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 opinion by written procedure on 16 May 2011

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).

SCHER

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 the 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.

Scientific Committee members

Ursula Ackermann-Liebrich, Herman Autrup, Denis Bard, Peter Calow, Stella Canna Michaelidou, John Davison, Wolfgang Dekant, Pim de Voogt, Arielle Gard, Helmut Greim, Ari Hirvonen, Colin Janssen, Jan Linders, Borut Peterlin, Jose Tarazona, Emanuela Testai, Marco Vighi.

Contact:

European Commission
DG Health & Consumers
Directorate C: Public Health and Risk Assessment
Unit C7 - Risk Assessment
Office: B232 B-1049 Brussels

Sanco-Sc8-Secretariat@ec.europa.eu

ISSN 1831-4775 ISBN 978-92-79-12781-6
doi:10.2772/38897 ND-AR-09-024-EN-N

ACKNOWLEDGMENTS

The members of the working group are acknowledged for their valuable contribution to the opinion:

Prof. U. Ackermann-Liebrich, University of Basel, CH

Prof. H. Autrup, University of Aarhus, DK (*Chair and Rapporteur human health part*)

Prof. D. Bard, National School of Public Health, Rennes, FR

Prof. P. Calow, University of Sheffield, UK

Prof. W. Dekant, University of Wurzburg, DE

Dr. A. Gard, Montpellier 1 University, FR

Dr. J. Linders, RIVM Bilthoven, NL (*Rapporteur environmental part)*

External experts:

Dr. C. Chambers, SCCS

Dr. P. Verger, EFSA

Dr. H. Przyrembel, EFSA

Prof. J. Ekstrand, Karolinska Institut, Stockholm, SE

ABSTRACT

Fluoride is not an essential element for human growth and development, and for most organisms in the environment.

A large variation in naturally occurring fluoride in drinking water is observed in EU Member States ranging from 0.1 to 8.0 mg/L. Fluoridation of drinking water is recommended in some EU Member States, and hexafluorosilicic acid and hexafluorosilicates are the most commonly used agents in drinking water fluoridation. These compounds are rapidly and completely hydrolyzed to the fluoride ion. No residual fluorosilicate intermediates have been reported. Thus, the main substance of relevance to be evaluated is the fluoride ion (F^-).

Systemic exposure to fluoride through 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 other adverse health effects following systemic fluoride exposure, e.g. carcinogenicity, developmental neurotoxicity and reproductive toxicity; however the application of the general rules of the weight-of-evidence approach indicates that these observations cannot be unequivocally substantiated.

The total exposure to fluoride was estimated for infants, children, and adults from all sources of fluoride, e.g. water based beverages, food, dietary supplements, and the use of toothpaste. Contribution from other sources is limited except for occupational exposure to dust from fluoride containing minerals.

The upper tolerable intake level (UL), as established by EFSA, was exceeded only in the worst case scenario for adults and children older than 15 years of age at a daily consumption of 2.8 L of drinking water, and for children (6-15 years of age) consuming more than 1.5 L of drinking water when the level of fluoride in the water is above 3 mg/L. For younger children (1-6 years of age) the UL was exceeded when consuming more than 1 L of water at 0.8 mg fluoride/L (mandatory fluoridation level in Ireland) and assuming the worst case scenario for other sources. For infants up to 6 months old receiving infant formula, if the water fluoride level is higher than 0.8 mg/L, the intake of fluoride exceeds 0.1 mg/kg/day, and this level is 100 times higher than the level found in breast milk (less than 0.001 mg/kg/day).

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 are less convincing. No obvious advantage appears in favour of water fluoridation as compared with topical application of fluoride. However, an advantage in favour of water fluoridation is that caries prevention may reach disadvantaged children from the lower socioeconomic groups.

In several environmental scenarios it was found that exposure of environmental organisms to levels of fluoride used for fluoridation of drinking water is not expected to lead to unacceptable risks to the environment.

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

Opinion to be cited as:

SCHER, Opinion on critical review of any new evidence on the hazard profile, health effects, and human exposure to fluoride and the fluoridating agents of drinking water – 16 May 2011.

TABLE OF CONTENTS

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 rinses), 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 upper tolerable intake levels (UL) 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 2008a, EFSA 2008b), and by 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 (NRC 2006).

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 to several countries discontinuing drinking water fluoridation and others expanding it.

Besides questioning the practice of intentional water fluoridation itself as being unnecessary or superfluous in the 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. Furthermore, they suggest that the presence of these chemicals in drinking water may cause adverse effects on 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 updated advice on the issue, the Commission considers it necessary to seek the advice of its Scientific Committee on Health and Environmental Risks (SCHER) 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.

In the preparation of this opinion, SCHER considered research articles and reviews published in peer-reviewed journals, reports from regulatory agencies and other organizations, as well as all papers submitted by different stakeholders following a public call on the internet for submission of relevant scientific information. The preliminary opinion was published for public consultation for a period of three months; it was discussed at a public hearing, and additional material was received. The scientific information available to the committee was evaluated using the weight-of-evidence approach developed by the EU Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). In general, the health risks of fluoridation of drinking water have been investigated within different areas such as epidemiologic studies, experimental studies in humans, experimental studies in animals, and cell culture studies. A health risk assessment evaluates the evidence within each of these areas and then weighs together the evidence across the areas to produce a combined assessment. The general rules of the weight-of-evidence approach were used to evaluate the documents on which the opinion is based.

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 (SCCP 2005) 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 consider evidence that has become available after 2005, but also evidence produced before 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 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-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 make a pronouncement as to whether there may be reasons for concern arising from the exposure of humans to fluoride and if so identify exposure scenarios that may give rise to particular concern for any population subgroup.

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.

2. Assess the health and environmental risks that may be associated with the use of the most common drinking water fluoridation agents, 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, whether 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, and the causal factors include microorganisms in dental plaque, fermentable carbohydrates (particularly 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 and occurs as fluoride, e.g. cryolite (Na_3AlF_6). Cryolite (used for the production of aluminium) and rock phosphates (used for the production of fertilizers) have 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. Fluoride has been detected in the ash from the Icelandic volcano eruption, but EFSA 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.

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 variations between and within countries, e.g. Ireland 0.01-5.8 mg /L, Finland 0.1-3.0 mg/L, and Germany 0.1-1.1 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 16th 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 requires that waters which contain more than 1.5 mg/L must be labelled as not suitable for the regular consumption by infants and children under 7 years of age and that by 1st January 2008, natural mineral waters shall, at the time of packaging, comply with the maximum concentration limit set out in Annex I for fluorides of 5 mg/L.

WHO established a guidance value for naturally occurring fluoride in drinking water of 1.5 mg/L based on a consumption of 2 L water/day, and recommended that artificial fluoridation of water supplies should not exceed the optimal fluoride levels of 1.0 mg/L (WHO 2006). In Europe, only Ireland and selected regions in the UK and Spain currently fluoridate drinking water at concentrations ranging from 0.8 to 1.2 mg/L (Mullen 2005). The Council Directive 98/83/EC of 3rd November 1998 (Council Directive 98/83/EC) determined a fluoride level (both natural and as a result of fluoridation) for water intended for human consumption of less than 1.5 mg/L. Recently, the US Department of Health and Human Services recommended a fluoride level in water of 0.7 mg/L "to balance the benefit of preventing tooth decay while limiting any unwanted health effects" (http://www.hhs.gov/news/press/2011pres/01/20110107a.html). The parametric value refers to the residual monomer concentration in the water as calculated according to specifications of the maximum release from the corresponding polymer in contact with the water.

Fluoride intake from food is generally low, except when food is prepared with fluoridated water or salt. However, some teas (e.g. *Camellia sinensis*) represent a significant source of fluoride intake. Fruit and vegetables, milk and milk products, bread and cereals contain between 0.02-0.29 mg/kg (EFSA 2005). Recently, EFSA (2008a, 2008b) has permitted 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 1,500 mg/kg (1,500 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 swallowed per application.

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.

An upper tolerable intake level (UL) of 0.1 mg/kg BW/day for fluoride has been derived by the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) (EFSA 2005) based on a prevalence of less than 5% of moderate dental fluorosis in children up to the age of 8 years as the critical endpoint, i.e. 1.5 mg/day for children 1-3 years of age, and 2.5 mg/day for children aged 4-8 years. For adults, an UL of 0.12 mg/kg BW/day was based on a risk of bone fracture, which converts on a body weight basis into 7 mg/day for populations aged 15 years 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 Department of Health (UK DoH 1994) concluded that 0.22 mg F/kg BW/day was safe.

Several pathologies have been linked to high levels of fluoride exposure but are 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 the 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 the fluoride ion was essentially complete. 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. 2006). $Si(OH)_4$ 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 following 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 sodium fluoride (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 if fluoride is naturally present in drinking water.

Hexafluorosilicic acids used as fluoridating agents may contain some impurities. Concerns have been raised about several heavy metals present as low-concentration impurities in commercial hexafluorosilicic acid. The average concentrations of arsenic, mercury, lead and cadmium present in hexafluorosilicic acid are low – between 10 and 400 mg/kg H_2SiF_6 (CEN 12175-2006). Therefore, fluoridation of drinking water only contributes to a limited extent to the total exposure to these contaminants (expected drinking water

concentrations are between 3.0 and 16.2 ng/L). These calculated concentrations are at least two orders of magnitude below drinking water guideline values for these metals established by WHO and other organizations, and therefore are not regarded as an additional health risk.

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 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 concern is the fluoride ion (F^-) and therefore the identification and the physico-chemical properties of sodium fluoride (NaF) given in Table 1 are considered applicable.

Table 1: Main physico-chemical properties of sodium fluoride (NaF).

Substance	**Sodium fluoride**
Elemental symbol	**NaF**
Ionic form	**Na^+, F^-**
CAS-number	**7681-49-4**
EINECS-number	**231-667-8**
Molecular weight (M)	**42 g/mol (Na: 23; F: 19)**
Melting point (MP)	**ca. 1,000°C**
Boiling point (BP)	**1,700°C**
Vapour pressure (VP)	**133 Pa at 1077°C**
Vapour pressure at 25°C (VP)	**1.97E-5 Pa (conversion by EUSES)**
Water solubility (WS)	**40,000 mg/L at 20°C**
Water solubility at 25°C (WS)	**42,900 mg/L (conversion by EUSES)**
Octanol-water partition (log K_{ow})	**Not appropriate**
Henry's Law constant (H)	**1.93E-8 Pa.m^3/mol (calculation by EUSES)**
Sorption capacity (K_d)	**0.0006–0.03 dm^3/kg (estimation) (Bégin et al. 2003) (see 3.1)**
Removal rate (R)	**1.39E-06 d^{-1} at 12°C (default)**
Bioconcentration factor (BCF)	**Not relevant**

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 occurs as hydrogen fluoride (HF) in the acidic environment of the stomach and is effectively absorbed from the gastrointestinal tract, although there is no proved absorption from the oral cavity. Peak plasma levels are typically seen within 30–60 minutes after ingestion. 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 expected to have low membrane permeability and limited absorption through the skin from dilute aqueous solutions at near neutral pH (such as water used for bathing and showering). This exposure pathway is unlikely to contribute to the fluoride body burden.

3.3.3. Inhalation

No systematic experimental data on the absorption of fluoride after inhalation are 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 of 3 to 10 hours. Fluoride is distributed between the plasma and blood cells, with plasma levels being twice as high as blood cell levels. The saliva fluoride level is about 65% of the level in plasma (Ekstrand 1977). 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 9.5 µg /L, compared to a mean plasma fluoride level of 19-28.5 µg/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 (more than 65 years of age), 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

Dental fluorosis

Dental fluorosis is a well-recognised condition and an indicator of overall fluoride absorption from all sources at a young age. Initially, fluorosis appears as white opaque striations across the enamel surface, and in more severe cases the porous areas increase in size and pitting occurs with secondary discoloration of the surface. The symptoms appear in a dose-response manner. 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. It is the daily total fluoride intake over a prolonged period of time, but only 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 utero*. Mineralisation of the permanent tooth buds starts 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 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 during the period of enamel formation.

Fluorosed enamel is composed of hypomineralized sub-surface 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 the effects of fluoride on the mineralizing matrix (Bronckers et al. 2009).

The EFSA NDA panel considered that an intake of less than 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 (Butler et al. 1985, Fejerskov et al. 1996, Richard et al. 1967). The plot shows a linear dose–response relationship and indicates that fluorosis may occur even 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 for more than 30 years.

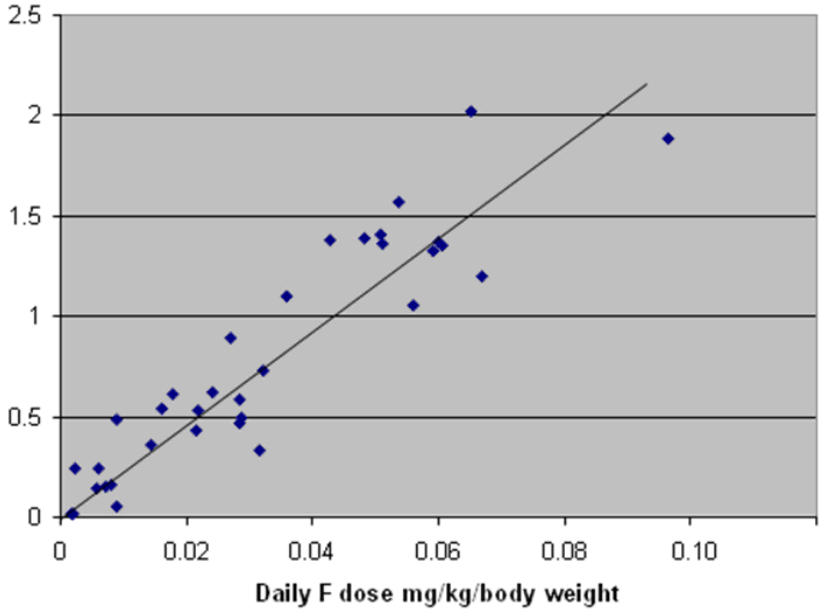

Figure 1: Regression line between Dean's Community Fluorosis Index* and daily fluoride dose from water per kg body weight.

* Individual scores are calculated by multiplying the frequency of each category in the population by the assigned weight. The sum of the weighted scores is then divided by the number of individuals examined (Dean 1942) (see also Fejerskov et al. (1988)).

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. due to high concentration of fluoride in drinking water and indoor burning of fluoride-rich coal resulting in a high indoor fluoride air concentration. In Europe, skeletal fluorosis has only been reported in workers in the aluminium industry, fluorospar processing and superphosphate manufacturing (Hodge and Smith 1977). The study design for most of the available studies is not suitable for estimating the dose-response relationship and development of a N/LOAEL for skeletal fluorosis because of other factors such as nutritional status and climate influence water intake (IPCS 2002).

Effect on bone strength and fractures

A large number of epidemiological studies have 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 proportion of ingested fluoride

will be deposited in the skeleton: up to 90% during the first year of life, which gradually decreases to 50% in children older than 15 years of age. There is no clear association of bone fracture risk with water fluoridation (McDonagh et al. 2000), and fluoridation at levels of 0.6 to 1.1 mg/L may actually lower overall fracture risk (AU-NHMRC 2007). It has been postulated that a high level of 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 (NRC 2006).

Conclusion

SCHER acknowledges that there is a risk for early stages of dental fluorosis in children in EU countries. A threshold cannot be detected.

The occurrence of endemic skeletal fluorosis has not been reported in the EU. SCHER concludes that there are insufficient data to evaluate the risk of bone fracture at the fluoride levels seen in areas with fluoridated water.

4.1.2. Genotoxicity and carcinogenicity

Genotoxicity studies

In general, fluoride is not mutagenic in prokaryotic cells, however sodium and potassium fluoride (500-700 mg/L) induced mutations 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 mutation frequency at the hypoxanthine-guanine phosphoribosyltransferase (HGPRT) locus (200-500 mg F/L). Chromosomal aberrations, mostly breaks/deletions and gaps, following exposure to NaF have been investigated in many *in vitro* assays, but no significant increase in frequency was observed in human fibroblasts at concentrations below 4.52 mg F/L and for Chinese hamster ovary (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 Webster mice (up to 18 mg F/kg BW), however no effects were observed in Swiss Webster mice following oral exposure for at least seven generations compared to low fluoride exposure (EFSA 2005). Fluoride has only been reported to be positive in genotoxicity tests at high concentrations (above 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 sister chromatid exchanges (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.

Carcinogenicity studies

Carcinogenesis studies have been conducted by the US National Toxicology Program (NTP). 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 Sprague Dawley (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 level, and no tumours in female rats.

In a bioassay in B6C3F1 mice receiving the high doses of 8.1 and 9.1 mg F/kg BW/day for males 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 consistent 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.

Epidemiological studies

Early epidemiological studies did not find a consistent relationship between mortality from all types of cancer and exposure for fluoride, including the consumption of fluoride-containing drinking water. Concerns regarding the potential carcinogenic effect of fluoride have been focused on bone cancer due to the known accumulation of fluoride in bones. Osteosarcoma is a rare form of cancer making it difficult to analyse risk factors using epidemiology.

Two studies from the US found a higher incidence of osteosarcoma among males less than 20 years of age living in fluoridated communities compared with non-fluoridated communities (Cohn 1992, Hoover 1991). However, two case-control studies did not find an increase in osteosarcoma in young males consuming fluoridated drinking water (above0.7 mg/L) (Eyre et al. 2009).

A recent study in the UK performed by McNally et al. did not find a statistically significant difference in osteosarcoma rates between areas with fluoride levels of 1 mg/L and those with lower fluoride levels. However, these results are described only in an abstract and the data cannot be assessed. In addition, the relevant age group does not seem to have been studied.

One 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 Harvard Fluoride Osteosarcoma study was conducted as a hospital based case-control study in 11 hospitals in the USA and was limited to subjects below the age of 20. The study consisted of 103 cases and 215 controls matched to the cases. The level of fluoride in drinking water was the primary exposure of interest, and the estimated exposure was on the source of the 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 the local climate, the fluoride exposure estimates were based on Centers for Disease Control and Prevention (CDC) recommendations for optimal target levels for the fluoride level in drinking water. The CDC target level for a warmer climate was 0.7 mg/L and for colder climate was 1.2 mg/L. The exposure estimate was expressed as the percentage of climate-specific target levels in drinking water at each age, and grouped into less than 30%, between 30-99% and above 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 on retrospectively collected data. A statistically significant increased risk was only observed for males exposed at the highest level (above100%) of the CDC optimal target level and when this exposure took place between 6 and 8 years of age. This coincides with the mid-childhood growth spurt in boys. The increased risk remained after adjustment, e.g. socioeconomic factors, use of fluoride products. No increased risk was observed in females. A preliminary conclusion was based upon an intermediate evaluation and further research was recommended to confirm or refute the observation that fluoride exposure was associated with development of osteosarcoma.

Conclusion

SCHER agrees that epidemiological studies do not indicate a clear link between fluoride in drinking water, and osteosarcoma and cancer in general. There is no evidence from animal studies to support the link, thus fluoride cannot be classified as carcinogenic.

4.1.3. Neurotoxicity

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 BW/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 which female rats were given doses of fluoride up to 11.5 mg/kg BW/day for 8 months, no significant differences 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 ingestion of fluoride at levels more than 200 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. The available information is inconsistent and no effects on the thyroid were observed in long-term studies with fluoride in rats. Apparently, fluoride does not interfere with iodine uptake into the thyroid. However, after long-term exposure to high fluoride content in food or water, the thyroid glands of some animals have been found to contain increased fluoride levels (EFSA 2005).

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 levels 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 in areas where there are likely to be less stringent controls over water quality. Thus it cannot be excluded that the water supply may be contaminated with other chemicals such as arsenic, which may affect intelligence quotient (IQ). The studies 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, and parents level of education 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 does not follow classical methodology of meta-analysis and only uses un-weighted means of study results without taking into account the difference between cross-sectional and case-control studies. Thus it does not comply with the general rules of meta-analysis. Furthermore the majority of these studies did not account for major confounders, a problem that cannot be solved in a summary.

Wang et al. (2007) carried out a study on the intelligence and fluoride exposure in 720 children between 8 and 12 years of age from a homogenous rural population in the Shanxi province, China. Subjects were drawn from control (fluoride concentration in drinking water 0.5 mg/L, n=196) and high fluoride (8.3 mg/L) areas. The high fluoride group was sub-divided according to arsenic exposure; low arsenic (n=253), medium arsenic (n=91), and high arsenic (n=180). The IQ scores in the high-fluoride group were significantly reduced compared to the control group, independent of arsenic exposure. The influence of socio-economic and genetic factors cannot be completely 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 three rural communities in Mexico with different levels of fluoride (0.8 mg/L, 5.3 mg/L and 9.4 mg/L; in the latter setting children were supplied with bottled water) and arsenic in drinking water. The children's 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 the type of water used for cooking (tap or bottled), health conditions, etc., was obtained by questionnaire. An inverse association was observed between fluoride in drinking water and IQ after adjusting for relevant confounding variables, including arsenic.

Conclusion

Available human studies do not clearly support the conclusion that fluoride in drinking water impairs children's neurodevelopment at levels permitted in the EU. 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. The limited animal data can also not support the link between fluoride exposure and neurotoxicity at relevant non-toxic doses.

SCHER agrees that there is not enough evidence to conclude that fluoride in drinking water at concentrations permitted in the EU may impair the IQ of children. SCHER also agrees that a biological plausibility for the link between fluoridated water and IQ has not been established.

4.1.4. Reproductive and developmental effects

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 to male rats in drinking water at levels of 2, 4, and 6 mg/L for 6 months adversely affected their fertility and reproductive system (Gupta et al. 2007). In addition, in male Wistar rats fed 5 mg/kg BW/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 caused 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 more than5.2 mg F/kg BW/day on days 6-15 after mating, no sign of adverse effect on pregnancy and implantation was

observed. Sperm mobility and viability were reduced in both mice and rats after 30 days of administration of 4.5 and 9.0 mg F/kg BW/day (ATSDR 2003).

Serum testosterone increased in rats after drinking water with a fluoride content of 45 and 90 mg/L for 2 weeks. Thereafter the level of serum testosterone decreased and was no different from the controls after 6 weeks. No effect was observed on several reproductive parameters in rats receiving up to 90.4 mg F/L for 14 weeks.

Human studies

The National Health Service (NHS) review on Public Water Fluoridation (McDonagh et al. 2000) did not find any evidence of reproductive toxicity in humans attributable to fluoride. Since then, no new evidence seems to be available other than abstracts without methodological details.

There is slight evidence that a high level of occupational exposure to fluoride affects male reproductive hormone levels. A significant increase in follicle-stimulating hormone ($p<0.05$) 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 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-Pérez et al. 2003). The alteration in the reproductive hormone levels after occupational fluoride exposure is not relevant for drinking water exposure.

Conclusion

There is no new evidence from human studies indicating that fluoride in drinking water influences male and female reproductive capacity. Few human studies have suggested that fluoride might be associated with alterations in reproductive hormones and fertility, but limitations in the study design make them of limited value for risk evaluation. Many experimental animal studies are of limited quality and no reproductive toxicity was observed in a multi-generation study.

SCHER concludes that fluoride at concentrations in drinking water permitted in the EU does not influence the reproductive capacity.

4.2. Question 1-b

Conduct an integrated exposure assessment of 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 hygiene products.

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 for the general population in the EU. However in some industrial areas exposure may occur, but no systematically collected data are available.

At present, there are no reliable biomarkers to assess fluoride exposure. Fluoride in blood, nails and hair samples has not been investigated systematically with respect to their use as an exposure biomarker. Urine is commonly used to measure fluoride exposure but is unreliable because of fluctuations in urinary flow and pH which will

influence fluoride output. Past fluoride exposure is also a factor that influences the urinary fluoride output due to the large fraction of fluoride accumulated in the bone that is slowly released. Measurement of plasma fluoride will only give information on recent fluoride intake.

4.2.1. Exposure to fluoride according to its source

Exposure to fluoride from food and water-based beverages

There are no new EU data on fluoride in food. The level will to a large extent depend on the fluoride concentration naturally present in, or artificially added to, the water used for processing. In lieu of new data, EFSA considered the German background exposure to fluoride from food based on intake of milk, meat, fish, eggs, cereals, vegetables, potatoes and fruit still to be valid. The exposure corresponds to 0.042, 0.114 and 0.120 mg/day for young children, older children, and adults, respectively (EFSA 2005). Exposure to fluoride from fruit juice, soft drinks, and mineral water was considered to be 0.011 and 0.065 mg F/day for younger and older children, respectively.

The current assessment of 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, i.e. coffee, tea, cocoa, ranges from about 400 mL to about 1,950 mL with a median value of 1,321 mL/day/person. These figures are consistent with the default value for water consumption (2,000 mL/day) used by WHO. The value for total consumption of liquids across European countries ranges from about 700 mL/day/person at the lowest reported mean to about 3,800 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 will thus mainly be driven by the level of fluoride in water for which the variability is about a factor of 30 (low fluoride levels in Germany vs. high fluoride levels in Finland).

The major sub-categories of water-based beverages are soft drinks, bottled water, stimulants, and tap water. The highest 97.5th percentiles for the consumption of a single category are 2,950, 2,400, 2,800 and 2,500 mL/day per adult respectively for tap water in Austria, stimulants in Denmark, soft drinks in Slovakia, 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 three other categories of water-based beverages for the whole population. Total consumption ranged from 3,300 to 3,800 mL/day/person.

Based on reported consumption of water-based beverages, several scenarios have been developed. Scenario 1 corresponds to the median of mean consumption for all water-based beverages across European countries (1,321 mL) with the mean occurrence level of fluoride (0.1 mg/L). Scenarios 2 and 3 correspond to the highest consumption for high consumers of one of the relevant categories (3,773 mL) with the mandatory water fluoridation in Ireland (0.8 mg/L) (scenario 2) and the WHO guideline value for fluoride in drinking water (1.5 mg/L) (scenario 3).

Scenario 4 is a worst-case scenario based on the highest 97.5th percentile for consumption of tap water (2,950 mL in 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 (older than 15 years of age) in the different scenarios is shown in Table 2.

Table 2: Adult and children (above 15 years of age) systemic exposure to fluoride from water-based beverages*.

Scenario	Consumption (mL/day)	Concentration of F (mg/L)	Exposure (mg/day)
1	1,321	0.1	0.13
2	3,773	0.8	3.02
3	3,773	1.5	5.66
4	2,800	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 are sparse. The consumption data of drinking water and other water based products used by EFSA (2005) are from 1994 and seem to be low (under 500 mL for children less than 12 years old and under 600 mL/day for children aged between 12 and 15 years).

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 compounds which are most commonly incorporated into toothpaste are sodium fluoride, sodium monofluoro-phosphate and stannous fluoride. Other over-the-counter oral hygiene products containing fluoride include mouthwashes, chewing gums, toothpicks, gels and dental floss.

These may contain up to a maximum of 1,500 mg F/kg (0.15% F). Toothpaste with lower fluoride content has been introduced onto the market to reduce fluoride ingestion by young children in order to minimize the risk of fluorosis. However, there is no evidence for its caries-reducing effect. Toothpaste containing a higher concentration of fluoride (more than 1,500 mg F/kg) is only available by prescription for patients with a high risk of dental caries.

It is estimated that in adults less than 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 ingestion has been reported to be as high as 48% in 2 to 3 year olds, 42% in 4 year olds, 34 in 5 year olds, and 25% in 6 year olds. In children aged between 8 and 12 years, the ingestion is reported to be around 10% (Ellewood et al. 2008). The recommended quantity of toothpaste per application is "pea size" (about 0.25 g), whereas the application corresponding to the length of the tooth brush head is considered a worst-case situation (0.75 g).

Table 3: 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 conc. (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.

Prescribed 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 fluoride supplements 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 mg) and fluoride containing chewing gums are available in some EU Member States.

Dietary supplements and fluoridated salts

Calcium fluoride can be added as a dietary supplement: 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 monofluorophosphate can be added as a dietary supplement: amounts between 0.25 and 2 mg fluoride per day have been considered to be safe (EFSA 2008b). Limits for the dietary supplements have not yet been set.

A value of 0.25 mg F/day from dietary supplements was used in the integrated fluoride exposure assessment described below because it is highly unlikely that these supplements will be used in areas with fluoridated water, or that both food supplements are used at the same time.

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

4.2.2. Integrated exposure to fluoride from all major sources

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

In order to achieve an integrated fluoride exposure assessment from all sources previously discussed, water, food and toothpaste are aggregated. Since the ingested fluoride ion is readily absorbed, it is assumed that there is 100% systemic bioavailability. Medicinal supplementation is not included in these assessments.

Four scenarios were used for the current assessment of exposure to fluoride from drinking water based on the EFSA concise database, compiling the results of consumption surveys across European countries (see Table 2). However, this database is only for adult exposure.

EFSA (2005) considered the German background exposure to fluoride from food based on intake of milk, meat, fish, eggs, cereals, vegetables, potatoes and fruit still to be valid. The fluoride concentration in food may be naturally present or acquired through food processing. In addition, EFSA (2008 a, 2008b) approved the addition of calcium fluoride and sodium monofluorophosphate for nutritional purposes as a source of fluoride in food by dietary supplementation to create supplemented foods.

Oral hygiene products (mainly toothpaste) are a further variable source of fluoride depending on four variables; the fluoride concentration of the toothpaste, the quantity applied to the toothbrush, the number of times teeth are brushed daily and the amount ingested after brushing and rinsing the teeth (see Table 3). The amount ingested after brushing is critical as it then becomes systemically available.

Exposure of adults and children above 15 years of age

Estimated fluoride exposures, from Table 2 for water-based beverages for adults and children (older than 15 years of age) in the different scenarios are used, and account for 18-95% of the total fluoride intake.

The fluoride intake from food and supplemented food with dietary additives is 0.37 mg/day (0.12 mg/day food and 0.25 mg/day fluoride supplemented food; EFSA 2005, EFSA 2008a, EFSA 2008b) and accounts for less than 1-6% of the total fluoride intake.

For these scenarios, also factored is ~10% systemically available fluoride from "adult" 0.15% F toothpaste. Thus 0.075 mg F/day is systemically available from 0.5 g/day (low end) toothpaste application and 0.225 mg F/day from 1.5 g/day (high end) toothpaste application.

Table 4: The aggregated daily systemic exposure to fluoride (mg/day) for adults and children older than 15 years of age.

Column A Fluoride levels estimated in water and water-based beverages from the scenarios in Table 2.

Column B Aggregated fluoride from water and food (the sum of fluoride intake from water given in Column A and fluoride intake from food of 0.37 mg F/day).

Column C Aggregated fluoride from water (Column A), food (0.37 mg F/day) and 0.075 mg F/day from toothpaste application (low end).

Column D Aggregated fluoride from water (Column A), food (0.37 mg F/day) and 0.225 mg F/day from toothpaste application (high end).

	F intake from water (mg/day)	**Aggregated F intake (mg/day): water and food**	**Aggregated F intake (mg/day): water, food, toothpaste 0.075 mg F/d**	**Aggregated F intake (mg/day): water, food, toothpaste 0.225 mg F/d**
Scenario	**A**	**B**	**C**	**D**
1	0.13	0.50	0.58	0.73
2	3.02	3.39	3.47	3.62
3	5.66	6.03	6.11	6.26
4	8.40	8.77	8.85	9.00

All calculations are rounded to 2 decimal places.

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

Exposure of children under 15 years old

This group is split into three age groups, children from 12-15 years old, children from 6-12 years old and children from 1–6 years old. For all age groups, data were sparse and there was the additional factor of behavioural development.

Calculations for the exposure to fluoride are performed for four different fluoride concentrations in water ranging from 0.1 mg/L to 3.0 mg/L. Since current data on water consumption for this age group are not available, the calculations are based on three different levels of daily consumption of water: 0.5 L, 1.0 L, and 1.5 L.

It must be noted that the EFSA estimates for total fluoride exposure of children in these age groups are limited, but were used to estimate the fluoride intake from food and supplemented food with dietary additives (EFSA 2005, EFSA 2008a, EFSA 2008b).

The contribution from fluoride toothpaste is variable, depending on how well the spitting response is developed. When well developed, ~10% of the toothpaste (systemically available fluoride) is ingested and if not developed, ~40% of the toothpaste (systemically available fluoride) is ingested. The fluoride concentration of the toothpaste and the quantity of toothpaste applied to the toothbrush is critical.

Exposure of children (12-15 years of age)

Estimates of total daily systemic exposure to fluoride for children from 12-15 years old are shown in Table 5. The fluoride intake from food and supplemented food with dietary additives is estimated at 0.43 mg/day (0.114 mg/day food, 0.065 mg/day water-based beverages and 0.25 mg/day dietary supplements; EFSA 2005, EFSA 2008a, EFSA 2008b).

The contribution from toothpaste is calculated for ~10% systemically available fluoride from "adult" 0.15% F toothpaste only, since the spitting and rinsing responses are well developed. Thus 0.075 mg F/d is systemically available from 0.5 g/day (low end) toothpaste application and 0.225 mg F/d from 1.5 g/day (high end) toothpaste application.

Table 5: Aggregated total daily systemic exposure to fluoride (mg/day) for children 12 up to 15 years of age**.**

Column A Fluoride intake from water at 0.1, 0.8, 1.5 and 3.0 mg F/L.

Column B Aggregated fluoride intake from water (Column A) and food (0.43 mg F/day).

Column C Aggregated fluoride intake from water (Column A), food (0.43 mg F/day) and systemically available fluoride (0.075 mg F/day) from the application of 0.15% F toothpaste (low end).

Column D Aggregated fluoride intake from water (Column A), food (0.43 mg F/day) and systemically available fluoride (0.225 mg F/day) from the application of 0.15% F toothpaste (high end).

Drinking water	F intake from water (mg/day)	Aggregated F intake (mg/day): water and food	Aggregated F intake (mg/day): water, food, 0.15% toothpaste	
			Low application 0.075 mg F/day	High application 0.225 mg F/day
	A	B	C	D
0.1 mg F/L				
Consumption 0.5 L	0.05	0.48	0.55	0.70
Consumption 1.0 L	0.1	0.53	0.60	0.75
Consumption 1.5 L	0.15	0.58	0.65	0.80
0.8 mg F/L				
Consumption 0.5 L	0.4	0.83	0.90	1.00
Consumption 1.0 L	0.8	1.23	1.30	1.45
Consumption 1.5 L	1.2	1.63	1.70	1.85
1.5 mg F/L				
Consumption 0.5 L	0.75	1.18	1.25	1.40
Consumption 1.0 L	1.5	1.93	2.00	2.15
Consumption 1.5 L	2.25	2.68	2.75	2.90
3.0 mg F/L				
Consumption 0.5 L	1.5	1.93	2.00	2.15
Consumption 1.0 L	3.0	3.43	3.50	3.65
Consumption 1.5 L	4.5	4.93	5.00	5.15

The estimated UL for children aged 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 bone fracture (EFSA 2005). This reference value was used for children aged 12-15 years despite the fact that not all molars will have erupted. The UL for children aged 12-15 years is only exceeded if 1.5 L water containing 3.0 mg F/L is consumed, and if 0.15% fluoride toothpaste and more than the recommended "pea size" application is used.

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.

Exposure of children (1-12 years of age)

The estimated total daily systemic exposure to fluoride for children between 6-12 years old and 1-6 years old is shown in Tables 6 and 7, respectively. Since current data on water consumption for children are sparse, the estimation of fluoride exposure is based upon water consumption at levels of 0.5 L, 1.0 L and 1.5 L. In warmer countries, the daily water consumption would be higher.

The intake of fluoride from food is estimated to be 0.303 mg/day. This figure is the sum from the following sources: 0.042 mg/day from food; 0.011 mg/day from water based beverages; and 0.25 mg/day from fluoridated dietary supplements(EFSA 2005, EFSA 2008a, EFSA 2008b).

Due to different tooth brushing behaviours, i.e. spitting and rinsing responses, two different exposures were developed for children aged 6-12 years and 1-6 years, respectively.

For children between 6 and 12 years old the contribution from toothpaste is ~10% systemically available fluoridebecause the spitting response is well developed. Both toothpaste for adults (0.15% F) and children (0.05% F) are considered. Thus for the "adult" toothpaste, 0.075 mg F/day is systemically available from 0.5 g/day (low end) toothpaste application and 0.225 mg F/day from 1.5 g/day (high end) toothpaste application, whereas for the "children's" toothpaste, 0.025 mg F/day is systemically available from 0.5 g/day (low end) toothpaste application and 0.075 mg F/day from 1.5 g/day (high end) toothpaste application.

Table 6: Total daily systemic exposure to fluoride (mg/day) for children 6-12 years of age.

Column A	Fluoride intake from water at 0.1, 0.8, 1.5 and 3.0 mg F/L.
Column B	Aggregated fluoride intake from water (Column A) and food (0.30 mg F/day).
Column C	Aggregated fluoride intake from water (Column A), food (0.30 mg F/day) and 0.025 mg F/day from the application of 0.05% F toothpaste (low end).
Column D	Aggregated fluoride intake from water (Column A), food (0.30 mg F/day) and systemically available fluoride (0.075 mg F/day) from either the application of 0.05% F toothpaste (high end) or the application of 0.15% F toothpaste (low end).
Column E	Aggregated fluoride intake from water (Column A), food (0.30 mg F/day) and systemically available fluoride (0.225 mg F/day) from the application of 0.15% F toothpaste (high end).

Drinking water	F intake from water	Aggregated F intake from water and food	Aggregated F intake: water, food, 0.05% toothpaste		Aggregated F intake: water, food, 0.15% toothpaste
			0.025 mg F/day	0.075 mg F/day	0.225 mg F/day
	A	B	C	D	E
0.1 mg F/L					
Consumption 0.5 L	0.05	0.35	0.38	0.43	0.58
Consumption 1.0 L	0.1	0.40	0.43	0.48	0.63
Consumption 1.5 L	0.15	0.45	0.48	0.53	0.68
0.8 mg F/L					
Consumption 0.5 L	0.4	0.70	0.73	0.78	0.93
Consumption 1.0 L	0.8	1.10	1.13	1.18	1.33
Consumption 1.5 L	1.2	1.50	1.53	1.58	1.73
1.5 mg F/L					
Consumption 0.5 L	0.75	1.05	1.08	1.13	1.28
Consumption 1.0 L	1.5	1.80	1.83	1.88	2.03
Consumption 1.5 L	2.25	2.55	2.58	2.63	2.78
3.0 mg F/L					
Consumption 0.5 L	1.5	1.80	1.83	1.88	2.03
Consumption 1.0 L	3.0	3.30	3.33	3.38	3.53
Consumption 1.5 L	4.5	4.80	4.83	4.88	5.03

The UL for children aged between 4 and 8 years is 2.5 mg/day based on a prevalence of less than 5% of moderate dental fluorosis as the critical endpoint (EFSA 2005). This value was used as the reference value for the children aged 6-12 years. Thus the UL for children in the 6-12 years category is exceeded if 1.5 L water containing 1.5 mg F/L is consumed, independent of tooth-brushing behaviour.

The spitting response is not well developed in children aged between 1 and 6 years and ~40% systemic fluoride availability from toothpaste will be used. Toothpastes for children (0.05% F) and for adults (0.15% F) are considered. Thus, for the 0.05% F toothpaste, 0.1 mg F/day is systemically available from 0.5 g/day (low end) toothpaste application and 0.3 mg F/day from 1.5 g/day (high end) toothpaste application. For the 0.15% toothpaste, 0.3 mg F/day is systemically available from 0.5 g/day (low end) toothpaste application and 0.9 mg F/day from 1.5 g/day (high end) toothpaste application.

Table 7: Estimate of total daily systemic exposure to fluoride for children 1 up to 6 years of age.

Column A Fluoride intake from water at 0.1, 0.8. 1.5 and 3.0 mg F/L.

Column B Aggregated fluoride intake from water (Column A) and food (0.30 mg F /day).

Column C Aggregated fluoride intake from water (Column A), food (0.30 mg F /day) and from the application of 0.05% F toothpaste (0.10 mg F /day) low end

Column D Aggregated fluoride intake from water (Column A), food (0.30 mg F /day) and systemically available fluoride (0.30 mg F/day) from either the application of 0.05% F toothpaste (high end) or the application of 0.15% F toothpaste (low end).

Column E Aggregated fluoride intake from water (Column A), food (0.30 mg F /day) and systemically available fluoride (0.9 mg F/day) from the application of 0.15% F toothpaste(high end).

Drinking water	F intake from water	Aggregated F intake from water and food	Aggregated F intake: water, food, 0.05% toothpaste		Aggregated F intake: water, food, 0.15% toothpaste
			0.10 mg F/day	0.30 mg F/day	0.90 mg F/day
	A	B	C	D	E
0.1 mg F/L					
Consumption 0.5 L	0.05	0.35	0.45	0.65	1.25
Consumption 1.0 L	0.1	0.40	0.50	0.70	1.305
Consumption 1.5 L	0.15	0.45	0.55	0.75	1.35
0.8 mg F/L					
Consumption 0.5 L	0.4	0.70	0.80	1.00	1.60
Consumption 1.0 L	0.8	1.10	1.20	1.40	2.00
Consumption 1.5 L	1.2	1.50	1.60	1.80	2.40
1.5 mg F/L					
Consumption 0.5 L	0.75	1.05	1.15	1.35	1.95
Consumption 1.0 L	1.5	1.80	1.90	2.10	2.70
Consumption 1.5 L	2.25	2.55	2.65	2.85	3.45
3.0 mg F/L					
Consumption 0.5 L	1.5	1.80	1.90	2.10	2.70
Consumption 1.0 L	3.0	3.30	3.40	3.60	4.20
Consumption 1.5 L	4.5	4.80	4.90	5.10	5.70

The estimated UL for children under 3 years old is 1.5 mg/day based on a prevalence of less than 5% of moderate dental fluorosis as the critical endpoint (EFSA 2005) and was used for children aged between 1-6 years. Thus, the UL is exceeded if more than 1.0 L water containing 0.8 mg F/L is consumed and tooth-brushing with the 0.15% fluoride toothpaste is included. If 1.5 L of water is consumed at this fluoride concentration, the UL is exceeded even without exposure to toothpaste.

Exposure of infants up to 12 months of age

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 prepare the infant formula products.

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), exposure to fluoride in breast-fed infants is low (less than 0.001 mg/kg/day).

Table 8 shows the wide range of fluoride intake depending on infant's feeding pattern.

Table 8: Estimated systemic fluoride exposure of infants from formulas (simplified from Fomon and Ekstrand (1999).

Drinking water	Infant 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	0.20	0.03	0.03	0.02
0.8	0.80	0.14	0.12	0.10
1.5	1.42	0.24	0.21	0.17
3.0	2.74	0.47	0.41	0.33

*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 of 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.

The fluoride concentration of the water is the main exposure source in formula-fed infants. An infant solely fed with an infant formula prepared using water containing 0.8 mg F/L ingests 0.137 mg F/kg/day compared with 0.001 mg F/kg/day for an infant who is solely breast fed. An accurate assessment of the fluoride intake of infants between 6 and 12 months old has not been addressed as such calculations would be full of assumptions, considering the variability of the different feeding patterns of infants in the EU Member States.

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.

4.2.3. Conclusion

Fluoride in drinking water is the major source of fluoride in the general population. However, in children aged between 2 and 6 years the contribution from the use of fluoridated 1,500 mg/kg toothpaste (1.5% fluoride) can account for up to 25% of the total systemic dose. As the water fluoride concentration increases, the percentage of the daily systemic exposure from fluoride in toothpaste decreases. As a worst case scenario, the daily exposure would be less than 40% (using 0.15% F toothpaste and unsupervised application), and if application is supervised and 0.05% F toothpaste is used, the daily exposure would be less than 10% of systemic fluoride from other sources.

There are no data of sufficiently high quality on sources and levels of fluoride to perform a full uncertainty analysis within the European context. The exposure assessment is very conservative both with respect to the level of fluoride in water either naturally present or artificially added, and the consumption data are based upon 95% of the highest intake of any water-based beverage.

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. Systemic fluoride is easily absorbed and is taken up into the enamel during the period of pre-eruptive tooth formation. The predominant beneficial cariostatic effects of fluoride in erupted teeth occur locally at the tooth surface. This could be achieved by fluoridated toothpaste, fluoride-containing water, fluoridated salt, etc. maintaining elevated intra-oral fluoride levels of the teeth, dental biofilm and saliva throughout the day.

4.3.2. Dental health and fluoridation

Figure 2 indicates that independent of the fluoridation policies across the EU Member States, there has been a consistent decline over time in tooth decay in 12 year old children from the mid-1970s, regardless of whether drinking water, milk or salt are fluoridated.

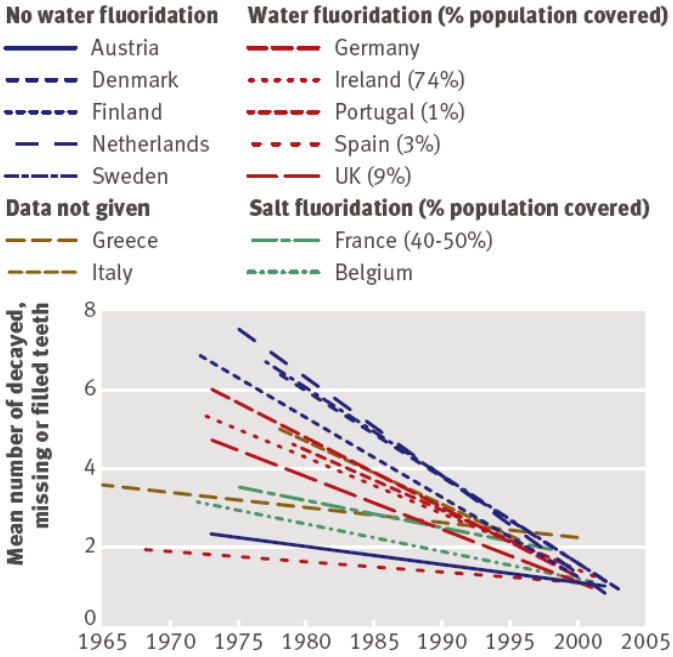

Figure 2 – Trends in tooth decay in 12 year olds in European Union countries (from Cheng et al. 2007).

It should be noted that there is a probable error regarding the figures from Germany because the data were 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, 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 water fluoridation, 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 improved wealth and education in these countries. This suggests that water fluoridation plays a relatively minor role in the improvement of dental health.

The role of fluoride on dental health has been demonstrated by comparing the efficiency of naturally occurring low and high fluoride concentrations in tap water to prevent dental caries. A recent study showed an inverse association between fluoride concentration in non-fluoridated drinking water and dental caries in both primary and permanent teeth in Denmark. The risk was reduced by approximately 20% at the lowest level of fluoride exposure (0.125-0.25 mg/L) compared to less than 0.125 mg, and the reduction was approximately 50% at the highest level of fluoride exposure (more than 1.0 mg/L) (Kirkeskov et al. 2010). The data were adjusted for socio-economic factors.

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 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 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 (UK-CRD 2003), supported by a Canadian review (Locker 1999), with the addition that the effect tends to be more pronounced in the deciduous dentition. The few studies of water fluoridation discontinuation do not suggest significant increases in dental caries.

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 recent review, Health Canada has concluded that the optimal concentration of fluoride in drinking water for dental health was 0.7 mg/L (http://www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/consult/_2009/fluoride-fluorure/consult_fluor_water-eau-eng.pdf).

In a study of students (16-year olds) living on the border between the Republic of Ireland (fluoridated water) and Northern Ireland (non-fluoridated water) 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 (CAWT 2008). 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. Furthermore water fluoridation offers additional benefits over alternative topical methods because its effect does not depend on individual compliance.

The benefits of water fluoridation for adult and elderly populations in terms of reductions in coronal and root decay are limited (Seppä et al. 2000a, Seppä et al. 2000b).

Fluoridated foods and dietary supplements

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 prevalence of 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

[1] DMFT/dmft score is 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.

reduction in the prevalence of 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 the 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).

The effectiveness of fluoride supplemented foods has not been investigated systematically. 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 years (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).

The benefits of preventive systemic supplementations (salt or milk fluoridation) are not proven. There is also only 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).

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 subjects with an adequate spitting response, only a percentage (adults 10%, young children 40%) of the fluoride applied becomes systemically available.

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, Marinho et al. 2003a, Marinho et al. 2003b, Marinho et al. 2003c, Marinho et al. 2004a, Marinho et al. 2004b, Salanti et al. 2009). Comparisons were made with a placebo treatment in children between 5 and 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 in children 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 (Petersson et al. 2004, Twetman et al. 2004) carried out additional reviews on the topic. The results do not challenge the above conclusions.

However, Twetman et al. (2004) point out that long-term studies in age groups other than children and adolescents are still lacking.

4.3.3. Conclusion

Water fluoridation as well as topical fluoride applications (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 effect of 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 helps to prevent caries, 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.

Fluoride is not essential for human growth and development. 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 as the critical endpoint for effect for children aged 1-3 years and 4-8 years, respectively. The estimated UL for children between 9 and 14 years is 5 mg/day extrapolated from the adult tolerable intake level. An UL of fluoride for adults of 7 mg/day was established using increased risk of non-vertebral bone fracture as the critical endpoint (EFSA 2005).

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 (more than 3 L) and living in areas with high natural concentrations of fluoride (more than 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 (less than 0.8 mg/L) did not exceed the UL under normal consumption and usage.

The UL for children 6-12 years old is exceeded if more than 1.0 L water containing 1.5 mg F/L is consumed and tooth-brushing with the 1.5% fluoride toothpaste is unsupervised.

For children aged between 1-6 years, the UL is exceeded if more than 1.0 L water containing 0.8 mg F/L is consumed and tooth-brushing is carried out with the 0.15% fluoride toothpaste. If 1.5 L of water is consumed at this fluoride concentration, the UL is exceeded even without exposure to toothpaste.

The UL for children between 12-15 years of age is exceeded if 1.5 L water containing 3.0 mg F/L is consumed, and if regular 1,500 mg/kg fluoride toothpaste and more than the recommended "pea size" application is used. In these older children, the spitting and rinsing response is better developed, so that ~10% of the fluoride present in toothpaste becomes systemically available.

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

The susceptibility to develop dental fluorosis depends on the timing of the systemic exposure and the uptake of circulating fluoride by developing teeth. Other subpopulations

susceptible to adverse effects of 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) have an increased risk for adverse health effects.

Conclusion

SCHER agrees that for adults and children over the age of 12 years the total intake of fluoride from all major sources is below the upper tolerable intake level (UL) in most parts of EU including areas with fluoridated drinking water, except for those living in areas with water naturally containing fluoride at high concentrations (above 3 mg/L) and with a high intake of water-based beverages.

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

There is no UL for infants up to 12 months of age. As shown in Table 8, when the fluoride concentration in drinking water is above 0.8 mg/L, the exposure to fluoride is estimated to exceed 0.1 mg/kg/day. This amount is 200 times higher than the amount found in breast milk.

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.

Fluoride in drinking water has been shown to have a beneficial effect on caries prevention, but could also induce enamel fluorosis within a very narrow margin of exposure, and the adverse effect depends on the period of exposure – windows of susceptibility.

Several other 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 on these endpoints is of limited quality with inaccurate exposure information, and the observed effects occur only at high exposure levels not relevant for the European situation.

Additional research on potential adverse health effects at realistic EU exposure levels may provide new data to support the risk assessment process.

Exposure assessment is the critical step for health effect studies, thus it is recommended to:

1) Develop and validate new biomarkers for long-term fluoride exposure.
2) Develop standardized methods for exposure assessment integrating all routes of exposure.
3) Collect information on fluoride in food and bioavailability of fluoride.
4) Conduct epidemiological studies, taking advantage of the existing mother-child cohorts 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 such as 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.

4.6.1. Introduction

The adverse effects of fluoride exposure in humans and the benefits for dental health have been discussed in sections 4.1 and 4.4, respectively and will not be discussed further.

As already indicated in section 3.1, the presence of fluorosilicates in drinking water 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 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 besides 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 available this approach would therefore consider the extent to which fluoridation adds to the 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).

The scenario of interest will therefore focus on the environmental exposures arising ofrom the use of fluoridated water as drinking water, personal hygiene, washing clothes and washing dishes. Most of this flows to the environment in drainage water and via sewage treatment works. SCHER did not consider losses due to leakages from water supply pipes and from the use of tap water in irrigation, and therefore soil contamination, since these outputs are not well documented. However, we have focussed on the losses through sewage treatment works. In this route most of the fluorides remain in solution during sewage treatment and pass to the aquatic environment in this way (Walton and Conway 1989). Therefore a negligible amount of fluorides may pass to the terrestrial environment if sludge is spread on land; and/or to atmosphere and land if sludge is subjected to incineration. In the aquatic environment water chemistry will drive distribution between water and sediments. Based on the physico-chemical characteristics of fluoride it is expected that the contamination of soil and the atmosphere are very limited. 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 and Conway 1989) and therefore this will be the focus of the 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 where water is fluoridated. 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 fluoride in water for human consumption of 1.5 mg/L in the EU. 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. Mechanism of action

Fluorides are not essential for most organisms. However, 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. The decrease of toxicity with calcium is mainly due to the formation/ precipitation of innocuous complexes such as $Ca_5(PO_4)_3F$, CaF_2 and MgF_2. An increase in the concentration of chloride ions might elicit a response in organisms for fluoride excretion. Based on observations in natural media, Camargo (2003) concluded that it should be evident that physiological and genetic adaptation to high fluoride concentrations can occur in wild fish populations.

4.6.3. Aquatic effects

The analysis of the aquatic effects was based on a bibliographic search. From this it appeared that the review of Camargo (2003) covered most of the relevant studies validated by the SCHER. Given the good quality of this review, SCHER has therefore based much of the following analysis of the effects on the information cited in this review. Additional information from field studies (Sigler and Neuhold 1972) did not lead to a conclusive safe level. SCHER concluded that the review of Camargo offered sufficient information of good quality to perform a risk assessment for the environment.

Fish

Freshwater

Acute effects

The most valid data available (96h tests with measured concentration) were reviewed by Camargo (2003) and Metcalfe-Smith 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 LC_{50} 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 a generally protective effect of chloride ions, Camargo (2003) listed some toxicity data in his review, which were taken as worst case.

Acute effects
Cyprinodon variegatus: LC_{50} 96h more than 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-Smith et al. (2003). The most sensitive species was an amphipod: *Hyalella azteca,* with an EC_{50} 48h of 14.6 mg F^-/L (measured concentrations) with hardness 140–150 mg $CaCO_3$/L (Metcalfe-Smith et al. 2003).

Chronic effects
Metcalfe-Smith et al. (2003) found an IC_{25} 28d of about 4 mg F^-/L on *Hyalella azteca* growth (calculated from the article data on controlled concentration in spiked sediment and overlaying water).

Marine water

Acute effects
Despite the general protective effect of Cl^- ions, Camargo (2003) reported some toxicity data, the lowest EC_{50} 96h being 10.5 mg F^-/L in the arthropod *Mysidopsis bahia*.

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

Algae

Freshwater

Acute effects
According to Camargo (2003), among algae species for which growth was not stimulated by fluoride ions, the lowest EC_{50} 96h was shown to be 123 mg F^-/L in *Selenastrum capricornutum.*

Chronic effects
In the same species selection, growth of an algae species *Scenedesmus quadricauda* with sensitivity generally similar that of *Selenastrum capricornutum,* 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
As a general observation marine algal species are less sensitive to fluoride ions. The

lowest EC_{50} 96h value of 82 mg F^-/L was shown 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, the growth of some species was inhibited, but at most at 30%. Therefore 50 mg/L can be taken as worst case NOEC 72h for algae.

Conclusion on effects

SCHER agreed to use the ecotoxicological data as presented in Table 11 and considered these data sufficiently reliable to be accepted and used in the risk assessment for the environment. From this data set based on the most sensitive taxa, it is evident that freshwater and marine organisms are of similar sensitivity. Therefore, the PNEC for both freshwater and marine water was derived from the whole data set, applying an Assessment Factor (AF) of 10 to the lowest NOEC. (SCHER and its predecessor do not accept the additional safety factor of 10 from freshwater to marine water stated in the TGD). The most sensitive trophic level is the invertebrate one. The chronic toxicity in *Hyalella azteca* is expressed as IC_{25} (juvenile growth). As the raw data set is not available in the publication, it is not possible to check if this value is close to the LOEC or NOEC. Therefore the data were not used to avoid excessive uncertainty. The chronic toxicity in *Grandidierella sp,* very close to the latter value, was used. It is expressed as MATC (female fecundity), from which an NOEC can be derived according to the REACH guidance (MATC/$\sqrt{2}$).

The PNEC such derived is 0.29 mg/L. However, this value has to be discussed in the light of fluoride ion character as essential oligo-element. Camargo (2003) reported from Connell and Airey (1982) that fluoride concentration below the defined 4.15 mg/L MATC might stimulate *Grandidierella sp* female fecundity. It is also likely that in most of organisms, fluoride ions stimulate growth and reproduction as essential element. Therefore, using a PNEC such derived has no real meaning, as concentrations below toxic concentrations are considered beneficial. In such a view, Camargo (2003) suggested to use ecologically relevant sensitive endpoints as direct quality levels for safe life in freshwater. Net-spinning caddisfly larvae and upstream-migrating adult salmons, living in soft waters with low ionic content, were found to be the most sensitive organisms, affected by fluoride concentrations higher than 0.5 mg/L. So it is assumed that concentrations lower than this threshold are safe for these extremely sensitive organisms, and therefore for aquatic ecosystems.

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

Organism	Endpoint	Value (mg/L)
Freshwater		
Fish (acute) (*Oncorhynchus mykiss)*	LC_{50} (96 h)	51
Invertebrates (acute) (*Hyalella azteca*)	EC_{50} (96 h)	14.6
Algae (acute) (*Selenastrum capricornutum*)	EC_{50} (96 h)	123
Freshwater		
Fish (chronic) (*Acipenser baerii*)	NOEC (90 d)	4
Invertebrates (chronic) (*Hyalella azteca*)	EC_{25} (28 d)	4
Algae (chronic) several species	NOEC (16 d)	50
Marine water		
Fish (acute) (*Cyprinodon variegatus*)	LC_{50} (96 h)	more than 500
Invertebrates (acute) (*Mysidopsis bahia*)	LC_{50} (48 h)	10.5

Algae (acute) (*Skeletonema costatum*)	EC_{50} (96 h)	82
Marine water		
Fish (chronic) (*Mugil cephalus*)	NOEC (113 d)	5.5
Invertebrates (chronic) (*Grandidierella sp.*)	NOEC (90 d) = MATC/√2	2.9
Algae (chronic)several species	NOEC (≥16 d)	50
No-effect in both waters	**PNEC**	**0.29**

Risk characterization

A 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 contain fluoride at 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 3.5 (only 2 if the sensitive species safety threshold is considered) for the fluoride concentration to be reduced below the worst case PNEC of 0.29 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 done by Osterman (1990) and 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 safe threshold of 0.5 mg/L, 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 the European Union System for the Evaluation of Substances (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 addition of fluoride to drinking water is analogous to the addition 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. addition 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 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 0.276 and case 2 to an RCR of 0.517 (see Appendix II).

From these different lines of evidence, SCHER deduces 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 from this source. There is still the possibility of direct soil contamination from leakage from the water supply system and by irrigation using tap water. SCHER was not able to carry out risk assessments here due to lack of exposure data. If there were the possibility of significant exposures in particular sites from these sources then more work would be necessary to asses risk to the soil ecosystem. Atmospheric releases from the incineration of sewage sludge are unlikely.

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 for 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 with systemic fluoride exposure, and a threshold cannot be detected.

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

There is not sufficient evidence linking fluoride in the drinking water to the development of osteosarcoma.

Fluoride intake from drinking water at the level occurring in the EU does not appear to hamper children’s neurodevelopment and IQ levels.

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

There is 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 years living in areas with fluoridated drinking water where the concentration of fluoride does not exceed 0.8 mg/L.

The UL was exceeded in children between 6 and 12 years living in areas with fluoridated drinking water (with levels above 0.8 mg/L) when consuming more than 1 L water/day and using adult toothpaste containing 0.15% fluoride.

The UL is exceeded in children between 1 and 6 years of age living in areas with fluoridated drinking water (at fluoride concentration levels above 0.8 mg/L) when consuming more than 0.5 L water and using adult toothpaste containing 0.15% fluoride. For infants, when the fluoride concentration in drinking water is above 0.8 mg/L, the exposure to fluoride is estimated to exceed 0.1 mg/kg/day.

Water fluoridation as well as topical fluoride applications, 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 beneficial effects of fluoride in caries prevention and the adverse effects of dental fluorosis.

Exposure of environmental organisms to the levels of fluoride used for fluoridation of drinking water is not expected to lead to unacceptable risks to the environment.

6. LIST OF ABREVIATIONS

AF	Assessment factor
AU NHMRC	Australian Government National Health and Medical Research Council
ATSDR	Agency for Toxic Substances and Disease Registry (US)
BW	Body weight
CAWT	Co-operation and Working Together
CDC	Centers for Disease Control and Prevention (US)
CHO	Chinese hamster ovary (cells)
dmft/DMFT	Decayed, missing or filled deciduous/permanent teeth
D(M)FS	Decayed (missing) or filled tooth surfaces
DNA	Deoxyribonucleic acid
ECDC	European Centre for Disease prevention and Control
ECHA	European Chemicals Agency
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
EMEA	European Medicines Evaluation Agency
EU	European Union
EUSES	European Union System for the Evaluation of Substances
F	Fluoride ion
FSH	Follicle-stimulating hormone
HGPRT	Hypoxanthine-guanine phosphoribosyltransferase
IPCS	International Programme for Chemical Safety (WHO)
IQ	intelligence quotient
MATC	Maximum allowable toxicant concentration
NHS	National Health Service
NMR	Nuclear Magnetic Resonance
N/LOAEL	No/lowest observed adverse effect level
NOEC	No observed effect concentration
NRC	National Research Council
NTP	National Toxicology Program (US)
PEC	Predicted environmental concentration
PNEC	Predicted no-effect concentration
PT5	Product-type 5: Drinking water disinfectants from the Biocidal Products Directive 98/88/EC ("BPD")
RCR	Risk characterisation ratio
SCCS	Scientific Committee on Consumer Safety
SCCP	Scientific Committee on Consumer Products
SCE	Sister chromatid exchanges
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SCHER	Scientific Committee on Health and Environmental Risks
SD	Sprague Dawley
SSCP	Scientific committee for consumer products
TGD	Technical guidance documents
TFT	Topical fluoride treatment
Tk	Thymidine kinase
UK	United Kingdom
UK DoH	UK Department of Health
UK COT	UK Committee of Toxicology
UL	Upper tolerable intake level
US	United States
US IOM	US Institute of Medicine
WHO	World Health Organization

7. REFERENCES

ATSDR. 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: Atlanta, Georgia; September 2003.

AU-NHMRC. Australian Government National Health and Medical Research Council: A systematic review of the efficacy and safety of fluoridation. PART A: review of methodology and results. Canberra; 2007.

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

Bégin L, Fortin J, Caron J. Evaluation of the fluoride retardation factor in unsaturated and undisturbed soil columns. Soil Sci Soc Am J 2003; 67:1635-46.

Bronckers AL, Lyaruu DM, DenBesten PK. The impact of fluoride on ameloblasts and the mechanisms of enamel fluorosis. J Dent Res 2009; 88:877-93.

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

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

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

CEN 12175-2006. Chemicals used for treatment of water intended for human consumption – Hexafluorosilicic acid. European Committee for Standardization; July 2006.

Cheng KK, Chalmers I, Sheldon TA. Adding fluoride to water supplies. BMJ 2007; 335:699-702.

Cohn PD. A brief report on the association of drinking water and incidence of osteosarcoma in young males. New Jersey Department of Health Environ. Health Service; 1992, p.1-17.

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

Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption. Official Journal of the European Communities. Available from: URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:330:0032:0054:EN:PDF (accessed 12 May 2011).

CAWT. Cross Border Fluoride Study commissioned by Co-operation and Working Together (CAWT) and jointly conducted by Social and Market Research (SMR) and the School of Dentistry at Queen's University Belfast; 2008. Available from: URL: http://borderireland.info/pubs/BI-01418.pdf (accessed 12 May 2011).

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

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

EFSA. 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 2008a; 882:1-15.

EFSA. 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 2008b; 886:1-18.

Ekstrand J. Fluoride concentrations in saliva after single oral doses and their relation to plasma fluoride. Scand J Dent Res 1977; 85:16-7.

Ellewood R, Fejerskov O, Cury JA, Clarkson B. Fluorides in caries control. In: Fejerskov O, Kidd E, editors. Dental Caries. Copenhagen, Denmark: Blackwell Munksgaard; 2008, Chapter 18.

European Commision (2004) European Union System for the Evaluation of Substances (EUSES) http://ecb.jrc.ec.europa.eu/euses/

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. Epidemiology of bone tumours in children and young adults. Pediatr Blood Cancer 2009; 53:941-52.

Fejerskov O, Baelun V, Manji F, Moller IJ. Dental fluorosis – a handbook for health workers. Copenhagen, Denmark: Munksgaard; 1988.

Fejerskov O, Baelun V, Richards A. Dose-resposonse and dental Fluorosis. In: Fejerskov O, Ekstrand J, Burt B, editors. Fluoride in Dentistry. 2nd ed. Copenhagen, Denmark: Munksgaard; 1996, Chapter 9, p.55-68.

Finney WF, Wilson E, Callender A, Morris MD, Beck LW. Reexamination of hexafluorosilicate hydrolysis by 19F NMR and pH measurement. Environ Sci Technol 2006; 40:2572-7.

Fomon S, Ekstrand J. Fluoride intake by infants. J Public Health Dent 1999; 59:229-34.

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

Götzfried F. Production of fluoridated salt. Schweiz Monatsschr Zahnmed 2006; 116:367-70.

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

Hodge HC, Smith FA. Occupational fluoride exposure. J Occup Med 1977; 19:12-39.

Hoover RN, Devesa SS, Cantor KP, Fraumeni JF Jr. 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, USA: DHHS; 1991, p.F1-F7.

IPCS. Fluorides – Environmetal Health Criteria 227. International Programme on Chemical Safety. Geneva, Switzerland: World Health Organization; 2002.

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

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

Kirkeskov L Kristiansen E, Bøggild H, von Platen-Hallermund F, Sckerl H, Carlsen A, et al. The association between fluoride in drinking water and dental caries in Danish children: Linking data from health registers, environmental registers and administrative registers. Community Dent Oral Epidemiol 2010. [Epub ahead of print]

Locker D. 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; 1999. Available from: URL: http://www.health.gov.on.ca/english/public/pub/ministry_reports/fluoridation/fluor.pdf (accessed 4 May 2011).

Maguire A, Zohouri FV, Mathers JC, Steen IN, Hindmarch PN, Moynihan PJ. Bioavailability of fluoride in drinking water: a human experimental study. J Dent Res 2005; 84:989-93.

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

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

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

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

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

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

Marthaler TM, Petersen PE. Salt fluoridation – an alternative in automatic prevention of dental caries. Int Dent J 2005; 55:351-8.

McDonagh M, Whiting P, Bradley M, Cooper J, Sutton A, Chestnut I, et al. A systematic report on public water fluoridation. NHS Centre for Reviews and Dissemination, University of York. York: York Publishing Services Ltd; 2000. Available from: URL: http://www.nofluoride.com/reports/York%20Review.pdf (accessed 4 May 2011).

Metcalfe-Smith JL, Holtze KE, Sirota GR, Reid JJ, de Solla SR. Toxicity of aqueous and sediment-associated fluoride to freshwater organisms. Environ Toxicol Chem 2003; 22:161-6.

Mullen J. History of water fluoridation. Br Dent J 2005; 199 (7 Suppl):1-4.

NRC. Fluoride in drinking water: a scientific review of EPA's standards. Committee on Fluoride in Drinking Water, National Research Council. The National Academies Press; 2006. Available from: URL: http://www.nap.edu/catalog/11571.html (accessed 4 May 2011).

Ortiz-Pérez D, Rodríguez-Martínez M, Martínez F, Borja-Aburto VH, Castelo J, Grimaldo JI, et al. Fluoride-induced disruption of reproductive hormones in men. Environ Res 2003; 93:20-30.

Osterman JW. Evaluating the impact of municipal water fluoridation on the aquatic environment. Am J Public Health 1990; 80:1230-5.

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

Petersson et al (2004), Petersson LG, Twetman S, Dahlgren H, Norlund A, Holm AK, Nordenram G, et al. Professional fluoride varnish treatment for caries control: a systematic review of clinical trials. Acta Odontol Scand 2004; 62:170-6.

Richard LF, Westmoreland JT, Tashiro M, McKay CH, Morrision JT. Determining optimum fluoride levels for community water supplies in relation to temperature. J Am Dent Assoc

1967; 74:389-97.

Rocha-Amador D, Navarro ME, Carrizales L, Morales R, Calderón J. Decreased intelligence in children and exposure to fluoride and arsenic in drinking water. Cad Saude Publica 2007; 23 Sup 4:S579-87.

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

SCCP. Opinion SCCP/0882/05 on the safety of fluorine compounds in oral hygiene products for children under the age of 6 years. Scientific Committee on Consumer Products; 20 September 2005. Available from: URL: http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_024.pdf (accessed 12 May 2011).

SCCP. 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. Scientific Committee on Consumer Products; 21 January 2009. Available from: URL: http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_169.pdf (accessed 12 May 2011).

Seppä L, Kärkkäinen S, Hausen H. Caries trends 1992-1998 in two low-fluoride Finnish towns formerly with and without fluoridation. Caries Res 2000a; 34:462-8.

Seppä L, Kärkkäinen S, Hausen H. Caries in the primary dentition, after discontinuation of water fluoridation, among children receiving comprehensive dental care. Community Dent Oral Epidemiol 2000b; 28:281-8.

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

Sigler WF, Neuhold JM. Fluoride intoxication in fish: a review. J Wildl Dis 1972; 8:252-4.

Tang QQ, Du J, Ma HH, Jiang SJ, Zhou XJ. Fluoride and children's intelligence: a meta-analysis. Biol Trace Elem Res 2008; 126:115-20.

TGD. 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; 2003.

Thylstrup A, Fejerskov O. Clinical appearance of dental fluorosis in permanent teeth in relation to histologic changes. Community Dent Oral Epidemiol 1978; 6:315-28.

Truman BI, Gooch BF, Sulemana I, Gift HC, Horowitz AM, Evans CA, et al. Reviews of evidence on interventions to prevent dental caries, oral and pharyngeal cancers, and sports-related craniofacial injuries. Am J Prev Med 2002; 23 (1 Suppl):21-54.

Twetman S, Petersson L, Axelsson S, Dahlgren H, Holm AK, Källestål C, et al. Caries-preventive effect of sodium fluoride mouthrinses: a systematic review of controlled clinical trials. Acta Odontol Scand 2004; 62:223-30.

UK-CRD. What the 'York review' on the fluoridation of drinking water really found. Centre for Reviews and Dissemination: York, UK; 2003.

UK-DoH. 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, Department of Health. London, UK: Stationary Office; 1994.

Urbansky ET, Schock MR. Can fluoridation affect lead(II) in potable water? Hexafluorosilicate and fluoride equilibra in aqueous solution. Int J Environ Stud 2000; 57:597-637.

US-IOM. 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, Institute of Medicine. Washington DC, USA: National Academy Press; 1999.

Walton BT, Conway RA. In: Bodek I, Lyman WJ, Reehl WF, Rosenblatt DH, editors. Environmental inorganic chemistry: properties, processes, and estimation methods (Society of Environmental Toxicology and Chemistry). New York, USA: Pergamon Press; 1989.

Wang SX, Wang ZH, Cheng XT, Li J, Sang ZP, Zhang XD, et al. Arsenic and fluoride exposure in drinking water: children's IQ and growth in Shanyin County, Shanxi province, China. Environ Health Perspect 2007; 115:643-7.

Whitford GM, Sampaio FC, Pinto CS, Maria AG, Cardoso VE, Buzalaf MA. Pharmacokinetics of ingested fluoride: lack of effect of chemical compound. Arch Oral Biol 2008; 53:1037-41.

Whitford GM, Whitford, JL, Hobbs SH. Appetitive-based learning in rats: lack of effect of chronic exposure to fluoride. Neurotoxicol Teratol 2009; 31:210-5.

WHO. Guidelines for drinking-water quality. Geneva, Switzerland: World Health Organization; 2006.

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

Appendix I Classification of dental 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 from an excessive intake of fluoride (usually from drinking water)". This is a very simplistic definition since mottling of the enamel of teeth is common and may have many causes including caries, childhood infections, developmental abnormalities and trauma. The generally applied classification of dental fluorosis is shown in Table A 1.

Table A 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 the 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 there is confluence of adjacent lines. **Occlusal surfaces**: Scattered areas of opacity less than 2 mm in diameter and pronounced opacity of the cuspal ridges.
3	**Smooth surface**: Merging and irregular cloudy areas of opacity. Accentuated drawing of the 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 the surface exposed to attrition appear 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) less than 2 mm in diameter.
6	**Smooth surfaces**: Pits are regularly arranged in horizontal bands less than 2 mm in vertical extension. **Occlusal surfaces**: Confluent areas less than 3 mm in diameter exhibit loss of enamel. Marked attrition.
7	**Smooth surfaces**: Loss of outermost enamel in irregular areas involving less than one-half of the 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 more than 1½ or one-half?
9	**Smooth and occlusal surfaces**: Loss of the main part of the enamel with a change in anatomical appearance of the surface. Cervical rim of almost unaffected enamel is often noted.

Appendix II

Case I Operational dose (0.8 mg F^-/L)

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 [1 "", 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])	S			

Rate constant for biodegradation in bulk soil (12[oC])	O	6.93E-07	[d-1]	
Rate constant for biodegradation in aerated sediment (12[oC])	O	6.93E-07	[d-1]	
Rate constant for hydrolysis in surface water (12[oC])	O	6.93E-07	[d-1]	
Rate constant for photolysis in surface water		6.93E-07	[d-1]	O
ENVIRONMENT-EXPOSURE				
SEWAGE TREATMENT				
LOCAL STP [1 "", 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				
RELEASE ESTIMATION				
Tonnage of substance in Europe	O	0	[tonnes.yr-1]	
Regional production volume of substance	O	0	[tonnes.yr-1]	
ENVIRONMENT-EXPOSURE				
DISTRIBUTION				
LOCAL SCALE				
[1 "", 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	O	0.0627	[mg.kgwwt-1]	
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	O	6.27E-03	[mg.kgwwt-1]	
Local PEC in agric. soil (total) averaged over 30 days	O	9.53E-06	[mg.kgwwt-1]	
Local PEC in agric. soil (total) averaged over 180 days	O	4.76E-06	[mg.kgwwt-1]	
Local PEC in grassland (total) averaged over 180 days	O	1.06E-06	[mg.kgwwt-1]	
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)	O	0	[mg.kgwwt-1]	
Continental PEC in pore water of agricultural soils		0	[mg.l-1]	O
Continental PEC in natural soil (total)	O	0	[mg.kgwwt-1]	
Continental PEC in industrial soil (total)	O	0	[mg.kgwwt-1]	
Continental PEC in sediment (total)	O	0	[mg.kgwwt-1]	
Continental PEC in seawater sediment (total)	O	0	[mg.kgwwt-1]	
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 "", 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		2.9	[mg.l-1]	S
NOEC for algae		50	[mg.l-1]	S
NOEC for additional taxonomic group		??	[mg.l-1]	D
PNEC for aquatic organisms		0.29	[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)		50	[mg.l-1]	S
NOEC for additional taxonomic group (marine)		??	[mg.l-1]	D
PNEC for marine organisms		0.029	[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		0.227	[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		0.0227	[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		0.0356	[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 "", IC=15/UC=39][INDUSTRIAL USE]				
RCR for the local fresh-water compartment		0.276	[-]	O
RCR for the local fresh-water compartment, statistical method		??	[-]	O
RCR for the local marine compartment		0.276	[-]	O
RCR for the local marine compartment, statistical method		??	[-]	O
RCR for the local fresh-water sediment compartment		0.276	[-]	O
RCR for the local marine sediment compartment		0.276	[-]	O
RCR for the local soil compartment		2.67E-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 "", 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 "", 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 "", 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 (1.5 mg F^-/L)

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]	[Pa.m3.mol-1]	1.93E-08	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 "", 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-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 (12[oC])	S	0	[d-1]	
Rate constant for biodegradation in bulk soil (12[oC])	O	6.93E-07	[d-1]	
Rate constant for biodegradation in aerated sediment (12[oC])	O	6.93E-07	[d-1]	
Rate constant for hydrolysis in surface water (12[oC])	O	6.93E-07	[d-1]	
Rate constant for photolysis in surface water		6.93E-07	[d-1]	O

ENVIRONMENT-EXPOSURE
SEWAGE TREATMENT
LOCAL STP [1 "", 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 "", 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 1]	0.117	[mg.kgwwt-	
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 1]	0.0117	[mg.kgwwt-	
Local PEC in agric. soil (total) averaged over 30 days 1]	1.79E-05	[mg.kgwwt-	
Local PEC in agric. soil (total) averaged over 180 days 1]	8.93E-06	[mg.kgwwt-	
Local PEC in grassland (total) averaged over 180 days 1]	1.98E-06	[mg.kgwwt-	
Local PEC in groundwater under agricultural soil	7.27E-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) 1]	0	[mg.kgwwt-	
Continental PEC in pore water of agricultural soils	0	[mg.l-1]	O
Continental PEC in natural soil (total) 1]	0	[mg.kgwwt-	
Continental PEC in industrial soil (total) 1]	0	[mg.kgwwt-	
Continental PEC in sediment (total) 1]	0	[mg.kgwwt-	
Continental PEC in seawater sediment (total) 1]	0	[mg.kgwwt-	

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
SECONDARY POISONING [1 "", 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-EXPOSURE				
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		2.9	[mg.l-1]	S
NOEC for algae		50	[mg.l-1]	S
NOEC for additional taxonomic group		??	[mg.l-1]	D
PNEC for aquatic organisms		0.29	[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)		50	[mg.l-1]	S
NOEC for additional taxonomic group (marine)		??	[mg.l-1]	D
PNEC for marine organisms		0.029	[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		0.227	[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		0.0227	[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		0.0356	[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 "", IC=15/UC=39][INDUSTRIAL USE]				
RCR for the local fresh-water compartment		0.517	[-]	O
RCR for the local fresh-water compartment, statistical method	?	?	[-]	O
RCR for the local marine compartment		0.517	[-]	O
RCR for the local marine compartment, statistical method		??	[-]	O
RCR for the local fresh-water sediment compartment		0.517	[-]	O
RCR for the local marine sediment compartment		0.517	[-]	O
RCR for the local soil compartment		5.01E-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 "", 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 "", 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 "", 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