OPINION OF THE SCIENTIFIC COMMITTEE ON COSMETIC PRODUCTS AND NON-FOOD PRODUCTS INTENDED FOR CONSUMERS

CONCERNING

THE SAFETY OF FLUORINE COMPOUNDS IN ORAL HYGIENE PRODUCTS FOR CHILDREN UNDER THE AGE OF 6 YEARS

adopted by the SCCNFP during the 24th plenary meeting
of 24-25 June 2003

1. Terms of Reference

1.1 Context of the question

Currently twenty fluorine compounds are approved as ingredients in cosmetic products and listed in Annex III Part 1. Entries 26 to 42, 47 and 56 allow these fluorine compounds to be used in oral hygiene products up to a maximum authorised concentration in the finished products of 0.15 % (1500 ppm), calculated as fluorine. When one fluorine compound is mixed with other fluorine compounds permitted in Annex III, total F concentration must not exceed 0.15 %.
The Commission has received a request from a Member State for the restriction of the concentration of fluorine compounds in oral hygiene products used by children under the age of 6 years. Although fluorides give an important aid in preventing dental caries, children might absorb an excessive amount of fluorine by swallowing toothpaste. This may cause fluorosis. Therefore, the Member State requests to limit the maximum authorised concentration in oral hygiene products used by children under the age of 6 years to 0.05 % (500 ppm) and to put the following conditions of use and warnings which must be printed on the label :

* The amount of the toothpaste on the brush must have the size of a pea.

* Children must rinse their mouth well and spit out the toothpaste after brushing.

A submission from industry (submission I, dated April 2003), was also forwarded from the Commission to be considered simultaneously by the SCCNFP.

1.2 Request to the SCCNFP

The SCCNFP is requested to answer the following questions:

* Is the use of fluorine compounds in oral hygiene products as regulated in 76/768/EEC safe when used by children under the age of 6 years, taking into account the risk of causing fluorosis?

* Does the SCCNFP propose any restrictions or conditions for the use of fluorine compounds in oral hygiene products for children under the age of 6 years?

1.3 Background

Fluoride in toothpaste is nowadays one of the most important sources for maintaining good oral health. The decline in dental decay began in the early 1970s in most industrialized countries, notably those European countries without water fluoridation. The explanation is the introduction, widespread use and daily exposure to fluoride from toothpaste. Fluoride toothpaste now account for over 90% of toothpaste sales in most economically developed countries. The reduction in caries is mirrored by the significant increase in the use of fluoride toothpaste by the public despite no paralleled reduction in sugar intake.

Ref. : S73

The link between fluoride and enamel changes in teeth was established in 1916. It was suggested that mottled enamel (dental fluorosis) could be related to the high fluoride levels endemic in the

water supply of these areas. Fluoride was then proved to be the cause both in man and in animal studies. About 40 years later it was established that a fluoride concentration of 1 mg/l drinking water gave a good protection of dental caries. Today about 280 million people have access to artificially fluoridated water mainly in the US. A further 300 million people use naturally fluoridated water. Alternatives to water fluoridation have arisen such as fluoride tablets, fluoridated salt and school rinse programs.

Ref.: S12

Fluoride became more available in the US and other industrial countries in the 1970s. Fluoride in infant formula became a problem as a consequence of water fluoridation. Fluoride supplement were recommended at an unsuitable high doses from the early 1960s in the US. Fluorosis only became apparent approximately 10 years later, due to the 6-7year lag-time of tooth development. Following the realisation of the increase in fluorosis in children, especially in the US, a series of studies, in the late 1980s and early 1990s, sought to identify risk factors for dental fluorosis.
Early use of infant formula and fluoridated toothpaste in fluoridated areas, and most significant, the use of fluoride supplements, were found to be risk factors in these studies. During the 1980s, reports from the US indicated an increase in mild forms of dental fluorosis both in fluoridated as well as in non-fluoridated areas. The increase of fluorosis in non fluoridated areas was believed to be a result from the so called 'halo' effect. That is, food products produced in fluoridated areas e.g. soft drinks and ready-meals, in non-fluoridated areas, increase fluoride exposure in some cases.
Accumulating scientific evidence over the last 20 years demonstrates that the cariostatic effect of fluoride is topical on the tooth surface. As a consequence, routine fluoride supplementation for infants and young children in particular has been re- evaluated during the last 10 -15 years.

2. Toxicological Evaluation and Characterisation

2.1. General

2.1.1. Primary names

Table 1 lists the 20 fluorine compounds currently in Annex III Part 1. These are approved as ingredients in oral hygiene products subject to the restrictions and conditions that allow these fluorine compounds to be used up to a maximum authorised concentration in the finished products of 0.15 % (1500 ppm), calculated as fluorine.

Table 1 Fluorine compounds in Annex III Part 1.

The Annex Substance name is given first, the INCI and/or IUPAC names are given only if different.

Annex III number	Substance	CAS no.	EINECS/ ELINECS No	Empirical formula & Mol. weight
26	Ammonium monofluorophosphate (not in INCI)	20859-38-5	-	
27	Sodium monofluorophosphate Disodium monofluorophosphate (IUPAC)	7631-97-2 0163-15-2	231-552-2 233-433-0	Na_2PO_3F 143.95
28	Potassium monofluorophosphate Dipotassium fluorophosphate (IUPAC)	14104-28-0	237-957-0	K_2PO_3F 176.17
29	Calcium monofluorophosphate Calcium fluorophosphate (IUPAC)	7789-74-4	232-187-1	$Ca\ F\ H_2\ O_3\ P$ 138.05
30	Calcium fluoride	7789-75-5	232-188-7	$Ca\ F_2$ 78.08
31	Sodium fluoride	7681-49-4	231-667-8	Na F 41.99
32	Potassium fluoride	7789-23-3	232-151-5	K F 58.10
33	Ammonium fluoride	12125-01-8	235-185-9	NH_4 F 37.05
34	Aluminium fluoride	7784-18-1	232-051-1	$Al\ F_3$ 83.98
35	Stannous fluoride (INCI), Tin difluoride	7783-47-3	231-999-3	$Sn\ F_2$ 156.69
36	Hexadecyl ammonium fluoride Cetylamine hydrofluoride (INCI), Hetaflur (IUPAC)	3151-59-5	221-588-7	$C_{16}H_{35}NHF$ 261.53
37	3-(N-hexadecyl-N-2-hydroxyethyl-ammonio)propylbis (2-hydroxyethyl) ammonium dihydrofluoride, Olaflur (INCI &IUPAC),	6818-37-7	229-891-6	$C_{27}H_{59}N_2O_3F_2$ 498.89
38	N,N',N'-tris(polyoxyethylene)-N-hexadecyl-propylenediamine dihydrofluoride (not in INCI)	-	-	
39	Octadecenyl-ammonium fluoride (not in INCI)	2782-81-2	-	

40	Sodium fluorosilicate (INCI) Disodium hexafluorosilicate (IUPAC)	16893-85-9	240-934-8	F_6-Si-Na_2 188.07
41	Potassium fluorosilicate Dipotassium hexafluorosilicate (IUPAC)	16871-90-2	240-896-2	F_6K_2Si- 220.29
42	Ammonium fluorosilicate Ammonium hexafluorosilicate (IUPAC)	16919-19	240-968-3	$F_6\,Si(NH_4)_2$- 178.19
43	Magnesium fluorosilicate Magnesium hexafluorosilicate (IUPAC)	16949-65-8	241-022-2	$MgSiF_6$ 166.40
47	Nicomethanol hydrofluoride (not in INCI)	62756-44-9	-	C_6H_8FNO 129.13
56	Magnesium fluoride	7783-40-6	231-995-1	MgF_2 62.31

Ref. : S47

2.1.7. Purity, composition and substance codes

No information available on the purity, stability or degradation products of the fluorine compounds used in oral products.

2.1.9. Solubility

Sodium fluoride : 4.22g/100g water at 18°C
Stannous fluoride : 30-39% in water at 20 °C

Ref. : S59, MS15

Magnesium fluoride : 0.009g/100g water or 0.009% in water at 18°C
Calcium fluoride : 0.0015g/100g water at 18°C

Ref. : S59

2.2. Function and uses

Fluorine compounds are used in oral hygiene products to reduce dental caries. They are approved for use in oral hygiene products up to a maximum authorised concentration in the finished product of 0.15% (1500ppm), calculated as fluorine. When a mixture of approved fluorine compounds is used, the total fluorine concentration must not exceed 0.15%. The American Dental Association list only three compounds for use in consumer oral hygiene products: sodium fluoride, stannous fluoride and sodium monofluorophosphate (MFP). No other fluorine compounds were on their list.

Ref. : S2

The ISO 11609 stipulates that the total fluoride concentration shall not exceed the limits by national laws and regulations and in no case shall the total fluoride concentration exceed 0.15%. In addition, this regulation specifies that when using containers, e.g., varieties of dispensing systems, the total fluoride content per single unit shall not exceed 300 mg.

Ref. : S46

In addition, there are medicinal products, such as toothpastes with fluoride concentration over 0.15%, gels and varnishes (used only by dental professionals) and over-the-counter systemic fluoride supplements (in the form of drops or tablets). The supplements have been recommended from birth in some European countries.
Olaflur and dectaflur (9-octadecenylamine hydrofluoride) are used in some prescribed oral hygiene products.

Ref. : S56

TOXICOLOGICAL CHARACTERISATION

2.3. Toxicity

The toxicological data is limited to sodium fluoride, unless specifically stated. No specific studies were presented, so the data has been taken from peer-reviews.

2.3.1. Acute oral toxicity

Animal studies

LD_{50} for sodium fluoride in feeding studies were between 11 and 52 mg/kg in mice and rats. The rat NOAEL is estimated at 1.1 mg/kg bw of sodium fluoride.

Ref. : MS1, MS12

In a 14 day study, rats and mice received sodium fluoride in drinking water at concentrations up to 800 ppm. Deaths occurred 5/5 male and 5/5 female rats and 2/5 male mice in the high-dose group and one female rat at 400 ppm before the end of the studies. No gross lesions were attributed to sodium fluoride administration.
Ref.: S63

Human data

All systems and organs are affected by a high dose of ingested fluoride, which induce at first nausea, abdominal pain, vomiting and diarrhoea, by the action of fluoride on gastro-intestinal mucosa. Death occurs by respiratory or cardiac failure.
Fifteen mg/kg of sodium fluoride has been fatal to humans. After an ingested dose of 5 mg/kg, the subject must be hospitalized.. "Numerous reports of accidental and intentional poisonings with fluoride concluded that a dose range of 5 to 10 grams of sodium fluoride can be cited as a

reasonable estimate of a "certainly lethal (single) dose" for a 70 kg man. They noted that this corresponds from 70 to 140 mg/kg".

Ref. : MS12, MS23

Based on some clinical reports it may be concluded that if a young child, under 6, ingests a fluoride dose in excess of 15 mg fluoride/kg (expressed as F^-), death is likely to occur. Therefore, the probably toxic dose, which can be defined as the threshold dose that could cause serious or life-threatening systemic signs and symptoms and will need immediate emergency treatment is considered to be 5 mg fluoride/kg (expressed as F^-).

Ref. : S86

In the USA, between 1989 and 1994, about 10,000 cases of suspected over-ingestion of fluoridated home use dental products in children from birth to 6 year of age were reported. The outcomes were generally not serious. Of these 10,000 cases, 2,000 were toothpaste-related and caused 1 major, 6 moderate and 387 minor outcomes.

Ref. : S 24

2.3.2. Repeated dose oral toxicity

Animal studies

60 day study

In a 60 day drinking water study, rats received sodium fluoride in as high as 300 ppm, and mice as high as 600 ppm. There were no deaths in rats during the studies. Deaths occurred in mice, (4/9 males, 9/11 females at 600 ppm and 1/8 male at 300 ppm before the end of the studies. Acute nephrosis and/or lesions in the liver and myocardium were observed in these mice. Weight gains were less than those of controls for rats receiving 300 ppm and mice receiving 200 to 600 ppm.
The teeth of rats and mice at the higher doses of sodium fluoride were chalky white and chipped or showed unusual wear patterns. Mice and male rats given the higher concentrations had microscopic focal degeneration of the enamel organ.

2-year study
Two year toxicology and carcinogenesis studies with sodium fluoride 0, 25, 100, and 175 ppm, (11, 45, or 79 ppm fluoride, expressed as F^-) in drinking water for 2 years in drinking water were conducted in F344/N rats (the daily amounts of sodium fluoride ingested were: males, 1.3, 5.2 and 8.6 mg/kg for low dose, mid-dose and high dose respectively, females, 1.3, 5.5 and 9.5 mg/kg for low dose, mid-dose and high dose, respectively) and B6C3F1 mice (the daily amounts of sodium fluoride ingested were: males, 2.4, 9.6 and 16.7 mg/kg for low dose, mid-dose and high dose respectively, females, 2.8, 11.3 and 18.8 mg/kg for low dose, mid-dose and high dose, respectively)of both sexes. These concentrations were selected from previous studies, based on decreased weight gain in rats at 300 ppm and in mice at 200 ppm and above. There was an increased incidence of gastric lesions in rats at 300 ppm in a 6 month study and an absence of significant toxic effects at sodium fluoride concentrations as high as 100 ppm in an earlier 2 year study.

Mean body weights of dosed and control groups of rats and mice were similar throughout the 2-year studies. Survival of rats and mice was not affected by sodium fluoride administration.

Ref. : S63

2.4.1. Irritation (skin)

No data

2.4.2. Irritation (mucous membranes)

Sodium fluoride (20 mg fluoride, expressed as F^-, in a litre solution) has been shown to result in slight disruption of the gastric mucosal layer if dosed whilst fasting. This concentration is equivalent to toothpaste containing 0.1% fluoride, expressed as F^-. Such effects are normally reversible within 24 hours.

Ref. : S79

2.5. Sensitisation

Toothpaste consist of abrasives, cleansing agents, binding agents, flavourings, humectants, preservatives, colouring agents, fluoride salts, antiseptics, sensitivity reducing agents and other, undefined substances, such as herbal extracts

Fluoride salts are still part of epidermal test kits of allergens designed for investigations of allergic reactions associated with toothpaste. The persistence of the suspicion that fluoride is an allergen in toothpaste appears to be based on a limited number of reports on allergic reactions. Only one case in 1967 was confirmed by double blind provocation tests to implicate the fluoride component as the allergen.

Ref. : S6, S54, S13, S39, S40, S19, S20

Allergies associated with the fluoride salts in toothpaste have not been reported in many years and the existence of such reactions has not been confirmed by modern scientific criteria. It is therefore concluded that the incidence of true allergic reactions to fluorides in toothpaste, if existent, is extremely low.

Ref. : S75

2.6. Teratogenicity

Sodium fluoride was administered ad libitum in drinking water to mated NZW rabbits (26/group) on gestation days (gd) 6 through 19 at levels of 0, 100, 200, or 400 ppm (0.1, 0.2, or 0.4 mg/ml). The detection limit of sodium fluoride in drinking water is less than 0.6 ppm. Animals were observed daily for clinical signs of toxicity. Food, water, and body weights were recorded for the animals in each group on gd 0 and every two days thereafter through gd 30. Blood samples were collected from 5 animals per group on gd 20. All animals were killed on gd 30 and examined for maternal body and organ weights, implant status, foetal weight, sex, and morphological development.

The average sodium fluoride/kg body weight/day per the low, mid and high concentration groups was 10, 18 or 29 mg calculated from water intake of animals. The rabbit feed contained an average of 15.6 ppm fluoride (range 14.6-16.6 ppm) and was a secondary source of fluoride

exposure. The average measured fluoride intake from both sources (food and water) was 3, 21, 34 and 52 mg fluoride per animal/day (or 0.8, 6, 9 and 14 mg fluoride/kg body weight/day) for the control through high concentration groups. Water intake provided approximately 84%, 91 % and 95% of the total F^- consumed for the low through high concentration groups in this study.
No maternal mortality occurred and pregnancy rates were similar. Maternal body weight change for the animals receiving 400 ppm sodium fluoride was significantly lower than the controls up to gd 8, but was similar by the end of the experiment.
There was significantly reduced food and water consumption initially. Maternal water consumption (g/kg/day) continued to be significantly decreased in the animals exposed to 400 ppm sodium fluoride, suggesting a possible palatability problem. No clear clinical signs of toxicity were observed. Serum fluoride levels were 0.06 ± 0.04, 0.24 ± 0.10, 0.39 ± 0.14, and 0.70 ± 0.33 ppm at the end of the exposure period for the control to high dose groups respectively. In utero sodium fluoride exposure did not affect the frequency of post-implantation loss, mean foetal body weight per litter, or external, visceral, or skeletal malformations. A NOAEL for maternal toxicity at 200 ppm sodium fluoride in drinking water (approximately 18 mg/kg/day) and a NOAEL for developmental toxicity of 400 ppm sodium fluoride in drinking water (approximately 29 mg/kg/day) was established for NZW rabbits. Effects on teeth were not specified.

Ref. : S63

Fluoride, expressed as F^-, does cross the placenta. Other animal data (dog, rat, mouse) showed defects in teeth in offspring of mothers exposed to high doses of fluoride, (F^-). There were no other significant differences in the occurrence of other congenital defects.

Ref. : S1

Human epidemiological studies have shown no association between the presence of fluorides in drinking-water and the incidence of Down's syndrome.

Ref. : MS15

2.7. Toxicokinetics

Absorption, Distribution & Excretion

The bioavailability of fluoride, (F^-) from all sources has not been studied in young children other than infants up to 420 days.
Readily water-soluble fluoride compounds, such as sodium fluoride tablets or aqueous solutions or that present in toothpaste, are almost completely absorbed via the G.I. tract. The ingestion of fluoride compounds with food inhibits the absorption significantly. In adults, when sodium fluoride tablets are taken with breakfast, the degree of fluoride absorption decreases by 30 to 40%. The timing of fluoride ingestion with respect to fluoride bioavailability is also an important factor. Bioavailability studies in human volunteers on toothpaste absorption have shown that brushing teeth soon after a meal will inhibit the rate and the degree of fluoride absorption. Fluoride enters the bloodstream via non-ionic diffusion from the G.I. tract. In the blood, fluoride is not bound to any blood constituents. Fluoride is not bound to any soft tissue and the fluoride concentration in most soft tissues mirrors that of plasma. Fluoride is accumulated in the bone. Of an ingested fluoride dose given to an adult, during steady state condition, approximately 50% is retained in the bone and the rest is excreted via the kidney. The rate of fluoride excretion via the kidney is predominantly determined by urinary flow but also urinary pH.

Ref. : S28, S29

2.8. Mutagenicity/Genotoxicity

2.8.1. Mutagenicity/Genotoxicity in vitro

Sodium fluoride has been tested extensively for gene mutation induction in *Salmonella typhimurium*. The results have uniformly been negative. Sodium fluoride is mutagenic in cultured mammalian cells and produces transformation of Syrian hamster embryo cells *in vitro.* The reports of *in vitro* cytogenetic studies are mixed, but the preponderance of the evidence indicates that sodium fluoride can induce chromosome aberrations and sister chromatid exchanges in cultured mammalian cells. These mutagenic and clastogenic effects in cultured cells are supported by positive effects in *Drosophila* germ cell tests that measure point mutations and chromosome breakage. *In vivo* tests in rodents for chromosome aberrations provide mixed results that cannot readily be resolved because of differences in protocols and insufficient detail in some study reports to allow a thorough analysis.

Ref. : S63

2.9. Carcinogenicity

Under the conditions of the NTP 2-year drinking water studies, (sodium fluoride at concentrations of 25, 100, or 175 ppm), there was equivocal evidence of carcinogenic activity of sodium fluoride in male F344/N rats, based on the occurrence of a small number of osteosarcomas treated at the two highest dose range. There was no evidence of carcinogenesis in female F344/N rats or in male or female mice at any sodium fluoride concentrations in drinking water for 2 years.

Ref. : S63

Human epidemiological data from more than 30 studies do not indicate any clear exposure-disease relationship. Only studies on water fluoridation and cancer have been considered. The relationship between cancer mortality or incidence and both natural and artificial fluoride in drinking-water has been investigated in a large number of descriptive epidemiological studies of population aggregates, carried out in Australia, Canada, New Zealand, Norway, the United Kingdom and the United States. Because of the uneven distribution of natural fluoride in the earth's crust, and the fact that local communities make independent decisions with regard to fluoridation, some of these studies could be viewed roughly as natural experiments. When proper account was taken of the differences among population units, in demographic composition, and in some cases also in their degree of industrialization and other social factors, none of the studies provided any evidence that an increased level of fluoride in water was associated with an increase in cancer mortality.

Sodium fluoride and the other fluoride salts are classified by IARC as Group 3, (The agent is not classifiable as to its carcinogenicity to humans).

Ref. : MS15

2.10. Special investigations

2.10.1 Mechanism of the cariostatic action of fluoride

Historically, it was believed that fluoride needed to become incorporated into the crystal lattice of enamel in order to effectively prevent the development of dental caries. Fluoride was considered to improve lattice stability and render the enamel less soluble to acid demineralization. Since the incorporation of fluoride into enamel, as partially fluoridated hydroxyapatite, was believed to be essential for its action, fluoride was thought best ingested.
There is now however, an increasing body of evidence to support the fact that the cariostatic activity of fluoride is mainly due to its effects on erupted teeth. The continual presence of fluoride in the saliva and in the fluid phase of dental plaque is critical to its mechanism of action. There is strong evidence that through its interaction with the surface of enamel, fluoride in saliva and dental plaque inhibits the demineralization, and promotes remineralization at the surface of the tooth. Hence, the predominant cariostatic effect is topical directly on the tooth surface.

Ref. : S28, S22

It has also become evident that the dramatic decline of caries in the western world during the last 30 years is primarily attributable to the widespread use of fluoridated toothpaste.

Ref. : S55

2.10.2. Efficacy and dose response

A recent meta–analysis, where over 42,300 children participated in 74 included studies, showed that fluoridated toothpaste resulted in an average 24 % reduction in decayed, missing and filled tooth surfaces in the permanent dentition.

Ref. : S55

This and other meta-analyses have reported that daily use of toothpaste with fluoride is an effective method of preventing caries in permanent teeth of children and adolescents. The effects are dose-related, i.e., toothpastes with a higher concentration of fluoride, 1500 ppm (0.15 % F^-) have a greater cariostatic effect than toothpastes with 1000 ppm (0.1 % F^-) The frequency of use also influences the effectiveness.

Ref. : S81, S66, S21, S22, S55

The effect of fluoride toothpaste on primary teeth has been insufficiently assessed. The scientific literature does not evaluate the preventive effects of fluoride toothpaste on primary teeth except for a few studies.

Ref. : S18, S45, S26

To reduce fluoride ingestion in young children, toothpaste with low F^- concentration (<500 ppm F^-) have been introduced on the market, with the hope of minimizing the risk of fluorosis, However, the efficacy of these low F^- toothpaste is questionable since convincing data on efficacy is lacking. Toothpaste, containing 400 ppm fluoride (F^-) have been available in Australia and New Zealand for approximately 20 years, but have not been tested in clinical trials. No data are available to assess whether toothpaste at this concentration has reduced the prevalence of enamel fluorosis in those countries. In a recent British study a 440 and a 1450 ppm F^- toothpaste were tested in 7,422 children from 12 months to 5-6 years. In the group that received the 1450

ppm F^- toothpaste there was significant less caries compared with the low fluoride paste and controls. There was no difference between the group of children using the low fluoride containing toothpaste (440 ppm F^-) and the control group.

Ref. : S3, S26

In a recent systematic review, the anti-caries efficacy of children's toothpaste containing 600 ppm of fluoride or less was compared with high fluoride toothpaste of 1000 ppm or above. Seven randomised controlled trials were included. In all five clinical trials using 250 ppm fluoride toothpaste, caries increments were greater than in the 1000 ppm groups. Two 500 ppm studies were found, but since no baseline level was presented in one of these studies, a meta-analysis was not carried out on the 500 ppm trials. Based on this and a few other studies, there is, so far, no strong scientific evidence that toothpaste with a fluoride concentration less then 1,000 ppm F (0.1 % F) is sufficient to prevent caries.

Ref. : S55

2.10.3 Fluoride exposure and bioavailability

Diet

The main sources of fluoride exposure are through diet including drinking water and toothpaste. The maximum level of fluoride (F^-) in drinking water is set at 1.5 mg/l by Directive 98/83/EC. In some Member states, drinking water is supplemented with fluoride. This is in line with WHO standards, set in 1984, reviewed in 1993 and currently being reassessed. This level is set irrespective of climate. Bottled mineral waters have been on the market with fluoride levels from 0.5 mg/l up to 9 mg/l, increasing the risk of fluorosis from consuming these mineral waters. Directive 2003/40/EC establishes concentration limits in mineral waters. It states that mineral waters with a fluoride concentration exceeding 1.5mg/l shall bear on the label 'contains more than 1.5mg/l of fluoride: not suitable for regular consumption by infants and children under 7 years of age'. Annex 1 of this directive sets a maximum limit of 5mg/l of fluoride, which if exceeded may pose a risk to public health. Member states shall bring this directive into force by 31 December 2003 at the latest.
Fluoridated salt is available in some Member States.

Ref. : S31,S32

Air

Airborne fluoride exists in gaseous and particulate forms emitted from both natural and anthropogenic sources. The gaseous fluorides include hydrogen fluoride, carbon tetrafluoride, hexafluoroethane and silicon tetrafluoride. Particulate fluorides include cryolite, chiolite , calcium difluoride , aluminum fluoride and sodium fluoride. Fluoride released as gaseous and particulate matter is deposited in the general vicinity of an emission source. The distribution and deposition of airborne fluoride is dependent upon emission strength, meteorological conditions, particulate size and chemical reactivity. Levels may be slightly higher in urban than in rural locations; however even in the vicinity of emission sources the levels of airborne fluoride usually do not exceed a few micrograms/m^3.

Ref. : S1

Sources of fluoride exposure in children

Fluoride exposure and intake in young children (0 – 6 years) are mainly determined by four factors. During the first year of life the major factor that determines the degree of fluoride exposure is the feeding pattern, i.e. if the child is breastfed or fed with water diluted baby formula. The fluoride dose from baby formula diluted with drinking water may be 30 to 150 times greater compared to the fluoride dose the child receive from breast milk.

Ref. : S36

After weaning the major exposure factors are: (i) the fluoride concentration of the drinking water used, (ii) if the child is given fluoride supplement and (iii) the use of fluoridated toothpaste. Studies on fluoride intake in young children are sparse. A few studies have been conducted in North America. There is limited information of fluoride intakes in young children from European countries. The MRC in the UK has recently published a report in which some estimates have been reported on fluoride consumption as related to drinking water. It has not been possible to identify the quantity of water consumed by different age groups. It should be pointed out that fluoride intakes in children from the studies conducted in the US cannot be directly transferred to the European situation. This is because a majority of the population in the US is being exposed to fluoridated water direct or indirect via food and beverages (the halo effect).

Ref. : S58

Table 2 (in Annex) summarise some data on fluoride concentration in infants' food mainly from the US. Similar data from the European market is lacking.

Ref. : S36

Studies on fluoride exposures in infants and young children are summarised in Table3, showing data from USA, Canada, Germany, Australia and New Zealand. The data indicate that the fluoride intake from food may range from 0.01 to 0.17 mg/kg/ day.

Fluoride exposure from toothpaste

Young children may swallow various amounts of toothpaste during brushing.

Ref. : S30, S7, S8, S27, MS6, S15, S77, S78, S61, S62, S50, S9, MS8

The amount of paste applied ranges from 0.05 to up to 0.8 gram, depending whether the toothpaste is applied by the parent or child. The recommended 'pea size' amount of toothpaste is taken as 0.25 gram. Most studies find oral retention figures in young children to be around 30 %. Table 4 shows a calculation of the amount fluoride ingested when a toothpaste of 0.1% or 0.15 % F^- is used. The estimation is based on a 20 or 40 % retention of the amount toothpaste used. The bioavailability factor was set to 100 or 80 %. The calculation shows that the absorbed amount of fluoride may range from as low as 0.03 mg up to as much as 0.15 mg per brushing.

Table 4: Estimated amount of fluoride absorbed (mg) using a 0.10 % or 0.15 % fluoridated toothpaste. 20 % or 40 % was assumed ingested of the applied toothpaste. The calculated numbers are based on an assumption of 100 % or 80 % bioavailability of the fluoride ingested. It should be noted that when tooth brushing is performed after a meal, the bioavailability of fluoride will be reduced considerably.

Paste used (g)	Fluoride concentration %	Fluoride dose F^-(mg)	Retained ingested fluoride dose			
			20 %		40%	
			100 %*	80 %*	100 %*	80 %*
0.10	0.10	0.10	0.02	0.016	0.04	0.03
0.10	0.15	0.15	0.03	0.02	0.06	0.05
0.25	0.10	0.25	0.05	0.04	0.10	0.08
0.25	0.15	0.37	0.07	0.06	0.15	0.12
* = bioavailability :100 % indicate 100 % absorption of swallowed fluoride dose						

Fluorides in dental restorative materials

Fluorides can be released from dental restorative materials, such as glass ionomer cements (polyalkenoates), modified composites and resin-modified glass ionomers containing fluoroaluminosilicate glasses as fillers, or as active ingredients. These products are widely used in young children with primary teeth. Most of the data on fluoride release are based on *in vitro* studies. The release rates of F^- and amounts depend on many variables, such as composition, setting mechanism(s), wear, local pH, consumption of acid soft drinks and other environmental factors. The glass ionomers show an initial burst of fluoride release, whereas the modified materials have a low and sustained level of fluoride release. The amount of fluoride release from dental restorative materials required in order to give a beneficial cariostatic effect is not known. However, this represents an insignificant source when assessing systemic effects.

Manufacturers state that these materials release fluoride, but rarely make direct claims about the therapeutic effect of fluoride release for glass ionomers or related products. To do so would result in the materials being classified in risk group III, according to the EC council directive concerning medical devices (EEC/92/43).

2.10.4 Fluorosis

The mechanisms by which systemic fluoride causes the changes leading to enamel fluorosis are not clear. The development of fluorosis is highly dependent on the dose, duration, and timing of fluoride exposure

Ref. : S4

Dental fluorosis is characterized by an alteration of dental enamel and results in white or in its severe state brownish spots on teeth resulting from hypomineralization and porosity of the enamel The inconvenience is generally more aesthetic than pathological. The first signs are light horizontal and parallel lines, extending progressively to opaque whitish spots, gradually

increasing in size. In severe stages, yellow or brownish spots appear, and, at the ultimate stage, eroded areas.

The effect of systemic fluoride exposure is dependent on the phase of the development of the dentition. Amelogenesis of primary teeth occurs *in utero* and the enamel formation is completed before eruption. For permanent teeth, amelogenesis seems to start approximately 3 months after a full-term birth. It continues slowly for years. Any disturbance, e.g., disease, infection and nutrition, may impair development of enamel in the pre-eruptive tooth. Systemic fluoride may result in fluorosis at this point. From an aesthetic view, the critical phase is from 20 months–5 years during the development of the most visible teeth, the incisors and canines.
Mild fluorosis can be induced by as low as 1 ppm fluoride in drinking water and are frequently seen in children who have been given fluoride supplementation from infancy up to the age of 6. In a French study that included over 6000 children, only one case of moderate fluorosis was seen, about 2.75% presented with very mild to mild fluorosis and a further 8.75% with questionable fluorosis.

Ref. : S33, MS13

During the past 20 years a large number of reports have shown the relation between intake of fluoride and the appearance of fluorosis.

Ref. : MS16, S36, S16, S85

Both water fluoridation studies and fluoride supplement studies indicate that a daily intake of 0.020 mg F^-/kg body weight may result in mild forms of fluorosis in the permanent dentition.

Ref. : S57, S53, S34

Mild form of enamel fluorosis seen in optimally fluoridated (0.7 – 1.2 ppm F) regions has been attributed to early tooth brushing behaviours, inappropriate fluoride supplementation and the use of infant formula in the form of a powdered concentrate.

Ref. : S17, S82, S69, S71, S82, MS22, S63

In several studies it has been shown that enamel fluorosis will occur in a non-fluoridated area and can be attributed to fluoride supplementation and early tooth brushing behaviours. In most studies where mild fluorosis has been recorded in conjunction with fluoridated toothpaste, this has been seen in combination with the use of fluoride supplements.

Ref. : S44, S48, S64, S89, S14, S88, S45, S24, S67, MS14, S49, MS21, S84, MS13

It must be emphasised that most of the studies reported have relied on retrospective assessment of fluoride exposure, often 8 to 10 years after the fluoride exposure occurred. Thus all studies where the use of fluoridated toothpaste has been related to fluorosis are prone to recall bias. Hence, convincing evidence that the use of fluoride toothpaste in young children causes fluorosis is rather weak.

The risk for fluorosis in young children, where the only fluoride exposure is through the recommended use of fluoridated toothpaste, therefore seems to be slight. This small risk must considered to be acceptable in light of the substantial reduction in the caries increment recorded during this period. This is attributed to the topical effect of daily use of fluoridated toothpaste.

Ref. : MS7, MS 9, MS11, MS13

2.11. Safety evaluation

NOT APPLICABLE

2.12. Conclusions

For children, the probable toxic dose, defined as the threshold that could cause serious symptoms and need immediate emergency treatment, is considered to be 5 mg fluoride/kg bw.
The incidence of true allergic reactions to fluorides in toothpaste, if existent, is extremely low. Genotoxic data is inconclusive. Sodium fluoride and the other fluoride salts are classified by IARC as Group 3, not classifiable as to their carcinogenicity to humans.
There are no reports on the teratogenicity of fluoride, other than the effects on teeth in animals.
Readily soluble fluoride compounds are almost completely absorbed systemically via the G.I. tract. In adults, approximately 50% is retained in the bone and the rest is excreted via the kidney. The rate of fluoride excretion via the kidney is determined by urinary flow but also urinary pH.
Amelogenesis of primary teeth occurs *in utero* and the enamel formation is completed before eruption. For permanent teeth, amelogenesis starts approximately 3 months after a full-term birth. It continues slowly for years.
Systemic fluoride may impair normal development of enamel in the pre-eruptive tooth and cause fluorosis.
The predominant cariostatic effect of sodium fluoride is a topical one directly on the tooth surface. Through its interaction with the surface of enamel, fluoride in saliva and dental plaque inhibits the demineralization, and promotes remineralization on the surface of the tooth.
There is, so far, no strong scientific evidence to support that fluoride toothpaste with a fluoride concentration less then 1,000 ppm F (0.1 % F^-) is sufficient to prevent caries.
The incidence of fluorosis increases with consumption of fluoride, and will therefore be higher in areas (member states or geographical areas) where supplementation (e.g. tablets, chewing gums, salts) or water fluoridation are instituted.

There is no scientific evidence of the impact of toothpaste "per se" in such areas. In these specific cases strategies should be implemented to reduce fluoride exposure considering any other source of fluoride.

3. Opinion of the SCCNFP

Based on the available pool of scientific evidence, the SCCNFP is of the opinion that the maximum permitted concentration of 0.15% (1500ppm) fluorine does not pose a safety concern when used by children under the age of 6 years.
The data used in this evaluation were generated from studies primarily on sodium fluoride. Extrapolation of this to the other fluoride compounds presently listed in Annex III can only be made with respect to fluorosis.
There is strong evidence that toothpaste containing 0.15 % (1500 ppm) is effective at preventing dental caries in all age groups, including children under the age of 6. This cariostatic effect decreases as the concentration is reduced. Below 1000 ppm, the cariostatic effect is not established. Further research is recommended in order to assess the effect under 1000 ppm.

If the sole source of fluoride exposure is toothpaste containing fluoride between 1000-1500 F^- ppm, used as recommended, there is minimal risk that children under the age of 6 will develop fluorosis. It is recommended that children under the age of 6 use a pea size amount of toothpaste with supervised brushing.

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Table 2 : Concentrations of Fluoride in infants food (a)

Food Item	Fluoride concentration (microgram/ litre	Reference
Human milk	5 – 10	a
Cow's milk	30 – 60	b
Formula		c
Ready to feed	100 – 300	
Concentrated liquid		
Milk-based	100 - 400	
Isolated Soybean-based	100 - 400	
Powdered		
Milk-based	400 - 1000	
Isolated Soybean-based	1000 - 1600	
Most products other than dry cereals	100 – 300	d
Fruit juices		d
Produced with non-fluoridated water	20 - 200	
Produced with fluoridated water	100 - 1700	
Dry cereals		d
Produced with non-fluoridated water	90 - 200	
Produced with fluoridated water	4000 - 6000	
Wet-pack cereal fruit products	2000 – 3000	d
Poultry-containing products	100 – 5000	d

(a) Fomon & Ekstrand (1993); Fomon et al. (2000)
(b) Esala et al. (1982); Spak et al. (1983); Elstrand et al. (1984)
(c) Ekstrand (unpublished data
(d) Johnson & Bawden (1987); McKnight-Hannes et al. (1988)
(e) Singer & Ophaug (1979);dabeka et al. (1982)

Table 3 Estimated intakes of fluoride

Country or region	*Age group*	*Sources of fluoride exposure*	*Estimated F intake mg/kg bw/day (mean)*	*Comment*	*Ref.*
USA	Children 16-40 months	Food, beverages and toothpaste	0.965 (0.07)	Drinking water level range 0.8-1.2mg F^-/l	S72
Canada	Infants (up to 6 months) Children 7 months - 4 years 5-11 years Adults (20 +years)	Ambient air, 109 foods (including infant formula or breast milk), fluoridated or non-fluoridated drinking water, soil, average F^- in toothpaste	<0.01-65<<0.001-0-09 0.6-2.1 (0.05-0.16) 0.7-2-1(0.03-0-08) 2.2-4.1 (0.03-0-06)	Multimedia exposure analysis using mean F^- concentration ranges as well as assigned reference values for body, inhalation, water consumption, soil and food, by age groups.	S41
USA	Infants (6 months) Children (1 year) Children (2-3 years)	Breast milk or formula Cereal, juices, toothpaste, fluoride supplements	0.4-1.4 (0.05-0.19) 0.32-0.73 (0.03-0.08) 0.76-1.23 (0.06-0.09)	Estimated intakes of F^- in breast milk or infant formulas made with fluoridated or non-fluoridated water, juices, cereals, toothpastes and supplements.	S52
Four regions of the USA	Infants (6 months): Children (2 years old)	Foodstuffs and water <0.3mg F^-/litre water >0.7mgF^-/l water <0.3mg F^-/litre water >0.7mgF^-/l	 0.226 (0.028) 0.418 (0.052) 0.207 (0.017) 0.621 (0.05)	Estimated consumption based on fluoride levels in market basket survey of foods and different drinking-water F^- levels	S68
North America	Children (up to 6 years)	Foods (including infant formulas), beverages, fluoridated or non-fluoridated drinking-water	0.05-l.23 (0.01-0.16)	Summary of 8 studies between 1943 and 1988	S51
Australia	Infants (6 months) Infants (1 year)	Infant formulas made with fluoridated or non-fluoridated drinking-water	0.13-1.35 (0.02-0.17)0.14-1.65 (0.02-0.17)	Estimated intakes from various infant formulas available in Australia	S76
Germany	Infants 1-12 months	Commercial foods and drinking-water	0.099-0.205	Estimate consumption based on food and drinking-water containing 0.13 mg fluoride/litre	S10
Germany	Infants 1-12 months	Breast milk and home prepared food	0.002-0.075 (0.0005-0.007)	Estimated F^- intake in breast milk and infant foods	S11

Table 3. Estimated intakes of fluoride continued

Country or region	Age group	Sources of fluoride exposure and estimated F intake						Comment	Ref
New Zealand	Infants 11 – 13 months, 65 consented, 60 completed study –32 in a fluoridated and 29 in a non-fluoridated area,	Fluoridated n=31			Non-fluoridated n=29			Duplicate-portionfor 3 days; leftovers & parts not eaten removed. Noted how children were fed. Toothpaste usage &supplements were monitored	S23*
		Mean	SD	Range	Mean	SD	Range		
		Food & drinks mg F^-/day							
		0.263	0.131	0.089-0.549	0.082	0.054	0.038-0.314		
		mg F/kg bw							
		0.028	0.013	0.009-0.056	0.009	0.006	0.004-0.038		
		From all sources mg F/day							
		0.305	0.032	0.093-1.299	0.195	0.174	0.039-0.720		
		mg F/kg bw							
		0.033	0.026	0.009-0.150	0.2020	0.017	0.004-0.061		
New Zealand	Children 3 and 4 years, selected for their caries & fluoridation status.. 66 children included	Fluoridated n=34			Non-fluoridated n=32			3x 24-h duplicate plates collected at 6 months intervals. Leftovers, skins and bones etc removed Toothpaste used and swallowed was determined by F^- spat out and left on the brush.	S42*
		Range	Mean± SD	95%CI	Range	Mean± SD	95%CI		
		Diet alone mg F/day mg							
		0.05- 0.31	0.15±0.06	0.13-0.17	0.09-0.74	0.36±0.17	0.30-0.42		
		mg F/kg bw							
		0.004-0.002	0.008±0.003	0.006-0.010	0.004-0.04	0.019±0.009	0.015-0.023		
		Diet and toothpaste F/day mg						and swallowed was	
		0.17-1.21	0.49±0.25	0.41-0.57	0.26-01.31	0.68±0.27	0.59-0.77	Determined by F	
		F/kg bw						spat out and left on	
		0.01-0.06	0.027±0.012	0.023-0.031	0.01-0.07	0.036±0.015	0.030-0.042	the brush.	

* The authors concluded that the current levels of fluoride intake of the infants studied from food and drink alone are not in excess of recommended optimal levels of intake. They noted that the use of toothpaste and supplements could push some infants above the recommended levels.