"Risk periods" associated with the development of dental fluorosis in maxillary permanent central incisors: a meta-analysis

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This systematic review of the dental literature (1966–98) concerns risk periods associated with dental fluorosis in the maxillary permanent central incisors. A literature search was organized through the MedLine and the ISI databases. In addition, one unpublished paper (in manuscript) was obtained, as well as one paper published before 1966. However, out of 143 catches, only 10 studies were included in this review. The main reason for exclusions was that the data presented did not meet the criteria given for the present meta-analysis. Among the included papers, 7 pertained to subjects whose exposure to fluoride *started at different ages* during the enamel formation (Group 1), and 3 were based on subjects who had been *exposed from birth* and then experienced an abrupt reduction in daily fluoride exposure at different ages during the amelogenesis period (Group 2). The meta-analysis for Group 1 found the odds ratio (OR) for dental fluorosis in children exposed to fluoride early in life (before 2 years of age) to be 7.24 (95% CI; 4.71–11.13) as compared to children exposed later in life (after 2 years of age). The meta-analysis for the studies in Group 2 found the overall OR to be 1.88 (95% CI; 1.35–2.61) for children who had a reduction in fluoride intake after 2 years of age, as compared to individuals who experienced reduction earlier (during the first 2 years). The studies from both groups were pooled and the duration of exposure to fluoride during the first 4 years of life was the independent variable. The meta-analysis now revealed an overall OR of 5.83 (95% CI; 2.83–11.94) for *long periods* of fluoride exposure (>2 out of the first 4 years) versus *shorter periods* of exposure (<2 out of the first 4 years of life) during the enamel formation in the maxillary central incisors. Based on the findings of the meta-analysis, no specific period of enamel formation is singled out as being *the most critical* for the development of dental fluorosis. *The duration of fluoride exposure* during the amelogenesis, rather than specific risk periods, would seem to explain the development of dental fluorosis in the maxillary permanent central incisor. □ *Dental fluorosis; fluoride exposure; meta-analysis; risk period; susceptibility*

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Excessive fluoride intake can cause dental fluorosis in developing teeth (1–3). While the clinical features of dental fluorosis are well known, the exact role of fluoride in the pathogenesis and the period(s) of maximum risk are still matters of debate. Relatively few studies have addressed the problem, and findings are inconsistent. Since fluorotic changes in teeth cannot be cured, but may easily be prevented if the fluoride intake is adequately controlled during the period of tooth formation, more information on the timing of dental fluorosis is urgently needed.

The start and duration of the mineralizing period vary among the different groups of teeth, so the period of maximum susceptibility would be expected to vary accordingly. In order to simplify the assessment of risk periods, the present study is restricted to maxillary permanent central incisors, in which mineralization of the crown is normally completed by 4 years of age (4).

The ideal study regarding fluorosis risk periods in the incisors would be a randomized clinical trial, including groups of subjects exposed to fluoride only during the 1st year of life, alternatively only the 2nd, 3rd or 4th year of life. Ethical and practical considerations make it impossible to conduct such experiments in humans. Information concerning risk periods in humans can, consequently, only be gathered retrospectively; from individuals who have been exposed to changes in the fluoride ingestion more or less by chance.

The literature concerning the timing of fluorosis includes at least two types of reports: (i) studies in individuals who have been introduced to fluoride at different ages during their first years of life (5–9) and (ii) studies in populations which, after having been exposed to fluoride (water fluoride) from birth, experience an abrupt reduction in daily fluoride intake at different periods during the amelogenesis (10–12).

Due to methodological differences in the studies (grouping, indices for scoring of dental fluorosis, sources of fluoride), interpretation and comparison of findings are difficult. Most of the studies in category (i) seem to indicate that the first year of life is a crucial period for the development of dental fluorosis. Pendrys et al. (7, 8), however, found that teeth exposed to fluoride supplements throughout the 3rd to the 6th year of life were equally at risk. Findings in category (ii) are more ambiguous, but a majority of reports support findings from animal studies stating that teeth in the transitional and early maturation stages (i.e. later stages of mineralization) rather than teeth in the secretory (early) stage are particularly susceptible

Table 1. The literature search strategy—MedLine*

No.	Records	Request
1	1,537	Fluorosis
2	215,462	Dental
3	1,178	Fluorosis dental
4	116,852	Risk factors
5	3,941	Risk assessment
6	9,146	Disease susceptibility
7	6,387	Dentition
8	39,210	Permanent
9	705	Dentition permanent
10	128,637	#4 or #5 or #6
11	2	#3 and #10 and #9
12	45	#3 and #10
13	311,912	Risk
14	57,166	Susceptible**
15	362,964	#13 or #14
16	109	#3 and #15
17	109	#16 or #12 or #11

* The same search strategy was used on the ISI database, and 69 studies were identified.
** Truncated request.

(13–15). Ishii and Suckling (16) found two 'at-risk periods' for the development of moderate to severe fluorosis in the incisors; (i) starting at birth and ending relatively early in the developmental period of the tooth, and (ii) starting later during the mineralization period and ending shortly before eruption.

The lack of agreement between results from these two study designs may be due to the fact that dental fluorosis mirrors not only the daily fluoride load, but also the duration of fluoride exposure. Thus, an early introduction, e.g. to high-fluoride water, in most cases also indicates a long period of exposure. For category (ii), a reduction in daily fluoride intake in children while the tooth is in the maturation phase of development reflects a longer duration of fluoride exposure as compared to children experiencing fluoride reduction while the teeth are in the secretory phase of enamel formation. One problem encountered in evaluating the studies was inherent differences in study design and lack of statistical power due to small sample sizes.

The present review of the literature was done in order to up-date present knowledge, especially regarding the existence or non-existence of special 'risk periods'. To avoid bias and confirm or refute individual findings, so-called meta-analytical methods have been developed to aggregate information from different studies and provide quantitative estimates of the effect. In the present study, data from relevant literature were combined statistically to provide a quantitative estimate of the strength of association between the period of exposure and risk of disease.

Hence, the purpose of this paper is threefold: (i) to present a systematic review of the existing dental literature dealing with periods of susceptibility to fluorosis in incisors, (ii) to assess the credibility of the various 'risk period' findings, and, finally, (iii) to test the hypothesis that these studies may measure *duration* of fluoride exposure rather than identify critical periods for developing dental fluorosis.

Material and methods

Literature search

A computerized literature search was made to identify relevant studies. A professional librarian specializing in literature search in medical topics carried out a search in the MedLine (WinSPIRS 2.0) and ISI databases (searches carried out May 8th, 1998). The strategy is given in *Table 1*. The databases cover the literature since 1966 (MedLine) and 1992 (ISI database). A classical study published in 1933 was also included (11).

A systematic search for unpublished studies was not carried out, but one manuscript was obtained and included in the meta-analysis (17). Authors of 2 papers were contacted in order to get information that was not easily deducible from their papers. However, a reply was obtained from the authors of one paper only (18).

Inclusion criteria

To be included in the meta-analysis, the following requirements had to be met: The study had to assess dental fluorosis according to periods of fluoride exposure for the incisors, either directly (hypothesis testing) or indirectly (hypothesis forming). The studies included were classified as follows: Group (i), studies in individuals who had been introduced to fluoride at different ages during the enamel formation, and Group (ii), studies in children who, after having been exposed to fluoride from birth experienced an abrupt reduction in daily fluoride intake at a given time during the first 4 years of life, e.g. when a high-fluoride water source was replaced by low-fluoride water.

Furthermore, the number of cases versus controls (fluorosis versus non-fluorosis) for the incisors had to be given, as well as the age when first exposed to fluoride (or removed from the relevant fluoride source), or this had to be deduced with certainty. Alternatively, papers had to give the odds ratio (OR), standard error (SE) and the 95% confidence interval (CI) for the different groups. All indices of dental fluorosis were allowed, as the dependent variable was the prevalence of dental fluorosis and not the severity. If one index was applied in several of the included studies, a separate analysis was carried out based on these studies. There was no restriction on fluoride sources. A separate analysis for each fluoride source was carried out if the number of included studies allowed this.

Group (i) reports were divided into: (1) exposure to fluoride during the first 2 years of life and (2) exposure to fluoride only after the 2nd year of life (Table 2). Because some studies made the distinction between "early

Table 2. Studies with the Group (i) design included in the meta-analysis (in chronological order)

Study no.	Authors (ref. no.)	Year	Index used for scoring dental fluorosis	Fluoride source*	*N*	Introduced to fluoride (age in months)	OR	SE	95% CI
1	Forsman (20) **	1974	Dean	1	7	Early (0–24); Late (>24)	0.0001	116	$0.00–1.10^{95}$
2	Holm & Andersson (6)	1982	TFI	2, 3	86	Early (6–23); Late (⩾24)	3.38	0.61	1.02–11.19
3	Osuji et al. (21)	1988	TFI	(1), 2	139	Early (0–24); Late (>24)	11.92	0.41	5.31–26.80
4	Lalumandier & Rozier (22)	1995	TSFI	2	113	Early (0–23); Late (⩾24)	3.05	0.50	1.17–8.01
5	Ismail & Messer (9)	1996	FRI	1	48	Early (0–23); Late (⩾24)	14.87	0.72	3.60–61.37
6	Wang et al. (18)	1997	TFI	2, 3	253	Early (0–20); Late (⩾21)	7.22	0.56	2.40–21.70
7	Bårdsen & Bjorvatn (17)	1998	TFI	1 (2, 3)	66	Early (0–24); Late (>24)	11.32	0.62	3.39–37.87

* 1: water, 2: fluoridated toothpaste, 3: fluoride supplements.
** The study contains an empty (zero) cell in the 2 × 2 table.

exposure" and "later exposure" at for example 23 months of age and some used the 24th month for the distinction, this dichotomizing will not be exhaustive and exclusive. For Group (ii) reports, the fluoride exposure was divided into: (1) reduction of fluoride intake early in life (exposure to fluoride only during the first 2 years of life) and (2) reduction in fluoride intake later in life (exposure to fluoride for more than 2 years out of the first 4 years of life) (Table 3).

As both types of reports may assess duration of fluoride exposure rather than critical periods for developing dental fluorosis in the incisors, alternative analyses were carried out. The grouping was as follows: (a) long exposure (exposed to fluoride for more than 2 of the first 4 years of life), (b) short exposure (exposed less than 2 of the first 4 years of life) (Table 4).

Analysing the data, meta-analysis

Results from each of the included studies were entered into a data matrix (SPSS-PC, Version 7.5). Logistic regression analysis was used to calculate the OR, the 95% CI and the SE of the OR for each study (dependent variable: fluorosis/not fluorosis, independent variables: groups according to age at start or age at end of fluoride exposure, as well as duration of fluoride exposure—weighted by the number of participants in each study).

If the data were homogeneous with respect to study features, the fixed effect model was applied to calculate the overall effect size (summary OR), as described by Fleiss (19). With lack of homogeneity, the random effects model was used to calculate the summary OR (19).

Results

Literature search

One-hundred-and-nine papers were identified through the MedLine search back to 1966, and 69 through the search in the ISI database. The findings overlapped in 37 cases, giving a total of 141 relevant papers. One unpublished paper (in manuscript) was obtained and included in the meta-analysis (17). Furthermore, one paper published before 1966 was included (11), giving a total of

Table 3. Studies with the Group (ii) design included in this meta-analysis (in chronological order)

Study no.	Authors (ref. no.)	Year	Index used for scoring dental fluorosis	Fluoride source*	*N*	Reduction in fluoride intake (age in months)	OR	SE	95% CI
8	McKay (11)	1933	–	1	43	Early (0–24) Late (>24)	10.12	0.91	1.70–60.2
9	Ishii & Suckling (12) **	1986	Dean	1 (2)	16	Early (0–24) Late (>24)	36670	85.64	$0.0–2.92^{77}$
10	Evans & Stamm (10)	1991	Dean	1 (2)	940	Early (0–24) Late (>24)	1.75	0.17	1.25–2.47

* 1: water, 2: fluoridated toothpaste, 3: fluoride supplements.
** The study contains an empty (zero) cell in the 2 × 2 table.

Table 4. The pool of Group (i) and (ii) design included in the meta-analysis controlling for duration of exposure

Study no.	Authors (ref. no.)	Year	Index used for scoring dental fluorosis	Fluoride source*	*N*	Duration of fluoride exposure (months)**	OR	SE	95% CI
1	Forsman (20)***	1974	Dean	1	7	Long (>23); Short (⩽23)	0.0001	116	$0.00–1.10^{95}$
2	Holm & Andersson (6)	1982	TFI	2, 3	86	Long (>24); Short (⩽24)	3.38	0.61	1.02–11.19
3	Osuji et al. (21)	1988	TFI	(1), 2	139	Long (>23); Short (⩽23)	11.92	0.41	5.31–26.80
4	Lalumandier & Rozier (22)	1995	TSFI	2	113	Long (>24); Short (⩽24)	3.05	0.50	1.17–8.01
5	Ismail & Messer (9)	1996	FRI	1	48	Long (>24); Short (⩽24)	14.87	0.72	3.60–61.37
6	Wang et al. (18)	1997	TFI	2	253	Long (>27); Short (⩽27)	7.22	0.56	2.40–21.70
7	Bårdsen & Bjorvatn (17)	1998	TFI	1, (2, 3)	66	Long (>23); Short (⩽23)	11.32	0.62	3.39–37.87
8	McKay (11)	1933	–	1	43	Long (>23); Short (⩽23)	10.12	0.91	1.70–60.20
9	Ishii & Suckling (12)***	1986	Dean	1	16	Long (>23); Short (⩽23)	36670	85.64	$0.0–2.92^{77}$
10	Evans & Stamm (10)	1991	Dean	1	940	Long (>23); Short (⩽23)	1.75	0.17	1.25–2.47

* 1: water, 2: fluoridated toothpaste, 3: fluoride supplements.
** Duration of exposure, out of the first four years.
*** The study contains an empty (zero) cell in the 2 × 2 table.

143 papers. Only 10 of the studies satisfied the criteria for inclusion in the meta-analysis; 7 were Group (i) (6, 9, 17, 18, 20–22) and 3 Group (ii) (10–12) studies (Tables 2 and 3, respectively). The excluded studies, and the main reason for exclusion, are listed in Table 5.

Table 5. Studies excluded and main reason for rejection

Main reason for exclusion, based on the topic described in the paper	References
Reporting on fluorosis, but not reporting age when introduced to fluoride (no control as to lifelong residency in high-fluoridated areas)	(8, 23–44)
Scores for dental fluorosis not recorded/specified in the maxillary central incisors	(5, 45–49)
Age groups not suitable or overlapping groups	(7, 50–52)
Overview/review papers or safety considerations/ guidelines	(53–81)
Histology/histopathology/morphology of fluorosed enamel	(82–86)
Reporting on dietary fluoride or fluoride concentrations in prophylactic fluoride products and/or the use of these	(37, 87–106)
Including only enamel defects in deciduous teeth	(107)
Reporting on enamel fluoride concentrations and/ or dental caries	(108–116)
Trends in prevalence of dental fluorosis	(117)
Aesthetic concerns of dental fluorosis	(118–120)
Material already presented in another included paper	(16, 121–123)
Environmental effects of fluoride and/or fluoride in waters	(124–129)
Describing index/indices/techniques for scoring of dental fluorosis	(130–132)
Non-English paper	(133–139)
Other reason	(140–151)

Studies including subjects introduced to fluoride at different ages during enamel formation

Children who were introduced to fluoride during the first 2 years of life had a significantly higher risk of developing dental fluorosis compared to those exposed after only 2 years of age. The material was homogeneous with respect to the effect size and, hence, the fixed effect model was used to calculate OR (19). Compared to children exposed to fluoride only after 2 years of age, those who were introduced to fluoride during the first 2 years of life had an OR of 7.24 (95% CI; 4.71–11.13) for developing dental fluorosis (Table 6).

When the meta-analysis was repeated, including only the 4 studies using the TF Index, the OR for early introduction to fluoride was 8.41 (95% CI; 5.05–14.01) (Table 6). Furthermore, separate analyses were carried out for studies including children who were (1) exposed to water fluoride and (2) exposed to fluoride supplements and fluoridated toothpaste. The summary OR and the 95% CI for these calculations are given in Table 6. Finally, new calculations were carried out after one study (18) had been excluded due to different age classification (20 months of age versus >20 months of age), and another (20) because of one empty (zero) cell in the 2 × 2 table (which gives an

Table 6. The summary OR for the studies in Group (i) where the subjects were exposed to fluoride at different age; early introduction versus late introduction*

Studies (ref. no.)	OR	95% CI
All (6, 9, 17, 18, 20–22)	7.24	4.71–11.13
All except the study by Wang et al.** (6, 9, 17, 20–22)	7.24	4.53–11.59
All except the study by Forsman*** (6, 9, 17, 18, 21, 22)	7.24	4.66–11.25
All except the studies by Forsman and Wang et al. (6, 9, 17, 21, 22)	7.24	4.53–11.59
Studies using the TF Index (6, 17, 18, 21)	8.41	5.05–14.01
Studies where the fluoride source was water (9, 17, 20)	12.26	6.69–22.65
Studies where toothpaste and supplement were the fluoride sources (6, 18, 21, 22)	3.60	2.20–5.87

* Fixed effect model.
** Excluded in the calculation due to the deviant way of dichotomizing the age groups.
*** Excluded in the calculation due to the empty cell (zero) cell in the 2 × 2 table.

unreliable OR). The results show that the inclusion of these 2 studies did not influence the outcome (Table 6).

Studies including subjects who, after having been exposed to fluoride from birth, experienced an abrupt reduction in daily fluoride intake at different ages during enamel formation

The Group (ii) studies included subjects who were cut off from the fluoride source or had a substantial reduction in fluoride intake at a certain age (6 months to 6 years) (Table 3). The Group (ii) children showed a significant overall effect of age at which the reduction in daily fluoride intake took place. Compared to children who experienced a reduction in daily fluoride intake as early as during the first 2 years of life, the OR was 1.88 (95% CI; 1.35–2.61) for children to develop dental fluorosis if the fluoride intake was reduced only *after* 2 years of age (i.e. the children had been exposed for more than 2 of the first 4 years of life).

Only 3 papers reported Group (ii) studies, all with water as the fluoride vehicle. One of the studies (11) was carried out before any fluorosis indices had been established, and findings are given as pure descriptions of the examined tooth surfaces. The other 2 studies used Dean's Index. Separate analyses for the different indices were not done, but an alternative calculation was carried out after excluding the study by Ishii & Suckling (9), which had one empty (zero) cell in the 2 × 2 table. The results are given in Table 7.

Table 7. The summary OR for the studies in Group (ii) where the subjects were introduced to fluoride at birth and then protected from the source at different age; reduction in fluoride intake late versus early*

Studies (ref. no)	OR	95% CI
All (10–12)	1.88	1.35–2.61
All except the study by Ishii & Suckling** (10, 11)	1.88	1.35–2.61

* Fixed effect model.
** Excluded in the calculation due to the empty (zero) cell in the 2 × 2 table.

Duration of fluoride exposure

The meta-analysis using duration of exposure as the independent variable (*long exposure*: >2 years out of the first 4 years, as compared to *short exposure*: <2 years) showed that children with a history of long exposure had a significantly higher risk of developing dental fluorosis compared with children with a short exposure. The summary OR was 5.83 (95% CI; 2.83–11.94) (Table 8).

When the meta-analysis was repeated including only the studies using the *TF Index* for scoring dental fluorosis (all studies from Group (i)), the OR was 8.41 (95% CI; 5.05–14.01) (Table 8). Similar analyses were carried out for studies using *Dean's Index*, for studies involving subjects *exposed to water fluoride*, and for studies related to children *exposed to fluoride toothpaste and supplements* only. The OR varied from 1.51 to 5.87 depending on the number of studies included and indices used (Table 8). All ORs were statistically significant at the 5% level.

Discussion

Meta-analyses can organize results and thereby facilitate new findings, or put old findings in a new perspective. However, they also raise problems. A frequent criticism is that the studies available for analysis will represent a *biased* sample of all relevant studies carried out (152). As pointed out by McNemar (153), published studies tend to have larger *effect size* than those remaining unpublished. Hence, the estimate of the effect size from meta-analysis will be biased upward. This kind of bias, however, applies also to the narrative review. In the present study, both the hypothesis-forming and the hypothesis-testing studies have been included, and it is postulated that the availability bias should thereby be reduced.

A meta-analysis based on several randomized controlled trials is, in fact, a systematic review providing *new* data of high quality. Case-control studies were the basis for this meta-analysis. Improvement in the design and analysis of case-control studies has recently improved the quality of these studies and thereby eliminated much of the criticism previously raised (154). A disease with a long latency period such as dental fluorosis is well suited for case-control studies (154).

For meta-analysis to function, well-defined criteria for the inclusion of studies are required. The selection of studies, then, will be based on strict distinctions ('ex-

Table 8. The summary OR for the duration of fluoride exposure; long exposure versus short exposure (Group (i) and (ii))

Studies (ref. no.)	Factor analysis	OR	95% CI
All (6, 9–12, 17, 18, 20–22)	Random effect	5.83	2.83–11.94
All except the study by Wang et al.* (6, 9–12, 17, 20–22)	Random effect	5.87	2.66–12.94
All except the studies by Forsman and Ishii & Suckling** (6, 9–11, 17, 18, 21, 22)	Random effect	5.87	2.83–12.18
All except the studies by Wang et al., Forsman and Ishii & Suckling (6, 9–11, 17, 21, 22)	Random effect	5.70	2.59–12.55
Studies using the TF Index (6, 17, 18, 21)	Fixed effect	8.41	5.05–14.01
Studies using the Dean's Index (10, 12, 20)	Random effect	1.51	1.11–2.05
Studies where the fluoride source was water (9–12, 17, 20)	Fixed effect	2.32	1.71–3.15
Studies where the fluoride sources were toothpaste and supplement (6, 18, 21, 22)	Fixed effect	3.60	2.20–5.87

* Excluded in the calculation due to the deviant way of dichotomizing the age groups.
** Excluded in the calculation due to the empty (zero) cell in the 2 × 2 table.

haustive and exclusive'), such as age. However, in the present study, the use of certain indefinite categories was accepted in the grouping of subjects according to months of fluoride exposure (overlapping at class boundaries). As there will always be some variation in the timing of enamel formation, deviation of 1 month (23 or 24 months of age) is not expected to influence the outcome significantly.

Despite the attempts to achieve objectivity in reviewing scientific data, considerable subjective judgement is required, not the least when deciding whether and how to use meta-analysis. Thus, as the quality of included studies can vary, meta-analyses may utilize different principles of weighting studies—thereby again introducing another subjective component. To avoid further bias, the present analysis was carried out considering only the criteria for inclusion as given in the material and method section.

The discrepancy between the number of papers identified in the literature search (143) and those actually included in the meta-analysis (10) might indicate too *wide* a search design compared to criteria for inclusion. This was accepted, however, as *risk periods* is not a *MESH term* in the MedLine database and the possibility for overlooking relevant papers was great.

The biochemical mechanisms leading to dental fluorosis in humans need further elucidation (15, 79, 155). According to DenBesten & Thariani (155), both animal and human studies indicate that teeth are particularly susceptible to fluoride during the transition/early-maturation stage of enamel formation. However, high fluoride intake during the secretory stage may also increase the risk. A study by Larsen et al. (50) showed that children starting to take fluoride supplements after the age of 2.5 years might develop dental fluorosis, i.e. even during the maturation stage teeth must be sensitive to fluoride exposure. The present qualitative and quantitative review found that early exposure to fluoride gave a significantly higher risk for developing dental fluorosis as compared to fluoride exposure later during the period of tooth formation. This would seem to support the theory that teeth are most susceptible to dental fluorosis during the secretory phase of enamel formation. The Group (ii) design of studies, however, indicated that the risk was high also in children who experienced the reduction in daily fluoride exposure later, i.e. during the transitional and maturation phase of enamel formation.

As demonstrated by Table 8, long-time exposure to fluoride during the time of tooth formation significantly increased the risk for developing dental fluorosis. However, fairly big differences exist in the effect size for the different analyses. The most marked difference in OR was found to be between studies where the TF Index was used and those where Dean's Index was used in the assessment of fluorosis (Table 8). This may be because the TF Index is more sensitive and specific than Dean's Index (3), hence the TF Index may give a higher number of cases with dental fluorosis than Dean's Index. As studies using the TF Index for scoring of dental fluorosis were found only in Group (i), the sensitivity of this index may explain some of the difference in OR values found between Groups (i) and (ii).

Fluoride is known to be absorbed by bone and may also easily be released from bone (156). Information related to the fluoride removal (back-exchange) after a reduction in daily fluoride intake is scarce. However, it has been indicated that fluoride-induced disturbances in the amelogenesis occurs in the absence of elevated plasma fluoride concentrations in rat (157, 158). If the skeleton acts as an internal fluoride source after cessation of fluoride intake, this may interfere with the findings—especially for the analysis based on the Group (ii) studies—and add to the difference in the summary OR between Groups I and II.

The literature discussing risk periods related to dental fluorosis is scarce and different study designs make comparison and interpretation difficult. However, the results from the two different study designs included in the present analysis are compatible when the duration of fluoride exposure is assessed: Long exposure time (more than 2 of the first 4 years) increased the risk for developing dental fluorosis in the maxillary permanent incisors. On the other hand, based on the available epidemiological studies in humans, neither the secretory phase nor the

maturation phase of enamel formation can be singled out as being *the* high-risk period for the development of dental fluorosis in maxillary permanent central incisors.

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