/person at the lowest reported mean to about 3800 mL/day/person at the highest reported 97.5th percentile. These values show that due to human physiology and European climatic conditions, the total variability attributable to liquid consumption is close to a factor of 5. The exposure assessment will thus mainly be driven by the level of fluoride in water for which the variability is about a factor of 30 (low Germany vs. high Finland).

The major sub-categories of water-based beverages are soft drinks, bottled water, coffee, tea and cacao (stimulants), and tap water. The highest 97.5th percentiles for the consumption of each single category in a single country are 2950, 2400, 2800 and 2500 ml/day per adult respectively for tap water in Austria, stimulants in Denmark, soft drinks and bottled water in Slovakia. For each of these countries, the consumption of one category at the 97.5th percentile for consumers only was summed with the mean consumption for the 3 other categories of water-based beverages for the whole population. Results are ranging from 3300 to 3800 ml/day/person.

Based on reported consumption of water-based beverages, several scenarios has been developed. Scenario 1 corresponds to the median of mean consumption for all water-based beverages across European countries (1321 ml) with the mean occurrence level (0.1 mg/L). Scenario 2 corresponds to the highest consumption for high consumer of one of the relevant categories (3773 ml) with the mandatory water fluoridation in Ireland (0.8 mg/L) (scenario 2a) and the WHO guidance value for fluoride in drinking water (1.5 mg/L) (scenario 2b).

Scenario 3 is a worst-case scenario based on the highest 97.5th percentile for consumption of tap water (2950 ml, Austria) with the upper range for fluoride concentration (3.0 mg/L in Finland).

Estimated fluoride exposure from water-based beverages for adults and children (>15 years old) in the different scenarios is shown in table 2.

Table 2 - Adult and children (>15 yrs) systemic exposure to fluoride from water-based beverages*

	Consumption	Concentration of F	Exposure
	ml/day	mg/L	mg/day
Scenario 1	1321	0.1	0.13
Scenario 2a	3773	0.8	3.02
Scenario 2b	3773	1.5	5.66
Scenario 3	2800	3.0	8.40

*Bottled mineral water was not included in these scenarios.

Data on daily consumption of drinking water and other water-based products by children is sparse. The estimates for fluoride exposure from tap-water for children was derived from the EFSA (2005) intake data, but recalculated to mirror the water fluoride levels in scenarios described for adults, (0.1, 0.8, 1.5 and 3.0 mg/L (table 3)). However, the consumption data of drinking water and other water based products used by EFSA (2005) is from 1994 and it would seem to be low (under 500 ml for children below 12 years and under 600 ml for children between 12 and 15 years).

Table 3 - Estimated systemic fluoride exposure of children below 12 years and children between 12 - 15 years from water and water based beverages

Fluoride intake (mg/day)		
Drinking water fluoride concentration (mg fluoride/L)	**Children 1-11.9 years consuming < 0.5 L water**	**Children 12-14.9 years consuming < 0.6 L water**
0.1	0.057	0.121
0.8	0.379	0.513
1.5	0.698	0.905
3.0	1.391	1.745

4.2.1.1. Fluoride content of dental hygiene products

In Annex III, part 1, of the amended Council Directive 76/768/EEC related to cosmetic products, 20 fluoride compounds are listed, that may be used in oral hygiene products. The most commonly incorporated in toothpaste are sodium fluoride, sodium monofluoro-phosphate and stannous fluoride. Other over-the-counter oral hygiene products with fluoride include mouthwashes, chewing gums, toothpicks, gels and dental floss. These may contain up to a maximum of 1500 mg F/kg (0.15 % F).

It is estimated that in adults <10% of the toothpaste is ingested as the spitting reflex is well developed, whereas the estimated intake in children may be up to 40%. In children aged 2 -3 years the ingestion has been reported to be as high as 48 % in 2 to 3 years old, 42% in 4 years old and in 5 and 6 years old 34 and 25% respectively. In children aged from 8 to 12 years the ingestion is reported to be ~10% (Ellewood et al., 2008).

The recommended quantity of toothpaste per application is "pea size" (about 0.25 g).

Toothpaste with lower fluoride content has been introduced on to the market to reduce fluoride ingestion by young children in order to minimize the risk of fluorosis.

Table 4- Estimated daily systemic fluoride exposure from the use of common toothpaste on the EU market (10% or 40% systemic fluoride absorption)

Type of toothpaste % F	Fluoride concentration mg /kg	Amount used* g /day	Total fluoride dose mg/day	Systemic fluoride absorption (mg) 10%	Systemic fluoride absorption (mg) 40%
0.05	500	0.5 — 1.5	0.25 — 0.75	0.025 — 0.075	0.100 — 0.300
0.10	1,000	0.5 — 1.5	0.50 — 1.50	0.050 — 0.150	0.200 — 0.450
0.15	1,500	0.5 — 1.5	0.75 — 2.25	0.075 — 0.225	0.300 — 0.900

* Estimated toothpaste use with twice daily brushing

4.2.1.2. Fluoride supplements

Prescribed fluoride supplements (tablets, lozenges, or drops) that are regulated as drugs, may be recommended by qualified professionals, based on a case-by-case evaluation of exposure to all other fluoride sources. As with any prescribed drug, patient compliance is a problem. It is estimated that they could be the source of up to 70% of the reasonable maximum dietary exposure value in infants and young children (EFSA, 2005). In addition, over the counter fluoride supplement tablets, lozenges (from 0.25 to 1.0 g) and fluoride containing chewing gums are available in some EU member states.

4.2.1.3. Fluoridated salt and food supplements

Many countries recommend the consumption of fluoridated salt and such products are available in at least 15 countries. The salt is fluoridated up to 350 mg/kg. Figures about the proportion of fluoridated salt sold are available (Gotzfried et al, 2006).

Calcium fluoride can be added as supplement to food: 1 mg CaF_2 /day would correspond to 0.5 mg F/day, but due to the low bioavailability, the anticipated absorbed daily amount is estimated to be 0.25 mg F/day (EFSA, 2008a).

Sodium monoflurophosphate can be added as a supplement to food: between 0.25 and 2 mg fluoride per day have been considered to be safe (EFSA, 2008b). Limits for additions to food supplements have not yet been set.

As a worst case scenario value of 0.5 mg F/day from food supplements was used in the integrated fluoride exposure assessment.

4.2.2. Integrated fluoride exposure from all major sources

Since ingested fluoride ion is readily absorbed, it is assumed that all ingested fluoride ion is 100 % bioavailable.

4.2.2.1. Adults and children above 15 years old

Water-based beverages are the major source of fluoride intake in adults in all scenarios, accounting for 18-95% of the total fluoride intake, while food and food supplements account for <1-6%. Toothpaste is an additional source of fluoride, with ~10% of the lower and upper ranges of daily toothpaste applied becoming systemically available. Table 5 gives the aggregated fluoride intake.

Table 5 - Total daily systemic fluoride exposure (mg/day) for adults and children above 15 years old

	Water *	**Food ****	**Food supplement*****	**Toothpaste********	**Total**
Scenario 1	0.13	0.12	0.5	0.075	0.825
	0.13	0.12	0.5	0.225	0.975

Scenario 2a	3.02	0.12	0.5	0.075	3.715
	3.02	0.12	0.5	0.225	3.865
Scenario 2b	5.66	0.12	0.5	0.075	6.355
	5.66	0.12	0.5	0.225	6.505
Scenario 3	8.40	0.12	0.5	0.075	9,095
	8.40	0.12	0.5	0.225	9.245

* Table 2

** EFSA 2005

*** Food supplement is based upon anticipated double of the upper level of use (EFSA, 2008)

****Contribution from toothpaste is based upon 0.15% fluoride concentration, 10% systemic absorption and the usage of 0.5 g/day (least case) and 1.5 g/day (worst case).

The upper tolerable intake limit (UL) for fluoride (7 mg/day) for adults and children over the age of 15 was only exceeded in areas with high level of natural fluoride in water, whereas the UL was not exceeded for adults and children over the age of 15 living in area with fluoridated drinking water.

4.2.2.2. Children (12-14.9 years)

Estimates of total daily systemic exposure to fluoride for children between 12 – 14.9 years old are shown in Table 6. These estimates are derived from the EFSA data on fluoride from food and food supplements. Calculations for water consumption, including water-based beverages, are provided at 0.5 L, 1.0 L and 1.5 L since current data on water consumption for this age group are not available. For this age group, systemically available fluoride is taken to be 10% of the 1.5% fluoride toothpaste applied (0.75 - 2.25 mg, table 4).

Table 6 - Estimate of total daily systemic exposure to fluoride from water and food for children between 12 – 14.9 years old.

	Fluoride intake in mg/day		**Toothpaste systemically available daily****	
			0.05 %	**0.15 %**
1	**SUM of food, beverages and supplements***	**0.679**	Range 0.025 – 0.075	Range 0.075– 0.225
	Drinking water 0.1 mg F/L			
2	Consumption 0.5 L + food intake	0.729	0.504- 0.554	0.554 – 0.704
3	Consumption 1.0 L + food intake	0.554	0.554 0.604	0.604 – 0.754
4	Consumption 1.5 L + food intake	0.579	0.604- 0.654	0.654 – 0.804
	Drinking water 0.8 mg F/L			
5	Consumption 0.5 L + food intake	0.829	0.854 – 0.904	0.904 – 1.054
6	Consumption 1.0 L + food intake	1.229	1.254 – 1.304	1.304 – 1.454
7	Consumption 1.5 L + food intake	1.629	1.654 – 1.704	1.704 – 1.854
	Drinking water 1.5 mg F/L			
8	Consumption 0.5 L + food intake	1.179	1.204 – 1.254	1.254 - 1.404
9	Consumption 1.0 L + food intake	1.929	1.954 – 2.004	2.004 – 2.154
10	Consumption 1.5 L + food intake	2.679	2.704 – 2.754	2.754 – 2.904
	Drinking water 3.0 mg F/L			
11	Consumption 0.5 L + food intake	1.929	1.954 – 2.004	2.004 – 2.154
12	Consumption 1.0 L + food intake	3.429	3.454 – 3.504	3.504 – 3.654
13	Consumption 1.5 L + food intake	4.929	4.954 – 5.004	5.04 – 5.154

*This value represents food 0.114 mg/day, beverages 0.065 mg/day and approved food supplement 0.50 mg/days based upon anticipated upper level of use (EFSA, 2008)

**Contribution based upon a fluoride concentration of 0.05% and 0.15%, toothpaste with 10% systemic absorption and the usage of 0.5 g/day (least case) and 1.5 g/day (worst case).

The estimated UL for children between 8 and 14 years is 5 mg/day extrapolated from the UL for adults for whom the critical endpoint is an increased risk of fracture (EFSA, 2005). This was used as the reference value for children 12-14.9 yrs despite the fact that not all molars will have erupted. The UL for children between 12 –14.9 is exceeded if 1.5 L water containing 3.0 mg F/L is consumed, and if 1.5% fluoride toothpaste (adult type) and more than the recommended "pea size" application is used unsupervised. In these older children the spitting and rinsing response would be better developed, resulting in ~ 10% of the fluoride present in toothpaste becomes systemically available.

However, the UL could be exceeded with additional exposure from two other sources: fluoridated salt as a condiment or in food preparation and/or from the consumption of bottled mineral water with high fluoride content.

4.2.2.3. Children (1-11.9 years)

It must be noted that EFSA (2005) did not estimate total fluoride exposure of children in Europe as there were so little reliable consumption data from different sources for this age group.

The estimated total daily systemic exposure to fluoride for children between 6.1 to 11.9 years old, and 1 and 6 years old is shown in table 7 and 8, respectively. Data on fluoride from food (0.042 mg F) and approved food supplements (0.50 mg F) are taken from EFSA (2005, 2008 a, b). Calculations for water consumption, including water-based beverages, are provided at 0.5 L, 1.0 L and 1.5 L, since current data on water consumption for children is poor. EFSA (2008 a, b) suggest a daily water consumption of approximately 0.5 L, whereas UK COT (2003) considers a higher daily consumption of between 0.8 and 1.3 L. In warmer countries, the daily water consumption would be even higher.

Table 7 - Estimate of total daily systemic exposure to fluoride for children between 6.1 – 11.9 years old.

	Fluoride intake in mg/day		**Toothpaste systemically available daily** 0.05 % F**	**0.15 % F**
1	**SUM of food, beverages and supplement***	**0.553**	**Range 0.025 – 0.075**	**Range 0.075 – 0.225**
	Drinking water 0.1 mg F/L			
2	Consumption 0.5 L + food intake	0.603	0.628 – 0.678	0.678 – 0.828
3	Consumption 1.0 L + food intake	0.653	0.678 - 0.728	0.728 – 0.878
4	Consumption 1.5 L + food intake	0.703	0.728 - 0.778	0.778 – 0.928
	Drinking water 0.8 mg F/L			
5	Consumption 0.5 L + food intake	0.953	0.978 – 1.028	1.028 – 1.178
6	Consumption 1.0 L + food intake	1.353	1.403 – 1.428	1.428 – 1.578
7	Consumption 1.5 L + food intake	1.753	1.788 – 1.828	1.828 - 1.978
	Drinking water 1.5 mg F/L			
8	Consumption 0.5 L + food intake	1.303	1.328 – 1.378	1.378 – 1.528
9	Consumption 1.0 L + food intake	2.053	2.078 – 2.128	2.128 – 2.278
10	Consumption 1.5 L + food intake	2.803	2.828 – 2.878	2.878 – 3.028
	Drinking water 3.0 mg F/L			
11	Consumption 0.5 L + food intake	2.053	2.078 – 2.128	2.128 – 2.278
12	Consumption 1.0 L + food intake	3.553	3.578 – 3.628	3.628 – 3.778
13	Consumption 1.5 L + food intake	5.053	5.078 – 5.128	5.128 – 5.278

*This value represents food (0.042 mg/day), beverages (0.011 mg/day) and food supplement (0.50 mg/day) based upon anticipated upper level of use (EFSA, 2008)

**Contribution based upon a fluoride concentration of 0.05% and 0.15%, toothpaste with 10% systemic absorption and the usage of 0.5 g/day (least-case) and 1.5 g/day (worst-case).

Table 8 - Estimate of total daily systemic exposure to fluoride for children between 1 - 6 years old.

	Fluoride intake in mg/day		Toothpaste systemically 40 % available daily** 0.05 % F	0.15 % F
1	**SUM of food, beverages and supplement***	**0.553**	**Range 0.100 – 0.300**	**Range 0.300 – 0.900**
	Drinking water 0.1 mg F/L			
2	Consumption 0.5 L + food intake	0.603	0.703- 0.903	0.903 – 1.503
3	Consumption 1.0 L + food intake	0.653	0.753 0.953	0.953 – 1.553
4	Consumption 1.5 L + food intake	0.703	0.803- 1.003	1.003 – 1.603
	Drinking water 0.8 mg F/L			
5	Consumption 0.5 L + food intake	0.953	1.053 – 1.253	1.253 – 1.853
6	Consumption 1.0 L + food intake	1.353	1.453 – 1.653	1.653 - 2.253
7	Consumption 1.5 L + food intake	1.753	1.853 – 2.053	2.053 - 2.653
	Drinking water 1.5 mg F/L			
8	Consumption 0.5 L + food intake	1.303	1.403 – 1.603	1.603 - 2.203
9	Consumption 1.0 L + food intake	2.053	2.153 – 2.353	2.353 – 2.953
10	Consumption 1.5 L + food intake	2.803	2.903 – 3.103	3.103 - 3.703
	Drinking water 3.0 mg F/L			
11	Consumption 0.5 L + food intake	2.053	2.153 - 2.353	2.353 – 2.953
12	Consumption 1.0 L + food intake	3.553	3.653 – 3.853	3.853 – 4.753
13	Consumption 1.5 L + food intake	5.053	5.153 – 5.353	5.353 – 5.953

*This value represents intake from food (0.042 mg/day), beverages (0.011 mg/day) and approved food supplement (0.50 mg/day) based upon anticipated upper level of use (EFSA, 2008)

**Contribution based upon a fluoride concentration of 0.5% and 0.15%, toothpaste with 40% systemic absorption and the usage of 0.5 g/day (least case) and 1.5 g/day (worst case).

The UL for children between 4 and 8 years is 2.5 mg/day based upon moderate dental fluorosis as the critical endpoint of (EFSA, 2005). This value was used as the reference value for the 6-12 years old children. Thus the UL for children 6-12 years old is exceeded if 1.0 L water containing 1.5 mg F/L is consumed and tooth-brushing, with the 1.5% fluoride toothpaste is unsupervised. If more water is consumed at this fluoride concentration, the UL is exceeded, even without exposure to toothpaste.

The toothpaste contribution of systemically available fluoride in children age 1 to 6 years, assuming ~40% ingestion of the daily applications, ranges from 0.1 – 0.3 mg fluoride using 'children's' toothpaste (0.05% fluoride), and 0.3 – 0.9 mg from 0.15% fluoride toothpaste. Intake of fluoride from 0.15% toothpaste may accounts for <20-50% of the total fluoride intake depending on the amount applied in areas with fluoridated water (0.8 mg F/L) or higher.

The estimated UL for children under 3 years is 1.5 mg/day based upon moderate dental fluorosis as the critical endpoint (EFSA, 2005) was used for children between 1-6 years. Thus the UL is exceeded if more than 1.0 L water containing 0.8mg F/L is consumed and tooth-brushing, with the 1.5% fluoride toothpaste. If 1.5 L of water is consumed at this fluoride concentration, the UL is exceeded, even without exposure to toothpaste.

4.2.2.4. Infants

Many infants are fully or partially breast fed during the early months of life. Fluoride intakes by fully breast-fed infants are low, but fluoride intakes by partially breast-fed infants and by formula-fed infants are different. This depends primarily on the fluoride content of the water used to dilute the infant formula products.

The food consumption scenario established by the EFSA NDA Panel was used for the exposure assessment (EFSA, 2005). A consumption of 174 ml/kg BW per day of infant formula for a 3 month infant weighing on average 6.1 kg would result in a total consumption of formula of 1060 ml per day (95th percentile). For an infant of 7.9 kg (mean BW at 6 month), the exposure from formula would be 1414 ml/day and for an

infant of 9.6 kg (mean BW at 12 month) 1718 ml/day. Thus the fluoride intake for infants in the respective age groups would be *circa* 0.9, 1.1 and 1.3 mg/day if the water used contained 0.8 mg F/L. These data was similar to the more recent exposure data from the German environmental survey (Schulz *et al*. 2002).

The Scientific Committee on Food (2003) had recommended a maximum fluoride level of 0.6-0.7 mg/L in infant formula, equivalent to an intake of about 0.1 mg/kg BW/day in infants during the first six months of life (body weight=5 kg). For powdered formula, this maximum will be exceeded if water containing more than 0.7 mg F/L is used for its preparation.

For infants, up to the age of 6 months, the main food source is milk, either solely breast milk or formula or a combination of both. Since the fluoride content of breast milk is low (~6 µg/L), fluoride exposure in breast-fed infants is low.

The wide range of fluoride intake depending on the infant's feeding pattern is shown in table 9.

Table 9 - Estimated systemic fluoride exposure of infants from milk and formulas

Drinking water	Baby formula	Fluoride intake mg/kg/day		
F conc. mg/L	F conc. as fed formula* mg/L	Formula intake 170 mL/kg/day**	Formula intake 150 mL/kg/day**	Formula intake 120 mL/kg/day**
0.1	0.200	0.034	0.030	0.024
0.8	0.804	0.137	0.121	0.096
1.5	1.420	0.241	0.213	0.170
3.0	2.740	0.466	0.411	0.329
Human Milk ***	---	0.001	0.001	0.001

(Modified from Fomon and Ekstrand 1996)

* Assumes that 145 g of formula with a fluoride concentration of 0.7 mg/kg is diluted with 880 mL of drinking water to make 1 litre formula.

** Mean energy intakes are approximately 114 kcal/kg/day from birth to 2 months of age and 98 kcal/kg/day from 2 to 4 months. An exclusively formula fed infant consuming 667 kcal/L formula will therefore consume approximately 0.17 L/kg/day from birth to 2 months of age and approximately 0.15 L/kg/day from 2 to 4 months.

*** Fluoride concentration in breast milk is approximately 6 µg/L

Fluoride concentration of the water is the main exposure source in formula-fed infants. An infant solely fed with a baby formula diluted with water containing 0.8 mg F/L ingest 0.137 mg F/kg/day compared with 0.001 mg F/kg/day for an infant, who is solely breast fed.

Tolerable upper intake levels for fluoride have not been established for infants (EFSA, 2005). For infants up to 6 months old, the UK DoH (1994) concluded that 0.22 mg F/kg BW/day was safe, while the US IOM (1999) derived an UL for fluoride of 0.1 mg/kg BW/day.

4.2.2.5. Conclusion

Fluoride in drinking water is the major source of fluoride in the general population. However, in children up to 6 yrs the contribution from the use of fluoridated toothpaste (1.5% fluoride) can account for up to 25% of the total systemic dose.

There is not enough quality data on sources and levels of fluoride to perform a full uncertainty analysis within the European context.

SCHER agrees that for adults and children over the age of 8 years the total intake of fluoride from all major sources is below the upper tolerable intake limit (UL) in most part of EU including areas with fluoridated drinking water, except for those living in areas with water containing natural high fluoride (> 3 mg/L) and with an high intake of water based beverages.

For children between 6-12 years the UL is not exceeded if the water consumption is less than 1.0 L water a day for children living in areas with fluoridated water (below 1.5 mg/L) and using regular fluoridated toothpaste unsupervised. For children between 1-6 yrs the UL is exceeded if they consume more than 0.5 L a day, and using more than the recommended quantity of regular fluoridated toothpaste.

For infants below 6 month of age the DoH (UK) recommended level was not exceeded in children exclusively fed infant formula and living in areas with fluoridated drinking water (<0.8 mg/L). The UL is exceeded when for the preparation of infant formula tap water with the maximum permitted fluoride level (1.5 mg/L) according to the Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption is used.

For infants, the WHO recommendation of breast feeding is the best option. If the infant's diet consists entirely of formulated food products the risk of developing dental fluorosis increases in areas with high level of fluoride in tap water.

4.3. Question 1-c1

To evaluate the evidence of the role of fluoride in tooth decay prevention and rank the various exposure situations as to their effectiveness in offering a potential tooth decay preventive action.

4.3.1. Mechanism of fluoride action in caries prevention

Fluoride treatment regimens have been developed to prevent dental caries. The concept was to make the enamel surface more resistant to a caries attack by incorporating fluoride, both systemically and topically in the outermost enamel. Systemic fluoride is easily absorbed and is particularly taken up during the period of enamel formation (pre-eruptive).

However, the predominant beneficial cariostatic effects of fluoride in erupted teeth occur locally at the tooth surface. This is achieved by maintaining the intra-oral fluoride levels of the teeth, dental plaque and saliva throughout the day. This limits the prevalence and severity of dental caries in erupted teeth.

4.3.2. Dental health and fluoridation

Figure 2 indicates that independent of the fluoridation policies across European countries, there has been a consistent decline over time in tooth decay in 12 years old children from the mid-seventies, regardless of whether drinking water, milk or salt are fluoridated.

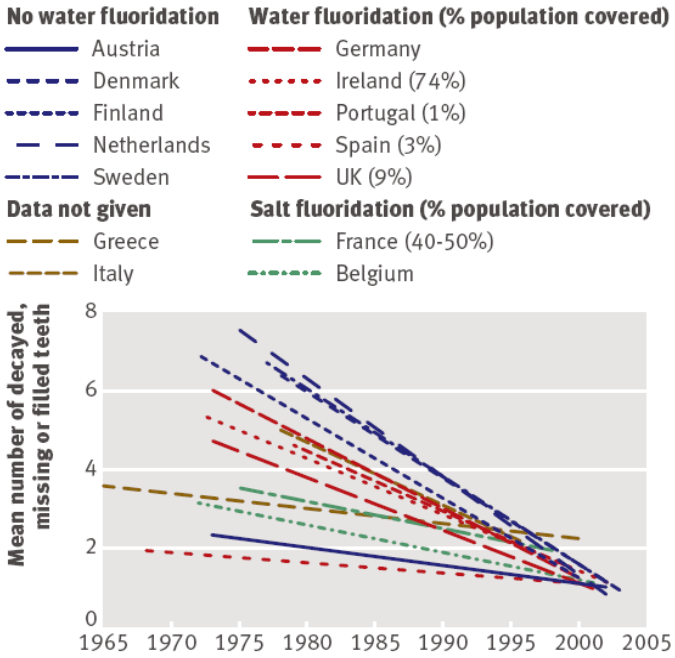

Figure 2 - Tooth decay in 12 year olds in European Union countries(from Cheng et al., 2007). It should be noted that there is a probable error as regard figures from Germany, as the data was collected during the unification period. Moreover water fluoridation was not practised in West Germany and in East Germany only in certain regions and intermittently – therefore, overall Germany should be placed under "no water-fluoridation".

A vast number of clinical studies have confirmed that topical fluoride treatment in the form of fluoridated toothpaste has a significant cariostatic effect. Other preventive regimens include fluoride supplement and fluoridated salt given during the period of tooth formation. In the 1970s, fluoridation of community drinking water, aimed at a particular section of the population, namely children, was a crude but useful public health measure of systemic fluoride treatment, however, the caries preventive effect of systemic fluoride treatment is rather poor (Ismael and Hasson, 2008).

In countries not using such additives, the improved dental health can be interpreted as the result of the introduction of topical fluoride preventive treatment (fluoridated toothpaste or mouth rinse or fluoride treatments within the dental clinic). Other preventive regimens include fluoride supplements, fluoridated salt, improved oral hygiene, changes in nutrition or care system practices, or any change that may result from an improved wealth and education in these countries. This suggests that water fluoridation plays a relatively minor role in the improved dental health.

The role of fluoride on dental health has been shown by comparing naturally occurring low and high fluoride concentration in tap water. An inverse association between fluoride concentration in non-fluoridated drinking water and dental caries was found in both primary and permanent teeth in Denmark. The risk was reduced by approximately 20% already at the lowest level of fluoride exposure (0.125-0.25 mg/L) compared to <0.125 mg, and the reduction was approximately 50% at the highest level of fluoride exposure (>1.0 mg/L) (Kirkeskov et al., 2010). The data was adjusted for socio-economic factors.

4.3.2.1. Water fluoridation

Water fluoridation was considered likely to have a beneficial effect, but the range could be anywhere from a substantial benefit to a slight risk to children's teeth with a the narrow margin between achieving the maximal beneficial effects of fluoride in caries prevention and the adverse effects of dental fluorosis (McDonagh et al., 2000). The available evidence suggests that fluoridation of drinking water supplies reduces caries

prevalence, both as measured by the proportion of children who are caries free and by the mean change in dmft/DMFT score[decayed, missing and filled deciduous –dfmt– or permanent –DFMT– teeth][1]. The studies were of moderate quality (CRD, 2003), but a similar conclusion is drawn by a Canadian review (Locker, 1999), adding that the effect tends to be more pronounced in the deciduous dentition. A few water fluoridation discontinuation studies do not suggest significant increases in dental caries. The benefits of fluoridation to adult and elderly populations in terms of reductions in coronal and root decay are limited (Seppä et al., 2000 a, b).

The effect of water fluoridation tends to be maximized among children from the lower socio-economic groups, so that this section of the population may be the prime beneficiary. There appears to be some evidence that water fluoridation reduces the inequalities in dental health across social classes in 5 and 12 year-olds, using the dmft/DMFT measure This effect was not seen in the proportion of caries-free children among 5 year-olds (McDonagh et al., 2000). In a study of students (16-year old) living on the border between the Republic of Ireland (fluoridated) and Northern Ireland (non-fluoridated) it was found that some of the variance in decay experience among the adolescents was explained by parental employment status. The higher decay experience in lower socio-economic groups was more evident within the non-fluoridated group, suggesting that water fluoridation had reduced oral health disparities (Cross Border Fluoride Study 2008; http://borderireland.info/pubs/BI-01418.pdf). Similarly, Truman et al. (2002)and Parnell et al. (2009) concluded that water fluoridation is effective in reducing the cumulative experience of dental caries within communities, and that the effect of water fluoridation tends to be maximized among children from the lower socio-economic groups.

4.3.2.2. Milk fluoridation

There is no consistent information on the efficiency of fluoridated milk compared with non-fluoridated milk on dental health. For permanent teeth, after 3 years there was a significant reduction in the DMFT (78.4%, $P < 0.05$) between the test and control groups in one trial, but not in the other. The latter study only showed a significant reduction in the DMFT until the fourth (35.5%, $P < 0.02$) and fifth (31.2%, $P < 0.05$) years. For primary teeth, again there was a significant reduction in the DMFT (31.3%, $P< 0.05$) in one study, but not in the other. The studies suggest that milk fluoridation is beneficial in the prevention or reduction of caries especially in permanent dentition, but available data are too limited to reach a conclusion (Yeung et al., 2005). However, recent studies have concluded that milk fluoridation may be an effective method for preventing dental caries (AU-NHMRC, 2007).

4.3.2.3. Salt fluoridation

The effectiveness of salt fluoridation at reducing dental caries has been assessed in cross-sectional studies in Mexico, Jamaica and Costa Rica. These studies are all considered of simplistic methodological quality. However, the data suggest that salt fluoridation reduces caries in populations of children aged 6-15 (AU-NHMRC, 2007).

Several studies from Switzerland suggest that the decline in caries after introduction of fluoridated salt is not drastically different from the one obtained by introducing dental hygiene in schools (Marthaler, 2005).

4.3.2.4. Topical fluoride treatments

Topical application of fluoride in the oral cavity has two advantages: a) application at the site of action and b) reducing the systemic exposure since in those with an adequate spitting response, only a percentage (adults 10%, young children 40%) of that applied becomes systemically available.

[1] calculated from the observation of the number of teeth with carious lesions, the number of extracted teeth, and the number of teeth with fillings or crowns

The effectiveness of topical fluoride treatments (TFT), i.e., fluoride varnish, gel, mouth rinse, or toothpaste on dental health have been compared (Marinho *et al.*, 2002; 2003a, b, c; 2004a, b; Salanti et al., 2009). Comparisons were made with placebo treatment in children from 5 to 16 years old for at least 1 year. The main outcome was caries increment measured by the change in decayed, missing and filled tooth surfaces. There was substantial heterogeneity, but the direction of effect was consistent. The effect of topical fluoride varied according to the type of control group used, the type of TFT used, mode/setting of TFT use, initial caries levels and intensity of TFT application, but was not influenced by exposure to water fluoridation or other fluoride sources. Supervised use of self applied fluoride increases the benefit. The relative effect of topical fluoride may be greater in those who have higher baseline levels of D(M)FS. These results are clearly in favour of a beneficial effect of topical fluoride treatment. There was no evidence of adverse effects of topical fluoride treatments (Marinho et al., 2003b). The authors did not consider analyses on specific time-windows or by regions.

The same authors also found that the combined regimens achieved a modest reduction (10%; 95% CI: 2%-17%) of dental caries compared with toothpaste used alone. (Marinho et al., 2004a). There was no clear evidence that any topical fluoride modality is more effective than any other (Salanti et al., 2009).

The AU-NHMRC (2007) and a group of Swedish scientists (Twetman et al., 2003; (Petersson et al., 2004) carried out additional reviews on the topic. The results do not challenge the above conclusions. However, Twetman et al., (2003) point out that long-term studies in age groups other than children and adolescents are still lacking.

The benefits of preventive systemic treatments (F drops in infants, salt or milk fluoridation) are not proven. There is weak and inconsistent evidence that the use of fluoride supplements prevents dental caries in primary teeth. Available evidence indicates that such supplements prevent caries in permanent teeth, but mild to-moderate dental fluorosis is a significant side effect (Ismail and Hasson, 2008).

4.3.2.5. Summary

Water fluoridation as well as topical fluoride treatments (e.g. fluoridated toothpaste or varnish) appears to prevent caries, primarily on permanent dentition. No obvious advantage appears in favour of water fluoridation compared with topical prevention. The continued systemic exposure of fluoride from whatever source is questionable once the permanent teeth have erupted.

SCHER agrees that topical application of fluoride is most effective in preventing tooth decay. Topical fluoride sustains the fluoride levels in the oral cavity and increased caries prevention, with reduced systemic availability. The efficacy of population-based policies, e.g. drinking water, milk or salt fluoridation, as regards the reduction of oral-health social disparities, remains insufficiently substantiated.

4.4. Question 1-c2

To pronounce itself as to whether there may be reasons for concern arising from the exposure of humans to fluoride and if so identify particular exposure scenarios that may give rise to concern in particular for any particular population subgroup.

EFSA (2005) has established upper tolerable intake levels of 1.5 and 2.5 mg fluoride/ day based upon the induction of moderate dental fluorosis for children aged 1-3 years and 4-8 years, respectively. For children aged 9-14 years an UL of 5 mg/day and for children > 15 years and adults an UL of 7 mg/day was established based upon the increase in non-vertebral bone fractures. There are no new scientific data that justify changing these values. Based upon the exposure scenarios discussed in 4.2.2 for infants, children, and adults and the intake of fluoride from water-based beverages, food, food supplement and the use of toothpaste, the UL was only exceeded in the worst case scenarios. Water-based beverages were the major fluoride sources and healthy adults and children over 15 years, consuming large quantities of drinking water (>3 L) and living in areas with high

natural concentrations of fluoride (> 3.0 mg/l) exceeded the UL. The contribution of fluoride from toothpaste was significant in children due to ingestion of a large proportion of the toothpaste used (40% absorption), thus for healthy children under the age of 15, the combination of high levels of fluoride in water and high water consumption would result in fluoride intakes that greatly exceed the ULs for the respective age groups. Children and adults when living in areas with fluoridated drinking water (<0.8 mg/L) did not exceed the UL under normal consumption and usage.

A special concern is for groups that have a high intake of food supplements containing fluoride, e.g. sodium monofluorophosphate, and living in areas where the level of fluoride is higher than 1 mg/L in drinking water.

The susceptibility to develop dental fluorosis depends on the timing of systemic exposure and the uptake of circulating fluoride by developing teeth. The period of the greatest susceptibility are shown in appendix II. Other subpopulations susceptible to systemic fluoride exposure include the elderly, with nutritional and metabolic deficiencies as these may alter bone composition leading to skeletal fluorosis. There is no strong evidence that fluoride exposure in sub-populations with endocrine disorders (diabetes, thyroid dysfunction) has an increased risk for adverse health effects.

4.5. Question 1-d

Identify any additional investigative work that needs to be done in order to fill data gaps in the hazard profile, the health effects and the exposure assessment of fluoride

Several adverse health effects have been postulated to be due to fluoride exposure, i.e. osteosarcoma, developmental neurotoxicity, and reproductive toxicity. However, most of the information is of limited quality and the observed effects mostly have been at high exposure levels not relevant for the European situation. Thus it is unlikely that additional research on potential adverse health effects will provide new data to support the risk assessment process.

Water fluoridation was intended to have a beneficial effect on caries prevention but could also induce fluorosis with a very narrow margin of exposure and may depend on windows of susceptibility.

Exposure assessment is critical for this type of studies

1) Develop and validate new biomarkers for long-term fluoride exposure.
2) Develop standardized methods for exposure assessment integrating all route of exposure.
3) Collect information on fluoride in food and bioavailability of fluoride.
4) Conduct an epidemiological study, taking advantage of the existing mother-child cohort to investigate the role of fluoride intake on incidence of dental fluorosis and dental health.

4.6. Question 2

Assess the health and environmental risks that may be associated with the use of the most common drinking water fluoridation agents like silicofluorides (e.g. (hydro)fluorosilicic acid, sodium silicofluoride, disodium hexafluorosilicate or hexafluorosilicate or hexafluorosilicic acid) taking into account their hazard profiles, their mode of use in water fluoridation, their physical chemical behavior when diluted in water, and the possible adverse effects they may have in exacerbating fluoride health effects as reported in some studies

4.6.1. Introduction

The adverse effect of fluoride exposure in humans and the benefit for dental health has been discussed in section 4.1 and 4.4, respectively and will not be discussed further

As already indicated in section 3.1, presence in drinking water of fluorosilicates due to the use of hexafluorosilicic acid or hexafluorosilicate for fluoridation, if any, is very low as fluorosilicates and other species are rapidly hydrolyzed in water to fluoride.

Therefore, this environmental risk assessment will focus only on the fluoride ion.

As also indicated in section 3, fluorides occur naturally and are ubiquitous; natural background levels vary with environmental compartments and geological circumstances. Fluorides also enter the environment from human activities, as well as the fluoridation of drinking water. These can involve: the production of aluminium, the production of some building bricks and the production and use of fertilizers.

Hence SCHER interprets this part of the request as follows: to what extent does the fluoridation of drinking water specifically lead to adverse ecological impacts?

If there were detailed information on exposure and physico-chemical conditions this approach should therefore consider the extent to which exposures due to fluoridation add to natural background, taking account of regional variations. It should also possibly take account of continental and regional backgrounds that integrate both natural and human sources. It would not consider the extent to which fluoridation might add to other anthropogenic sources at specific sites (e.g. point source emissions from aluminium smelting or diffuse emissions from agricultural use of fertilizers) since these raise difficult questions about exposure scenarios and also responsibilities.

The scenario of interest will, therefore, focus on the environmental exposures arising out of the use of fluoridated water in drinking, personal hygiene, washing clothes and washing dishes. All of this flows to the environment in drainage water and via sewage treatment works. At the sewage treatment works, some of the fluorides partition into the sewage sludge and may then pass to the terrestrial environment if sludge is spread on land; and/or to atmosphere and land if sludge is subjected to incineration. However, most of the fluorides remain in solution during sewage treatment and pass to the aquatic environment in this way (Walton & Conway, 1989). In the aquatic environment there will be a distribution between water and sediments depending on water chemistry. Fluoride is the most electronegative chemical in the Periodic Table and is highly reactive. Hence in the aquatic environment fluorides are likely to occur as the fluoride anion (Walton & Conway, 1989) and so this will be the focus of exposure and effect assessments for the aquatic ecosystems.

To carry out this risk assessment effectively would have required detailed information on ambient exposures and physico-chemical conditions at sites receiving fluoridated waters. Hence as a pragmatic approach SCHER has assumed further: (1) that the fluoride concentrations in waters used as a source of drinking water reflect local background concentrations and (2) that those authorities that practice fluoridation would not add fluoride if these background levels exceeded the legally-specified concentrations for fluoridation. Hence worst case environmental exposure concentrations will be equal to these legally-specified maxima. On that basis SCHER has used the legally defined concentration for Ireland (0.8 mg/L) and the WHO standard (1.5 mg/L) as appropriate total exposure levels – see section 4.2.1. The value of 3.0 mg/L (Scenario 3 in the human health assessment – see section 4.2.1) has not been used in this environmental assessment since this was based on natural concentrations in Finland – i.e. there is no added environmental risk here. Finally, indirect side effects, such as the possible increase in concentrations of lead from the action of fluoride in lead water pipes (section 3.1) are not considered since these scenarios are speculative and difficult to anticipate.

Therefore, SCHER is of the opinion that 1) fluoride as F^- should be considered as the only acting agent, 2) the only source of fluoride in this opinion is the application of fluoride in water supply systems and other sources of fluoride are excluded with respect to potential effects in the environment, 3) as a pragmatic approach it is assumed that the worst-case exposure from fluoridation will be no greater than the allowed legal limits, and 4) the focus of attention for the risk assessment should be the aqueous phase of the aquatic environment.

The physico-chemical properties are mentioned in Section 3.2.

4.6.2. Effects

4.6.2.1. Mechanism of action

Fluorides are not essential for most organisms. That said, there is evidence that at low concentrations fluorides can enhance the population growth rates of some aquatic algal species (Camargo, 2003). Some algae are able to tolerate fluoride levels as high as 200 mg F^-/L.

The adverse effects of fluoride on organisms seem to arise from the disruption of key metabolic pathways through the impairment of enzymes, including those involved in nucleic acid synthesis. However, the mechanistic details are as yet unclear.

In fish and invertebrates, fluoride toxicity decreases with increasing calcium and chloride concentrations in the water. Decrease with calcium is mainly due to the formation/ precipitation of innocuous complexes such as $Ca_5(PO_4)_3F$, CaF_2 and MgF_2. And an increase in the concentration of chloride ions might elicit a response in organisms for fluoride excretion. From observation in natural medium, Camargo (2003) concluded that it should be evident that physiological and genetic adaptation to high fluoride concentrations can occur in wild fish populations.

4.6.2.2. Aquatic effects

The analysis of the aquatic effects was based on a bibliographic search. From this it was clear that the review of Camargo (2003) covered most of the relevant studies. SCHER has, therefore, based much of the following analysis of effects on the information in this review.

Fish

Freshwater

Acute effects

The most valid data available (96h tests with measured concentration) were reviewed by Camargo (2003) and Metcalfe et al. (2003). The most sensitive fish was *Oncorhynchus mykiss*. In worst case soft water conditions (total hardness of 17 mg $CaCO_3$/L) the LC50 96h was 51 mg/L fluoride ion (Camargo, 2003).

Chronic effects

Among valid data in the literature, Shi et al. (2009) found the lowest NOEC in fish in 90 days in *Acipenser baerii* (sturgeon): 4 mg F^-/L (measured).

Marine water

Despite of generally protective effect of chloride ions, Camargo (2003) got some toxicity data in his review, which was taken as worst case.

Acute effects

Cyprinodon variegatus: LC50 96h > 500 mg/L (NOEC lethality 500 mg/L).

Chronic effects

Mugil cephalus: NOEC 113d on juvenile development = 5.5 mg/L.

Invertebrates

Freshwater

Acute effects

A large number of valid toxicity values in invertebrates at 48h were described in Camargo (2003) and Metcalfe et al. (2003). The most sensitive species was an amphipod: *Hyalella azteca,* with an EC50 48h of 14.6 mg F^-/L (measured concentrations) with hardness 140 – 150 mg $CaCO_3$/L (Metcalfe et al., 2003).

Chronic effects

Metcalfe et al. (2003) found an IC25 28d on *Hyalella azteca* growth of about 4 mg F^-/L (calculated from the article data on controlled concentration in spiked sediment and overlaying water).

Marine water

Acute effects

Despite of the general protective effect by Cl^- ions, Camargo review (2003) reported some toxicity data, the lowest EC50 96h being 10.5 mg F^-/L in the arthropod *Mysidopsis bahia*.

Chronic effects

Camargo (2003) reported that *Grandidierella lutosa* and *lignorum* estuarine amphipods female fecundity was shown to be the most sensitive endpoint in a 90 day life-cycle test, with a MATC of 4.15 mg F^-/L. It is noticeable that below this value it was observed that F^- was stimulating female fecundity.

Algae

Freshwater

Acute effects

In Camargo (2003), among algae species for which growth was not stimulated by fluoride ions, the lowest EC50 96h was shown to be 123 mg F^-/L in *Selenastrum capricornutum.*

Chronic effects

In the same species selection, growth of an algae species with sensitivity generally similar to this of *Selenastrum capricornutum, Scenedesmus quadricauda,* was shown not to be inhibited by 50 mg F^-/L in 175h. This value can therefore be taken as worst case NOEC for algae.

Marine water

Acute effects

Despite of the general observation that marine algal species were less sensitive to fluoride ions, again a lowest EC50 96h was shown a value of 82 mg F^-/L in *Skeletonema costatum*.

Chronic effects

In the chronic exposure experiments with marine algae cited in Camargo (2003), the lowest tested concentrations of fluoride was 50 mg/L, and the duration was more than 16 days. For algae tested at this concentration, no inhibition was observed. At 100 mg/L, some species growth was inhibited, but at most at 30 %. 50 mg/L can therefore be taken as worst case NOEC 72h for algae.

4.6.2.3. Conclusion on effects

SCHER agreed to use the ecotoxicological data as presented in Table 11 and considered these data sufficiently reliable and accepted to be used in risk assessment for the environment.

Table 11 - Summary of effect data for fluoride in mg/L.

Toxicity to organism	L(C)(D)(E)50 NOEC (... h or d)	Value
Freshwater		
fish (acute) (*Oncorhynchus mykiss)*	LC50 (96 h)	51
Invertebrates (acute) (*Hyalella azteca*)	EC50 (96 h)	14.6

Algae (acute) (*Selenastrum capricornutum*)	EC50 (96 h)	123
Freshwater		
Fish (chronic) (*Acipenser baerii*)	NOEC (90 d)	4
Invertebrates (chronic) (*Hyalella azteca*)	EC25 (28 d)	4
Algae (chronic) several species	NOEC (16 d)	50
No-effect freshwater	**$PNEC_{fresh}$**	**0.4***
Marine water		
Fish (acute) (*Cyprinodon variegatus*)	LC50 (96 h)	> 500
Invertebrates (acute) (*Mysidopsis bahia*)	LC50 (48 h)	10.5
Algae (acute) (*Skeletonema costatum*)	EC50 (96 h)	82
Marine water		
Fish (chronic) (*Mugil cephalus*)	NOEC (113 d)	5.5
Invertebrates (chronic) (*Grandidierella sp.*)	MATC (90 d)	4.15
algae (chronic)several species	NOEC (>=16 d)	50
No-effect marine water	**$PNEC_{marine}$**	**0.04***

*. The PNEC was derived by taking the lowest effect level observed and applying a safety factor of 10 for freshwater and 100 for marine water. These PNEC-values may also be found in the EUSES output in Appendix III. SCHER and its predecessor do not accept the additional safety factor of 10 from freshwater to marine water. However, if the TGD is applied the risk is even lower.

4.6.3. Risk characterization

A very simplistic risk characterisation can be carried out by assuming that the fluoridation level is 1 mg/L, that all domestic waters entering sewage treatment works have fluoride to this level and that most of this flows through the system. This means that worst case fluoride ion concentration in a typical output would be no more than 1 mg/L due to fluoridation – though this will be diluted to a variable extent by rainwater inputs. This means that the effluent would only have to be diluted in receiving water by a factor of at least 2.5 for the fluoride concentration to be reduced below the PNEC of 0.4 for freshwaters – something which seems extremely plausible for most circumstances (default dilution factor taken in the TGD is 10 (TGD, 2003)). Dilution for effluents entering the marine environment would have to be greater; but again that seems plausible (the default dilution factor taken in TGD for marine ecosystems is 100 (TGD, 2003)).

The only detailed work that has been carried out on the consequences of fluoridation of drinking water for concentrations of F in sewage treatment effluents was in Osterman (1999) and this supports the conclusion from the simplistic assessment. This paper presents a mass balance approach to develop a series of mathematical equations that describe the fate of fluoride added to drinking water in a typical municipal water management system. The ionic mass of fluoride entering the aquatic system from all sources was calculated, its distribution followed and its fate examined. The city of Montreal in Canada was used as an example but it is SCHER's view that this approach can be applied broadly. In this system fluoride was added to obtain levels between 0.7 and 1.2 mg/L. Based on the fluoridation level and the characteristics of the water supply situation in Montreal, the estimated daily average fluoride concentration at less than 1km distance from the effluent outfall was 0.22 to 0.34 mg/L. If this is compared with the PNEC of 0.4 (from table 11) no unacceptable risk for aquatic organisms is expected.

Clearly this study is focused on a particular site. To check the generality of the results, SCHER further has carried out an analysis using EUSES (EC, 2004).

SCHER recognizes that this model has been designed to be applied for organic and hydrophobic substances in the framework of new and existing substances and biocides (EC, 2004) but is of the view that treated cautiously; the model can give further insight into the likely consequences of fluoride for aquatic systems.

The application of fluoride to drinking water is analogous to the application of disinfectants to drinking water and this version of EUSES has been adopted in the following analyses.

In addition it should be kept in mind that the scenarios included in EUSES are conservative.

The following assumptions have been adopted by SCHER:

1. application of fluoride according to PT5 in analogy to drinking water disinfection;
2. the dose applied is 0.8 (normal dose) and 1.5 mg/L, based on the Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption (see section 4.2.1, human part);
3. the physico-chemical characteristics are as indicated in table 1;
4. the effect data are as indicated in table 11.

The following 2 cases are presented:

1. Case 1: a dose of 0.8 mg F^-/L as is the normal dose for fluoridation of drinking water,
2. Case 2: a dose of 1.5 mg F^-/L, based on the reference dose of WHO (2006),

The main results of the calculation of the risk characterisation ratios (RCR), defined as the ratio between the Predicted Environmental Concentration (PEC) and the Predicted No-Effect Concentration (PNEC) are that case 1 leads to an RCR of 0.2 and case 2 to an RCR of 0.375. (see Appendix III)

From these different lines of evidence, SCHER is of the opinion that fluoridation of drinking water will not result in unacceptable effects to the environment as RCR-values are below 1.

4.6.4. Conclusions

Based on three lines of evidence, a simplistic risk assessment, mass balance modelling and a modified EUSES analysis SCHER is of the opinion that adding fluoride to drinking water at concentrations between 0.8 mg F^-/L and the reference dose level of WHO (1.5 mg F^-/L) does not result in unacceptable risk to water organisms. Due to the electronegativity of the F ion SCHER is of the view that there will be little partition to solids in the sewage treatment process. It follows that sewage sludge is unlikely to become contaminated and, in turn, this means that the contamination of soils and terrestrial systems is unlikely. Similarly atmospheric releases from the incineration of sewage sludge are unlikely. Hence SCHER concludes that the risks from fluoridation to soils and atmospheric compartments do not give any cause for concern.

5. Summary

Fluoride, either naturally present or intentionally added to water, food and consumer products, e.g. toothpaste, is generally considered beneficial to prevent dental caries. Considering previous opinions from EFSA and SCCP, SCHER has reviewed the newest information in the area on risk and benefit of using fluoridated drinking water and intake of fluoride from all sources.

SCHER concludes:

Hydrolysis of hexafluorosilicates used to drinking water fluoridation to fluoride was rapid and the release of fluoride ion was essentially complete. Therefore, the fluoride ion is considered the only relevant substance with respect to this opinion.

There is a risk for dental fluorosis in children in EU countries with systemic fluoride exposure, but a threshold cannot be detected.

The occurrence of endemic skeletal fluorosis has not been reported in EU.

There is equivocal evidence linking fluoride in drinking to the development of osteosarcoma

Fluoride intake from drinking water does not hamper children's neurodevelopment and impairs IQ at the level occurring in EU.

Human studies do not suggest adverse thyroid effects at realistic human exposures to fluoride.

No new evidence from human studies indicating that fluoride in drinking water influences male and female reproductive capacity.

The upper tolerable intake level (UL) is not exceeded for adults and children between 12 and 15 living in areas with fluoridated drinking water (<0.8 mg/L).

The UL was exceeded in children between 6 and 12 years living in areas with fluoridated drinking water (<0.8 mg/L) when consuming up to 1 L water and using adult toothpaste (1.5%) unsupervised.

The UL is exceeded in children between 1 and 6 years living in areas with fluoridated drinking water (<0.8 mg/L) when consuming up to 0.5 L water and using adult toothpaste (1.5%) unsupervised.

Water fluoridation as well as topical fluoride treatments (e.g. fluoridated toothpaste or varnish) appears to prevent caries, primarily on permanent dentition, but topical application is the more efficient measure.

In children a very narrow margin exists between achieving the maximal beneficial effects of fluoride in caries prevention and the adverse effects of dental fluorosis.

Exposure of environmental organisms to levels of fluoride as used in fluoridation of drinking waters are not expected to lead to unacceptable risks to the environment.

6. LIST OF ABREVIATIONS

ATSDR	Agency for Toxic Substances and Disease Registry (US)
BW	body weight
CDC	Center for Disease Control (US)
DFMT	missing and filled deciduous teeth
D(M)FS	decayed (missing) filled tooth surfaces
EFSA	European Food Safety Authority
EFSA CONTAM	EFSA's panel on contaminants in the food chain
EFSA NDA	EFSA's panel on dietetic products, nutrition and allergies
EUSES	European Union System for the Evaluation of Substances
F	fluoride ion
IPCS	International Program for Chemical Safety (WHO)
IQ	intelligence quotient
MATC	Maximum Allowable Toxicant Concentration
NOEC	no observed effect concentration
NTP	National Toxicology Program (US)
PNEC	predicted no-effect concentration
PT5	Product type 5 from the biocides directive (8/8/EC
RCR	Risk Characterisation Ratio
SSCP	Scientific committee for consumer products
TGD	Technical guidance documents
TFT	topical fluoride treatment
UK DoH	UK Department of Health
UK COT	UK Committee of Toxicology
UL	upper tolerable intake level
US IOM	US Institute of Medicine
WHO	World Health Organisation

REFERENCES:

ASTDR (Agency for Toxic Substances and Disease Registry) (2003) Toxicological Profile for Fluorides, Hydrogen Fluoride, and Fluorine U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. Division of Toxicology/Toxicology Information Branch. September 2003. Atlanta, Georgia.

AU-NHMRC (2007) National Health and Medical Research Council (Australia): A systematic review of the efficacy and safety of fluoridation. PART A: review of methodology and results. Canberra: 187

Bassin EB, Wypij P, Davis RB, Mittleman MA (2006) Age-specific fluoride exposure in drinking water and osteosarcoma(United States); Cancer Causes Control 17:421–8

Bégin L, Fortin J, and Caron J (2003) Evaluation of the Fluoride Retardation Factor in unsaturated and undisturbed Soil Columns. Soil Science Society of America Journal, 67:1635-1646.

Bronckers AL, Lyaruu DM, DenBesten PK (2009) The Impact of Fluoride on Ameloblasts and the Mechanisms of Enamel Fluorosis. Journal of Dental Research, 88: 877-93.

Burt BA (1992) The Changing Patterns of Systemic Fluoride Intake. Journal of Dental Research 71: 1228-37

Butler WJ, Segreto V, Collins E (1985) Prevalence of dental mottling in school-aged lifetime residents of 16 Texas communities. American Journal of Public Health 75:1408-12

Camargo JA (2003) Fluoride toxicity to aquatic organisms: a review. Chemosphere 50: 251-64

Catanese J, and Keavney TM (1996) Role of collagen and hydroxyapatite in the. mechanical behavior of bone tissue. J Bone Miner Res 11:S295

Cohn PD (1992) A brief report on the association of DW and incidence of osteosarcoma in young males New Jersey Department of Health Environ. Health Service: 1- 17

Coplan MJ, Patch SC, Masters RD, Bachman MS, (2007) Confirmation of and explanations for elevated blood lead and other disorders in children exposed to water disinfection and fluoridation chemicals, Neurotoxicology, 28:1032-42

Dean HT, Arnold FA, Elvovoe. E (1942) Domestic water and dental caries. Public Health Rep 57:1155 – 79.

EFSA (2005) Scientific Opinion of the Panel on Dietetic Products, Nutrition, and Allergies (NDA) on the tolerable upper intake level of fluoride. The EFSA Journal 192, 1-65.

EFSA (2008a) Opinion of the Panel on Food Additives and Nutrient Sources added to Food on Calcium fluoride as a source of fluoride added for nutritional purposes to food. The EFSA Journal 882, 1-15

EFSA (2008b) Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food on Sodium monofluorophosphate as a source of fluoride added for nutritional purposes to food supplements. The EFSA Journal 886, 1-18

EFSA (2010) Statement of EFSA on the possible risks for public and animal health from the contamination of the feed and food chain due to possible ash-fall following the eruption of the Eyjafjallajökull volcano in Iceland – urgent advice. The EFSA Journal 8 (4), 1593.

Ellewood R, Fejerskov O, Cury JA, Clarkson B. (2008) Fluorides in caries control. IN: Dental Caries. Eds O Fejerskov & E. Kidd. Blackwell & Munksgaard Chapter 18

Erdal S and Buchanan SN (2005) A Quantitative Look at Fluorosis, Fluoride Exposure, and Intake in Children Using a Health Risk Assessment Approach. Environ. Health Perspect. 113:111–7.

European Commission (1998). Directive 98/8/EC Of The European Parliament And Of The Council of 16 February 1998 concerning the placing of biocidal products on the market, Official Journal of the European Communities L 123/1

European Commission (2001). European Union – Risk Assessment Report on Hydrogen Fluoride, Office for Official Publications of the European Communities, ISBN 92-894-0485-X, 135pp.

EUSES (2003) Uniform System for the Evaluation of Substances 2.1 (EUSES 2.1) National Institute of Public Health and the Environment (RIVM), Ministry of Housing, Spatial Planning and the Environment (VROM), Ministry of Health, Welfare and Sports (VWS), The Netherlands.

Eyre R, Feltbower RG, Mubwandarikwa E, Eden TO, McNally RJ (2009) Epidemiology of bone tumours in children and young adults. Pediatr Blood Cancer. 53:941-52. Review.

Fejerskov O, Baelun V, Richards A. Dose-resposonse and dental Fluorosis. (1996) Chapter 9. IN: Fluoride in Dentistry (second edition) Eds., O. Fejerskov**,** J. Ekstrand & B. Burt, Munksgaard, Copenhagen , 55-68

Finney WF. Wilson Erin, Callender, Morris MD, Beck LW (2006) Reexamination of Hexafluorosilicate Hydrolysis by 19F NMR and pH Measurement. Environ. Sci. Technol., 40, 2572-2577

Fomon S, Ekstrand J. (1999) Fluoride intake by infants. J Publ Health Dent. Vol 59 (No 4) :229 –234

Forsman B (1977) Early supply of fluoride and enamel fluorosis. Scand J Dent Res. 85:22-30.

Forum on Fluoridation Ireland Report (2002) Presented to Micheál Martin TD, Minister for Health and Children. ISBN: 0755-711-572

Gupta RS, Khan TI, Agrawal D, Kachhawa JB (2007) The toxic effects of sodium fluoride on the reproductive system of male rats. Toxicol Ind Health 23:507-13

Hoover RN, Devesa SS, Cantor KP, Fraumeni JF Jr. (1991) Time trends for bone and joint cancers and osteosarcomas in the Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. Review of fluoride benefits and risks. Report of the Ad Hoc Subcommittee on Fluoride of the Committee to Coordinate Environmental Health and Related Problems. Washington, DC; DHHS p. F1-F7.

IPCS (2002) International Programme on Chemical Safety. Environmetal Health Criteria 227, Fluorides WHO

Ismail AI, Hasson H (2008) Fluoride supplements, dental caries and fluorosis: A systematic review. J Am Dent Assoc. 139:1457-68.

Izquierdo-Vega JA, Sánchez-Gutiérrez M, Del Razo LM (2008) Decreased in vitro fertility in male rats exposed to fluoride-induced oxidative stress damage and mitochondrial transmembrane potential loss. Toxicol Appl Pharmacol. 230: 352-7.

Jobson MD, Grimm SE III, Banks K, Henley G (2000) The effects of water filtration systems on fluoride: Washington, DC metropolitan area. ASDC J Dent Child 67:350-4

Kirkeskov L Kristiansen E, Bøggild H, von Platen-Hallermund F, Sckerl H, Carlsen A, Larsen MJ, Poulsen S (2010) The association between fluoride in drinking water and dental caries in Danish children: Linking data from health registers, environmental registers and administrative registers Community Dentistry Oral Epi. (in press)

Locker, D (1999) The benefits and risks of water fluoridation: An Update of the 1996 Federal-Provincial Sub-committee Report Toronto, Community Dental Health Services Research Unit, Faculty of Dentistry, University of Toronto: 83

Lowry R, Steen N, Rankin J (2003) Water fluoridation, stillbirths, and congenital abnormalities. J Epidemiol Community Health 57:499-500.

Maguire A, Zohouri FV, Mathers JC, Steen IN, Hindmarch PN, Moynihan PJ (2005) Bioavailability of Fluoride in Drinking Water: a Human Experimental Study. J Dent Res 84:989-93

Marinho VC, Higgins JP, Logan S, Sheiham A (2002) Fluoride gels for preventing dental caries in children and adolescents. Cochrane Database Syst Rev (2): CD002280.

Marinho VC, Higgins JP, Logan S, Sheiham A (2003a). Fluoride mouthrinses for preventing dental caries in children and adolescents. Cochrane Database Syst Rev (3): CD002284.

Marinho VC, Higgins JP, Logan S, Sheiham A (2003b). Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries in children and adolescents. Cochrane Database Syst Rev (4): CD002782.

Marinho VC, Higgins JP, Sheiham A, Logan S (2004b). One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus another for preventing dental caries in children and adolescents. Cochrane Database Syst Rev (1): CD002780.

Marinho VC, Higgins JP, Sheiham A, Logan S (2003c) Fluoride toothpastes for preventing dental caries in children and adolescents. Cochrane Database Syst Rev (1): CD002278.

Marinho VC, Higgins JP, Sheiham A, Logan S (2004a). Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus single topical fluoride for preventing dental caries in children and adolescents. Cochrane Database Syst Rev (1): CD002781.

Marthaler TM, Petersen PE (2005) Salt fluoridation-an alternative in automatic prevention of dental caries. International Dental Journal. 55:351-8

McDonagh M, Whiting P, Bradeley M, Cooper J, Sutton A, Chestnut I, Misso K, Wilson P, Treasure E, Kleijnen J (2000) A systematic report on public water fluoridation. NHS Center for Reviews and Dissemination. York, UK, University of York: 259.

Metcalfe-Smith JL, Holtze KE, Sirota GR, Reid JJ and de Solla SR (2003). Toxicity of Aqeous and Sediment-associated Fluoride to Freshwater Organisms. Environmental Toxicology and Chemistry, Vol 22 no. 1 pp 161 – 166.

Ortiz-Pérez D, Rodríguez-Martínez M, Martínez F, Borja-Aburto VH, Castelo J, Grimaldo JI, de la Cruz E, Carrizales L, Díaz-Barriga F (2003) Fluoride-induced disruption of reproductive hormones in men. Environ Res 93:20-30.

Osterman JW (1999) Evaluating the Impact of Municipal Water Fluoridation on the Aquatic Environment. Am J Public Health 80: 1230-1235.

Parnell C, Whelton H, O'Mullane D (2009) Water fluoridation. Eur Arch Paediatr Dent. 10:141-8.

Richard LF, Westmoreland JT, Tashiro M, McKay CH, Morrision JT (1967) Determining optimum fluoride levels for community water supplies in relation to temperature. J Am Dent Assoc 74:389 -397

Rocha-Amador D, Navarro ME, Carrizales L, Morales R, Calderón J (2007) Decreased intelligence in children and exposure to fluoride and arsenic in drinking water; Cad. Saúde Pública, Rio de Janeiro, 23 Sup 4:S579-S587

Salanti G, Marinho V, Higgins JP (2009) A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered. J Clin Epidemiol 62: 857-64

SCCP (2005) Opinion SCCP/0882/05 on the safety of fluorine compounds in oral hygiene products fro children under the age of 6 years, 20 September 2005

SCCP (2009) Clarification on the Opinions SCCNFP/0653/03 and SCCP/0882/05 on the Safety of Fluorine Compounds in Oral Hygiene Products for Children under the Age of 6 Years, 21 January 2009
http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_169.pdf

Schulz C, Conrad A, Becker K, Kolossa-Gehring M, Seiwert M, Seifert B (2007) Twenty years of the German Environmental Survey (GerES): human biomonitoring--temporal and spatial (West Germany/East Germany) differences in population exposure. Int J Hyg Environ Health 210(3-4): 271-97

Scientific Committee on Food (1996) Opinion on arsenic, barium, fluoride, boron and manganese in natural mineral water.

Scientific Committee on Food (2003) Report on the Revision of Essential Requirements of Infant Formulae and Follow-on Formulae, adopted on 4 April 2003http://ec.europa.eu/food/fs/sc/oldcomm7/out09_en.html

Seppa, L, Karkkainen, S Hausen, H (2000a) Caries trends 1992-1998 in two low-fluoride Finnish towns formerly with and without fluoridation. Caries research 34(6): 462-8.

Seppa, L, Karkkainen, S Hausen, H (2000b) Caries in the primary dentition, after discontinuation of water fluoridation, among children receiving comprehensive dental care. Community dentistry and oral epidemiology 28(4): 281-8

Shi X, Zhuang P, Zhang L, Feng G, Chen L, Liu J, Qu L, Wang R (2009) The bioaccumulation of fluoride ion (F^-) in Siberian sturgeon (*Acipenser baerii*) under laboratory conditions. Chemosphere 75:376-80

Singer L and Armstrong WD (1977) Fluoride in treated sewage and in rain and snow. Arch Environ Health. 32:21-3.

Singer L, Ophaug R (1979) Total Fluoride Intake of Infants. Pediatrics 63: 460-6

Tang Q-q; Du J, Ma H-h,Jiang S-j, Xiao-jun ZhouX-j (2008) Fluoride and Children's Intelligence: A Meta-analysis. Biol Trace Elem Res 126:115–20

TGD, 2003. Technical Guidance Document on Risk Assessment *in support of* Commission Directive 93/67/EEC on Risk Assessment for new notified substances Commission Regulation (EC) No 1488/94 on Risk Assessment for existing substances Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market

Truman, BI, Gooch, BF, Sulemana, I, Gift, HC, Horowitz, AM, Evans, CA, Griffin, SO Carande-Kulis, VG (2002) Reviews of evidence on interventions to prevent dental caries, oral and pharyngeal cancers, and sports-related craniofacial injuries. American Journal of Preventive Medicine 23(1 Suppl): 21-54.

Twetman S, Petersson L, Axelsson S, Dahlgren H, Holm AK, Källestål C, Lagerlöf F, Lingström P, Mejàre I, Nordenram G, Norlund A, Söder B. Caries-preventive effect of sodium fluoride mouthrinses: a systematic review of controlled clinical trials. Acta Odontol Scand. 2004 Aug;62(4):223-30.

UK-COT, (2003) Committee on toxicity of chemical in food, consumer products and the environment. COT Statement on fluorine in the 1997 total diet study. September 2003.

UK-CRD 2003Center for reviews and dissemination. What the 'York review' on the fluoridation of drinking water really found. In: York U, editor. York, UK,

UK-DoH (Department of Health) (1994) Dietary reference values for food energy and nutrients for the United Kingdom. Report of the Panel on Dietary Reference Values of the Committee on Medical Aspects of Food Policy. London, Stationary Office.

Urbansky ET, Schock MR (2000) Can Fluoridation Affect Lead(II) in Potable Water? Hexafluorosilicate and Fluoride Equilibra in Aqueous Solution. International Journal of Environmental Studies 57: 597-637.

US-IOM (Institute of Medicine) (1999) Dietary reference values for calcium, phosphorus, magnesium, Vitamin D and fluoride for the United Kingdom. Standing Committee on the Scientific Evaluation on Dietary Reference Intakes, Food and Nutrition Board, Washington, National Academy Press.

US-NRC (2006) National Research Council Fluoride in drinking water A scientific review of EPA´S standard. The national Academic Press.

Walton BT & Conway RA (1989) In: Environmental Inorganic Chemistry: Properties, Processes, and Estimation Methods (Society of Environmental Toxicology and Chemistry) Eds: Bodek I, Lyman WJ, Rehl WF & Rosenblatt DH. Pergamon Press, ISBN-13-978-0080368337.

Wang S-X Wang SX, Wang ZH, Cheng XT, Li J, Sang ZP, Zhang XD, Han LL, Qiao XY, Wu ZM, Wang ZQ (2007) Arsenic and Fluoride Exposure in Drinking Water: Children's IQ and Growth in Shanyin County, Shanxi Province, China. Environ Health Perspect. 115: 643-7

Whelton H, Crowley E, O'Mullane D, Donaldson M, Cronin M, Kelleher V (2006) Dental caries and enamel fluorosis among the fluoridated population in the Republic of Ireland and non fluoridated population in Northern Ireland in 2002. Community Dent Health 23:37-43.

Whitford G, Sampaio F, Pinto C, Maria A, Cardoso V, Buzalaf M (2008) Pharmacokinetics of ingested fluoride: Lack of effect of chemical compound. Arch Oral Biol 53: 1037-41

Whitford GM, Whitford, JL, Hobbs SH, (2009) Appetitive-based learning in rats: Lack of effect of chronic exposure to fluoride. Neurotox Teratol 31: 210-5

Whiting P, MacDonagh M, Kleijnen J (2001) Association of Down's syndrome and water fluoride level: a systematic review of the evidence. BMC Public Health 1:6. doi:10.1186/1471-2458-1-6

WHO (2006) Guidelines for Drinking-water Quality. World Health Organization. Geneva,

Yeung, CA, Hitchings, JL, Macfarlane, TV, Threlfall, AG, Tickle, M Glenny, AM (2005) Fluoridated milk for preventing dental caries. Cochrane Database Syst Rev(3): CD003876

Appendix I Classification of fluorosis

The dictionary definition of fluorosis is " an abnormal condition (as mottled enamel of human teeth) caused by fluorine or its compounds" or "a pathological condition resulting for an excessive intake of fluoride (usually from drinking water)". This is a very simplistic, since mottling of the enamel of teeth is common and may have many aetiologies, including caries, childhood infections, developmental abnormalities and trauma. The generally applied classification of fluorosis is shown in table 1.

Table 1: Classification of the clinical appearance of fluorotic enamel changes characterising the single tooth surface (Thylstrup and Fejerskov, 1978)

Score	Clinical appearance
0	Normal translucency of enamel remains after prolonged air drying
1	Narrow white lines located corresponding to the perichymata
2	**Smooth surface**: More pronounced lines of opacity which follow the perichymata. Occasionally confluence of adjacent lines. **Occlusal surfaces**: Scattered areas of opacity <2 mm in diameter and pronounced opacity of cuspal ridges
3	**Smooth surface**: Merging and irregular cloudy areas of opacity. Accentuated drawing of perichymata often visible between opacities. **Occlusal surfaces**: Confluent areas of marked opacity. Worn areas appear almost normal but usually circumscribed by a rim of opaque enamel.
4	**Smooth surfaces:** The entire surface exhibits marked opacity or appears chalky white. Parts of surface exposed to attrition appears less affected **Occlusal surfaces**: Entire surface exhibits marked opacity. Attrition is often pronounced shortly after eruption.
5	**Smooth and occlusal surfaces:** Entire surface displays marked opacity with focal loss of outermost enamels (pits)<2mm in diameter
6	**Smooth surfaces**: Pits are regular arranged in horizontal bands <2mm in vertical extension **Occlusal surfaces**: Confluent areas <3 mm in diameter exhibits loss of enamel. Marked attrition.
7	**Smooth surfaces**: Loss of outermost enamel in irregular areas involving less than one-half of entire surface **Occlusal surfaces**: Changes in the morphology caused by merging pits and marked attrition
8	**Smooth and occlusal surfaces**: Loss of outermost enamel involving >1½ of surface
9	**Smooth and occlusal surfaces**: Loss of main part of enamel with change in anatomic appearance of surface. Cervical rim of almost unaffected enamel is often noted.

The classification mild fluorosis used in the opinion corresponds to score 1- 2, and moderate fluorosis 3-4.

Appendix II - Critical exposure timing for teeth

Effect	Age	Fluoride exposure
Early ossification of jaw and development of deciduous teeth	~ 4 – 6 months In utero	In uterus maternal intake crossing placenta
Ameliogenesis of deciduous teeth	~ 5 – 8 months In utero	
Eruption Deciduous teeth Enamel surface	6 - 24 months	Ingested Systemic - Milk (mother's or formula) Biofilm uptake in buccal cavity
Ameliogenesis of unerupted permanent teeth	~3 months post partum – 5 years old	Ingested milk (mother's/formula/dairy) initially + increasing quantity food, water, dental products
Eruption permanent teeth Enamel surface	5 –16 years old	Food, water, soft drinks, beverage, dental products Biofilm uptake in buccal cavity
Permanent teeth	16+ years old	Food, water, soft drinks, beverage, dental products Biofilm uptake in buccal cavity

Appendix III

Case I Operational dose

IDENTIFICATION OF THE SUBSTANCE

General name	Sodium fluoride		S
CAS-No	7681-49-4		S
EC-notification no.	NA		S
EINECS no.	231-667-8		S
Molecular weight			

PHYSICO-CHEMICAL PROPERTIES

Melting point	1000	[oC]	S
Boiling point	1.7E+03	[oC]	S
Vapour pressure at test temperature	1.33	[hPa]	S
Temperature at which vapour pressure was measured	1.077E+03	[oC]	S
Vapour pressure at 25 [oC]	1.97E-05	[Pa]	O
Water solubility at test temperature	4E+04	[mg.l-1]	S
Temperature at which solubility was measured	20	[oC]	S
Water solubility at 25 [oC]	4.29E+04	[mg.l-1]	O
Octanol-water partition coefficient	??	[log10]	D
Henry's law constant at 25 [oC]	1.93E-08	[Pa.m3.mol-1]	O

ENVIRONMENT-EXPOSURE			
RELEASE ESTIMATION			
Tonnage of substance in Europe	0	[tonnes.yr-1]	O
Regional production volume of substance	0	[tonnes.yr-1]	O
ENVIRONMENT-EXPOSURE			
RELEASE ESTIMATION			
[1 "SCHER FLUORIDATION", IC=15/UC=39]			
Industry category	15/0 Others		D
Use category	39 Biocides, non-agricultural		D
Fraction of tonnage for application	1	[-]	D
ENVIRONMENT-EXPOSURE			
RELEASE ESTIMATION			
[INDUSTRIAL USE]			
Use specific emission scenario	Yes		D
Emission tables	A3.16 (general table), B3.14 (general table)		S
Emission scenario			D
Main category industrial use	III Non-dispersive use		D
Scenario choice for biocides	(5) Drinking water		S
Fraction of tonnage released to air	1E-05	[-]	O
Fraction of tonnage released to wastewater	0.75	[-]	O
Fraction of tonnage released to surface water	0	[-]	O
Fraction of tonnage released to industrial soil	1E-03	[-]	O
Fraction of tonnage released to agricultural soil	0	[-]	O
Fraction of the main local source	1	[-]	O
Number of emission days per year	365	[-]	O
Local emission to air during episode	0	[kg.d-1]	O
Local emission to wastewater during episode	1.6	[kg.d-1]	O
Intermittent release	No		D
ENVIRONMENT-EXPOSURE			
RELEASE ESTIMATION			
TOTAL REGIONAL EMISSIONS TO COMPARTMENTS			
Total regional emission to air	0	[kg.d-1]	O
Total regional emission to wastewater	0	[kg.d-1]	O
Total regional emission to surface water	0	[kg.d-1]	O
Total regional emission to industrial soil	0	[kg.d-1]	O
Total regional emission to agricultural soil	0	[kg.d-1]	O
ENVIRONMENT-EXPOSURE			
PARTITION COEFFICIENTS			
SOLIDS-WATER PARTITION COEFFICIENTS			
Solids-water partition coefficient in soil	6E-03	[l.kg-1]	S
Solids-water partition coefficient in sediment	1.5E-03	[l.kg-1]	S
Solids-water partition coefficient suspended matter	3E-03	[l.kg-1]	S
Solids-water partition coefficient in raw sewage sludge	9E-03	[l.kg-1]	S
ENVIRONMENT-EXPOSURE			
DEGRADATION AND TRANSFORMATION			
Characterization of biodegradability	Not biodegradable		D
Degradation calculation method in STP	First order, standard OECD/EU tests		D
Rate constant for biodegradation in STP	0	[d-1]	O
Rate constant for biodegradation in surface water	0	[d-1] (12[oC])	O
Rate constant for biodegradation in bulk soil	6.93E-07	[d-1] (12[oC])	O
Rate constant for biodegradation in aerated sediment	6.93E-07	[d-1] (12[oC])	O
Rate constant for hydrolysis in surface water	6.93E-07	[d-1] (12[oC])	O
Rate constant for photolysis in surface water	6.93E-07	[d-1]	O
ENVIRONMENT-EXPOSURE			
SEWAGE TREATMENT			
LOCAL STP [1 "SCHER FLUORIDATION", IC=15/UC=39][INDUSTRIAL USE]			
OUTPUT			
Fraction of emission directed to air by STP	1.85E-08	[%]	O
Fraction of emission directed to water by STP	100	[%]	O
Fraction of emission directed to sludge by STP	3.73E-04	[%]	O
Fraction of the emission degraded in STP	0	[%]	O
Concentration in untreated wastewater	0.8	[mg.l-1]	O
Concentration of chemical (total) in the STP-effluent	0.8	[mg.l-1]	O
Concentration in effluent exceeds solubility	No		O
Concentration in dry sewage sludge	7.55E-03	[mg.kg-1]	O
PEC for micro-organisms in the STP	0.8	[mg.l-1]	O

ENVIRONMENT-EXPOSURE
DISTRIBUTION
LOCAL SCALE
[1 "SCHER FLUORIDATION", IC=15/UC=39][INDUSTRIAL USE]

Concentration in air during emission episode	8.23E-14	[mg.m-3]	O
Annual average concentration in air, 100 m from point source	8.23E-14	[mg.m-3]	O
Concentration in surface water during emission episode (dissolved)	0.08	[mg.l-1]	O
Annual average concentration in surface water (dissolved)	0.08	[mg.l-1]	O
Local PEC in surface water during emission episode (dissolved)	0.08	[mg.l-1]	O
Annual average local PEC in surface water (dissolved)	0.08	[mg.l-1]	O
Local PEC in fresh-water sediment during emission episode	0.0627	[mg.kgwwt-1]	O
Concentration in seawater during emission episode (dissolved)	8E-03	[mg.l-1]	O
Annual average concentration in seawater (dissolved)	8E-03	[mg.l-1]	O
Local PEC in seawater during emission episode (dissolved)	8E-03	[mg.l-1]	O
Annual average local PEC in seawater (dissolved)	8E-03	[mg.l-1]	O
Local PEC in marine sediment during emission episode	6.27E-03	[mg.kgwwt-1]	O
Local PEC in agric. soil (total) averaged over 30 days	9.53E-06	[mg.kgwwt-1]	O
Local PEC in agric. soil (total) averaged over 180 days	4.76E-06	[mg.kgwwt-1]	O
Local PEC in grassland (total) averaged over 180 days	1.06E-06	[mg.kgwwt-1]	O
Local PEC in groundwater under agricultural soil	3.88E-05	[mg.l-1]	O

ENVIRONMENT-EXPOSURE
DISTRIBUTION
REGIONAL AND CONTINENTAL SCALE
CONTINENTAL

Continental PEC in surface water (dissolved)	0	[mg.l-1]	O
Continental PEC in seawater (dissolved)	0	[mg.l-1]	O
Continental PEC in air (total)	0	[mg.m-3]	O
Continental PEC in agricultural soil (total)	0	[mg.kgwwt-1]	O
Continental PEC in pore water of agricultural soils	0	[mg.l-1]	O
Continental PEC in natural soil (total)	0	[mg.kgwwt-1]	O
Continental PEC in industrial soil (total)	0	[mg.kgwwt-1]	O
Continental PEC in sediment (total)	0	[mg.kgwwt-1]	O
Continental PEC in seawater sediment (total)	0	[mg.kgwwt-1]	O

ENVIRONMENT-EXPOSURE
DISTRIBUTION
REGIONAL AND CONTINENTAL SCALE
REGIONAL

Regional PEC in surface water (dissolved)	0	[mg.l-1]	O
Regional PEC in seawater (dissolved)	0	[mg.l-1]	O
Regional PEC in air (total)	0	[mg.m-3]	O
Regional PEC in agricultural soil (total)	0	[mg.kgwwt-1]	O
Regional PEC in pore water of agricultural soils	0	[mg.l-1]	O
Regional PEC in natural soil (total)	0	[mg.kgwwt-1]	O
Regional PEC in industrial soil (total)	0	[mg.kgwwt-1]	O
Regional PEC in sediment (total)	0	[mg.kgwwt-1]	O
Regional PEC in seawater sediment (total)	0	[mg.kgwwt-1]	O

ENVIRONMENT-EXPOSURE
BIOCONCENTRATION

Bioconcentration factor for earthworms	??	[l.kgwwt-1]	D
Bioconcentration factor for fish	??	[l.kgwwt-1]	O

ENVIRONMENT-EXPOSURE
SECONDARY POISONING [1 "SCHER FLUORIDATION", IC=15/UC=39][INDUSTRIAL USE]

Concentration in fish for secondary poisoning (freshwater)	??	[mg.kgwwt-1]	O
Concentration in fish for secondary poisoning (marine)	??	[mg.kgwwt-1]	O
Concentration in fish-eating marine top-predators	??	[mg.kgwwt-1]	O
Concentration in earthworms from agricultural soil	??	[mg.kg-1]	O

ENVIRONMENT - EFFECTS
MICRO-ORGANISMS

Test system	Respiration inhibition, EU Annex V		
C.11, OECD 209	D		
EC50 for micro-organisms in a STP	??	[mg.l-1]	D
EC10 for micro-organisms in a STP	??	[mg.l-1]	D
NOEC for micro-organisms in a STP	??	[mg.l-1]	D
PNEC for micro-organisms in a STP	??	[mg.l-1]	O
Assessment factor applied in extrapolation to PNEC micro	??	[-]	O

ENVIRONMENT - EFFECTS
FRESH_WATER ORGANISMS

LC50 for fish	51	[mg.l-1]	S
L(E)C50 for Daphnia	14.6	[mg.l-1]	S
EC50 for algae	123	[mg.l-1]	S
LC50 for additional taxonomic group	??	[mg.l-1]	D
NOEC for fish	4	[mg.l-1]	S
NOEC for Daphnia	4	[mg.l-1]	S
NOEC for algae	40	[mg.l-1]	S
NOEC for additional taxonomic group	??	[mg.l-1]	D
PNEC for aquatic organisms	0.4	[mg.l-1]	O
PNEC for aquatic organisms, intermittent releases	0.146	[mg.l-1]	O

ENVIRONMENT - EFFECTS
MARINE ORGANISMS

LC50 for fish (marine)	500	[mg.l-1]	S
L(E)C50 for crustaceans (marine)	10.5	[mg.l-1]	S
EC50 for algae (marine)	82	[mg.l-1]	S
LC50 for additional taxonomic group (marine)	??	[mg.l-1]	D
NOEC for fish (marine)	5.5	[mg.l-1]	S
NOEC for crustaceans (marine)	4.2	[mg.l-1]	S
NOEC for algae (marine)	20	[mg.l-1]	S
NOEC for additional taxonomic group (marine)	??	[mg.l-1]	D
PNEC for marine organisms	0.04	[mg.l-1]	O

ENVIRONMENT - EFFECTS
FRESH-WATER SEDIMENT ORGANISMS

LC50 for fresh-water sediment organism	??	[mg.kgwwt-1]	D
EC10 for fresh-water sediment organism	??	[mg.kgwwt-1]	D
EC10 for fresh-water sediment organism	??	[mg.kgwwt-1]	D
EC10 for fresh-water sediment organism	??	[mg.kgwwt-1]	D
NOEC for fresh-water sediment organism	??	[mg.kgwwt-1]	D
NOEC for fresh-water sediment organism	??	[mg.kgwwt-1]	D
NOEC for fresh-water sediment organism	??	[mg.kgwwt-1]	D
PNEC for fresh-water sediment-dwelling organisms	0.313	[mg.kgwwt-1]	O

ENVIRONMENT - EFFECTS
MARINE SEDIMENT ORGANISMS

LC50 for marine sediment organism	??	[mg.kgwwt-1]	D
EC10 for marine sediment organism	??	[mg.kgwwt-1]	D
EC10 for marine sediment organism	??	[mg.kgwwt-1]	D
EC10 for marine sediment organism	??	[mg.kgwwt-1]	D
NOEC for marine sediment organism	??	[mg.kgwwt-1]	D
NOEC for marine sediment organism	??	[mg.kgwwt-1]	D
NOEC for marine sediment organism	??	[mg.kgwwt-1]	D
PNEC for marine sediment organisms	0.0313	[mg.kgwwt-1]	O

ENVIRONMENT - EFFECTS
TERRESTRIAL ORGANISMS

LC50 for plants	??	[mg.kgwwt-1]	D
LC50 for earthworms	??	[mg.kgwwt-1]	D
EC50 for microorganisms	??	[mg.kgwwt-1]	D
LC50 for other terrestrial species	??	[mg.kgwwt-1]	D
NOEC for plants	??	[mg.kgwwt-1]	D
NOEC for earthworms	??	[mg.kgwwt-1]	D
NOEC for microorganisms	??	[mg.kgwwt-1]	D
NOEC for additional taxonomic group	??	[mg.kgwwt-1]	D
NOEC for additional taxonomic group	??	[mg.kgwwt-1]	D
PNEC for terrestrial organisms	0.0492	[mg.kgwwt-1]	O
Equilibrium partitioning used for PNEC in soil?	Yes		O

ENVIRONMENT - EFFECTS
BIRDS AND MAMMALS

Duration of (sub-)chronic oral test	28 days		D
NOEC via food for secondary poisoning	??	[mg.kg-1]	O
PNEC for secondary poisoning of birds and mammals	??	[mg.kg-1]	O

ENVIRONMENT - RISK CHARACTERIZATION

LOCAL [1 "SCHER FLUORIDATION", IC=15/UC=39][INDUSTRIAL USE]			
RCR for the local fresh-water compartment	0.2	[-]	O
RCR for the local fresh-water compartment, statistical method	??	[-]	O
RCR for the local marine compartment	0.2	[-]	O
RCR for the local marine compartment, statistical method	??	[-]	O
RCR for the local fresh-water sediment compartment	0.2	[-]	O
RCR for the local marine sediment compartment	0.2	[-]	O
RCR for the local soil compartment	1.94E-04	[-]	O
RCR for the local soil compartment, statistical method	??	[-]	O
RCR for the sewage treatment plant	??	[-]	O
RCR for fish-eating birds and mammals (fresh-water)	??	[-]	O
RCR for fish-eating birds and mammals (marine)	??	[-]	O
RCR for top predators (marine)	??	[-]	O
RCR for worm-eating birds and mammals	??	[-]	O
ENVIRONMENT - RISK CHARACTERIZATION			
REGIONAL			
RCR for the regional fresh-water compartment	0	[-]	O
RCR for the regional fresh-water compartment, statistical method	??	[-]	O
RCR for the regional marine compartment	0	[-]	O
RCR for the regional marine compartment, statistical method	??	[-]	O
RCR for the regional fresh-water sediment compartment	0	[-]	O
RCR for the regional marine sediment compartment	0	[-]	O
RCR for the regional soil compartment	0	[-]	O
RCR for the regional soil compartment, statistical method	??	[-]	O
HUMAN HEALTH - EXPOSURE ASSESSMENT			
HUMANS EXPOSED VIA THE ENVIRONMENT			
LOCAL SCALE			
Purification factor for surface water	1	[-]	O
HUMAN HEALTH - EXPOSURE ASSESSMENT			
HUMANS EXPOSED VIA THE ENVIRONMENT			
LOCAL SCALE			
CONCENTRATIONS IN INTAKE MEDIA [1 "SCHER FLUORIDATION", IC=15/UC=39][INDUSTRIAL USE]			
Local concentration in wet fish	??	[mg.kg-1]	O
Local concentration in root tissue of plant	??	[mg.kg-1]	O
Local concentration in leaves of plant	??	[mg.kg-1]	O
Local concentration in grass (wet weight)	??	[mg.kg-1]	O
Local concentration in drinking water	0.08	[mg.l-1]	O
Local concentration in meat (wet weight)	??	[mg.kg-1]	O
Local concentration in milk (wet weight)	??	[mg.kg-1]	O
HUMAN HEALTH - EXPOSURE ASSESSMENT			
HUMANS EXPOSED VIA THE ENVIRONMENT			
LOCAL SCALE			
DOSES IN INTAKE MEDIA [1 "SCHER FLUORIDATION", IC=15/UC=39][INDUSTRIAL USE]			
Daily dose through intake of drinking water	2.29E-03	[mg.kg-1.d-1]	O
Daily dose through intake of fish	??	[mg.kg-1.d-1]	O
Daily dose through intake of leaf crops	??	[mg.kg-1.d-1]	O
Daily dose through intake of root crops	??	[mg.kg-1.d-1]	O
Daily dose through intake of meat	??	[mg.kg-1.d-1]	O
Daily dose through intake of milk	??	[mg.kg-1.d-1]	O
Daily dose through intake of air	2.35E-14	[mg.kg-1.d-1]	O
HUMAN HEALTH - EXPOSURE ASSESSMENT			
HUMANS EXPOSED VIA THE ENVIRONMENT			
LOCAL SCALE			
FRACTIONS OF TOTAL DOSE [1 "SCHER FLUORIDATION", IC=15/UC=39][INDUSTRIAL USE]			
Fraction of total dose through intake of drinking water	??	[-]	O
Fraction of total dose through intake of fish	??	[-]	O
Fraction of total dose through intake of leaf crops	??	[-]	O
Fraction of total dose through intake of root crops	??	[-]	O
Fraction of total dose through intake of meat	??	[-]	O
Fraction of total dose through intake of milk	??	[-]	O
Fraction of total dose through intake of air	??	[-]	O
Local total daily intake for humans	??	[mg.kg-1.d-1]	O

HUMAN HEALTH - EXPOSURE ASSESSMENT
HUMANS EXPOSED VIA THE ENVIRONMENT
REGIONAL SCALE
CONCENTRATIONS IN INTAKE MEDIA

Regional concentration in wet fish			??	[mg.kg-1]	D
Regional concentration in root tissue of plant			??	[mg.kg-1]	D
Regional concentration in leaves of plant			??	[mg.kg-1]	D
Regional concentration in grass (wet weight)			??	[mg.kg-1]	D
Regional concentration in drinking water			??	[mg.l-1]	D
Regional concentration in meat (wet weight)			??	[mg.kg-1]	D
Regional concentration in milk (wet weight)	??	[mg.kg-1] D			

HUMAN HEALTH - EXPOSURE ASSESSMENT
HUMANS EXPOSED VIA THE ENVIRONMENT
REGIONAL SCALE
DOSES IN INTAKE MEDIA

Daily dose through intake of drinking water	??	[mg.kg-1.d-1]	D
Daily dose through intake of fish	??	[mg.kg-1.d-1]	D
Daily dose through intake of leaf crops	??	[mg.kg-1.d-1]	D
Daily dose through intake of root crops	??	[mg.kg-1.d-1]	D
Daily dose through intake of meat	??	[mg.kg-1.d-1]	D
Daily dose through intake of milk	??	[mg.kg-1.d-1]	D
Daily dose through intake of air	??	[mg.kg-1.d-1] D	

HUMAN HEALTH - EXPOSURE ASSESSMENT
HUMANS EXPOSED VIA THE ENVIRONMENT
REGIONAL SCALE
FRACTIONS OF TOTAL DOSE

Fraction of total dose through intake of drinking water	??	[-]	D
Fraction of total dose through intake of fish	??	[-]	D
Fraction of total dose through intake of leaf crops	??	[-]	D
Fraction of total dose through intake of root crops	??	[-]	D
Fraction of total dose through intake of meat	??	[-]	D
Fraction of total dose through intake of milk	??	[-]	D
Fraction of total dose through intake of air	??	[-]	D
Regional total daily intake for humans	??	[mg.kg-1.d-1] D	

HUMAN HEALTH - RISK CHARACTERIZATION CURRENT CLASSIFICATION

Corrosive (C, R34 or R35)	No	D
Irritating to skin (Xi, R38)	No	D
Irritating to eyes (Xi, R36)	No	D
Risk of serious damage to eyes (Xi, R41)	No	D
Irritating to respiratory system (Xi, R37)	No	D
May cause sensitisation by inhalation (Xn, R42)	No	D
May cause sensitisation by skin contact (Xi, R43)	No	D
May cause cancer (T, R45)	No	D
May cause cancer by inhalation (T, R49)	No	D
Possible risk of irreversible effects (Xn, R40)	No	D

Case II WHO reference use

IDENTIFICATION OF THE SUBSTANCE

General name	Sodium fluoride		S
CAS-No	7681-49-4		S
EC-notification no.	NA		S
EINECS no.	231-667-8		S
Molecular weight 42 [g.mol-1] S			

PHYSICO-CHEMICAL PROPERTIES

Melting point	1000	[oC]	S
Boiling point	1.7E+03	[oC]	S
Vapour pressure at test temperature	1.33	[hPa]	S
Temperature at which vapour pressure was measured	1.077E+03	[oC]	S
Vapour pressure at 25 [oC]	1.97E-05	[Pa]	O
Water solubility at test temperature	4E+04	[mg.l-1]	S
Temperature at which solubility was measured	20	[oC]	S
Water solubility at 25 [oC]	4.29E+04	[mg.l-1]	O
Octanol-water partition coefficient	??	[log10]	D
Henry's law constant at 25 [oC] 1.93E-08 [Pa.m3.mol-1] O			

ENVIRONMENT-EXPOSURE
RELEASE ESTIMATION

Tonnage of substance in Europe	0	[tonnes.yr-1]	O
Regional production volume of substance	0	[tonnes.yr-1]	O

ENVIRONMENT-EXPOSURE
RELEASE ESTIMATION
[1 "SCHER FLUORIDATION", IC=15/UC=39]

Industry category	15/0 Others		D
Use category	39 Biocides, non-agricultural		D
Fraction of tonnage for application	1	[-]	D

ENVIRONMENT-EXPOSURE
RELEASE ESTIMATION
[INDUSTRIAL USE]

Use specific emission scenario	Yes		D
Emission tables	A3.16 (general table), B3.14 (general table)		S
Emission scenario			D
Main category industrial use	III Non-dispersive use		D
Scenario choice for biocides	(5) Drinking water		S
Fraction of tonnage released to air	1E-05	[-]	O
Fraction of tonnage released to wastewater	0.75	[-]	O
Fraction of tonnage released to surface water	0	[-]	O
Fraction of tonnage released to industrial soil	1E-03	[-]	O
Fraction of tonnage released to agricultural soil	0	[-]	O
Fraction of the main local source	1	[-]	O
Number of emission days per year	365	[-]	O
Local emission to air during episode	0	[kg.d-1]	O
Local emission to wastewater during episode	3	[kg.d-1]	O
Intermittent release	No		D

ENVIRONMENT-EXPOSURE
RELEASE ESTIMATION
TOTAL REGIONAL EMISSIONS TO COMPARTMENTS

Total regional emission to air	0	[kg.d-1]	O
Total regional emission to wastewater	0	[kg.d-1]	O
Total regional emission to surface water	0	[kg.d-1]	O
Total regional emission to industrial soil	0	[kg.d-1]	O
Total regional emission to agricultural soil	0	[kg.d-1]	O

ENVIRONMENT-EXPOSURE
PARTITION COEFFICIENTS
SOLIDS-WATER PARTITION COEFFICIENTS

Solids-water partition coefficient in soil	6E-04	[l.kg-1]	S
Solids-water partition coefficient in sediment	1.5E-03	[l.kg-1]	S
Solids-water partition coefficient suspended matter	3E-03	[l.kg-1]	S
Solids-water partition coefficient in raw sewage sludge	9E-03	[l.kg-1]	S

ENVIRONMENT-EXPOSURE
ENVIRONMENT-EXPOSURE
DEGRADATION AND TRANSFORMATION

Characterization of biodegradability	Not biodegradable		D
Degradation calculation method in STP	First order, standard OECD/EU tests		D
Rate constant for biodegradation in STP	0	[d-1]	O
Rate constant for biodegradation in surface water	0	[d-1] (12[oC])	O
Rate constant for biodegradation in bulk soil	6.93E-07	[d-1] (12[oC])	O
Rate constant for biodegradation in aerated sediment	6.93E-07	[d-1] (12[oC])	O
Rate constant for hydrolysis in surface water	6.93E-07	[d-1] (12[oC])	O
Rate constant for photolysis in surface water	6.93E-07	[d-1]	O

SEWAGE TREATMENT
LOCAL STP [1 "SCHER FLUORIDATION", IC=15/UC=39][INDUSTRIAL USE]
OUTPUT

Fraction of emission directed to air by STP	1.85E-08	[%]	O
Fraction of emission directed to water by STP	100	[%]	O
Fraction of emission directed to sludge by STP	3.73E-04	[%]	O
Fraction of the emission degraded in STP	0	[%]	O
Concentration in untreated wastewater	1.5	[mg.l-1]	O
Concentration of chemical (total) in the STP-effluent	1.5	[mg.l-1]	O
Concentration in effluent exceeds solubility	No		O
Concentration in dry sewage sludge	0.0141	[mg.kg-1]	O
PEC for micro-organisms in the STP	1.5	[mg.l-1]	O

ENVIRONMENT-EXPOSURE
DISTRIBUTION
LOCAL SCALE
[1 "SCHER FLUORIDATION", IC=15/UC=39][INDUSTRIAL USE]

Concentration in air during emission episode	1.54E-13	[mg.m-3]	O
Annual average concentration in air, 100 m from point source	1.54E-13	[mg.m-3]	O
Concentration in surface water during emission episode (dissolved)	0.15	[mg.l-1]	O
Annual average concentration in surface water (dissolved)	0.15	[mg.l-1]	O
Local PEC in surface water during emission episode (dissolved)	0.15	[mg.l-1]	O
Annual average local PEC in surface water (dissolved)	0.15	[mg.l-1]	O
Local PEC in fresh-water sediment during emission episode	0.117	[mg.kgwwt-1]	O
Concentration in seawater during emission episode (dissolved)	0.015	[mg.l-1]	O
Annual average concentration in seawater (dissolved)	0.015	[mg.l-1]	O
Local PEC in seawater during emission episode (dissolved)	0.015	[mg.l-1]	O
Annual average local PEC in seawater (dissolved)	0.015	[mg.l-1]	O
Local PEC in marine sediment during emission episode	0.0117	[mg.kgwwt-1]	O
Local PEC in agric. soil (total) averaged over 30 days	1.77E-05	[mg.kgwwt-1]	O
Local PEC in agric. soil (total) averaged over 180 days	8.67E-06	[mg.kgwwt-1]	O
Local PEC in grassland (total) averaged over 180 days	1.91E-06	[mg.kgwwt-1]	O
Local PEC in groundwater under agricultural soil	7.33E-05	[mg.l-1]	O

ENVIRONMENT-EXPOSURE
DISTRIBUTION
REGIONAL AND CONTINENTAL SCALE
CONTINENTAL

Continental PEC in surface water (dissolved)	0	[mg.l-1]	O
Continental PEC in seawater (dissolved)	0	[mg.l-1]	O
Continental PEC in air (total)	0	[mg.m-3]	O
Continental PEC in agricultural soil (total)	0	[mg.kgwwt-1]	O
Continental PEC in pore water of agricultural soils	0	[mg.l-1]	O
Continental PEC in natural soil (total)	0	[mg.kgwwt-1]	O
Continental PEC in industrial soil (total)	0	[mg.kgwwt-1]	O
Continental PEC in sediment (total)	0	[mg.kgwwt-1]	O
Continental PEC in seawater sediment (total)	0	[mg.kgwwt-1]	O

ENVIRONMENT-EXPOSURE
DISTRIBUTION
REGIONAL AND CONTINENTAL SCALE
REGIONAL

Regional PEC in surface water (dissolved)	0	[mg.l-1]	O
Regional PEC in seawater (dissolved)	0	[mg.l-1]	O
Regional PEC in air (total)	0	[mg.m-3]	O
Regional PEC in agricultural soil (total)	0	[mg.kgwwt-1]	O
Regional PEC in pore water of agricultural soils	0	[mg.l-1]	O
Regional PEC in natural soil (total)	0	[mg.kgwwt-1]	O
Regional PEC in industrial soil (total)	0	[mg.kgwwt-1]	O
Regional PEC in sediment (total)	0	[mg.kgwwt-1]	O
Regional PEC in seawater sediment (total)	0	[mg.kgwwt-1]	O

ENVIRONMENT-EXPOSURE
BIOCONCENTRATION

Bioconcentration factor for earthworms	??	[l.kgwwt-1]	D
Bioconcentration factor for fish	??	[l.kgwwt-1]	O

ENVIRONMENT-EXPOSURE
SECONDARY POISONING [1 "SCHER FLUORIDATION", IC=15/UC=39][INDUSTRIAL USE]

Concentration in fish for secondary poisoning (freshwater)	??	[mg.kgwwt-1]	O
Concentration in fish for secondary poisoning (marine)	??	[mg.kgwwt-1]	O
Concentration in fish-eating marine top-predators	??	[mg.kgwwt-1]	O
Concentration in earthworms from agricultural soil	??	[mg.kg-1]	O

ENVIRONMENT - EFFECTS
MICRO-ORGANISMS

Test system	Respiration inhibition, EU Annex V		
C.11, OECD 209	D		
EC50 for micro-organisms in a STP	??	[mg.l-1]	D
EC10 for micro-organisms in a STP	??	[mg.l-1]	D
NOEC for micro-organisms in a STP	??	[mg.l-1]	D
PNEC for micro-organisms in a STP	??	[mg.l-1]	O
Assessment factor applied in extrapolation to PNEC micro	??	[-]	O

ENVIRONMENT - EFFECTS
FRESH_WATER ORGANISMS

LC50 for fish	51	[mg.l-1]	S
L(E)C50 for Daphnia	14.6	[mg.l-1]	S
EC50 for algae	123	[mg.l-1]	S
LC50 for additional taxonomic group	??	[mg.l-1]	D
NOEC for fish	4	[mg.l-1]	S
NOEC for Daphnia	4	[mg.l-1]	S
NOEC for algae	40	[mg.l-1]	S
NOEC for additional taxonomic group	??	[mg.l-1]	D
PNEC for aquatic organisms	0.4	[mg.l-1]	O
PNEC for aquatic organisms, intermittent releases	0.146	[mg.l-1]	O

ENVIRONMENT - EFFECTS
MARINE ORGANISMS

LC50 for fish (marine)	500	[mg.l-1]	S
L(E)C50 for crustaceans (marine)	10.5	[mg.l-1]	S
EC50 for algae (marine)	82	[mg.l-1]	S
LC50 for additional taxonomic group (marine)	??	[mg.l-1]	D
NOEC for fish (marine)	5.5	[mg.l-1]	S
NOEC for crustaceans (marine)	4.2	[mg.l-1]	S
NOEC for algae (marine)	20	[mg.l-1]	S
NOEC for additional taxonomic group (marine)	??	[mg.l-1]	D
PNEC for marine organisms	0.04	[mg.l-1]	O

ENVIRONMENT - EFFECTS
FRESH-WATER SEDIMENT ORGANISMS

LC50 for fresh-water sediment organism	??	[mg.kgwwt-1]	D
EC10 for fresh-water sediment organism	??	[mg.kgwwt-1]	D
EC10 for fresh-water sediment organism	??	[mg.kgwwt-1]	D
EC10 for fresh-water sediment organism	??	[mg.kgwwt-1]	D
NOEC for fresh-water sediment organism	??	[mg.kgwwt-1]	D
NOEC for fresh-water sediment organism	??	[mg.kgwwt-1]	D
NOEC for fresh-water sediment organism	??	[mg.kgwwt-1]	D
PNEC for fresh-water sediment-dwelling organisms	0.313	[mg.kgwwt-1]	O

ENVIRONMENT - EFFECTS
MARINE SEDIMENT ORGANISMS

LC50 for marine sediment organism	??	[mg.kgwwt-1]	D
EC10 for marine sediment organism	??	[mg.kgwwt-1]	D
EC10 for marine sediment organism	??	[mg.kgwwt-1]	D
EC10 for marine sediment organism	??	[mg.kgwwt-1]	D
NOEC for marine sediment organism	??	[mg.kgwwt-1]	D
NOEC for marine sediment organism	??	[mg.kgwwt-1]	D
NOEC for marine sediment organism	??	[mg.kgwwt-1]	D
PNEC for marine sediment organisms	0.0313	[mg.kgwwt-1]	O

ENVIRONMENT - EFFECTS			
TERRESTRIAL ORGANISMS			
LC50 for plants	??	[mg.kgwwt-1]	D
LC50 for earthworms	??	[mg.kgwwt-1]	D
EC50 for microorganisms	??	[mg.kgwwt-1]	D
LC50 for other terrestrial species	??	[mg.kgwwt-1]	D
NOEC for plants	??	[mg.kgwwt-1]	D
NOEC for earthworms	??	[mg.kgwwt-1]	D
NOEC for microorganisms	??	[mg.kgwwt-1]	D
NOEC for additional taxonomic group	??	[mg.kgwwt-1]	D
NOEC for additional taxonomic group	??	[mg.kgwwt-1]	D
PNEC for terrestrial organisms	0.0473	[mg.kgwwt-1]	O
Equilibrium partitioning used for PNEC in soil?	Yes		O

ENVIRONMENT - EFFECTS			
BIRDS AND MAMMALS			
Duration of (sub-)chronic oral test	28 days		D
NOEC via food for secondary poisoning	??	[mg.kg-1]	O
PNEC for secondary poisoning of birds and mammals	??	[mg.kg-1] O	

ENVIRONMENT - RISK CHARACTERIZATION			
LOCAL [1 "SCHER FLUORIDATION", IC=15/UC=39][INDUSTRIAL USE]			
RCR for the local fresh-water compartment	0.375	[-]	O
RCR for the local fresh-water compartment, statistical method	??	[-]	O
RCR for the local marine compartment	0.375	[-]	O
RCR for the local marine compartment, statistical method	??	[-]	O
RCR for the local fresh-water sediment compartment	0.375	[-]	O
RCR for the local marine sediment compartment	0.375	[-]	O
RCR for the local soil compartment	3.75E-04	[-]	O
RCR for the local soil compartment, statistical method	??	[-]	O
RCR for the sewage treatment plant	??	[-]	O
RCR for fish-eating birds and mammals (fresh-water)	??	[-]	O
RCR for fish-eating birds and mammals (marine)	??	[-]	O
RCR for top predators (marine)	??	[-]	O
RCR for worm-eating birds and mammals	??	[-]	O

ENVIRONMENT - RISK CHARACTERIZATION			
REGIONAL			
RCR for the regional fresh-water compartment	0	[-]	O
RCR for the regional fresh-water compartment, statistical method	??	[-]	O
RCR for the regional marine compartment	0	[-]	O
RCR for the regional marine compartment, statistical method	??	[-]	O
RCR for the regional fresh-water sediment compartment	0	[-]	O
RCR for the regional marine sediment compartment	0	[-]	O
RCR for the regional soil compartment	0	[-]	O
RCR for the regional soil compartment, statistical method	??	[-] O	

HUMAN HEALTH - EXPOSURE ASSESSMENT			
HUMANS EXPOSED VIA THE ENVIRONMENT			
LOCAL SCALE			
Purification factor for surface water	1	[-]	O

HUMAN HEALTH - EXPOSURE ASSESSMENT			
HUMANS EXPOSED VIA THE ENVIRONMENT			
LOCAL SCALE			
CONCENTRATIONS IN INTAKE MEDIA [1 "SCHER FLUORIDATION", IC=15/UC=39][INDUSTRIAL USE]			
Local concentration in wet fish	??	[mg.kg-1]	O
Local concentration in root tissue of plant	??	[mg.kg-1]	O
Local concentration in leaves of plant	??	[mg.kg-1]	O
Local concentration in grass (wet weight)	??	[mg.kg-1]	O
Local concentration in drinking water	0.15	[mg.l-1]	O
Local concentration in meat (wet weight)	??	[mg.kg-1]	O
Local concentration in milk (wet weight)	??	[mg.kg-1]	O

HUMAN HEALTH - EXPOSURE ASSESSMENT
HUMANS EXPOSED VIA THE ENVIRONMENT
LOCAL SCALE
DOSES IN INTAKE MEDIA [1 "SCHER FLUORIDATION", IC=15/UC=39][INDUSTRIAL USE]

Daily dose through intake of drinking water	4.29E-03	[mg.kg-1.d-1]	O
Daily dose through intake of fish	??	[mg.kg-1.d-1]	O
Daily dose through intake of leaf crops	??	[mg.kg-1.d-1]	O
Daily dose through intake of root crops	??	[mg.kg-1.d-1]	O
Daily dose through intake of meat	??	[mg.kg-1.d-1]	O
Daily dose through intake of milk	??	[mg.kg-1.d-1]	O
Daily dose through intake of air	4.41E-14	[mg.kg-1.d-1]	O

HUMAN HEALTH - EXPOSURE ASSESSMENT
HUMANS EXPOSED VIA THE ENVIRONMENT
LOCAL SCALE
FRACTIONS OF TOTAL DOSE [1 "SCHER FLUORIDATION", IC=15/UC=39][INDUSTRIAL USE]

Fraction of total dose through intake of drinking water	??	[-]	O
Fraction of total dose through intake of fish	??	[-]	O
Fraction of total dose through intake of leaf crops	??	[-]	O
Fraction of total dose through intake of root crops	??	[-]	O
Fraction of total dose through intake of meat	??	[-]	O
Fraction of total dose through intake of milk	??	[-]	O
Fraction of total dose through intake of air	??	[-]	O
Local total daily intake for humans	??	[mg.kg-1.d-1]	O

HUMAN HEALTH - EXPOSURE ASSESSMENT
HUMANS EXPOSED VIA THE ENVIRONMENT
REGIONAL SCALE
CONCENTRATIONS IN INTAKE MEDIA

Regional concentration in wet fish	??	[mg.kg-1]	D
Regional concentration in root tissue of plant	??	[mg.kg-1]	D
Regional concentration in leaves of plant	??	[mg.kg-1]	D
Regional concentration in grass (wet weight)	??	[mg.kg-1]	D
Regional concentration in drinking water	??	[mg.l-1]	D
Regional concentration in meat (wet weight)	??	[mg.kg-1]	D
Regional concentration in milk (wet weight)	??	[mg.kg-1]	D

HUMAN HEALTH - EXPOSURE ASSESSMENT
HUMANS EXPOSED VIA THE ENVIRONMENT
REGIONAL SCALE
DOSES IN INTAKE MEDIA

Daily dose through intake of drinking water	??	[mg.kg-1.d-1]	D
Daily dose through intake of fish	??	[mg.kg-1.d-1]	D
Daily dose through intake of leaf crops	??	[mg.kg-1.d-1]	D
Daily dose through intake of root crops	??	[mg.kg-1.d-1]	D
Daily dose through intake of meat	??	[mg.kg-1.d-1]	D
Daily dose through intake of milk	??	[mg.kg-1.d-1]	D
Daily dose through intake of air	??	[mg.kg-1.d-1]	D

HUMAN HEALTH - EXPOSURE ASSESSMENT
HUMANS EXPOSED VIA THE ENVIRONMENT
REGIONAL SCALE
FRACTIONS OF TOTAL DOSE

Fraction of total dose through intake of drinking water	??	[-]	D
Fraction of total dose through intake of fish	??	[-]	D
Fraction of total dose through intake of leaf crops	??	[-]	D
Fraction of total dose through intake of root crops	??	[-]	D
Fraction of total dose through intake of meat	??	[-]	D
Fraction of total dose through intake of milk	??	[-]	D
Fraction of total dose through intake of air	??	[-]	D
Regional total daily intake for humans	??	[mg.kg-1.d-1]	D

HUMAN HEALTH - RISK CHARACTERIZATION
CURRENT CLASSIFICATION

Corrosive (C, R34 or R35)	No	D
Irritating to skin (Xi, R38)	No	D
Irritating to eyes (Xi, R36)	No	D
Risk of serious damage to eyes (Xi, R41)	No	D
Irritating to respiratory system (Xi, R37)	No	D
May cause sensitisation by inhalation (Xn, R42)	No	D
May cause sensitisation by skin contact (Xi, R43)	No	D
May cause cancer (T, R45)	No	D
May cause cancer by inhalation (T, R49)	No	D
Possible risk of irreversible effects (Xn, R40)	No	D