Statement to the discussion paper on the setting of maximum and minimum amounts for vitamins and minerals in foodstuffs

The “Informationsstelle für Kariesprophylaxe” (IFK) is a non-governmental non-profit-organisation which is coordinating caries prevention by means of fluoridated salt in Germany. It is represented by a scientific board which consists of scientists with expertise in caries prevention, dentists, paediatrics as well as representatives of the public health service.
The introduction of fluoridated salt, which is available as Iodine-salt with fluoride, was started in 1991 and has until now reached a marked share of 66.7% of all domestic salt sold in Germany. Salt fluoridation has substantially contributed to a remarkable drop in caries prevalence in Germany since the early 1990ies. This development is very well documented and resulted in a 76% caries reduction in 12-years-old children. Consequently, in order to stabilize and to promote oral health on a public health basis, there is a strong interest in Germany to make salt fluoridation possible also under EU-legislation.
In seven European countries there are national legal regulations, or salt producers have obtained individual authorisation for the production and marketing of fluoridated edible salt. On the basis of EU mutual recognition rules, there are other countries which import fluoridated edible salt (Götzfried 2006).

The main issues that need to be addressed can be summarised as follows:

- The addition of fluoride to foodstuffs should be limited to fluoride salt.
- The expansion of fluoride addition to other food should be rejected due to the risk of overdosing fluoride in young children.

Rationale:

Even if there is no health threatening risk caused by fluoride overdosing in children up to six years a dental fluorosis which can be seen as white spots on the tooth surface, may appear. If the addition of fluoride should be expanded to other foodstuffs, such as vitamin and mineral supplements, it would be impossible for the dentist to calculate the total fluoride intake and to give the patient advice for the optimal use of fluoride. Salt is the only food which is consumed within narrow limits (in Germany: 6-8 g/pay) and therefore an overdosing of fluoride can be excluded if salt is the carrier material for fluoride.
It is known, that the effect of fluoride in caries prevention is mainly caused by local mechanisms at the tooth surface. Therefore the addition of fluoride to vitamins and mineral supplements, which are usually swallowed, will not result in a measurable effect in caries prevention but in an elevated fluorosis-risk, if children up to six years are consuming these supplements.

- In order to ensure effectiveness in caries prevention, the minimum concentration of fluoride in salt should be fixed at 250 mg per kg salt (tolerance +/- 25 %).
- The use of fluoride salt should be allowed not only in households but also in public kitchens and bakeries, as recommended by the WHO.

Rationale:
Projects in Switzerland, where salt fluoridation started in 1955 with a concentration of 90 mg fluoride / kg Salt (=90 ppm) clearly show, that 250 ppm fluoride in all edible salt is the optimal concentration. Based on theses findings, the WHO recommends the use of fluoridated salt with 200 ppm fluoride for use in households, public kitchens, restaurants and bakeries (WHO 1994).

Background information

1. Introduction

Etiology of caries may be regarded as general knowledge in industrialized countries. As a matter of principle, it is possible to fight the disease by avoiding ingestion of sugar or by applying perfect oral hygiene. However, in practice this seems extraordinarily difficult. Scientific examinations and practical experience showed repeatedly that a significant reduction of sugar consumption and perfect oral hygiene cannot be attained in wide sections of the population (Marthaler 1990, Micheelis and Schroeder 1999, Bauch et al. 1991). Therefore, for the population a regular supply of fluoride is the most important measure in caries prevention to strengthen the resistance of dental hard tissues. For a long time, the systemic effect of fluoride was regarded to be most important, resulting in recommendations to use fluoride supplements such as tablets or drops. However, there is increasing evidence that the local effect of fluoride at the surface of erupted teeth is by far more important.

2. Fluoride - its value to man

Fluorides are chemical compounds of fluorine and organic or anorganic cations. Fluoride can be found everywhere in nature in the soil, the air, and the water, either as lightly soluble salt (sodium- or potassiumfluoride) or as barely soluble mineral (fluorspar, fluorite or fluorapatite). Fluoride is a natural element within the fauna and flora and their food chain. In this context it is also up taken into the human body (Smith and Ekstrand 1988). Fluoride is regarded as an important trace element, which has a high impact on growth of bone and teeth because it serves as core of mineralisation (Karlson 1984). It is mainly up taken with food and 90% are absorbed. Approximately half is estimated to be eliminated via urine, less in children, more in adults. 99% are incorporated into bone and teeth (Ekstrand and Whitford 1988), the rest is spread over the other tissues. In total, an adult human body contains about 2.6g of fluoride (Hopfenzitz 1996). According to its primary location in bone and teeth fluoride has a major impact on the stability of bone and it has a leading role in caries prevention.

3. Caries preventive mechanisms of fluoride

The action of fluoride is based on chemical and possibly on antibacterial effects. The chemical effect is by far the most important and will be discussed more in detail than the antibacterial effect.

Chemical action of fluoride

From a chemical point of view, a tooth may be regarded as a barely soluble salt (enamel and dentine) which is exposed to an aqueous solution (saliva). Ideally, there is a well-balanced equilibrium between de- and remineralisation. However, this balance is lost when dental plaque and sugar is frequently present in the oral cavity. In such a case demineralisation will prevail due to acidic metabolites from bacteria. This will first result in microscopically detectable carious lesions with characteristical appearance (subsurface lesion) which later will merge into cavities. Demineralisation is initiated by protonation of phosphate in apatite of enamel and/or dentine ($PO_4^{3-} + H^+ \rightarrow HPO_4^{2-}$). Calcium will therefore not be bound to an adequate extent but rather will be lost (König 1987). The presence of fluoride promotes the opposite reaction catalyzing remineralisation using the calcium of saliva and thus reverses the loss of substance before it can be detected microscopically. Furthermore, lesions which are already visible as white spots and already spread into dentine can be remineralised and healed with fluoride (Itthagarun et al. 2000, ten Cate 2001, Wefel et al. 1995). On a molecular basis, fluoride is capable to remove protons (H^+-ions) from the demineralised hard tissues which allows a re-embedding of calcium (König 1987). In an acidic solution, ten Cate and Duijsters could show a dose-response relationship between the concentration of fluoride and the calcium loss of enamel specimens (Cate ten and Duijsters 1983).
Another yet less important action of fluoride is the stabilisation of the present hard tissues. Apatite in enamel and dentine is chemically not a pure hydroxy-apatite ($Ca_{10}\ (PO4)_6\ (OH)_2$). Amongst other, there is a constant lack of OH^-ions. These “vacancies” within the crystalline structure can be occupied by fluoride. This will result in hydroxy-fluorapatite ($Ca_{10}\ (PO4)_6\ (OH)F$) or ideally in fluorapatite ($Ca_{10}\ (PO4)_6\ (OH)F$) which both are more stable against acidic attacks. However, under in vivo conditions, fluor-apatite develops rather scarcely (König 1987, Featherstone and Ten Cate 1988, Cate ten 1979). Moreno et al detected fluoride replacement of OH^--ions in less than 10% of the outer surface of enamel; in a depth of 50µm it was only 1% (Moreno et al. 1977).

Antibacterial action of fluoride

Fluoride may hamper the carbohydrate metabolism of streptococcus mutans by incorporating fluoride as hydrofluoric acid (HF) and therefore cytoplasmatic acidification (Whitford et al. 1977). This may result in a non-specific inhibition of the glycolysis because several enzymes including Enolase have their optimum efficacy in a neutral environment. Moreover the sugar transport system is sensitive to acidification of the cytoplasma (Belli and Marquis 1994). Both mechanisms reduce the generation of energy in the bacterial cell and the production of lactate (Hamilton and Bowden 1988, Loveren van 2001). However, the antibacterial effect of fluoride is of inferior importance unless the fluoride is not bound to cations which have their own specific antibacterial activity. It is even not yet clearly proven to be existent under in vivo conditions (Loveren van 2001).

Systemic and local effect of fluoride

For years, the major caries-preventive effect of fluoride has been ascribed to its ability to form fluorapatite. With this comprehension the systemic fluoridation, practiced mostly through daily tablet intake was favoured assuming that this would result in internal formation of fluor-apatite during tooth development. This would render teeth resistant to carious attacks on a long-term basis. This concept was disproved in in-vitro-studies using shark teeth. Those teeth are built from pure fluorapatite with a fluoride concentration of 32,000 ppm. Ögaard et al. compared the solubility of these teeth with human enamel in vitro. In their study, the human enamel showed a fluoride concentration of 1270 ppm at the surface, which decreased rapidly in the more central areas of enamel (Ögaard et al. 1988). With the comprehension of the “indestructible” enamel containing a high amount of fluorapatite, it should have been impossible to create carious lesions in shark teeth. However, it has been shown that in an in vitro caries model, shark teeth developed lesions with almost similar depth and mineral loss as human teeth (Ögaard et al. 1988). These findings reinforce the apprehension that the beneficial action of fluoride is much more eminent in its ability to enhance remineralisation than in its ability to form stable apatite and thus resist acidic attacks. The lack of benefit of pre-eruptive systemic fluoride application has been shown by Reich and coworkers, which performed a prospective study in newborn children (Reich et al. 1992). The authors demonstrated that there was no difference in caries development at the age of five years if fluoride was administered as tablets right after birth as opposed to an application starting in the age of seven month, i.e. with the eruption of the first deciduous tooth (Reich et al. 1992).

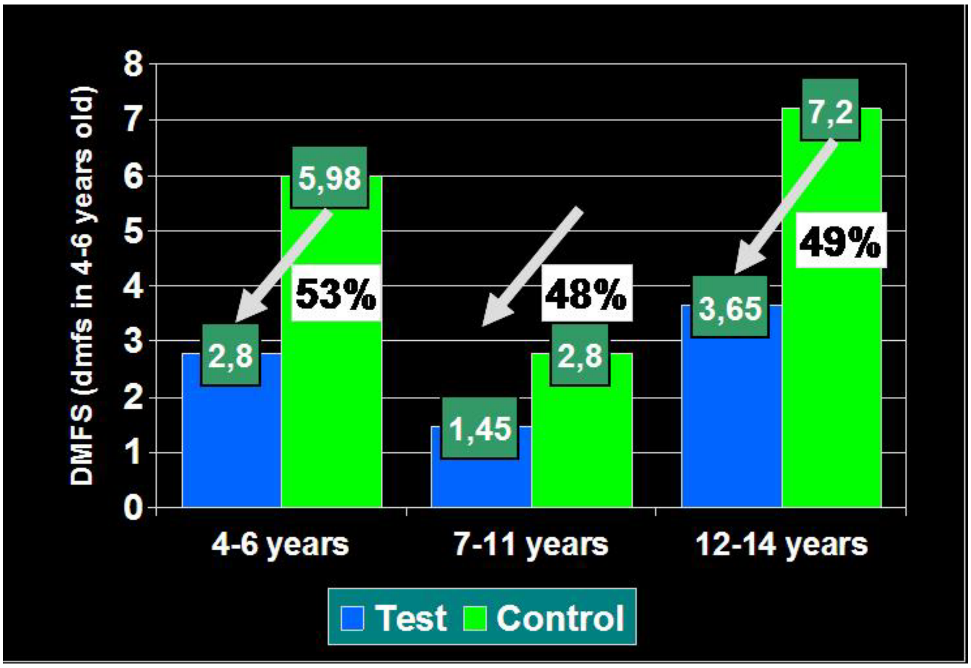
Increasing knowledge about the importance of fluoride in the process of de- and remineralisation has lead to the fact that topical application of fluoride is preferred to the systemic one (Riordan 1999, Limeback 1999, DGZMK 2000). However, it has to be taken into consideration that every systemic intake of fluoride has also a topical aspect if there are already teeth in the oral cavity: First, during its passage through the mouth (e.g. as fluoridated salt) it will have local contact to the teeth. Second, after its resorption in the gastro-intestinal tract it will gain access to the blood circulation and to the saliva. In this manner, fluoride is in low concentrations but over a relatively long time period locally available. In vitro studies have shown that concentrations of 0.1 ppm may already be effective for caries prevention (ten Cate and Duijsters 1983, Amjad and Nancollas 1979). If food had been prepared with fluoridated salt at 250 ppm the above mentioned or even higher concentrations can be measured in saliva during and after its ingestion (Macpherson and Stephen 2001, Hetzer and Korn 1997, Sjögren and Birkhed 1993).

4. Effectiveness of fluoridated salt

The caries preventive effect of fluoridated salt is of local nature, even if it is swallowed with food. When food prepared with fluoride-salt is passing the oral cavity it gets in contact with the tooth surfaces and provides fluoride just in the moment, when it is needed. Fluoride is mostly needed if the pH at the tooth surface drops to values below 5.5, which is usually the case if bacterial plaque present at teeth is "fed" with low molecular carbohydrates containing in nearly every food.

Controlled clinical trials have shown the efficacy of fluoride salt. For example, Toth (1973) could demonstrate 58% less caries in 2-6 years old Hungarian children using fluoride salt when compared to a control group who did not. Fluoride salt was introduced in Hungary in 1966. After ten years of salt fluoridation, the results were as shown in Figure 1. Overall, a 50 % caries reduction was found after life-time use of fluoridated salt (Toth 1978).

Figure 1 (DMFT=Number of Decayed, Missing or Filled Teeth in permanent teeth, dmft = Number of decayed, missing or filled teeth in deciduous teeth)



Switzerland is the country with the longest tradition in salt fluoridation. The addition of fluoride started already in 1955, with a fluoride concentration of 90 ppm (Marthaler 2000). In 1983, the concentration was elevated to 250 ppm. Already in 1974, salt fluoridation was extended to nearly all bakeries in the county of Glarus. While caries prevalence in Glarus was 6.84 DMFT (Decayed Missing Filled Teeth) in 1974, it dropped to 1.84 until 1987 and to 1.1 until 1992 (Menghini et al. 1995). While it is obvious, that not the whole caries drop could be explained by the introduction of fluoridated salt, statistical analyses showed it's important contribution (Steiner et al.1989)

5. Toxicological aspects

Compared to other substances which are regularly ingested by humans, fluoride has a high therapeutical safety. The lethal dose ranges between 32 and 64 mg F^-/kg body weight (Hodge and Smith 1965) which would imply 3,500 mg F^- (3.5 g) for an adult of 75 kg. Other sources even report lethal doses of 5,000–10,000 mg (5-10 g) in adults (Mühlendahl et al. 1995). The German society for nutrition recommends a daily fluoride intake of about 3.5 mg for an adult (Przyrembel 1998). Therefore the factor between recommended and lethal dose is at least 1,000. In contrast, the lethal dose for sodium chloride which is usually consumed in an amount of 6-8 g/day is 40-75 g for an adult. This is less than the ten fold of the average daily ingested amount (Mühlendahl et al. 1995).

For practical purposes the knowledge about the lethal dose of fluoride is not very helpful. More important is the question which dose will lead to first undesired effects. The toxicological assessment of any substance has to be done dose-related. The ingested amount of the substance and the body weight of the patient has to be known as well as the sensitivity of humans against the substance. It has to be distinguished between chronic and acute toxicity. Acute toxicity describes the immediate toxic effects after one single ingestion whereas the chronic toxicity relates to effects which appear slowly as a consequence of slight over dosage over a long period.

Acute toxicity

The minimal fluoride dose which may cause toxic signs and symptoms and which requires an immediate therapeutical intervention is found to be 5 mg/kg body weight. It is defined as probably toxic dose (PTD) (Whitford 1996). For example, there is a risk of toxic signs if a six-year-old child with a body weight of 20 kg has ingested the whole content of a tube of toothpaste with 1,500 ppm F^- (75 ml with 112.5 mg F^-). For fluoridated salt, the PTD is reached if this child ingests 400 g of salt. However, the lethal dose of sodium chloride for a child of this age is about 15-20 g if ingested at one time (Mühlendahl et al. 1995).

Chronic toxicity

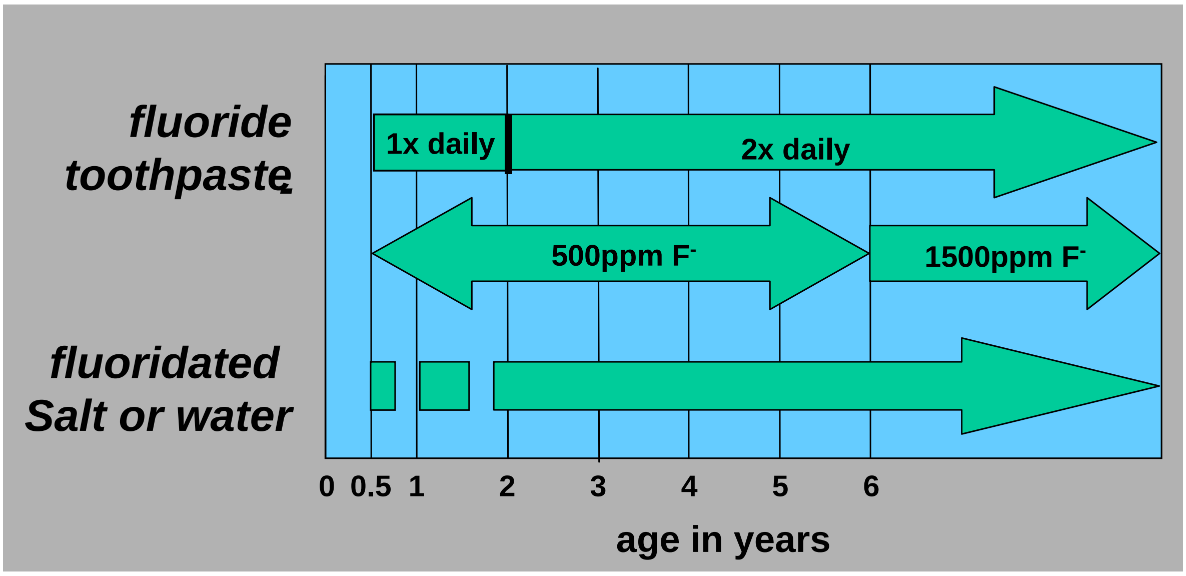
If fluoride is ingested in elevated doses over longer time-periods, changes in teeth and bone can result. These changes are called fluorosis. In teeth, they are the result of some disturbance in mineralization, resulting in a higher organic proportion. Dental fluorosis can only occur during tooth formation. In contrast, fluorosis of the bones is the result of an over mineralization and can occur during the entire life. First signs of skeletal fluorosis can be observed after the ingestion of more than 10 mg F^-/day over a period of at least ten years. These changes do not yet have any impact on health (Whitford 1996). Because of dose and exposure time, fluoride containing caries preventive agents, such as fluoridated salt, cannot be considered as risk factor for skeletal fluorosis. However, already a slight over dose of fluoride during tooth formation may result in a dental fluorosis. The primary effects occur during the early maturation stage of enamel (Evans and Stamm 1991, DenBesten and Thariani 1992, DenBesten 1999, Zhou et al. 1996, Lyaruu et al. 1987, DenBesten et al. 1985). It is not possible to define a threshold value for the formation of dental fluorosis. In the literature, values between 0.03 and 1.0 mg F-/kg body weight and day can be found (Mascarenhas 2000). A fluoride uptake of 0.05 mg F-/kg bodyweight and day is regarded as optimal (Villa et al. 1999). Recommendations for the use of fluoride in caries prevention have always to be based on the best compromise between preventive efficacy and fluorosis risk. Since there are individual varying predisposing factors for fluorosis (Mascarenhas 2000) and since it is not possible to exactly determine the individual fluoride uptake, it has to be considered that an effective caries prevention with fluoride is always associated with a slight prevalence of mild fluorosis. In the US an increase of fluorosis is reported (Pendrys and Stamm 1990, Clark 1994). In Europe the situation is varying among the countries. An increase in fluorosis was shown in Belgian (Carvalho et al. 2001), whereas a low fluorosis level and no increase was found in France, Great Britain, and Germany (Dünninger and Pieper 1991, Einwag 1993, Reich and Beermann 1996, Obry-Musset 1998, Holloway and Ellwood 1997). Except for its severe forms which show large enamel defects (Thylstrup and Fejerskov 1978), fluorosis is an issue of at most esthetical concern. Interestingly, a study in Great Britain showed that mild forms of dental fluorosis (TF-index 1 and 2 (Thylstrup and Fejerskov 1978)) are not considered to be aesthetically disturbing. On the contrary, its perception is rather positive (Hawley et al. 1996). The risk of the formation of dental fluorosis on anterior teeth ends at the age of six years, because only posterior teeth, second premolars and particularly second molars are not fully mineralized at this age.

6. Recommendations for the use of fluoride

The multiple use of various fluoride products leads to an increased protection against caries. Figure 2 shows a fluoride time-table which is based on the guidelines of the European

Academy of Paediatric Dentistry (EAPD) and the German Dental Association (DGZMK) (DGZMK 2000, Oulis et al. 2000). The adherence to this recommendations will supply a good caries prevention with a low risk of fluorosis only. The recommendations are based on the principle that only one type of systemic fluoride should be applied. Fluoride tablets are only indicated for children who are deemed to be at increased caries risk and do not use fluoride toothpaste or fluoridated salt.

Figure 2



The guidelines are based on the finding that the local effect of fluoride is by far exerting the systemic one (Featherstone 1999). Apparently, a caries preventive effect on unerupted teeth does not exist (Reich et al. 1992). Therefore, from a caries preventive viewpoint it makes no sense to provide children with fluoride before the first tooth appears in the oral cavity. On erupted teeth, the so called systemic fluoridation has some beneficial effect. However, this is not based on a systemic but local effect, for example if food with fluoridated salt or water is chewed. The fluoride uptake of infants from fluoridated salt or water is low and therefore, the benefit from these fluoride sources may be little. But on the other hand, the entire population will benefit from these fluoride sources and therefore, the use of fluoridated water or salt can be considered as an important public health measure.

It is recommended that children up to the age of six years should use a toothpaste with reduced fluoride content (500 ppm) (DGZMK 2000, Oulis et al. 2000). The use of this toothpaste should start with the first deciduous tooth erupting. A pea sized amount should be used once and from the second birthday on twice a day. Starting with the sixth birthday, a “normal” toothpaste with 1,500 ppm fluoride should be used. If an increased caries protection is required, e.g. at high caries risk, a highly concentrated fluoride gel (12,500 ppm F^-) can be used weekly. Alternatively, fluoride mouthrinses with 200-500 ppm F^- can be used on a daily basis. Both preparations are not recommended for children under the age of six.

7. Conclusion

Since the main effect of fluoride results from reactions at the tooth surface, it should only be applied if teeth are already present in the oral cavity. This means the fluoride prevention should start with the erupting first deciduous tooth. The combination of various forms, e.g. fluoridated salt, toothpaste, and gel enhances the effect of fluoride. If properly used it can be considered as effective and safe.

8. Literature

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