European Food Safety Authority

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SCIENTIFIC OPINION

Sodium monofluorophosphate as a source of fluoride added for nutritional purposes to food supplements [1]

Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food

(Question No EFSA-Q-2006-277, EFSA-Q-2006-295)

Adopted on 27 November 2008

PANEL MEMBERS

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SUMMARY

Following a request from the European Commission to the European Food Safety Authority (EFSA), the Scientific Panel on Food Additives and Nutrient Sources added to Food (ANS) was asked to provide a scientific opinion on the safety of sodium monofluorophosphate added for nutritional purposes as a source of fluoride in food supplements and on bioavailability of fluoride from this source.

The present opinion deals only with the safety of sodium monofluorophosphate as a source of fluoride and the bioavailability of the fluoride from this source. The safety of fluoride itself, in term of amounts that may be consumed, is outside the remit of this Panel.

Available literature on sodium monofluorophosphate and sodium fluoride suggests that sodium monofluorophosphate is hydrolysed in fluoride and phosphate ions and the Panel concludes that fluoride bioavailability will be to an extent comparable to the one from sodium fluoride. The most sensitive effect of fluoride exposure in humans is dental fluorosis and conclusions of comprehensive evaluations indicate that genotoxicity and carcinogenicity are not of concern for fluoride exposure in humans. Long-term clinical interventions trials have suggested that monofluorophosphate is better tolerated than other common sources of fluoride

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such as sodium fluoride. Based on toxicity data from readily soluble forms of fluoride tolerable upper intake levels (ULs) for fluoride have been established in Europe. The proposed supplementation foresees that sodium monofluorophosphate will be added to food supplements to supply between 0.25 and 2 mg fluoride per day, corresponding to approximately 2.5 to 16 mg sodium monofluorophosphate.

Daily sodium exposure estimates (1.7–14 mg) and phosphate (1.1–8.8 mg) arising from the proposed supplementations with sodium monofluorophosphate would be of no safety concern. Sodium exposure from this source represents at most only 0.3% of the estimated dietary intake of sodium in Europe (4500–11000 mg/day) whereas phosphate exposure would be at most approximately 460 times lower than the Maximum Tolerable Daily Intake (MTDI) of 70 mg/kg bw established for phosphates.

The ANS Panel concludes that the use of sodium monofluorophosphate as food supplement would be of no safety concern provided that fluoride tolerable upper intake levels established in Europe are not exceeded by the combined exposure from food supplements and the diet.

The ANS Panel noticed that most of these proposed levels of supplementation are below tolerable upper intake levels established for different populations in Europe. However, when the potential fluoride contribution of sodium monofluorophosphate supplementation is added to the total fluoride daily exposures estimates in Europe for children, in most cases fluoride tolerable upper intake levels will be exceeded. For adults, the proposed fluoride supplementation levels will not exceed the tolerable upper intake level with the exception of the supplementation value 2 mg/day.

The Panel notes that according to Commission Regulation (EC) No 629/2008 the maximum levels of respectively lead, mercury and cadmium in food supplements as sold should be respectively 3.0 mg/kg, 0.1 mg/kg and 1 mg/kg.

Key words:

Food supplements, sodium monofluorophosphate, disodium fluorophosphates, CAS number 10163-15-2.

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BACKGROUND AS PROVIDED BY THE COMMISSION

The European Community legislation lists nutritional substances that may be used for nutritional purposes in certain categories of foods as sources of certain nutrients.

The Commission has received a request for the evaluation of disodium fluorophosphate added for nutritional purposes to food supplements. The relevant Community legislative measure is:

- Directive 2002/46/EC of the European Parliament and of the Council on the approximation of the laws of the Member States relating to food supplements[2].

TERMS OF REFERENCE AS PROVIDED BY THE COMMISSION

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority to provide a scientific opinion, based on its consideration of the safety and bioavailability of disodium fluorophosphate added for nutritional purposes in food supplements.

ACKNOWLEDGEMENTS

The European Food Safety Authority wishes to thank the members of the Working Group for the preparation of this opinion: F. Aguilar, N Bemrah, P. Galtier, J. Gilbert, S. Grilli, R. Guertler, G.E.N. Kass, C. Lambré, J.C. Larsen, J-C. Leblanc, A. Mortensen, I. Pratt, I. Stankovic.

[2] OJ L 183, 12.7.2002, p. 51.

ASSESSMENT

1. Introduction

The present opinion deals with sodium monofluorophosphate, a synonym of disodium fluorophosphate, the latter terminology is used in the terms of references provided by the Commission. The term sodium monofluorophosphate is used here since it is the term employed in all the scientific publications provided.

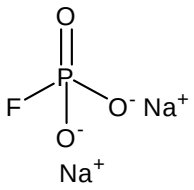
Fluoride supplementation has been used for years essentially to prevent dental caries, especially if the fluoride concentration in drinking water is low. Sodium monofluorophosphate is commonly used in toothpaste and the widespread use of fluoridated toothpaste in the western world has been associated with an effective decline in caries prevalence. The Scientific Panel on Dietetics Products, Nutrition and Allergies (NDA) (EFSA, 2005a) established tolerable upper intake levels of fluoride that include intake from water, beverages, foodstuffs, fluoride salt, dental health products and fluoride tablets for caries prevention. Similarly, the Food and Nutrition Board (FNB) of the National Academies in the US established tolerable upper intake levels of fluoride representing total intake from food, water, and food supplements (FNB, 2002). The Scientific Committee on Cosmetic Product and Non-Food Products intended for consumers evaluated the safety of fluoride compounds in oral hygiene products for children (SCCNFP, 2003).

The present opinion deals only with the safety of sodium monofluorophosphate and the bioavailability of fluoride from this source. The safety of fluoride itself, in term of amounts that may be consumed, is outside the remit of this Panel.

2. Technical data

2.1. Chemistry

Sodium monofluorophosphate has a molecular formula of Na_2FPO_3, a molecular weight of 143.95 g/mol and is identified by CAS Registry number 10163-15-2 (Technical dossiers, 2005a; 2005b). Its structural formula is:



Other synonyms proposed by the petitioners are disodium fluorophosphate, phosphorofluoridic acid disodium salt and disodium phosphorofluoridate.

2.2. Specifications

Sodium monofluorophosphate is described as a white powder, being freely soluble in water with a pH in solution in the range of 6 to 8. The main described impurities are free fluoride

(≤1.2%), sodium orthophosphate and various complexes of sodium phosphates (Technical dossiers, 2005a; 2005b). Proposed chemical specifications are as follows:

Table 1. **Chemical specifications proposed by the applicants for sodium monofluorophosphate**

	Assay (% w/w)	Heavy metals	Arsenic	Free fluoride ions
Technical dossier 2005a	91.7-100.5	≤5 mg/kg as lead	≤3 mg/kg	n.p.
Technical dossier 2005b	91.7-100.5	≤50 mg/kg	n.p.	≤1.2 %

n.p.: none proposed

The Panel notes that according to Commission Regulation (EC) No 629/2008 (EC, 2008) the maximum levels of respectively lead, mercury and cadmium in food supplements as sold should be respectively 3.0 mg/kg, 0.1 mg/kg and 1 mg/kg.

2.3. Manufacturing process

No detailed manufacturing process has been provided by one of the petitioners. The other petitioner described a manufacturing process using sodium fluoride, phosphorus pentoxide and sodium polyphosphate as raw materials.

2.4. Methods of analysis in foods

No method of analysis in food was provided. One of the petitioners describes a High Performance Liquid Chromatography (HPLC) analytical method for the determination of the sodium monofluorophosphate in food supplements. The other petitioner describes a HPLC analytical method for the determination of the total fluoride content in food supplements.

2.5. Reaction and fate in foods

No specific results on reaction and fate in foods have been provided. Stability tests of the food supplements containing sodium monofluorophosphate as ingredient have been provided. No significant changes of the fluoride and sodium monofluorophosphate contents have been observed in 12- and 24-month stability studies.

2.6. Case of need and proposed uses

Sodium monofluorophosphate is intended to be used by both petitioners in food supplements as a source of fluoride in the forms of multi-vitamin, multi-mineral supplements, solid tablets or tablets dispersible in liquid.

2.7. Exposure

According to one of the petitioners sodium monofluorophosphate is to be added to prepare tablets with different dosages 0.25, 1.0 and 2.0 mg fluoride equivalents (given as examples) (Technical dossier, 2005b). These amounts of fluoride would correspond to approximately 2, 8 and 16 mg of sodium monofluorophosphate.

The second petitioner proposed to supply between 0.3–0.6 mg fluoride per day from this source corresponding to 2.4–4.8 mg sodium monofluorophosphate (Technical dossier, 2005a). This petitioner estimated the human exposure to sodium monofluorophosphate based on annual product sales. According to the data provided the typical dosage of the products was 1-2 tablets per day corresponding to an upper exposure estimate of approximately 0.6 mg fluoride/day (or 4.8 mg sodium monofluorophosphate per day).

The most recent available exposure estimates to fluoride from all sources in Europe show total intakes from 0.5 to 1.2 mg/day for adults, when no fluoridated salt is used, no fluoride containing tooth paste is used and no supplements are taken (EFSA, 2005a). In the case where fluoride salt would be used, fluoride water would be drunk and used for the preparation of food and tea, the sum of fluoride intake could reach 6 mg/day, without taking into consideration toothpaste use. For children, given that only very few reliable data were available on fluoride content from different sources it was not possible to estimate total exposure to fluoride in the European children population in the NDA opinion (EFSA, 2005a).

The Scientific Panel on Contaminants in the Food Chain (CONTAM) mentions in its opinion on fluoride in mineral waters that exposure values to fluoride from sources other than mineral waters are 1 mg/day for the age group 9 to 14 years and 3 mg fluoride/day for the population of 15 years and older (EFSA, 2005b).

In the UK total dietary exposure in children to fluoride from food and fluoride water was calculated assuming two water fluoride concentration scenarios (Table 2). In the same report it is mentioned that breast milk contains only trace amounts of fluoride, providing less than 0.01 mg fluoride/day to infants.

Table 2. **Total exposure estimates to fluoride from the diet and drinking water in UK children (adapted from COT, 2003)**

Population group (years old)	**Fluoride concentration of drinking water**			
	0.7 mg/l		**1 mg/l**	
	Mean intake (mg/kg bw/day) ~ (mg/day)	97.5th percentile intake (mg/kg bw/day) ~ (mg/day)	Mean intake (mg/kg bw/day) ~ (mg/day)	97.5th percentile intake (mg/kg bw/day) ~ (mg/day)
1.5 to 4.5	0.066 ~ 0.86[a]	0.096 ~1.25[a]	0.085 ~1.10[a]	0.115 ~1.49[a]
4 to 6	0.054 ~1.46 [b]	0.083 ~2.24[b]	0.064 ~1.73[b]	0.093 ~2.51[b]
7 to 10	0.047 ~1.27[b]	0.070 ~1.89[b]	0.057 ~1.54[b]	0.080 ~2.16[b]

(a) assuming an average 13 kg bw

(b) 27 kg bw

For infants and children it has been estimated in the USA that total daily intakes of fluoride from all sources can amount in non-fluoride areas to 0.08 and 0.11 mg/kg bw/day, respectively, and to 0.06 and 0.23 mg/kg bw/day for fluoride areas, respectively (EFSA, 2005a).

Daily sodium and phosphate exposure from the proposed supplementations would be in the range of approximately 2–14 mg and 1–9 mg, respectively.

2.8. Information on existing authorisations and evaluations

The Scientific Panel on Dietetics Products, Nutrition and Allergies (NDA) established upper tolerable intake levels for fluoride of 1.5 mg/day for 1-3 years children, of 2.5 mg/day for 4-8 year children, of 5 mg/day for 9-15 year children and of 7 mg/day for ≥ 15 year adults (EFSA, 2005a). These tolerable upper intake levels apply to fluoride intake from water, beverages, foodstuffs, including fluoride salt, dental health products and fluoride tablets for caries prevention. The NDA panel considered that an intake of 0.1 mg fluoride/kg bw/day in children up to 8 years old is a dose at which no significant occurrence of moderate forms of fluorosis in permanent teeth will occur.

The Scientific Panel on Contaminants in the Food Chain (CONTAM) issued an opinion on concentration limits for fluoride in natural mineral waters (EFSA, 2005b). The Panel applied different scenarios for setting maximum limits for fluoride in mineral waters and concluded that at a concentration of 1 mg/l exposure to fluoride in the whole population including young children from all sources would be unlikely to reach the tolerable upper intake levels. A second scenario using higher fluoride concentration value (5 mg/l) exposure to fluoride would exceed tolerable upper intake levels for the populations under 15 years old.

The Food and Nutrition Board (FNB) of the National Academies in the US established tolerable upper intake levels of fluoride of 0.7 and 0.9 mg/day for infants (up to 12 months), of 1.3 and 2.2 mg/day for children (1–8 years) and of 10 mg/day for adults including pregnant and lactating women (FNB, 2002). These tolerable upper intake levels apply to fluoride intake from food, water and food supplements.

The Scientific Committee on Cosmetic Product and Non-Food Products (SCCNFP) intended for consumers evaluated the safety of fluoride compounds (mainly sodium fluoride) in oral hygiene products for children under the age of 6 years (SCCNFP, 2003). This committee concluded that the *threshold that could cause serious symptoms and need immediate emergency treatment* was *5 mg fluoride/kg bw* for these children. Based on available data the SCCNFP was of the opinion that toothpaste containing up to 0.15% of fluoride does not pose a safety concern for children under this age.

The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) in UK considered an intake of 0.05 mg/kg bw/day to be a no observable adverse effect level (NOAEL) for moderate dental fluorosis (COT, 2003). This Committee pointed out that the threshold dose at which fluoride causes moderate dental fluorosis was 0.1 mg/kg bw/day.

Sodium and potassium fluorides are authorised substances in Europe that may be added for specific nutritional purposes in foods for particular nutritional uses (EC, 2001).

The World Health Organisation (WHO) established a guideline value for naturally occurring fluoride in drinking-water of 1.5 mg/l (WHO, 2006). According to the WHO recommended artificial fluoridation of water supplies is usually 0.5–1 mg/l.

The US FDA evaluated the safety and effectiveness of a sodium monofluorophosphate 6% solution as anticaries ingredient offered as over-the-counter (OTC) drug product (CFR, 2007).

No tolerable upper intake level could be established for sodium from dietary sources by the NDA Panel (EFSA, 2005c). This Panel estimated that the dietary intake of sodium in Europe lie between 4500–11000 mg/day (EFSA, 2005c).

Trisodium phosphate is a permitted food additive in Europe identified as E 339 (iii) (EC, 1995). A MTDI of 70 mg/kg body weight for phosphates was established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (WHO, 1982). The SCF (1991) confirmed this MTDI value for phosphates used as food additives.

3. Biological and toxicological data

3.1. Bioavailability

In humans, the dominating route of fluoride absorption is via the gastrointestinal tract. Sodium monofluorophosphate dissociates into sodium and monofluorophosphate ions $(FPO_3)^{2-}$ in the intestinal tract, the latter being absorbed mainly in the upper small intestine (Setnikar and Ringe, 1995). Once absorbed sodium monofluorophosphate is rapidly and completely hydrolysed by enzymes (alkaline phosphatase) into fluoride and phosphate ions (Setnikar and Ringe, 1995; Farley *et al.*, 1987). After intake only fluoride is found in plasma and some evidence suggests that in humans it can be transported as a globulin-bound form which disappears from plasma within 5 to 8 hours following intake (ATSDR, 2003; Rigali *et al.*, 1996).

In a study with five volunteers received oral doses of 10 mg per day of either a placebo, sodium fluoride (NaF), sodium monofluorophosphate, calcium fluoride (CaF_2), tin fluoride (SnF_2) or aluminium fluoride (AlF_3) for one week over a 6-week experimental period (Shannon and Edmonds, 1977). The 10 mg dosing was divided into five 2 mg portions taken with 5 ml flavoured water. Parotid saliva samples were taken for fluoride analysis, samples before treatment serving as subjects' internal controls. Samples were collected over the first hour after dosage and then at 2, 3, and 4 hour time-points. Urine excreted during the saliva collection periods was also collected. A fluoride peak concentration was reached in saliva within 30 – 40 minutes after ingestion of sodium monofluorophosphate, similar to that observed after sodium fluoride administration. Absolute peak concentration value was higher after sodium monofluorophosphate intake compared to sodium fluoride (0.258 ppm *vs.* 0.205) but the difference was not significant. In this study urinary excretion of fluoride after sodium monofluorophosphate intake was 1 fold (SnF), 1.4 fold (AlF_3, NaF) and 6 fold (CaF_2) higher, which tends to indicate a greater bioavailability.

In contrast to these findings, a triple cross-over study showed no significant difference in urine fluoride excretion in twelve volunteers administered either 29 mg sodium fluoride water solution, 100 mg sodium monofluorophosphate water solution or 100 mg sodium monofluorophosphate calcium carbonate tablets (Setnikar and Maurer, 1990). The authors concluded that fluoride bioavailability was similar for sodium monofluorophosphate and sodium fluoride.

In a review on fluoride pharmacokinetics and bioavailability it has been reported that after oral administration of 100 mg of sodium monofluorophosphate (equivalent to 13.2 mg fluoride) to twelve male healthy volunteers, fluoride increased in plasma within 7 minutes, reaching a peak concentration after 0.62 h. Clearance from plasma was biphasic, occurring first with an initial half-life of 0.08 h (constant 0.92 h^{-1}) and with a terminal half-life of 5.3 h (constant 0.13 h^{-1})

(Setnikar and Ringe, 1995 Fluoride bioavailability from sodium monofluorophosphate was estimated to be 100% relative to fluoride bioavailability from a 100 mg sodium fluoride solution.

Overall soluble forms of fluoride salts, including sodium monofluorophosphate, have reported absorption efficiencies of between 80 to 100 % (ATSDR, 2003).

The degree of fluoride absorption from soluble sources, especially sodium fluoride, may be altered by interactions with food components (Pratz *et al*., 1977; Ekstrand and Ehrnebo, 1979; Trautner and Einwag, 1987; EHC, 2002; ATSDR, 2003). In laboratory animals, the presence of food and fluoride-binding ions (i.e., aluminium, calcium, magnesium) in the gastrointestinal tract has been reported to significantly reduce the amount of fluoride absorbed (EHC, 2002). However, fluoride absorption from sodium monofluorophosphate appears to be less affected by these parameters.

A comparative study was carried out with 80 Wistar rats, divided into three groups for a fist series of experiments and into five groups for a second series of experiments. In the first series lasting 3 weeks, 10 ppm of fluoride (equivalent to approxymately 1 mg/kg bw/day) was administered daily in tap water as sodium fluoride or as a sodium monofluorophosphate powdered milk (third group acted as control). In the second series of experiments lasting 7 weeks the same amount of fluoride was administered daily in the above mentioned vehicules and additionally in distilled water and tea. With the exception of tea, fluoride bioavailability was 100 % in all vehicules as measured by femur fluoride concentration as compared to that of sodium fluoride in tap water.

In the same publication is reported a study done with eight pre-school children (3–5 years old) supplemented with 1 mg fluoride as sodium fluoride tablets in drinking water and as monofluorophosphate powdered milk[3]. Fluoride concentrations were measured in 24 h urine samples, each child serving as its own control. The study design included administration of the fluoride sources 5 min before lunch (in presence of meal) or under fasting conditions, each experiment was separated from its predecessor by at least 1 week recovery period. Results showed that in the presence of a meal of sodium monofluorophosphate powdered milk fluoride urine excretion was significantly increased compared to sodium fluoride suggesting that under these conditions fluoride availability from sodium monofluorphosphate is less influenced by the meal. This was confirmed when both supplementations were done under fasting conditions, in which no significant differences were observed between sodium monofluorophosphate powdered milk and sodium fluoride tablets (Villa *et al.,* 1989).

A two-treatment, randomised, cross-over study was conducted with 8 volunteers (26 to 32 years old) administered with 10 mg fluoride as sodium monofluorophosphate in combination with 300 mg of calcium as calcium D-gluconate monohydrate and calcium citrate tetrahydrate, either in fasting conditions or immediately after intake of a standard meal (Warneke and Setnikar, 1993). The meal group showed a delay in the time to maximal fluoride concentration (> 11 min), a slowing of the absorption rate, a prolonged t_{max} and mean residence time[4] and a decrease in C_{max} (reached > 2.4 h), but similar fluoride AUC profiles and cumulated urine fluoride excretion to those of the fasted group. The fasting group showed that fluoride appeared in plasma very rapidly (< 4 min), reaching a C_{max} after 34 min and returning to the average plasma pre-dosing values after 48 h, the last being similar to the meal group. Similar results have been reported in animal studies (Setnikar and Ringe, 1995).

[3] industrially (pilot scale) manufactured monofluorophosphate-powdered milk, freshly diluted daily with tap water.
[4] time for 63,2 % of the dose to be eliminated from blood

3.2. Toxicological data

Most of the available data on fluoride toxicity comes from exposure to sodium fluoride. Only scarce toxicity literature is available specifically on sodium monofluorophosphate. LD_{50} values for rats and mice in the range of 54 to 146 mg/kg bw/day have been reported for sodium monofluorophosphate (EHC, 2002).

A number of expert bodies (IARC, 1982; EHC, 2002; COT, 2003; ATSDR, 2003; EFSA, 2005a) have reviewed the toxicity of fluorides in general. The following text summarises the major toxicological findings on fluorides reported in these evaluations.

Overall, acute exposure to soluble fluoride can induce vomiting, diarrhoea, respiratory arrest, cardiac depression and gastric mucosal changes. The latter have been reported following exposure to 18 mg fluoride/kg bw administered as sodium fluoride. Haematological changes (reduced numbers of blood cellular constituents), reduced collagen synthesis, signs of trabecular bone mineralisation and increased bone matrix formation have been reported on short-term studies in animals exposed to sodium fluoride. Body weight reduction, dental fluorosis, histological changes in the kidney, liver, testes and myocardium have been reported in medium-term studies in animals exposed to high-doses of fluoride (up to 270 mg/l of water). In long-term toxicity studies in animals exposed to high doses of sodium fluoride signs of hyperkeratosis of the stomach mucosa, changes in blood chemistry and bone composition disturbances have been reported. Chronic exposure to fluoride has not been related to reproductive or teratogenic effects in animals. Some studies have found behavioural or brain abnormalities in mice exposed to fluoride, however these findings could not be fully assessed and results on well conducted long-term studies in rodents at high doses did not show neurotoxicity. In general it is considered that exposure to fluoride by the oral route has no effect upon the frequency of chromosomal aberrations, micronuclei, sister chromatid exchange, DNA strand breaks or sperm morphology. On animal carcinogenicity, there was a reported occurrence of small numbers of osteosarcomas in a long-term study on male F344/N rats at doses of approximately 5 and 8 mg sodium fluoride/kg bw/day. However, there was no evidence of carcinogenicity in female F344/N rats and male or female $B6C3F_1$ mice at any of the same doses. The EFSA 2005 opinion on fluoride concluded that *there is equivocal evidence of carcinogenicity in male rats and no evidence of carcinogenicity in mice* (EFSA, 2005a). Fluoride salts have been classified by IARC as Group 3 (The agent is not classifiable as to its carcinogenicity to humans). In humans, many epidemiological studies on drinking-water consumption containing naturally or artificially added fluoride have not related fluoride exposure to an increased risk of developing cancer. The main effect reported in these type of studies was dental or enamel fluorosis and in some populations skeletal fluorosis. The most sensitive population to dental fluorosis is children under the age of eight particularly during the pre-eruptive formation and maturation of enamel in teeth. It has been considered that exposure to up to 0.1 mg/kg bw/day in children under eight years old does not result in dental fluorosis in permanent teeth. Very mild forms of dental fluorosis are of aesthetic concern only. No epidemiological association was reported between fluorides in drinking-water and the incidence of Down's syndrome. There was no evidence identified of increased incidence of allergic reactions after fluoride exposure.

3.2.1. Other studies

In a long term, randomised, double-blind controlled intervention trial in 80 women on a pre-existing hormone replacement therapy and calcium supplementation, administration of 20 mg per day of glutamine monofluorophosphate over 4 years did not show signs of adverse effects other than those expected on bone mineral density (BMD) following fluoride intake (17%

BMD increase above placebo group) (Reid *et al.,* 2007). A high mineralisation of bone, which could adversely change bone strength, was reported in women on monofluorophosphate treatment but the authors suggested that lower doses of monofluorophosphate (5-10 mg/day) could avoid this effect without impairing its desired anabolic action on bones. Calcium, phosphate, vitamin D levels in serum as well as levels of urinary calcium did not differ significantly between the placebo and treatment groups and reported cases of gastrointestinal pain, back pain, lower limb pain were similarly frequent in both groups as reported in other therapeutical studies (EFSA, 2005a), suggesting that long intake of monofluorophosphate is well tolerated.

In a randomised doubled-blind placebo study 20 male volunteers (10 per group) aged 21-35 years old were administered daily for 7 days either 76 mg sodium monofluorophosphate or 22 mg sodium fluoride as tablets, equivalent to approximately 10 mg fluoride (Müller *et al.,* 1992). Volunteers underwent gastroduodenoscopy monitoring and serum fluoride analysis and each subject served as its own control. Results showed that two hours after intake of sodium fluoride the body of the stomach and the antrum had petechiae and the presence of free blood in the gastric lumen, lasting during the seven day treatment but without significant lesion scores changes. The oesophagus and the duodenal bulb were not affected by the treatment. The gastroscopic findings after one day of treatment were related to high mean serum fluoride levels. Treatment with sodium monofluorophosphate did not induce any significant gastric mucosal injury after one hour treatment or 7 days treatment. Only erythema of the stomach fundus and antrum was observed though serum fluoride levels were as high as those found after sodium fluoride treatment. After seven days subjects in the sodium fluoride group reported neither gastric pain, diarrhea, gastric pressure, nausea or a combination whereas in the sodium monofluorophosphate group one subject showed signs of weakness considered by the authors to be unlikely related to the treatment. No correlation was found between the gastric lesion scores and the development of the symptoms. This study suggests that sodium monofluorophosphate is less irritant to the gastric mucosal and better tolerated than sodium fluoride.

4. Discussion

Most of the available toxicity data comes from exposure to sodium fluoride and the results of comprehensive evaluations carried out on these substances conclude that the most sensitive effect of fluoride exposure in humans is dental fluorosis. Conclusions of comprehensive evaluations indicate that genotoxicity and carcinogenicity are not of concern for fluoride exposure in humans.

Fluoride from sodium monoflurorophosphate does not appear to form insoluble calcium complexes as has been suggested with sodium fluoride supplementation and comparative studies have shown that fluoride from sodium monofluorophosphate in the presence of milk powder and sources of calcium is efficiently absorbed from the diet.

Available literature on sodium monofluorophosphate and sodium fluoride suggests that sodium monofluorophosphate is hydrolysed in fluoride and phosphate ions and the Panel concludes that fluoride bioavailability will be to an extent comparable to the one from sodium fluoride. In general, absorption of fluoride from sodium monofluorophosphate appears to be less affected by meal components or by the presence of calcium than from sodium fluoride .

Tolerable upper intake level for fluoride have been established in Europe amounting to 1.5 mg/day for 1-3 years children, of 2.5 mg/day for 4-8 year children, of 5 mg/day for 9-15 year children and of 7 mg/day for ≥ 15 year adults. Proposed supplementation data foresees that

sodium monofluorophosphate will be added to food supplements to supply, according to one petitioner, 0.25, 1.0 and 2.0 mg fluoride equivalents (given as examples), amounting to approximately 2, 8 and 16 mg of sodium monofluorophosphate. The second petitioner proposed to supply between 0.3–0.6 mg fluoride per day from this source corresponding to 2.4–5 mg sodium monofluorophosphate. These levels of supplementation are below tolerable upper intake levels established for different populations in Europe with the exception of the UL established for 1-3 years children (1.5 mg/day) which would be exceeded by the highest supplementation proposed (2 mg/day).

However, when the potential contribution of fluoride from the proposed supplementation with sodium monofluorophosphate is added to the total fluoride daily exposure estimates in Europe for UK children (assuming 1 mg/l fluoride supplementation of drinking water), tolerable upper intake levels for the 97.5th percentile population of 1.5 to 10 years old children will be exceeded by most of the foreseen supplementations. Only the lowest proposed fluoride supplementation (0.3 mg/day) will not exceed tolerable upper intake levels when added to the total fluoride exposure estimated for the 97.5th percentile 7-10 years old children (4.56 mg/day).

For adults, the proposed fluoride supplementation levels will not exceed the tolerable upper intake level (7 mg/day) when added to the daily fluoride intake (6 mg/day), except for one proposed fluoride supplementation level (2 mg/day) which will exceed this tolerable upper intake level.

Daily sodium exposure from the proposed supplementations will be low (1.7–14 mg) compared to the estimated dietary intake of sodium in Europe estimated to be between 4500–11000 mg/day. Daily exposure to phosphate ions at the proposed supplementations (1.1 mg–8.8 mg) would be at most approximately 470 times lower than the MTDI of 70 mg/kg bw established for phosphates.

CONCLUSIONS

The present opinion deals only with the safety of sodium monofluorophosphate as a source of fluoride and the bioavailability of the fluoride from this source. The safety of fluoride itself, in term of amounts that may be consumed, is outside the remit of this Panel.

Available literature on sodium monofluorophosphate and sodium fluoride suggests that sodium monofluorophosphate is hydrolysed in fluoride and phosphate ions and the Panel concludes that fluoride bioavailability will be to an extent comparable to the one from sodium fluoride. The most sensitive effect of fluoride exposure in humans is dental fluorosis and conclusions of comprehensive evaluations indicate that genotoxicity and carcinogenicity are not of concern for fluoride exposure in humans. Additionally, long-term clinical intervention trials have suggested that monofluorophosphate is better tolerated than other common sources of fluoride such as sodium fluoride.

Proposed supplementation data foresees that sodium monofluorophosphate will be added to food supplements to supply between 0.25 and 2 mg fluoride per day, corresponding to approximately 2.5 to 16 mg sodium monofluorophosphate.

Daily exposure estimates to sodium (1.7–14 mg) and phosphate (1.1–8.8 mg) arising from the proposed supplementations with sodium monofluorophosphate would be of no safety concern. Sodium exposure from this source represents at most only 0.3% of the estimated dietary intake of sodium in Europe (4500–11000 mg/day) whereas phosphate exposure would be at most

approximately 460 times lower than the maximum tolerable daily intake of 70 mg/kg bw established for phosphates.

The ANS Panel concludes that the use of sodium monofluorophosphate as food supplement would be of no safety concern provided that fluoride tolerable upper intake levels established in Europe are not exceeded by the combined exposure from food supplements and the diet.

The ANS Panel noticed that most of these proposed levels of supplementation are below tolerable upper intake levels established for different populations in Europe. However, when the potential fluoride contribution of sodium monofluorophosphate supplementation is added to the total fluoride daily exposures estimates in Europe for children, fluoride tolerable upper intake levels will be exceeded in most cases. For adults, the proposed fluoride supplementation levels will not exceed the tolerable upper intake level with the exception of the supplementation value of 2 mg/day.

The Panel notes that according to Commission Regulation (EC) No 629/2008 the maximum levels of respectively lead, mercury and cadmium in food supplements as sold should be respectively 3.0 mg/kg, 0.1 mg/kg and 1 mg/kg.

DOCUMENTATION PROVIDED TO EFSA

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2. Technical dossier, 2005b. Dossier for safety evaluation of Sodium monofluorophosphate for use in the manufacture of Isifluor® 0.25 mg and Isifluor® 1.00 mg. July 2005. Submitted by Rottapharm S.p.A., Italy.

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GLOSSARY / ABBREVIATIONS

ANS Panel	The Scientific Panel on Food Additives and Nutrient Sources added to Food
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	Bone Mineral Density
CONTAM Panel	Scientific Panel on Contaminants in the Food Chain
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
EFSA	European Food Safety Authority
FAO	Food and Agriculture Organization of the United Nations
EHC	Environmental Health Criteria
FNB	Food and Nutrition Board
HPLC	High Performance Liquid Chromatography
IARC	International Agency for Research on Cancer
JECFA	Joint FAO/WHO Expert Committee on Food Additives
MTDI	Maximum Tolerable Daily Intake
NDA Panel	Scientific Panel on Dietetics Products, Nutrition and Allergies
NOAEL	No observable adverse effect level
OTC	over-the-counter
SCCNFP	Scientific Committee on Cosmetic Product and Non-Food Products
UL	Tolerable Upper Intake Level
WHO	World Health Organisation