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FLUORIDE EXPOSURES AND DENTAL FLUOROSIS: A LITERATURE REVIEW

EXPOSIÇÃO AO FLÚOR E FLUOROSE DENTAL: UMA REVISÃO DE LITERATURA

Marília Afonso Rabelo BUZALAF
Department of Biological Sciences, Bauru Dental School, University of São Paulo, Brazil.

Jaime Aparecido CURY
Department of Physiological Sciences, Piracicaba Dental School, University of Campinas, Brazil.

Gary Milton WHITFORD
Department of Oral Biology, School of Dentistry, Medical College of Georgia, Augusta, GA ,USA.

The decline in dental caries prevalence and incidence in the last two decades is considered to be largely due to the widespread use of fluoride. However, the prevalence of dental fluorosis has increased simultaneously. The increase is in the mild and very mild forms of fluorosis, both in fluoridated and in non-fluoridated areas. A large amount of epidemiological data demonstrates that the occurrence of dental fluorosis is associated with excessive fluoride intake throughout the period of tooth development. Multiple sources of fluoride intake have been identified. This review describes the condition and summarizes the recent literature on the risk factors for dental fluorosis. Four major risk factors have been consistently identified: use of fluoridated drinking water, fluoride supplements, fluoride dentifrice and infant formulas. In addition, some manufactured children foods and drinks may also be important contributors to total daily fluoride intake.

UNITERMS: Fluoride; Dental fluorosis, risk.

INTRODUCTION

There has been a decline in dental caries prevalence and incidence during the last two decades, both in economically developed[36,60,61,69] and in economically developing countries[37,67,107]. This decrease is considered to be largely due to the widespread use of fluoride. Concurrent with the decline in caries, an increase in the prevalence of dental fluorosis has been documented, in communities with[43,55,101,103] and without fluoridated drinking water[43,55,80,101]. Concern with the increase in the prevalence of fluorosis has led to many studies on the reasons for the increase, and in identifying the important risk factors. These studies have had different designs and employed different populations, many with multiple sources of fluoride exposure. Further, they have used different indices to diagnose and score dental fluorosis. This has made it difficult to compare the results of these studies. The purpose of this review is to summarize the recent literature on risk factors for dental fluorosis.

Dental fluorosis is a fluoride-induced disturbance in tooth formation, which results in hypomineralized enamel with increased porosity[25]. It is caused by excessive fluoride intake but only during the period of tooth development[13,15,74,99]. The most important risk factor for fluorosis is the total amount of fluoride consumed from all sources during the critical period of tooth development[15,17,31,63].

The clinical appearance of mild dental fluorosis is characterized by bilateral, diffuse (not sharply demarcated) opaque, white striations that run horizontally across the enamel. These may be invisible to the individual and the clinician but often can be seen after the enamel has been dried. The opacities may coalesce to form white patches. In the more severe forms the enamel may become discolored and/or pitted[24,26,97,98]. Upon eruption into the mouth, fluorosed enamel is not discolored – the stains develop over time due to the diffusion of

exogenous ions (eg, iron and copper) into the abnormally porous enamel.

The mechanism underlying the development of dental fluorosis has not been conclusively determined. It was believed previously that excessive fluoride intake interfered with the function of ameloblasts, perhaps inhibiting the secretion of, or altering the composition of enamel matrix proteins. It now appears that this is unlikely for several reasons including the fact that the risk of dental fluorosis is lowest during the secretory stage of enamel development [16,17,27,28].

Microscopically, the structural arrangement of the crystals appears normal, but the width of the intercrystalline spaces is increased, causing pores. The degree and extent of porosity depends on the concentration of fluoride in the tissue fluids during tooth development[25,102]. In fact, the risk of dental fluorosis, based on animal studies, is directly related to the interaction of circulating fluoride concentrations and time, i.e., the area under the time-concentration curve. Thus it appears that dental fluorosis can result from a range of plasma fluoride concentrations provided that they are maintained for sufficiently long periods[111]. With increasing severity of fluorosis, the fluoride concentration throughout the enamel, the depth of enamel involvement, and the degree of porosity also increases[25,85]. Clinical studies of dental fluorosis have demonstrated that the most critical period for development of fluorosis is during the post-secretory or early maturation phase of tooth development[22,26,52,74,84,102].

Fluorosis is less prevalent and less apparent in primary teeth than in permanent teeth, and, in any case, fluorosis of the primary teeth has only short-term rather than long-term consequences. Therefore, the major concern about fluorosis is with the permanent teeth. Since the different permanent teeth are developing at different times, the critical period for the whole dentition extends from eleven months to seven years of age. The permanent maxillary central incisors are of greatest cosmetic importance and they appear most at risk of fluorosis between ages of fifteen and twenty-four months for males and between twenty-one and thirty months for females[23]. However, a meta-analysis of the risk periods associated with the development of dental fluorosis in maxillary permanent central incisors showed that the duration of excessive fluoride exposure throughout amelogenesis, rather than specific risk periods, would seem to explain the development of dental fluorosis[4].

Some authors regard to 0.1 mg F/kg body weight per day as the exposure level above which dental fluorosis occurs[33], although studies in Kenya have found fluorosis with a daily fluoride intake of less than 0.03 mg F/kg body weight per day from water[3,59]. In these latter studies, however, the teeth were dried in order to detect the mildest forms of fluorosis. A daily fluoride intake between 0.05 and 0.07 mg/kg body weight per day is generally regarded as optimum for prevention of dental caries[70]. Other factors that may increase the susceptibility of individuals to dental fluorosis are altitude[1,42,57-59,93,110,111,114], renal insufficiency[45,46,82,104], and malnutrition[91,114]. Some of these factors, however, can produce enamel changes that resemble dental fluorosis in the absence of significant exposure to fluoride.

Studies of dental fluorosis, done in areas with and without fluoridated drinking water, have identified four major risk factors: use of fluoridated drinking water, fluoride supplements, fluoride dentifrice, and infant formulas before the age of seven years. Some manufactured children foods and drinks may also be important contributors to total daily fluoride intake.

Fluoridated drinking water

Dean[14], in 1942, stated that some 10% of children in optimally fluoridated (1.0 ppm) areas were affected by mild or very mild fluorosis in the permanent teeth and that less than 1% were so affected in low-fluoride areas. These degrees of prevalence were recorded prior to the availability of fluoridated dental products when fluoridated drinking water was the only significant source of fluoride intake[2,92]. In North America, the prevalence of dental fluorosis now ranges between 7.7% to 69% in fluoridated communities, and from 2.9% to 42% in non-fluoridated communities. The studies done after the 1980s have shown the highest prevalences[63]. The studies by Spuznar; Burt[99] and Riordan[88] are in agreement that the risk of fluorosis in areas where the water fluoride concentration is 0.8 ppm is four times higher than in non-fluoridated communities[87,88,99]. However, water fluoride probably has its greatest impact on fluorosis prevalence indirectly, through being used in the processing of infant formulas, other children's foods and soft drinks[8]. In a systematic review of 214 studies on water fluoridation, McDonagh et al.[64] observed an increase in the proportion of caries-free children and a reduction in the number of teeth affected by caries. They also noted a dose-dependent

increase in dental fluorosis. At a fluoride level of 1 ppm in the drinking water, they estimated that 12.5% of exposed people would have fluorosis that they would find of esthetic concern, a prevalence much higher than that reported by Dean[14] in 1942 who found virtually no cases of moderate or severe fluorosis. The present-day prevalence of fluorosis indicates that some young children are ingesting fluoride from sources in addition to that in drinking water.

Dietary fluoride supplements

Fluoride supplements are recommended for children living in fluoride deficient areas. The recommended daily dose is based on the age of the child and on the fluoride concentration in the drinking water. However, there are many reports showing that supplements are prescribed inappropriately to children in fluoridated areas[51,75,100]. Many studies have identified fluoride supplements as risk factors for dental fluorosis, both in fluoridated[49,76,79] and non-fluoridated areas[40,43,49-51,74,78,108]. In fluoridated areas the risk of dental fluorosis from use of fluoride supplements is almost 4 times higher than in non-fluoridated areas[63,87]. Hence, the risk of dental fluorosis from the use of fluoride supplements is well established. Clinicians must be sure of the water fluoride concentrations, as well as of the caries risk of the child, before prescribing fluoride supplements. The U.S. Centers for Disease Control and Prevention has recently published guidelines for the judicious prescription of dietary fluoride supplements[11].

Infant Formulas

Because of its very low fluoride contcentration, human breast milk is a poor source of fluoride. In infancy the major source of fluoride is considered to be infant formulas. A number of studies have implicated the consumption of infant formulas as a risk factor for dental fluorosis, particularly in fluoridated areas[10,44,53,71,88,94,105], but not in non-fluoridated areas[78]. Soy-based formulas have been reported to have somewhat higher fluoride concentrations than milk-based formulas[10,94,105] and this has been attributed to higher endogenous levels of fluoride in the soy extract[44,54,65]. However, the most important factor when considering infant formulas as risk factors for dental fluorosis is the water used to reconstitute them. When infant formulas are reconstituted with optimally fluoridated water, they provide a daily fluoride intake above that likely to cause some degree of dental fluorosis[10,94]. Therefore, to reduce the risk of fluorosis the recommendation is to use ready-to-feed formulas whose fluoride concentrations are known to be low, or low-fluoride bottled water to dilute the formula concentrate.

Fluoride dentifrice

Ripa[89] reviewed studies that investigated the possible association between the use of fluoride dentifrice and prevalence of dental fluorosis. He concluded that of the ten studies reviewed, nine[7,9,18,39,49,74,96,99,113] failed to find an association. These studies, however, were not designed with fluoride dentifrice effects as the major focus or used surrogate measures to evaluate fluoride dentifrice exposure. From this group of studies, the only one[71] used case control methodologies to assess the relationship between dental fluorosis and dentifrice use. The authors identified only two factors, tooth brushing with fluoride containing dentifrice prior to 25 months of age and prolonged use of infant formula beyond 13 months of age, as being significantly associated with dental fluorosis in a fluoridated community.

More recent studies specifically addressed dentifrice use in more detail, with most finding a relationship between early dentifrice use and dental fluorosis[21,62,66,80]. Moreover, other studies have used case control methods to assess the relationship between dental fluorosis and the early use of fluoride dentifrices. All these studies have demonstrated significant relationships between fluoride dentifrice use and dental fluorosis. A study of 157 patients aged 8-17-years attending a university pediatric dentistry clinic in Iowa City identified exposure to fluoride water and fluoride dentifrice as risk factors for dental fluorosis[95]. A larger study of a similar design was conducted in a pediatric dental practice in Asheville, North Carolina[51]. This study found that initiating tooth brushing with fluoride dentifrice prior to age two was significantly associated with dental fluorosis. In addition, for those drinking non-fluoridated water, daily fluoride supplement use was strongly associated with dental fluorosis.

Of particular interest are a series of well-designed case control studies conducted by Pendrys and co-workers[74,76-78] in both fluoridated and non-fluoridated areas in New England. In these studies, parents completed detailed, self-administered questionnaires regarding infant feeding patterns,

residence history, fluoride supplement use, brushing (with fluoride dentifrice) frequency, and amount of dentifrice used per brushing up to eight years of age. Among residents in fluoridated areas, mild-to-moderate dental fluorosis was associated with (inappropriate) supplement use, frequent brushing prior age of eight, and use of larger than pea-sized amounts of dentifrice. The estimated percentage of cases of dental fluorosis attributable to greater dentifrice use was 21%[76,77]. (Pendrys et al., 1994, 1995).

Among residents of non-fluoridated areas, Pendrys; Katz[74] found that mild-to-moderate dental fluorosis was strongly associated with fluoride supplement use and high household income, but the use of infant formula and fluoride dentifrice were not associated with increased risk for fluorosis. However, a later study[78] identified fluoride supplement use and frequent, early toothbrushing habits as significantly associated with mild-to-moderate fluorosis in both early and late enamel forming surfaces in the permanent teeth.

As a follow up to their trial of low fluoride dentifrice in children between the ages of three to five years in a fluoridated area[112] Holt and co-workers[40] compared the prevalence of dental fluorosis among high (1,055 ppm fluoride) and low (550 ppm fluoride) fluoride dentifrice groups, when children were 9-10 years of age. This study found that use of fluoride supplements and use of standard dentifrice (1,055 ppm fluoride) significantly increased the risk of dental fluorosis in the permanent teeth.

In their study of eight-year-old Norwegian children whose water was not fluoridated, Wang and co-workers[108] identified regular supplement use and use of fluoride toothpaste prior to age 14 months as the only significant risk factors for dental fluorosis.

Rock; Sabieha[90] conducted a study of 325 8-9-year-old children living in optimally-fluoridated Birmingham, England and found a strong association between fluorosis in the maxillary central incisors and early dentifrice use and use of dentifrice with a high (1,500 ppm) fluoride concentration. It was also observed that a higher proportion of children without fluorosis had used a commercially available low-fluoride dentifrice.

While case control methodologies, more detailed survey instruments, and multivariate analysis used in many of these recent studies lend more credence to the conclusions than the earlier studies, all of these studies have relied on retrospective assessment of fluoride exposures, often eight to ten years after the exposures had occurred. Thus, all studies relating dentifrice use to dental fluorosis are prone to recall bias. Nevertheless, there is now compelling evidence that the early use of fluoride dentifrice is an important risk factor for dental fluorosis, as young children swallow considerable amounts of dentifrice. In fact, the amount of fluoride ingested is inversely related to the age of the child.

Dentifrices with a fluoride concentration of 1,000 ppm contain 1.0 mg of fluoride per gram. In children younger than 6 years of age, the mean quantity of dentifrice per brushing episode is about 0.55 g[86], corresponding to a fluoride exposure of about 0.55 mg. An average of 48% of this amount is ingested by 2- to 3-year olds, 42% by 4-year-olds and 34% by 5-year-olds[5,20,38,86]. Assuming mean body weights of 15, 18 and 20 kg, respectively, fluoride intake from one brushing per day results in ingestion of 18, 13 and 9 mg/kg/day, respectively. So, it is evident that toothbrushing substantially increases the fluoride exposure, particularly for 2- to 3-year-old children, and, of course, especially for children that brush more than once daily[31]. Information like this for economically developing countries is rare[12]. Studies conducted with 2-3-year-old Brazilian children, that lived in areas with fluoridated water, showed that they ingested 0.061 mg fluoride/kg body weight per day (range 0.011-0.142) from dentifrice[73] and that dentifrice contributed with 55% of the total amount of fluoride ingested daily[56].

Based on these findings, it is clear that measures to reduce fluoride intake by children at risk of dental fluorosis are necessary. Two alternatives have been suggested. The first one would be to reduce the amount of dentifrice used. This is an important measure, but we cannot forget that nowadays in most families both parents work and people who take care of the children not always follow parents' instructions. In addition, the flavor of most children dentifrices encourages ingestion. Because of this, it has been proposed that dentifrices with lower fluoride concentrations should be developed and marketed for use by young children, as has been done in many countries[6,41]. The European Academy of Paediatric Dentistry[72] advises the use of a very small amount of low fluoride dentifrice from 6 months to 2 years of age and the use of a pea-sized amount of 500 ppm fluoride twice daily from 2 to 6 years. A higher fluoride concentration dentifrice (1,000-1,500 ppm) should be used as soon as the first permanent molars erupt. However, in some countries (like Brasil and USA) the sale of low fluoride dentifrices is not allowed until large clinical

trials have demonstrated safety and efficacy. It is possible that reducing the fluoride concentration of dentifrices could reduce the anti-caries effectiveness. Therefore, the ideal lower fluoride dentifrice should not only reduce fluoride ingestion, but also be equally effective in caries prevention as currently marketed formulations of 1,000-1,100 ppm fluoride. Some researchers have developed low fluoride formulations (550 ppm, NaF) that were as effective as the "gold-standard" Crest (1,100 ppm) in terms of reducing enamel demineralization and enhancing enamel remineralization in situ[81]. The cariostatic effectiveness of this formulation, however, has not yet been tested in longitudinal clinical studies.

There have been many longitudinal clinical trials of the effectiveness of dentifrices with lower fluoride concentrations. Some of them found no significant differences between standard (1,000-1,100 ppm) and low fluoride dentifrices (250-550 ppm fluoride)[32,35,47]. In contrast, Reed[83], Mitropoulos and co-workers[68] and Koch and co-workers[48] found the low-fluoride dentifrices to be somewhat less effective than the 1,000 ppm dentifrices.

At first glance, these studies might suggest that low-fluoride dentifrices are less effective in terms of caries prevention than standard 1,000 ppm dentifrices. However, of these studies, only one[35] was conducted on the appropriate, preschool age group. This study did not find a statistically significant difference between 250 ppm and 1,000 ppm dentifrices. In view of the negative results of the studies cited above, however, it may be that a fluoride concentration of 250 ppm is too much of a departure from the standard 1,000 ppm dentifrice. A more practical formulation may have fluoride concentrations in the range of 500-550 ppm[109].

The only study of low-fluoride dentifrice that used both a sample of young, preschool children and a 500-550 ppm dentifrice was reported by Winter and co-workers[112]. This three-year, double blind trial compared effectiveness of 550 and 1,055 ppm fluoride dentifrices in children who were two years of age at baseline by measuring dmf increments. The caries increment was slightly higher (10%) in the low-fluoride dentifrice group after three years, but the difference was not statistically significant. The authors concluded that "the low fluoride toothpaste possessed a similar anticaries activity to the control paste and could therefore be recommended for use by young children." However, their conclusion was based on a single study and additional trials of such dentifrices should be conducted.

Thus, even without corroborating studies, it appears that the best balance between prevention of caries and dental fluorosis favors reduced concentrations of about 500-550 ppm fluoride for preschoolers. However, those groups or individuals judged to be at increased risk for dental caries might have a more favorable benefit/risk ratio with the use of standard 1,000-1,100 ppm fluoride dentifrices. While additional studies are needed for young children that are not at high risk for caries but may be at risk for dental fluorosis, it is appropriate to consider recommendations that dentifrices containing 500-550 ppm fluoride be marketed and endorsed for use by preschool children.

Any decision taken by official health organs should take into account both anti-caries effectiveness and risk for dental fluorosis. In addition, official health organs should review labeling requirements for dentifrice to make the fluoride concentrations more apparent and should formulate guidelines for instructions regarding prudent use in young children. The Support Agencies should finance additional well-controlled clinical trials of low-fluoride dentifrices of sufficient duration and follow-up to assess both dental caries and fluorosis prevention. Such trials should be conducted with populations of children in the targeted preschool age group. Furthermore, manufacturers should be encouraged to aggressively market dentifrice dispensers with small orifices or fixed amount "pumps" for use by young children. They should be encouraged or required also to warn parents concerning excessive use and ingestion of dentifrices flavored for children. Dentists, physicians, and other professionals, as well as dentifrice manufacturers should continue to recommend the use of a small "pea-sized" amount of dentifrice (no more than 0.25 g) for young children. In addition, preschool children should be well-supervised in their use of fluoride dentifrice, and the dentifrice should be placed on a child-size toothbrush by a parent or other adult[109].

Infant foods and drinks

During infancy the main sources of fluoride are considered to be commercially available foods and beverages. Many studies have shown that the fluoride concentrations of infant foods and beverages span a wide range and depends mainly on the fluoride concentration in the water used to manufacture them[29,30,106].

Beikost is a collective term for foods other than milk or formula fed to infants. The fluoride concentration of most beikost is quite modest[30]. However, some cereals in Brazil have been shown to have higher fluoride concentrations than would be expected. This was the case for Mucilon and Neston, both manufactured by Nestlé, which had fluoride concentrations of 2.44 and 6.2 ppm, respectively. A relatively high fluoride concentration was also found in a ready-to-drink chocolate milk (1.2 ppm, Toddynho, Quaker). When one of these products is consumed just once a day it can provide as much as 25% of the fluoride intake believed to be associated with increased risk for dental fluorosis of esthetic concern (0.1 mg F/kg body weight/day) for a 2-year-old child[19]. Of especial concern are also some teas, especially the black tea (Camelliia sinensis), which has high fluoride concentrations[34]. Thus, these products may be important contributors to total daily fluoride intake and their consumption by children at the age of risk for dental fluorosis must be controlled[19]. In addition, the manufacturers should inform the fluoride content on the label.

RESUMO

O declínio na prevalência e incidência de cárie dentária nas duas últimas décadas é considerado ser devido, em grande parte, ao amplo uso do flúor. Entretanto, a prevalência de fluorose dentária aumentou simultaneamente. O aumento foi nas formas de fluorose suave e muito suave, tanto em áreas fluoretadas como não fluoretadas. Uma grande quantidade de dados epidemiológicos mostra que a ocorrência de lesões fluoróticas está associada à ingestão excessiva de flúor durante o período de desenvolvimento dental. Muitas fontes de flúor têm sido identificadas. Esta revisão descreve a condição e sumariza a literatura recente acerca dos fatores de risco para fluorose dentária. Quatro fatores de risco maiores foram consistentemente identificados: uso de água fluoretada, suplementos de flúor, dentifrícios fluoretados ou fórmulas infantis. Em adição alguns alimentos e bebidas manufaturados podem ser importantes contribuintes para a ingestão diária total de flúor.

UNITERMOS: Flúor; Fluorose dentária, risco.

REFERENCES

1- ANGMAR-MANSSON, B.; WHITFORD, G.M. Environmental and physiological factors affecting dental fluorosis. **J. dent. Res.**, v. 69, p. 706-13, Feb 1990. Special Issue.

2- AST, D.B. et al. Newburgh-Kingston caries fluorine study XIV. Combined clinical and roentgenographic dental findings after ten years of water fluoride experience. **J. Amer. dent. Ass.**, v. 52, p. 314-25, 1956.

3- BAELUM, V. et al. Daily dose of fluoride and dental fluorosis. **Tandlaegebladet**, v. 91, n. 10, p. 452-6, 1987.

4- BARDSEN, A. "Risk periods" associated with the development of dental fluorosis on maxillary permanent central incisors. **Acta Odont. Scand.**, v. 57, n. 5, p. 247-56, 1999.

5- BARNHART, W.E. et al. Dentifrice usage and ingestion among four age groups. **J. dent. Res**., v. 53, n. 6, p. 1317-22, 1974.

6- BELTRAN, E.D.; SZPUNAR, S.M. Fluoride in toothpastes for children: suggestions for change. **Pediatr. Dent**., v. 10, p. 185-8, 1988.

7- BOHATY, B.S. et al. Prevalence of fluorosis-like lesions associated with topical and systemic fluoride usage in an area of optimal water fluoridation. **Pediatr. Dent.**, v. 11, n. 2, p. 125-8, 1989.

8- BURT, B.A. The changing patterns of systemic fluoride intake. **J. dent. Res.**, v. 71, n. 5, p. 1228-37, May 1992.

9- BUTLER, W.J.; SEGRETO, V.; COLLINS, E. Prevalence of dental mottling in school-aged lifetime residents of 16 Texas communities. **Amer. J. Public Health**, v. 75, n. 12, p. 1408-12, 1985.

10- BUZALAF, M.A.R. et al. Fluoride content of infant formulas prepared with deionized, bottled mineral and fluoridated drinking water. **ASDC J. Dent. Child**., v. 68, n. 1, p. 37-41, 2001.

11- CDC. Recommendations for using fluoride to prevent and control dental caries in the United States. **Morbidity and mortality weekly report**, v. 50, n. RR-14, Atlanta, GA, USA, August 17, 2001.

12- CURY, J.A. Determination of appropriate exposure of fluoride in non-EME countries in the future. J. **dent. Res.**, v. 79, n. 4, p. 901, 2000.

13- DEAN, H.T. Classification of mottled enamel diagnosis. **J. Amer. dent. Ass**., v. 21, p. 1421-6, 1934.

14- DEAN, H.T. The investigation of physiological effects by the epidemiological method. In: Moulton, F.R., edit. **Fluorine and dental health**. Washington, DC, American Association for the Advancement of Science, 1942. p. 23-31.

15- DEAN, H.T.; ARNOLD, F.A.; ELVOVE, E. Domestic water and dental caries V. Additional studies of the relation of fluoride domestic waters to dental caries experience in 4,425 white children aged 12-14 years in 13 cities in 4 states. **Public Health Rep**., v. 57, p. 1155-79, 1942.

16- DENBESTEN, P.K. Dental fluorosis: its use as a biomarker. **Adv. dent. Res.**, v. 8, n. 1, p. 105-10, 1994.

17- DENBESTEN, P.K. Biological mechanisms of dental fluorosis relevant to the use of fluoride supplements. **Comm. Dent. oral Epidemiol**., v. 27, n. 1, p. 41-7, 1999.

18- DRISCOLL, W.S. et al. Prevalence of dental caries and dental fluorosis in areas with optimal and above-optimal water fluoride concentrations. **J. Amer. dent. Ass**., v. 107, n. 1, p. 42-7, 1983.

19- DUARTE, J.L. et al. Concentração de flúor em alimentos infantis e risco de fluorose dental. **Pesq. Odont. Bras**., v. 15, p. 34, 2001. Supplement. Abst. I101.

20- ERICSSON, Y.; FORSMAN, B. Fluoride retained from mouthrinses and dentifrices in preschool children. **Caries Res.**, v. 3, n. 3, p. 290-9, 1969.

21- EVANS, D.J. A study of developmental defects in enamel in 10-year-old high social class children residing in a non-fluoridated area. **Comm. Dent. Health**, v. 8, n. 1, p. 31-8, 1991.

22- EVANS, R.W. Changes in dental fluorosis following an adjustment to the fluoride concentration of Hong Kong's water supplies. **Adv. dent. Res**., v. 3, n. 2, p. 154-60, 1989.

23- EVANS, R.W.; DARVELL, B.W. Refining the estimate of the critical period for susceptibility to enamel fluorosis in human maxillary central incisors. **J. Public Health Dent**., v. 55, n. 4, p. 238-49, 1995.

24- FEJERSKOV, O. et al. Clinical and structural features and possible pathogenic mechanisms of dental fluorosis. **Scand. J. dent. Res**., v. 85, n. 7, p. 510-34, 1977.

25- FEJERSKOV, O.; MANJI, F.; BAELUM, V. The nature and mechanisms of dental fluorosis in man. **J. dent. Res.**, v. 69, p. 692-700, 1990. Special Issue.

26- FEJERSKOV, O. et al. Posteruptive changes in human dental fluorosis – a histological and ultrastructural study. **Proc. Finn. Dent. Soc**., v. 87, n. 4, p. 607-19, 1991.

27- FEJERSKOV, O.; BAELUM, V.; RICHARDS, A. Dose-response and dental fluorosis. In: Fejerskov, O.; Ekstrand, J.; Burt, B.A., edit. **Fluoride in Dentistry**. 2. ed. Copenhagen, Munksgaard, 1996. p. 153-66.

28- FEJERSKOV, O.; RICHARDS, A.; DENBESTEN, P.K. The effect of fluoride on tooth mineralization. In: Fejerskov, O.; Ekstrand, J.; Burt, B.A., edit. **Fluoride in Dentistry**. 2. ed. Copenhagen, Munksgaard, 1996. p. 112-52.

29- FERNANDES, C.M.; TABCHOURY, C.M.; CURY, J.A. Fluoride concentration in infant foods and risk of dental fluorosis. **J. dent. Res**., v. 80, p. 224, 2001. Special Issue. Abst 1505.

30- FOMON, S.J.; EKSTRAND, J. Fluoride intake by infants. **J. Public Health Dent**., v. 59, n. 4, p. 229-34, 1999.

31- FOMON, S.J.; EKSTRAND, J.; ZIEGLER, E.E. Fluoride intake and prevalence of dental fluorosis: trends in fluoride intake with special attention to infants. **J. Public Health Dent**., v. 60, n. 3, p. 131-9, 2000.

32- FORSMAN, B. Studies on the effect of dentifrices with low fluoride content. **Comm. dent. oral Epidemiol**., v. 2, n. 4, p. 166-75, 1974.

33- FORSMAN, B. Early supply of fluoride and enamel fluorosis. **Scand. J. dent. Res**, v. 85, n. 1, p. 22-30, 1977.

34- FUJIMAKI, M. et al. Fluoride and aluminium in Brazilian and imported teas and oral health. **J. dent. Res**., v. 79, (Spec. Issue), p. 405, 2000.

35- GERDIN, P. Studies in dentifrices, VIII: Clinical testing of an acidulated, nongrinding dentifrice with reduced fluoride contents. **Swed. dent. J**., v. 67, n. 5, p. 283-97, 1974.

36- GLASS, R.L. INTRODUCTION – the first international conference on the declining prevalence of dental caries. **J. dent. Res.**, v. 61, p. 1304, 1982.

37- GRIMALDO, M. et al. Endemic fluorosis in San Luis Potosi, Mexico. I. Identification of risk factors associated with human exposure to fluoride. **Environ. Res.**, v. 68, n. 1, p. 25-30, 1995.

38- HARGREAVES, J.A.; INGRAM, G.S.; WAGG, B.J. A gravimetric study of the ingestion of toothpaste by children. **Caries Res.**, v. 6, n. 3, p. 237-43, 1972.

39- HOLM, A.K.; ANDERSON, R. Enamel mineralization disturbances in 12-year old children with known early exposure to fluorides. **Comm. dent. oral Epidemiol**., v. 10, n. 6, p. 335-9, 1982.

40- HOLT, R.D. et al. Enamel opacities and dental caries in children who used a low fluoride toothpaste between 2 and 5 years of age. **Int. dent. J.**, v. 44, n. 4, p. 331-41, 1994.

41- HOROWITZ, H.S. The need for toothpastes with lower than conventional fluoride concentrations for preschool-aged children. **J. Public Health Dent**., v. 52, p. 216-21, 1992.

42- IRIGOYEN, M.E.; MOLINA, N.; LUENGAS, I. Prevalence and severity of dental fluorosis in a Mexican community with above-optimal fluoride concentration in drinking water. **Comm. dent. oral Epidemiol.**, v. 23, n. 4, p. 243-5, 1995.

43- JACKSON, R.D. et al. Dental fluorosis in children residing in communities with different water fluoride levels: 33-month follow-up. **Pediatr. Dent**., v. 21, n. 4, p. 248-54, 1999.

44- JOHNSON JR, J.; BAWDEN, J.W. The fluoride content of infant formulas available in 1985. **Pediatr. Dent.**, v. 9, n. 1, p. 33-7, 1987.

45- JUNCOS, L.I.; DONADIO, J.V.Jr. Renal failure and fluorosis. **J. Amer. dent. Ass.**, v. 222, n. 7, p. 783-5, 1972.

46- KAMINSKY, L.S. et al. Fluoride: benefits and risks of exposure. **Crit. Rev. oral Biol. Med**., v. 1, n. 4, p. 261-81, 1990.

47- KOCH, G. et al. Effect of 250 and 1000 ppm fluoride dentifrice on caries. A three-year clinical study. **Swed. dent. J**., v. 6, n. 6, p. 233-8, 1982.

48- KOCH, G. et al. Caries-preventive effect of fluoride dentifrices with and without anticalculus agents: a 3-year controlled clinical trial. **Caries Res.**, v. 24, n. 1, p. 72-9, 1990.

49- KUMAR, J.V. et al. Trends in dental fluorosis and dental caries prevalences in Newburgh and Kingston, NY. **Amer. J. Public Health**, v. 79, n. 5, p. 565-9, 1989.

50- KUMAR, J.V.; SWANGO, P.A. Fluoride exposure and dental fluorosis in Newburgh and Kingston, New York: policy implications. **Comm. dent. oral Epidemiol**., v. 27, n. 3, p. 171-80, 1999.

51- LALUMANDIER, J.A.; ROZIER, G.R. The prevalence and risk factors of fluorosis among patients in a pediatric dental practice. **Pediatr. Dent.**, v. 17, n. 1, p. 19-25, 1995.

52- LARSEN, M.J.; RICHARDS, A.; FEJERSKOV, O. Development of dental fluorosis according to age at start of fluoride administration. **Caries Res**., v. 19, n. 6, p. 519-27, 1985.

53- LARSEN, M.J. et al. Dental fluorosis in the primary and the permanent dentition in fluoridated areas with consumption of either powdered milk or natural cow's milk. **J. dent. Res**., v. 67, n. 5, p. 822-5, 1988.

54- LATIFAH, R.; RAZAK, I.A. Fluoride levels in infant formulas. **J. Pedod.**, v. 13, n. 4, p. 323-7, 1989.

55- LEVERETT, D.H. Prevalence of dental fluorosis in fluoridated and in non-fluoridated communities-a preliminary investigation. **J. Public Hlth. Dent**., v. 46, p. 184-7, 1986.

56- LIMA, Y.B.O.; CURY, J.A. [Fluoride intake by children from water and dentifrice]. **Rev. Saude Publ.**, 2001 (in press).

57- MABELYA, L. et al. Dental fluorosis, altitude and associated dietary factors (short communication). **Caries Res**., v. 26, n. 1, p. 65-7, 1992.

58- MABELYA, L. et al. Dental fluorosis and the use of a high fluoride-containing trona tenderizer (magadi). **Comm. dent. oral Epidemiol**., v. 25, n. 2, p. 170-6, 1997.

59- MANJI, F. et al. Enamel changes in two low-fluoride areas of Kenya. **Caries Res**., v. 20, n. 4, p. 371-80, 1986.

60- MARTHALER, T.M. Caries status in Europe and predictions of future trends. **Caries Res**., v. 24, p. 381-96, 1990.

61- MARTHALER, T.M.; O'MULLANE, D.M.; VRBIC, V. The prevalence of dental caries in Europe 1990-1995. **Caries Res**., v. 30, n. 4, p. 237-55, 1996.

62- MASCARENHAS, A.K.; BURT, B.A. Fluorosis risk from early exposure to fluoride toothpaste. **Comm. dent. oral Epidemiol**., v. 26, n.4, p. 241-8, 1998.

63- MASCARENHAS, A.K. Risk factors for dental fluorosis: A review of the recent literature. **Pediatr. Dent.**, v. 22, n. 4, p. 269-77, 2000.

64- McDONAGH, M.S. et al. Systematic review of water fluoridation. **Brit. med. J.**, v. 321, n. 7265, p. 844-5, Oct 2000.

65- McKNIGHT-HANES, M.C. et al. Fluoride content of infant formulas: soy-based formulas as a potential factor in dental fluorosis. **Pediatr. Dent**., v. 10, n. 3, p. 189-94, 1988.

66- MILSOM, K.; MITROPOULOS, C.M. Enamel defects in 8-year-old children in fluoridated and non-fluoridated parts of Cheshire. **Caries Res.**, v. 24, n. 4, p. 286-9, 1990.

67- MINISTÉRIO DA SAÚDE. Secretaria de Políticas Especiais de Saúde. Área Técnica de Saúde Bucal. Levantamento epidemiológico em saúde bucal. (available in www.datasus.gov.br/cgi/sbucal/sbdescr.htm).

68- MITROPOULOS, C.M. et al. Relative efficacy of dentifrices containing 250 or 1000 ppm F in preventing dental caries – report of a 32-month clinical trial. **Comm. dent. Health**, v. 1, n. 3, p. 193-200, 1984.

69- MURRAY, J.J. Comments on results reported at the Second International Conference "Changes in caries prevalence". **Int. dent. J**., v. 44, n. 4, p. 457-8, 1994. supplement 1.

70- OPHAUG, R.H.; SINGER, L.; HARLAND, B.F. Estimated fluoride intake of 6-month-old infants in four dietary regions of the United States. **Amer. J. Clin. Nutr**., v. 33, n. 2, p. 324-7, 1980.

71- OSUJI, O.O. et al. Risk factors for dental fluorosis in a fluoridated community. **J. dent. Res.**, v. 67, n. 12, p. 1488-92, 1988.

72- OULIS, C.; RAADAL, M. MARTENS, L. Guidelines on the use of fluoride in children: An EAPD policy document. **Eur. J. Paediatr. Dent.**, v. 1, p. 7-12, 2000.

73- PAIVA, S.M.; CURY, J.A. Dentifricio fluoretado e risco de fluorose dentária. **Rev. Pós Grad.** (in press).

74- PENDRYZ, D.G.; KATZ, R.V. Risk of enamel fluorosis associated with fluoride supplementation, infant formula, and fluoride dentifrice use. **Amer. J. Epid**., v. 130, n. 6, p. 1199-208, 1989.

75- PENDRYZ, D.G.; MORSE, D.E. Use of fluoride supplementation by children living in fluoridated communities. **ASDC J. Dent. Child**., v. 57, n. 5, p. 343-7, 1990.

76- PENDRYZ, D.G.; KATZ, R.V.; MORSE, D.E. Risk factors for enamel fluorosis in a fluoridated population. **Amer. J. Epidemiol.**, v. 140, n. 5, p. 461-71, 1994.

77- PENDRYS, D.G. Risk of fluorosis in a fluoridated population. Implications for the dentist and hygienist. **J. Amer. dent. Ass**., v. 126, n. 12, p. 1617-24, 1995.

78- PENDRYS, D.G.; KATZ, R.V.; MORSE, D.E. Risk factors for enamel fluorosis in a nonfluoridated population. **Amer. J. Epidemiol.**, v. 143, n. 8, p. 808-15, 1996.

79- PENDRYZ, D.G.; KATZ, R.V. Risk factors for enamel fluorosis in optimally fluoridated children born after the US manufacturer's decision to reduce the fluoride concentration of infant formula. **Amer. J. Epidemiol**., v. 148, n. 10, p. 967-74, 1998.

80- PEREIRA, A.C. et al. Dental caries and fluorosis prevalence study in a nonfluoridated Brazilian community: trend analysis and toothpaste association. **ASDC J. dent. Child**., v. 67, n. 2, p. 132-5, 2000.

81- PERES, P.E.C.; DEL BEL CURY, A.A.; CURY, J.A. Avaliação in situ de uma formulação de dentifrício com concentração reduzida de flúor. **Pesq. Odont. Bras.**, v. 15, p. 83, 2001. (Abs A103).

82- PORCAR, C. et al. Fluorosis, osteomalacia and pseudohyperparathyroidism in a patient with renal failure. **Nefron**, v. 79, n. 2, p. 234-5, 1998.

83- REED, M.W. Clinical evaluation of three concentrations of sodium fluoride in dentifrices. **J. Amer. dent. Ass**., v. 87, n. 7, p. 1401-3, 1973.

84- RICHARDS, A. et al. Dental fluorosis developed in post-secretory enamel. **J. dent. Res.**, v. 65, n. 12, p. 1406-9, 1986.

85- RICHARDS, A.; FEJERSKOV, O.; BAELUM, V. Enamel fluoride in relation to severity of human dental fluorosis. **Adv. dent. Res.**, v. 3, n. 2, p. 147-53, 1989.

86- RICHARDS, A; BANTING, D.W. Fluoride toothpastes. In: Fejerskov, O.; Ekstrand, J.; Burt, B.A. eds. **Fluoride in dentistry**. Copenhagen, Munksgaard, 1996, p. 328-46.

87- RIORDAN, P.J.; BANKS, J.A. Dental fluorosis and fluoride exposure in Western Australia. **J. dent. Res**., v. 70, n. 7, p. 1022-8, 1991.

88- RIORDAN, P.J. Dental fluorosis, dental caries and fluoride exposure among 7-years-olds. **Caries Res**., v. 27, n. 1, p. 71-7, 1993.

89- RIPA, L.W. A critique of topical fluoride methods (dentifrices, mouthrinses, operator-, and self-applied gels) in an era of decreased caries and increased fluorosis prevalence. **J. Public Health Dent.**, v. 51, n. 1, p. 23-41, 1991.

90- ROCK, W.P.; SABIEHA, A.M. The relationship between reported toothpaste usage in infancy and fluorosis of permanent incisors. **Brit. dent. J**., v. 183, n. 5, p. 165-70, 1997.

91- RUGG-GUNN, A.J.; al-MOHAMMADI, S.M.; BUTLER, T.J. Effects of fluoride level in the drinking water, nutritional status and socio-economic status on the prevalence of developmental defects of dental enamel in permanent teeth in Saudi 14-year-old boys. **Caries Res**., v. 31, n. 4, p. 259-67, 1997.

92- RUSSELL, A.L. Dental fluorosis in Grand Rapids during the seventeenth year of fluoridation. **J. Amer. dent. Ass.**, v. 65, p. 608-12, 1962.

93- RWENYONYI, C. et al. Altitude as a risk indicator of dental fluorosis in children residing in areas with 0.5 and 2.5 mg fluoride per litre in drinking water. **Caries Res**., v. 33, n. 4, p. 267-74, 1999.

94- SILVA, M.; REYNOLDS, E.C. Fluoride content of infant formulae in Australia. **Austr. dent. J.**, v. 41, n. 1, p. 37-42, 1997.

95- SKOTOWSKI, M.C.; HUNT, R.J.; LEVY, S.M. Risk factors for dental fluorosis in pediatric dental patients. **J. Public Health Dent.**, v. 55, n. 3, p. 154-9, 1995.

96- SOPARKAR, P.M.; DEPAOLA, P.F. History of fluoride ingestion among children diagnosed with and without fluorosis. **J. dent. Res**., v. 64, p. 230, 1985. Special Issue. Abst.

97- SUNDSTROM, B.; MYHRBERG, H. Light and scanning electron microscopy of fluorosed enamel from human permanent teeth. **Caries Res.**, v. 12, n. 6, p. 320-9, 1978.

98- SUNDSTROM, B. et al. Morphology of outer regions of fluorosed deciduous enamel. **Caries Res.**, v. 14, n. 6, p. 381-8, 1980.

99- SZPUNAR, S.M.; BURT, B.A. Dental caries, fluorosis, and fluoride exposure in Michigan schoolchildren. **J. dent. Res**., v. 67, n. 5, p. 802-6, 1988.

100- SZPUNAR, S.M.; BURT, B.A. Fluoride exposure in Michigan schoolchildren. **J. Public Health Dent.**, v. 50, n. 1, p. 18-23, 1990.

101- TABARI, E.D. et al. Dental fluorosis in permanent incisor teeth in relation to water fluoridation, social deprivation and toothpaste use in infancy. **Brit. Dent. J.**, v. 189, n. 4, p. 216-20, 2000.

102- THYLSTRUP, A.; FEJERSKOV, O. Clinical appearance of dental fluorosis in permanent teeth in relation to histological changes. **Comm. dent. oral Epidemiol.**, v. 6, n. 6, p. 315-28, 1978.

103- TSUTSUI, A.; YAGI, M. HOROWITZ, A.M. The prevalence of dental caries and fluorosis in japanese communities with up to 1.4 ppm of naturally occurring fluoride. **J. Public Hlth. Dent.**, v. 60, n. 3, p. 147-53, Summer 2000.

104- TURNER, C.H. et al. High fluoride intakes cause osteomalacia and diminished bone strength in rats with renal deficiency. **Bone**, v. 19, n. 6, p. 595-601, 1996.

105- VAN WINKLE, S. et al. Water and formula fluoride concentrations: significance for infants fed formula. **Pediatr. Dent.**, v. 17, n. 4, p. 305-10, 1995.

106- VLACHOU, A.; DRUMMOND, B.K.; CURZON, M.E.J. Fluoride concentrations of infant foods and drinks in the United Kingdom. **Caries Res.**, v. 26, n. 1, p. 29-32, 1992.

107- VRBIC, V.L. The prevalence of dental caries in Slovenia in 1987 and 1993. **Comm. Dent. Health**, v. 12, v. 1, p. 39-41, 1995.

108- WANG, N.J.; GROPEN, A.M.; OGAARD, B. Risk factors associated with fluorosis in a non-fluoridated population in Norway. **Comm. dent. oral Epidemiol.**, v. 25, n. 6, p. 396-401, 1997.

109- WARREN, J. J.; LEVY, S.M. A review of fluoride dentifrice related to dental fluorosis. **Pediatr. Dent**., v. 21, n. 4, p. 265-71, 1999.

110- WHITFORD, G.M. The physiological and toxicological characteristics of fluoride. **J. dent. Res**., v. 69, p. 539-49, 1990. Special issue.

111- WHITFORD, G.M. Determinants and mechanisms of dental fluorosis. **CIBA Found. Symp.**, v. 205, p. 226-45, 1997.

112- WINTER, G.B.; HOLT, H.D.; WILLIAMS, B.F. Clinical trial of a low-fluoride toothpaste for young children. **Int. dent. J.**, v. 39, n. 4, p. 227-35, 1989.

113- WOOLFOLK, M.W.; FAJA, B.W.; BAGRAMIAN, R.A. Relation of sources of systemic fluoride to prevalence of dental fluorosis. **J. Public Health Dent**., v. 49, n. 2, p. 78-82, 1989.

114- YODER, K.M. et al. Severe dental fluorosis in a Tanzanian population consuming water with negligible fluoride concentrations. **Comm dent. oral Epidemiol.**, v. 26, n. 6, p. 382-93, 1998.

Corresponding author:

MARÍLIA AFONSO RABELO BUZALAF
Al. Octávio Pinheiro Brisolla, 9-75
Departamento de Ciências Biológicas/Bioquímica
Bauru-SP Brazil
17012-901
e-mail: mbuzalaf@fob.usp.br