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Fluoride Intake Levels in Relation to Fluorosis Development in Permanent Maxillary Central Incisors and First Molars

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Key Words
Dental fluorosis · Fluoride intake · Maxillary central incisors · First molars

Abstract
Gaps remain in our knowledge about the levels of fluoride intake that cause dental fluorosis. The purpose of this study was to report the fluorosis prevalence by levels of estimated fluoride intake in an effort to understand the importance of different levels of daily fluoride intake. As part of the longitudinal Iowa Fluoride Study, subjects were followed from birth to 36 months with questionnaires every 3–4 months to gather information on fluoride intake from various sources. Daily fluoride intake in mg per kg body weight (BW) was estimated from water, beverages and selected foods, fluoride supplements and dentifrice. Six hundred and twenty-eight subjects were examined for fluorosis on permanent incisors and first molars at about age 9 by two calibrated examiners using the Fluorosis Risk Index categories. Fluorosis prevalence rates were determined separately for maxillary central incisors and first molars by levels of estimated fluoride intake. There were significant positive associations between fluorosis prevalence and levels of fluoride intake. Cumulatively from birth to 36 months, average daily intake of 0.04 mg F/kg BW or less carried relatively low risk for fluorosis (12.9% for maxillary central incisors, 6.8% for first molars). Average daily intake of 0.04–0.06 mg F/kg BW showed a significantly elevated risk for fluorosis (23.0% for maxillary central incisors, 14.5% for first molars), while fluorosis risk was even higher for average intake above 0.06 mg F/kg BW (38.0% for maxillary central incisors, 32.4% for first molars). The study suggests that fluorosis prevalence is related to elevated fluoride intake when averaged over the first 3 years of life, but is even more strongly related to fluoride intake that is elevated for all of the first 3 years of life.

Dental fluorosis results from excessive fluoride intake during the enamel-forming periods early in life. In the United States and other developed countries, the marked decline in dental caries has been accompanied by an apparent increase in dental fluorosis due to the widespread use of fluoride [Rozier, 1999; CDC, 2001]. Over the past 40+ years, the number of different sources of ingested fluoride has increased and includes a variety of sources such as foods, beverages, dietary supplements, fluoride dentifrices, and other therapeutic fluoride products [Pendrys and Morse, 1990; Warren and Levy, 1999, 2003]. Using the data collected in the Iowa Fluoride Study, we have described the patterns of fluoride intake and exposure among children from birth to 72 months [Levy et al., 2001, 2003]. The mean total fluoride intakes appeared to

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be relatively stable very early in life and then at 20 months and later, with a transitional period between 6 and 20 months. There is considerable variation in fluoride intake across ages and among individuals, with some individuals' intakes greatly exceeding the means. A modest seasonal variation in fluoride intake from beverages was also found from 12 to 72 months, with higher intake in summer [Broffitt et al., 2004]. Dietary fluoride supplement intake was low and stable, fluoride ingested from dentifrice increased substantially from 6 to 24 months and then generally leveled off, and fluoride from water (from water itself and added to foods/beverages) generally increased with age [Levy et al., 2001, 2003]. Furthermore, we reported that early-erupting permanent teeth, such as maxillary central incisors, appear most at risk for fluorosis during the first 2 years, although the 3rd and 4th year of life were also individually important [Hong et al., 2006]. The data also indicated that fluorosis development relates not only to the time periods of fluoride intake relative to the stages of enamel formation, but also to the cumulative duration of an elevated level of fluoride intake.

A question of fundamental importance in fluoride use is the level of fluoride intake necessary for fluorosis development. McClure [1943] originally suggested an 'optimal' fluoride intake in the 1940s to be about 0.05 mg F/kg body weight (BW) from a cross-sectional sample of children from 1 to 12 years old. Although a number of studies attempted to estimate the mean daily fluoride intake of children using a variety of techniques, as reviewed by Warren and Levy [1999, 2003], there are very few studies that have specifically linked amounts of fluoride intake from all major sources to fluorosis occurrence. A better understanding of fluoride intake levels in relation to fluorosis development is crucial in efforts to maximize fluoride's caries-preventive benefits and minimize fluorosis risk. Using longitudinal data on individuals' fluoride intake collected in the Iowa Fluoride Study, we report the prevalence of dental fluorosis on maxillary central incisors and permanent first molars at various levels of estimated fluoride intake.

Methods

Data were collected from participants in the Iowa Fluoride Study, a prospective study of fluoride intake and exposures among a cohort recruited at birth from March 1992 to February 1995, using Institutional Review Board-approved informed consent procedures. Demographic characteristics at baseline were described previously [Levy et al., 1997]. Briefly, this cohort was 98% Caucasian, from families of relatively high socioeconomic status (71% having a family income of USD 30,000 or more and 46% of mothers having completed 4 years of college), 44% were first children, 32% were breast-fed for at least 6 months, 4% had low birth weight (<2,500 g) and 3% had developmental disorders such as congenital heart diseases. Study methodologies have been described in detail previously [Levy et al., 2001, 2003]. Subjects were followed from birth to 36 months (and beyond) with questionnaires every 3–4 months that included a series of items concerning children's fluoride exposures and ingestion from various sources during the preceding time period. Fluoride intake in mg per kg BW per day was estimated from water, beverages and selected foods, dietary fluoride supplements, and fluoride dentifrice based on parents' responses to the series of questions. Parents' responses were not validated, but reliability was assessed for selected questions [Levy et al., 2001, 2003]. Fluoride intake for cumulative time periods was calculated by the area under curve (AUC) [Hanley and McNeil, 1982] trapezoidal method.

Children (319 males and 309 females) were examined for dental fluorosis on early-erupting permanent teeth at about 8–10 years of age (mean age 9.3 years, SD 0.7, range 7.7–12.0) by two trained and calibrated dentist examiners using the Fluorosis Risk Index (FRI) [Pendrys, 1990]. Subjects who continued participation in the study and completed the mixed dentition exam were more often of Caucasian descent (98 vs. 91% for dropouts), more educated (45% of mothers with college degrees vs. 26%), had higher family incomes (33% above USD 50,000 vs. 18%), and older parents (mean age of mothers: 30 vs. 26, mean age of fathers: 32 vs. 30). Twelve early-erupting permanent teeth were examined in each subject: eight incisors and four first molars. A mouth mirror and exam light were used, and teeth were dried lightly with gauze. Fluorosis was differentiated from nonfluorosis opacities based on Russell's criteria [Russell, 1961]. Fluorosis was also distinguished from enamel demineralization ('white spot' lesions) based on color, texture, demarcation and relationship to the gingival margin [Slayton et al., 2001]. The FRI was adapted to include assessment of all visible enamel surfaces, with four zones scored separately on each buccal surface (the incisal edge/occlusal table, the incisal/occlusal third, the middle third, and the cervical third). The scoring criteria differentiated no fluorosis, questionable fluorosis (less than 50% of zone with white striations), definitive fluorosis (greater than 50% of zone with white striations), and severe fluorosis (zone displays pitting/staining/deformity) [Pendrys, 1990]. Cervical zones were excluded from the analyses in this report because of lack of consistent full eruption.

A case of incisor fluorosis was defined as having FRI definitive/severe fluorosis (FRI score 2 or 3) on both maxillary central incisors; and a case of first molar fluorosis was defined as having FRI definitive/severe fluorosis on at least two first molars. All other subjects were classified as nonfluorosis.

The correlations among fluoride intakes for the first 3 years were assessed using Spearman rank correlation analyses. The sample sizes varied depending on questionnaire response rates for each time period. Fluoride intake for cumulative time periods (AUC) was calculated for the 1st year (0–12 months), 2nd year (12–24 months), 3rd year (24–36 months), and all 3 years (0–36 months).

Logistic regression was used to assess the relationships between estimated fluoride intakes and fluorosis. Estimated daily fluoride intake was subsequently categorized into three catego-

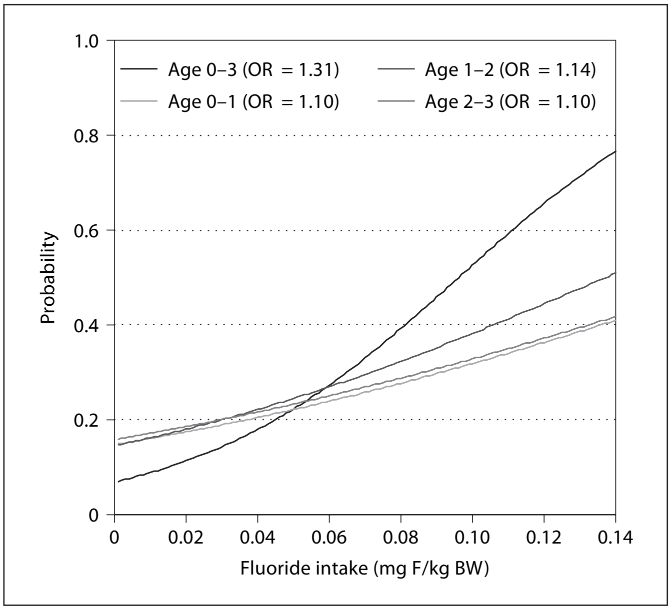

Fig. 1. Probability of permanent maxillary central incisor fluorosis case by level of fluoride intake (from logistic regression). ORs for increments of 0.01 mg F/kg BW. p values for fluoride intakes were all statistically significant ($p < 0.05$).

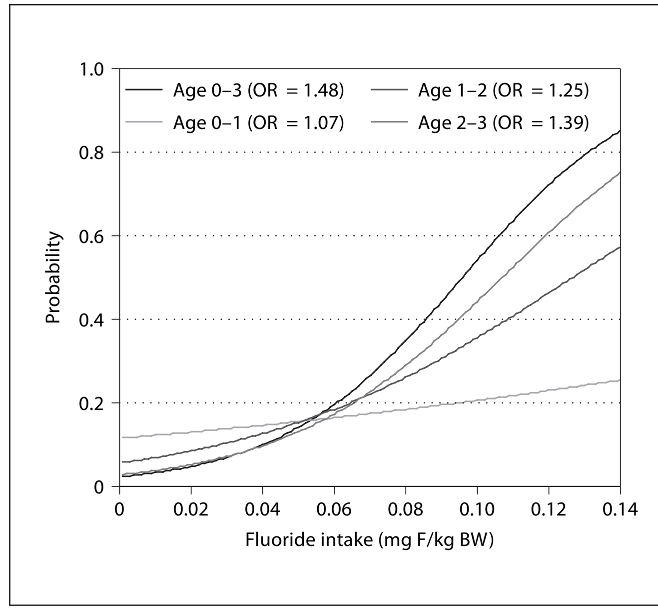

Fig. 2. Probability of permanent first molar fluorosis case by level of fluoride intake (from logistic regression). ORs for increments of 0.01 mg F/kg BW. p values for fluoride intakes were all statistically significant ($p < 0.05$).

ries: <0.04 mg F/kg BW, 0.04–0.06 mg F/kg BW, and >0.06 mg F/kg BW. Fluorosis prevalence rates were calculated by fluoride intake category, and relationships were assessed using Cochran-Armitage tests for linear trend, using scores equal to the median fluoride intake for each group. Using the subjects with fluoride intake <0.04 mg F/kg BW as the reference group, the relative risks (RRs) for fluorosis were calculated for 0.04–0.06 mg F/kg BW intake, and >0.06 mg F/kg BW intake. Similar categorical analyses were used to compare subjects who consistently stayed within the same fluoride intake category for the first 2 years and those who were consistent for all 3 years.

The significance level was set at $\alpha = 0.05$. The data were analyzed with SAS statistical software for Windows version 9.1 (SAS Institute Inc., Cary, N.C., USA).

Results

Most dental fluorosis in this study was mild to moderate (FRI score 2), with only 8 individuals (1.3%) having severe fluorosis (FRI score 3). Prevalence rates were 24.0% for fluorosis on both maxillary central incisors (FRI score 2 or 3), and 16.2% for fluorosis on at least two first molars (FRI score 2 or 3). The Spearman correlation between 1st and 2nd year fluoride intake was 0.38 ($p < 0.001$), between 1st and 3rd year it was 0.17 ($p < 0.001$), and between 2nd and 3rd year it was 0.61 ($p < 0.001$).

Figures 1 and 2 present the predicted probability of fluorosis from logistic regression using levels of fluoride intake for different time periods (individual yearly intake and 0–3-year AUC intake) for maxillary central incisors and first molars, respectively. Logistic regression results show that at an average intake of 0.04 mg F/kg BW during the first 3 years, 18% of children are predicted to have fluorosis on both maxillary central incisors, and 10% to have fluorosis on 2 or more permanent first molars. At an average fluoride intake of 0.06 mg/kg BW during the first 3 years, 27% of children are predicted to have fluorosis on the maxillary central incisors, and 20% to have fluorosis on the permanent first molars. At an average F intake of 0.10 mg/kg BW during the first 3 years, 53% of children are predicted to have fluorosis on the maxillary central incisors, and 54% to have fluorosis on the permanent first molars.

The unit of increment for odds ratio (OR) calculations in the logistic regressions was set at 0.01 mg F/kg BW. For the maxillary central incisor fluorosis logistic curve based on 0- to 36-month AUC fluoride intake, the lower change point in curvature was located at 0.047 mg F/kg BW. For 0- to 36-month AUC fluoride intake and for each yearly intake, the upper change point in curvature occurred at fluoride levels beyond those seen in this study.

Table 1. Prevalence of fluorosis on both permanent maxillary central incisors by estimated total fluoride intake

Fluoride intake period	Subjects	<0.04 mg F/kg/day		0.04–0.06 mg F/kg/day			>0.06 mg F/kg/day			p value[1]
		n	% fluorosis	n	% fluorosis	RR (95% CI)	n	% fluorosis	RR (95% CI)	
0–12 months	405	185	15.7	67	25.4	1.62 (0.95, 2.75)	153	32.7	2.08 (1.39, 3.12)[2]	0.001
12–24 months	405	178	16.3	144	27.8	1.70 (1.12, 2.61)[2]	83	32.5	2.00 (1.27, 3.15)[2]	0.002
24–36 months	405	136	18.4	148	19.6	1.07 (0.66, 1.73)	121	34.7	1.89 (1.23, 2.90)[2]	0.002
0–36 months	405	132	12.9	165	23.0	1.79 (1.06, 3.02)[2]	108	38.0	2.95 (1.78, 4.88)[2]	0.001
2 years steady[3]	202	121	12.4	32	28.1	2.27 (1.09, 4.70)[2]	49	46.9	3.79 (2.16, 6.63)[2]	0.001
3 years steady[4]	113	67	13.4	16	25.0	1.86 (0.66, 5.29)	30	50.0	3.72 (1.84, 7.54)[2]	0.001

[1] Cochran-Armitage test for linear trend.
[2] RR significantly greater than 1.0 ($p < 0.05$) when compared to group with <0.04 mg F/kg/day.
[3] This group had the same intake category (<0.04, 0.04–0.06 or >0.06 mg F/kg/day) for years 1 and 2.
[4] This group had the same intake category (<0.04, 0.04–0.06 or >0.06 mg F/kg/day) for years 1, 2, and 3.

We chose to use 3 categories for subsequent comparisons of subjects with <0.04, 0.04–0.06, and >0.06 mg F/kg BW intake which corresponded to the intakes of 32, 41 and 27% of the sample, respectively, for 3-year fluoride intake. Individual yearly fluoride intake was less predictive of central incisor fluorosis (ORs ≤ 1.14) than age 0–3 (OR = 1.31) AUC intake. All ORs for maxillary central incisors were statistically significant at $p < 0.05$. For fluorosis on first molars, the lower change point in curvature for age 0–36 months AUC intake was at 0.062 mg F/kg BW. Three-year AUC fluoride intake was also the best single predictor of first molar fluorosis (OR = 1.48). The ORs were 1.07, 1.25, and 1.39 for 1st year, 2nd year, and 3rd year AUC fluoride intake, respectively. All first molar fluorosis ORs were statistically significant at $p < 0.05$.

Table 1 presents actual prevalence of fluorosis on both maxillary central incisors and estimated RRs. Table 2 presents actual prevalence and estimated RRs for first molar fluorosis cases. Linear trends for fluorosis prevalence by fluoride intake levels were all statistically significant for both maxillary central incisors and first molars.

Table 1 shows that the RR of maxillary central incisor fluorosis was significantly greater than 1.0 for subjects with 0.04–0.06 mg F/kg BW intake compared to subjects with under 0.04 mg F/kg BW intake at 12–24 months, 0–36 months and first 2 years steady intake. RR of fluorosis for subjects with fluoride intake above 0.06 mg/kg BW was significantly greater than 1.0 compared to subjects with less than 0.04 mg F/kg BW intake at all yearly and cumulative intervals. With 3-year averages from AUC calculations, fluorosis prevalence of both maxillary central incisors was 12.9, 23.0, and 38.0% for fluoride intake of <0.04, 0.04–0.06, and >0.06 mg F/kg BW, respectively. Using intake categories of <0.05, 0.05–0.07, and >0.07 mg F/kg BW for 3-year AUC fluoride intake, the fluorosis prevalence was 13.9, 30.8 and 40.9%, respectively (data not included in table 1). For subjects with all 3 years within the same category (3 years steady), fluorosis prevalence of both maxillary central incisors was 13.4, 25.0 and 50.0% for fluoride intake of <0.04, 0.04–0.06, and >0.06 mg F/kg BW, respectively.

Table 2 shows that the RR for first molar fluorosis cases was significantly greater than 1.0 for subjects with 0.04–0.06 mg F/kg BW intake compared to subjects with under 0.04 mg F/kg BW intake at 0–12 months, 12–24 months, 24–36 months, 0–36 months and first 2 years steady intake. RR of fluorosis for subjects with fluoride intake above 0.06 mg/kg BW was also significantly greater than 1.0 compared to subjects with less than 0.04 mg F/kg BW intake at all yearly and cumulative intervals. With 3-year averages from AUC calculations, fluorosis prevalence on first molars was 6.8, 14.5 and 32.4% for fluoride intakes of <0.04, 0.04–0.06, and >0.06 mg F/kg BW, respectively. Using intake categories of <0.05, 0.05–0.07, and >0.07 mg F/kg BW for 3-year AUC fluoride intake, the fluorosis prevalence was 7.7, 21.5 and 36.4%, respectively (data not included in table 2). For subjects with all 3 years within the same category (3 years steady), fluorosis prevalence on first molars was 7.5, 18.8, and 46.7% for fluoride intakes of <0.04, 0.04–0.06, and >0.06 mg F/kg BW, respectively.

The effect of sustained fluoride intakes on fluorosis prevalence of the maxillary central incisors and first molars is further summarized in table 3, which cross-tabulates prevalence for 3 categories of fluoride intake during

Table 2. Prevalence of fluorosis on two or more permanent first molars by estimated total fluoride intake

Fluoride intake period	Subjects	<0.04 mg F/kg/day		0.04–0.06 mg F/kg/day			>0.06 mg F/kg/day			p value[1]
		n	% fluorosis	n	% fluorosis	RR (95% CI)	n	% fluorosis	RR (95% CI)	
0–12 months	405	185	8.6	67	25.4	2.93 (1.57, 5.47)[2]	153	22.9	2.65 (1.52, 4.59)[2]	0.001
12–24 months	405	178	10.7	144	19.4	1.82 (1.06, 3.12)[2]	83	25.3	2.37 (1.35, 4.16)[2]	0.002
24–36 months	405	136	6.6	148	14.2	2.14 (1.02, 4.52)[2]	121	31.4	4.75 (2.39, 9.41)[2]	0.002
0–36 months	405	132	6.8	165	14.5	2.13 (1.03, 4.43)[2]	108	32.4	4.75 (2.39, 9.45)[2]	0.001
2 years steady[3]	202	121	8.3	32	25.0	3.03 (1.30, 7.04)[2]	49	30.6	3.70 (1.79, 7.67)[2]	0.001
3 years steady[4]	113	67	7.5	16	18.8	2.51 (0.67, 9.44)	30	46.7	6.25 (2.48, 15.78)[2]	0.001

[1] Cochran-Armitage test for linear trend.
[2] RR significantly greater than 1.0 ($p < 0.05$) when compared to group with <0.04 mg F/kg/day.
[3] This group had the same intake category (<0.04, 0.04–0.06 or >0.06 mg F/kg/day) for years 1 and 2.
[4] This group had the same intake category (<0.04, 0.04–0.06 or >0.06 mg F/kg/day) for years 1, 2, and 3.

Table 3. Fluorosis case prevalence by 0- to 12-month and 12- to 36-month fluoride intake levels

0- to 12-month daily F intake mg F/kg	Maxillary central incisor fluorosis 12- to 36-month daily F intake, mg F/kg			First molar fluorosis 12- to 36-month daily F intake, mg F/kg		
	<0.04	0.04–0.06	>0.06	<0.04	0.04–0.06	>0.06
0.04	14.3% (13/91)	14.5% (8/55)	20.5% (8^{x}/39)	6.6% (6/91)	3.6% (2/55)	20.5% (8/39)
0.04–0.06	12.5% (2/16)	29.4% (10/34)	29.4% (5/17)	12.5% (2/16)	23.5% (8/34)	41.2% (7^{x}/17)
0.06	19.0% (8/42)	36.2% (21^{xx}/58)	39.6% (21^{x}/53)	7.1% (3/42)	19.0% (11^{x}/58)	39.6% (21/53)

Each 'x' denotes a subject with severe (FRI = 3) fluorosis. All other subjects with fluorosis were rated mild to moderate (FRI = 2).

the 1st year vs. the following 2 years (12- to 36-month AUC). Relatively low maxillary central incisor fluorosis prevalence was found for subjects having at least one interval of intake below 0.04 mg F/kg BW (12.5–20.5%). Subjects with intake consistently above 0.04 mg F/kg BW had a higher fluorosis prevalence (29.4% and above), with the highest prevalence found for subjects who stayed above 0.06 mg F/kg BW during both intervals (39.6%). Although very few subjects had severe fluorosis on the maxillary central incisors (n = 4), all of them had high levels of fluoride intake (>0.06 mg/kg) at either 0–12 months or 12–36 months.

Prevalence of first molar fluorosis was low for subjects with 12- to 36-month intake below 0.04 mg F/kg BW (6.6–12.5%) and for subjects with low 1st year intake and moderate (0.04–0.06 mg F/kg BW) 12- to 36-month intake (3.6%). Subjects with intakes above 0.04 mg F/kg BW during both intervals, or 12- to 36-month fluoride intakes above 0.06 mg F/kg BW had a higher prevalence of first molar fluorosis (19.0–41.2%), with the highest prevalence among subjects with 12- to 36-month intake above 0.06 mg F/kg BW and 0- to 12-month intake at 0.04 mg F/kg BW or above. The two subjects with severe fluorosis on the first molars recorded both moderate (0.04–0.06 mg/kg) and high (>0.06 mg/kg) fluoride intake over the first 3 years.

Discussion

With longitudinal data on fluoride intake for individual subjects collected from birth to 36 months, we attempted to assess the levels of fluoride intake associated with fluorosis development on permanent teeth. Considering the paucity of studies in this area, particularly the lack of studies on longitudinal assessment of fluoride intake [Burt, 1992; Warren and Levy, 1999, 2003], the results from this study are important in helping provide a more thorough understanding of the levels of fluoride intake linked to fluorosis development. Since the study assessed fluoride intake from all major sources at the individual level from birth to 36 months (and beyond), it provides a unique opportunity to advance our knowledge concerning this critical aspect of fluoride use.

The present study provided strong evidence for a significant positive relationship between total fluoride intake and fluorosis prevalence, and the positive relationship is apparent for all yearly and extended time periods for both maxillary central incisor fluorosis and first molar fluorosis. The prevalence rates increased with increasing fluoride intake levels, although the rates varied substantially across different time periods. The data showed that when the cumulative average daily fluoride intake was greater than 0.04 mg F/kg BW, fluorosis prevalence was substantially higher (statistically significant) than at lower fluoride intake levels, with highest fluorosis rates for >0.06 mg F/kg BW. Statistical significance of the risk increase was observed for both maxillary central incisor fluorosis and first molar fluorosis relating to 2-year and 3-year cumulative fluoride intake duration. This dose-response relationship between fluoride intake and fluorosis prevalence is not surprising, considering that similar relationships between fluoride levels in drinking water, which was then the major source of fluoride intake, and fluorosis prevalence were repeatedly found since Dean's time [Dean and McKay, 1939].

Subjects with daily fluoride intake of <0.04 mg F/kg BW had less than 20% probability of developing fluorosis (18.5% on maxillary central incisors and 10.0% on first molars) and almost all fluorosis was of mild severity. Therefore, daily intake <0.04 mg F/kg BW apparently bears low risk for fluorosis. Collectively from linear trend tests, RR, and logistic regression analyses on both maxillary central incisors and first molars, daily intake of 0.04–0.06 mg F/kg BW carries a significant, elevated risk for fluorosis, while daily intake >0.06 mg F/kg BW is associated with high risk for fluorosis on early-erupting permanent teeth (incisors and first molars). However, our data also showed different susceptibility for fluorosis by tooth type, with maxillary central incisors having greater fluorosis prevalence than first molars.

The choice of 0.04 mg F/kg BW as the cutoff point is both from the statistical model and clinical considerations, as described above. However, this is different from the concept of a threshold. Fluorosis susceptibility varies substantially between subjects within similar fluoride intake categories and by tooth type, such as the differences seen between primary and permanent teeth or between maxillary and mandibular incisors (data not shown). Therefore, the use of a common threshold might not be appropriate. The cut point of 0.04 mg F/kg BW from this study applies only to the early-erupting permanent teeth. Its generalizability may be quite limited, and further research is definitely needed, such as studies on different populations and different tooth types.

Although it is possible that an acute, short-term high dose of fluoride could induce fluorosis [Angmar-Mansson and Whitford, 1985; Suckling et al., 1988], our study did not assess this. Rather, our data support the importance of cumulative, long-term fluoride intake. As reported regarding the critical stage of tooth development for fluorosis etiology [Hong et al., 2006], the first 2 years of life generally were found to be more important compared to later years. However, effects of fluoride intake during any critical period or window of maximum susceptibility is confounded by fluoride intake at other ages. Thus, this window of importance should be viewed as the period when risk of fluorosis may be maximal, but not as the only time when there is fluorosis susceptibility. This report clearly shows that subjects with ingestion of high levels of fluoride for longer duration had higher fluorosis prevalence, with daily intakes >0.06 mg F/kg BW during each of the 3 years having the highest risk for fluorosis. Therefore, fluorosis development appears to relate not only to the timing of fluoride intake relative to the stages of enamel formation, but also to the duration of such a fluoride intake level. This result is consistent with the possible mechanisms of fluorosis etiology suggested by other researchers [Evans and Darvell, 1996; Den Besten, 1999; Robinson et al., 2004].

Given the dynamic nature of fluoride intake [Levy et al., 1995; Warren and Levy, 1999, 2003], including daily fluctuation [Bawden, 1996; Levy et al., 2001, 2003] and seasonal changes [Broffitt et al., 2004], estimating a critical level of fluoride intake necessary for fluorosis development is inherently difficult. Studies have shown the considerable variation in fluoride intake at various ages both between individuals and within individuals across time [Rojas-Sanchez et al., 1999; Levy et al., 2001, 2003]. In an effort to simplify the numerous combinations of fluoride intake levels at different ages that could be important in determining an individual's fluorosis risk, we elected to use cumulative 1-, 2- and 3-year estimates of fluoride intake. Most other research studies and clinicians would have much more limited fluoride intake data available.

The findings from this study should be interpreted within the limitations of the study. The cohort was a convenience sample of families with relatively high socioeconomic status. Incomplete questionnaire data, which is an unavoidable problem in longitudinal studies, resulted in only 113 subjects being available for the analyses of 3-year steady intake. Fluoride intake data were obtained through self-administered questionnaires from parents without direct verification. These estimates were based on assessment at 3–4 intervals during each year and do not fully account for within-period variations in intake. Daily fluctuation was also not assessed. Some less frequent sources of fluoride exposure, such as fluoride mouth rinses and gels, were not included in these analyses. Also, only 6 subjects (~1.5%) had more severe fluorosis (FRI scores of 3), so our results are limited primarily to mild fluorosis (white opacity). Any recommendation or change of the so-called 'optimal level' of fluoride intake for the public seems to be premature not only because of the study limitations, but also because the appropriate use of fluoride must take into account the caries-preventive effects. Thus, the goal is finding the maximal balance of benefit and risk from fluoride use. Also, these analyses have not controlled for other potential risk factors in fluorosis development, including amoxicillin use during infancy [Hong et al., 2005]. Nevertheless, because of the unique longitudinal data on fluoride intake from all major sources at the individual level, the study provides important insights into the levels of fluoride intake associated with dental fluorosis.

In conclusion, this study showed significant positive associations between fluorosis prevalence and levels of fluoride intake during the first 3 years. Considering from birth to 36 months, on first molars and maxillary central incisors, an average daily intake of <0.04 mg F/kg BW carries a low risk for fluorosis, a daily intake of 0.04–0.06 mg F/kg BW generally produces a significant, increased risk for fluorosis, and a daily intake of >0.06 mg F/kg BW is associated with a high risk for fluorosis. Fluorosis development appears also to relate to the duration of cumulative exposure to high levels of fluoride intake.

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