Infant formula and enamel fluorosis

A systematic review

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ABSTRACT

Background. Researchers have considered infant formula consumption a potential risk factor for enamel fluorosis in the U.S. population. The authors conducted a systematic review of controlled studies regarding the risk of developing enamel fluorosis associated with use of infant formula.

Methods. One reviewer independently conducted systematic searches in eight databases. The authors then abstracted information, assessed study quality and combined odds ratios (ORs), when obtainable, by using a random-effects model.

Results. After evaluating 969 potentially eligible published studies, the reviewers found that the authors of 41 studies had evaluated the effect of infant formula on enamel fluorosis risk. Authors of 14 of the 41 studies did not report their findings in their results. The authors of the remaining 27 published studies reported the findings of 19 observational studies; authors of 17 of these 19 studies reported ORs and, among these, infant formula consumption was associated with a higher prevalence of enamel fluorosis in the permanent dentition (summary OR 1.8, 95 percent confidence interval [CI] 1.4-2.3). There was significant heterogeneity among studies (I^2 66 percent) and evidence of publication bias (P = .002). A metaregression analysis indicated that the ORs associating infant formula with enamel fluorosis increased by 5 percent for each 0.1–part-per-million increase in the reported levels of fluoride in the water supply (OR 1.05, 95 percent CI 1.02-1.09).

Clinical Implications. Infant formula consumption may be associated with an increased risk of developing at least some detectable level of enamel fluorosis, which depends on the level of fluoride in the water supply. The evidence that the fluoride in the infant formula caused enamel fluorosis was weak, as other mechanisms could explain the observed association.

Key Words. Infant formula; fluorosis; mottled teeth.
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Infant formula is a substitute for breast milk. It can be purchased as either a powder or a liquid that has to be reconstituted with water before use, or as a ready-to-feed formulation. Unlike breast milk, in which fluoride concentration is approximately 0.02 parts per million (ppm)[1] owing to the pH gradient between milk and the interstitial fluid,[2] the fluoride levels in infant formula are determined by the industrial processes involved in preparing the infant formula itself and, when applicable, the fluoride levels in the water used for reconstitution. The intake of fluoride from infant for-

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mula may exceed the tolerable upper intake levels that were established by the Institute of Medicine[3] in 1997: 0.7 milligrams per day for infants from birth to 6 months of age and 0.9 mg/day for infants aged 7 to 12 months.

Professional dental organizations have provided variable advice regarding the use of infant formula as it relates to enamel fluorosis.[4-6] Reports from countries in which the fluoride levels in the water are low typically indicate low levels of fluoride in infant formula, and some researchers in these countries have recommended the use of fluoride supplements for infants.[7,8] Advice about infant formula use is more complex for people living in countries in which higher natural or adjusted fluoride levels in the water supply can increase fluoride concentrations in both the infant formula itself and in the water used to reconstitute it. In Canada, where water fluoride content generally ranges from 0.5 to 0.8 ppm,[4] the country's dental association has made no recommendations regarding infant formula preparations and fluorosis. In the United States, where water fluoride levels typically range from 0.7 to 1.2 ppm, the interim guidance by the American Dental Association[5] suggested that those who are concerned about their children's exposure to fluoride and those whose children receive most of their nutrition from infant formula should use ready-to-feed formula or should use nonfluoridated water when reconstituting powdered formula. The U.S. Centers for Disease Control and Prevention reported that parents should follow the advice of the infant formula's manufacturer and the child's physician.[9] Public health officials in both Australia[10] and Ireland[11] consider it safe to reconstitute infant formula using fluoridated water.

International agencies such as the World Health Organization have not provided specific guidelines with respect to fluoride content of infant formulas.[12,13] U.S. manufacturers have voluntarily reduced the fluoride levels of ready-to-feed and concentrated formulas since 1979.[14] Since this change, formulas' fluoride content reportedly has ranged between 0.03 and 0.34 ppm.[15] Investigators have assessed the maintenance of this decrease intermittently.[16,17] In other countries, such as Brazil, investigators have reported fluoride concentrations as high as 0.70 ppm in soy-based infant formula.[18]

With the increasing prevalence of enamel fluorosis,[19] researchers have placed more emphasis on preventing infants' and children's overexposure to fluorides. As a result, they are scrutinizing the fluoride content of food and liquid, including infant formula, as potential sources of fluoride overexposure. Our primary aim in conducting the systematic review we describe here was to search the literature for evidence on the association between infant formula consumption from birth to the age of 24 months, as well as the risk of developing dental fluorosis by comparing children who are fed with formula with children who are fed with breast milk or cow's milk. A secondary aim was to evaluate any available evidence implicating the fluoride in the infant formula as the cause of fluorosis.

MATERIALS AND METHODS

Selection of articles. We considered for inclusion in this systematic review studies of humans in which investigators evaluated fluorosis and the use of infant formula, breast-feeding or both during infancy. We excluded studies that focused exclusively on primary teeth. One reviewer (L.G.Z.) searched eight databases for randomized or observational studies without language restriction in October and November 2007: PubMed; the Cochrane Library; the Web of Science; Controlled Trials; Clinical Trials, a service of the U.S. National Institutes of Health; ProQuest UMI; National Institute for Health and Clinical Excellence; and Virtual Health Library (Bireme-PAHO-WHO, Latin America and Caribbean Center on Health Sciences Information). Another reviewer (P.P.H.) searched reference lists of relevant reports and review articles.

The first reviewer used the following strategy to search PubMed in October 2007: ((fluorosis OR Fluorosis, Dental[mh] OR mottled teeth) AND (bottlefeed* OR bottle feed* OR bottle-feed* OR bottlefed OR bottle fed OR bottle-fed OR infant formula* OR (Formula* AND feeding) OR Formula fed OR "reconstituted milk" OR Infant Food OR "bottled water" OR breastfeed* OR breast feed* OR breast-feed* OR breastfed OR breast fed OR Nutrition Physiology OR Diet OR Feeding

ABBREVIATION KEY. BF: Breast-feeding. **DDE:** Development Defects of Enamel Index. **EBF:** Exclusive breast-feeding. **EIF:** Exclusive infant formula. **FRI:** Fluorosis Risk Index. **IF:** Infant formula. **NA:** Not applicable. **NR:** Not reported. **ppm:** Parts per million. **TFI:** Thylstrup and Fejerskov index. **TSIF:** Tooth Surface Index of Fluorosis.

Behavior OR Food Analysis OR epidemiologic Factors OR time factors)) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]). She used similar search strategies for the Cochrane Library and Web of Science databases. She searched the remaining databases using the following key words: "dental fluorosis," "white spots," "fluoride," "infant formula" and "breast-feeding."

The first reviewer evaluated studies for inclusion. (Appendix 1 in the supplemental data online [found at "http://jada.ada.org"] provides a list of excluded reports.) Two reviewers (L.G.Z. and P.P.H.) assessed a sample of 120 reports and calculated agreement regarding exclusion by using the κ statistic.

Study description. Two reviewers (L.G.Z. and J.C.-C.) extracted descriptive data independently and resolved questions regarding the abstracted data by means of discussion. They extracted data on study design; country and setting; publication language; type, frequency and amount of infant formula consumption; fluoride concentration in infant formula; comparison group; fluorosis measurements (index used, type of teeth examined); the contribution of fluoride intake to the infant formula-fluorosis association; and adjustment for confounding. They made two attempts, in November and December 2007, to e-mail the authors of the 14 studies in which investigators evaluated infant formula without reporting findings regarding the infant formula–fluorosis association. Authors of two of the studies responded that the data no longer were available.

Study design. The studies' authors classified study designs as historical-control, cross-sectional, case-control, retrospective cohort, prospective cohort and randomized controlled trial. In historical-control studies, investigators compared children born in different calendar years and with different feeding practices with respect to fluorosis. In cross-sectional studies, investigators sampled groups of children of similar age regardless of fluorosis status and related fluorosis to infant feeding practices. In case-control studies, investigators separately sampled children with and without fluorosis (case subjects and control subjects, respectively). In retrospective cohort studies, investigators compared populations with different levels of fluoride in the water supply with respect to fluorosis. In prospective cohort studies, researchers obtained information regarding infant feeding practices and subsequently followed the children for the incidence of fluorosis. In randomized controlled trials, researchers randomly assigned mothers to either breast-feeding or different types of infant formula. In historical-control, case-control, cross-sectional and retrospective cohort studies, investigators obtained information on past infant feeding practices from interviews with the mothers of the examined children (in person, by mail or by phone) or assumed the data on the basis of the caretaker's place of residence (without questionnaire).

Infant feeding practices. In this report, we use the term "infant formula" to describe ready-to-feed formulations or powder or liquid infant formula that requires reconstitution with water. We abstracted information on frequency, quantity and fluoride concentration of the infant formula as follows:

- ***Frequency of infant formula consumption.*** Qualitative information indicated whether the mother reported exclusive infant formula use, exclusive breast-feeding or use of both feeding practices. Quantitative information indicated an estimate of the amount of feeding with infant formula during infancy on either a continuous scale (for example, ranging from 0 percent to 100 percent) or a discrete scale (for example, none, occasionally, frequently, always).
- ***Quantity of infant formula consumption.*** The authors obtained the specific quantity of infant formula consumption per day (for instance, from one to three bottles of infant formula per day) through data from diet diaries compiled by mothers or during interviews with mothers.
- ***Fluoride concentration of infant formula.*** We classified the fluoride concentration of infant formulas as "fluoride concentration reported" when the fluoride level in the infant formula was assayed within the period during which infant feeding took place, as "historical estimates" if the fluoride level was assayed many years after infant feeding actually occurred and as "not reported" if no data regarding fluoride levels of infant formula were available.

Enamel fluorosis outcome. Throughout this article, when we use the term "fluorosis," we mean enamel fluorosis, not skeletal fluorosis. We abstracted information about the fluorosis index used and the type of teeth examined. We further classified studies depending on whether the investigators had categorized the fluorosis meas-

ure used into discrete levels (binary/polytomous) or had used it as a continuous variable.

Covariates and adjustment for confounding. We also abstracted the number and type of confounders for which investigators had adjusted in their analysis. We classified the fluoride concentration in the water supply as "fixed" if there was no variation among the participants' water supply (for instance, the study was restricted to a city with a low fluoride level in its water supply), as having "geographical variability" if participants lived in areas with different levels of fluoride in the water supply and as having "secular variability" if the level of fluoride in the water supply changed across time.

Fluoride as the cause of the infant formula–fluorosis association. The extent to which the fluoride content in infant formula is in the causal pathway between infant formula and fluorosis can be determined using either the method of surrogate endpoint evaluation or the method of testing the significance of a statistical interaction term.

Surrogate endpoint evaluation. One such method is surrogate endpoint evaluation.[20] Such an approach is possible if for each subject there is information on the fluoride concentration of the infant formula used. According to regression models, the percentage change in the size of the regression coefficient associated with infant formula—with and without adjustment for individual fluoride concentration in the infant formula—determines the percentage of the effect of infant formula on fluorosis that could be fluoride-related.

Significance of statistical interaction. A second method of assessing the extent to which fluoride in the infant formula is responsible for fluorosis is to make two assumptions:

- that the caregivers used the reported water supply to reconstitute infant formula;
- that the caregivers used primarily concentrated infant formula (powder or liquid), not ready-to-feed infant formula.

If these two assumptions hold, the fluoride concentration in the water supply can be considered a proxy for the fluoride content of the infant formula. Stratification of the data by fluoride concentration or a test for statistical interaction can help one assess whether the risk of developing fluorosis that is associated with infant formula use depends on the fluoride concentration assumed present in the infant formula.

Assessment of methodological quality. Two independent reviewers (L.G.Z. and J.C.-C.) performed the quality assessment, and they resolved disagreements by means of discussion. To assess the quality of studies, they used a modification of the Newcastle-Ottawa Scale.[21] This scale has nine items for prospective and retrospective cohort studies and eight items for case-control, historical-control and cross-sectional studies. They used the following four items to assess the quality of all studies:

- ascertainment of infant feeding practices;
- ascertainment of fluorosis status;
- adjustment for use of fluoridated toothpaste and socioeconomic status;
- reporting of sample size, point estimates and measure of variability.

The reviewers used the following five items to assess the quality of cohort studies:

- representativeness of groups exposed to fluoride;
- representativeness of groups not exposed to fluoride;
- blinding of the examiner;
- follow-up sufficient to enable diagnosis of fluorosis on permanent teeth;
- subjects' drop-out rate.

The reviewers used the following four items to assess the quality of case-control, historical-control and cross-sectional studies:

- representativeness of subjects with fluorosis;
- representativeness of subjects without fluorosis;
- blinding of interviewers as to severity of fluorosis;
- subjects' rate of response to the questionnaire and the clinical examination.

Synthesis of results. We calculated a summary odds ratio (OR) and 95 percent confidence intervals (CIs) by using a random-effects model. We ignored the clustering of data in two studies.[36,37] We selected ORs as the measure of association between infant formula and fluorosis because they either were reported or could be calculated across the largest number of studies. When the investigators reported several ORs for infant formula, or when they did not report the OR, we made the following assumptions to select or calculate the OR to be included in the meta-analysis:

- when investigators reported duration of breast-feeding, we assumed that the shortest duration of breast-feeding reported corresponded to the

longest duration of infant formula use;
- when investigators reported breast-feeding as a yes/no variable, we assumed that an absence of breast-feeding corresponded to exclusive infant formula consumption;
- when investigators reported data on different types of infant formula (soy-based, milk-based), we calculated a weighted summary OR;
- when study reports provided information about breast-feeding only, infant formula consumption only and use or consumption of both, we calculated a summary OR combining infant formula and use or consumption of both compared with breast-feeding only (that is, any consumption of infant formula versus no consumption of infant formula);
- when investigators reported different intervals (such as from birth to age 6 months and older than 6 months), we calculated a summary OR combining all time intervals compared with no consumption of infant formula (that is, any consumption of infant formula versus no consumption of infant formula).

We quantified heterogeneity between studies using the I^2 statistic.[22] We assessed the influence of studies on the summary OR by computing the random-effect summary OR, omitting one study at a time. We assessed publication bias by visually inspecting asymmetry in a funnel plot[23] and by using the Egger test.[24] We used random-effect metaregression models to explain and quantify variation in ORs according to study characteristics such as the reported fluoride levels in the water supply, study quality, fluorosis index used, adjustment for dietary fluoride supplement use and socioeconomic status.[25] We plotted and regressed the log of the OR for fluorosis associated with infant formula against the average fluoride level in the water supply. We analyzed data using SAS version 9.1 (SAS Institute, Cary, N.C.) and Stata 10 (StataCorp LP, College Station, Texas).

RESULTS

Selection of articles. The reviewers' online search retrieved 499 references from PubMed, 163 from the Web of Science, 19 from the Cochrane Library and 377 from other sources (Figure 1). We identified one additional study from the reference lists of the included studies.[26-32] We identified 969 unique reports and titles and read abstracts, when available. The agreement between the two systematic reviewers regarding the appropriateness of abstracted publications for full evaluation was excellent (κ coefficient = 0.81). We selected 41 publications but could not include 14 of them in the presentation of the data because they did not provide reports of results. The 27 published studies we selected for the final review covered 19 original studies that included reports of the effect of infant feeding on fluorosis.

Study description. The authors of the 19 studies included in this review reported data for approximately 17,429 subjects (8,454 participants included in the analyses), with ages ranging from 2 to 17 years (Table, pages 848 and 849).[26-52] Most studies involved participants who were enrolled in school. We identified no studies published in languages other than English.

Study design. Among the studies we selected, there was one prospective cohort study,[17,33-35] five retrospective cohort studies,[31,36-39] six case-control studies,[28-30,32,40-44] four cross-sectional studies[26,45-49] and three historical-control studies.[27,50-52] We identified no randomized controlled trials.

Infant feeding practices. The authors of seven studies defined children who were breast-fed as the exposure group.[26,31,34,36,37,42,45] The authors of 12 studies[27-30,32,38-40,47,48,51,52] defined children who were fed infant formula as the exposure group (Table).

Frequency and quantity of infant formula use. The authors of 10 studies did not report the frequency of infant formula consumption[26,27,31,34,36-39,48,52] and authors of nine studies provided qualitative data (for example, exclusive breast-feeding)[28-30,32,40,42,45,47,51] (Table). None of the study reports included data regarding quantity of infant formula consumed.

Fluoride concentration of infant formula. The authors of 16 studies[17,26,28-32,34,36,38-40,42,45,48,51,52] did not report the fluoride content of the infant formula. The authors of three studies[27,37,47] provided historical estimates of fluoride concentration in infant formula and reported the concentration as 0.03 to 0.04 ppm[27] (measured 10 years after usage) and 0.4 to 5.0 ppm[47] (the authors provided no information as to when they had measured reported fluoride values). The authors of one study provided estimates of typical fluoride consumption from breast milk and powdered formula diluted in water with varying fluoride levels[37] (Table). None of the 19 study reports included information on the fluoride level of the infant formula measured at the time of consumption.

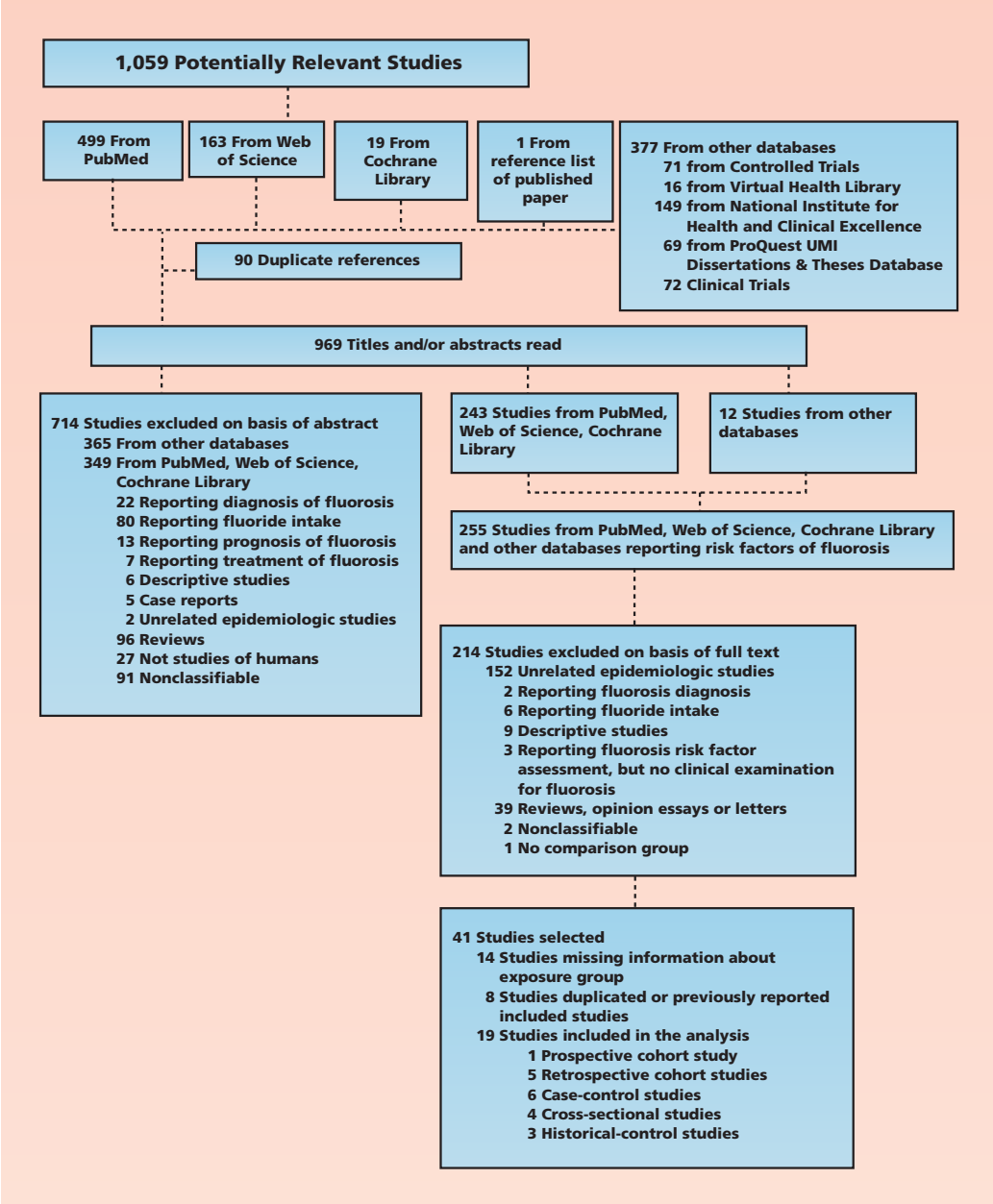

Figure 1. Flow diagram showing the process of selecting published articles about infant formula, breastfeeding and fluorosis.

Fluorosis outcome. The studies' authors used different criteria for presence of fluorosis: a Thylstrup & Fejerskov[53] index score greater than 0 (very mild to severe fluorosis),[27,31,32,51,52] a Thylstrup & Fejerskov index score greater than 2 (mild to severe fluorosis),[39] a Fluorosis Risk Index classification I (mild to severe fluorosis in tooth zones forming at or shortly after birth)[29,30,34,42] and the combination of Fluorosis Risk Index classifications I and II (mild to severe fluorosis in tooth zones forming at or shortly after birth and/or after 2 years of age).[28] Other fluorosis indexes used were Dean's fluorosis index[53] (used in four studies[36.37,40,47]), Moller's Index[54] (used in one study[26]), the Development Defects of Enamel Index[53] (used in one study[48]) and the Tooth Surface Index of Fluorosis[53] (used in two studies[38,45]). Authors of two studies reported scores on the fluorosis index as a continuous variable,[26,47] and we did not include the results in our meta-analyses. The authors of 17 studies reported the impact of infant formula use on the permanent dentition. In two studies, the authors did not report whether fluorosis was measured on primary or permanent teeth,[32,38] and we made an assumption that they measured it on the subjects' permanent teeth (Table). Because researchers in 17 of the 19 studies dichotomized the underlying continuous fluorosis scale differently, we decided that in this systematic review, the term "fluorosis" would refer to the presence of at least some detectable level of enamel fluorosis.

Water supply information. In six studies, researchers reported a fixed level of fluoride in the water supply (Table).[28-30,32,42,47] The reported fluoride levels of water in four of these six studies were < 0.1 ppm[42] (assumption of 0.1 ppm for metaregression), 0.3 ppm,[28] 0.95 ppm[32] and 1.2 ppm.[47] Authors of two studies reported that the

water supply was optimally fluoridated (assumption of 1.00 ppm for meta-regression).[29,30]

In two studies, the investigators compared fluorosis during periods in which the level of fluoride in the public water supply was changed (secular variability) (Table).[40,51] The reported changes in fluoride concentrations in the water supply were 0.93 ppm (value used in metaregression) versus nonfluoridated water (no results reported for the latter)[40] and 1.0 ppm versus 0.1 ppm[51] (assumption of 1.0 ppm for meta-regression because 0.1 ppm was present for only 11 months of the participant's life).

In 10 studies,[26,27,31,36-39,45,48,52] the investigators evaluated the effect of infant formula use on fluorosis in geographical regions that had different fluoride levels (Table). The contrasting fluoride levels in seven studies were 1.1 ppm versus 1.4 to 1.6 ppm[27] (assumption of 1.32 ppm for metaregression), < 0.3 ppm versus 0.3 to 0.69 ppm versus ≥ 0.7 ppm[45] (assumption of 0.28 ppm derived as [(0.1 × 521 + 125 × 0.50 + 1.2 × 72.0) ÷ 718]), ≤ 0.3 ppm versus 0.31 to 0.5 ppm versus 0.51 to 0.99 ppm versus ≥ 1.0 ppm[48] (assumption of 0.68 ppm for metaregression), ≤ 0.1 ppm versus 1.2 ppm[38] (assumption of 0.65 ppm for metaregression), 0.5 ppm versus 2.5 ppm[39] (reported infant formula effect only for the 2.5-ppm group, which is the value included in the metaregression), 1.0 ppm versus 5.0 ppm versus 10.0 ppm[36] (assumption of 1.00 ppm and 7.5 ppm for metaregression) and < 0.2 ppm versus 1.2 ppm[37] (assumption of 0.2 ppm and 1.2 ppm for metaregression). The authors of three of the 10 studies did not report the different fluoride levels in water.[26,31,52] The authors of the original studies described what we refer to in this study as "the water supply" by using the following terms: "water supply," "community water," "(household) drinking water," "municipal water supply," "piped water system" and "water." One study had individual information about the average daily fluoride intake during the first 12 months estimated from consumption of drinking water, beverages, selected foods and dietary fluoride supplements and from ingestion of fluoride toothpaste.[34]

Fluoride as the cause of the infant formula–fluorosis association. None of the investigators used the method of surrogate marker evaluation to assess the extent to which the fluoride in the infant formula explains significant infant formula–fluorosis associations. In seven studies, we could not evaluate whether the effect of infant formula depended on the fluoride level in the water supply (as a proxy for fluoride content), because the authors did not report the fluoride levels in the water supply[34] or there was no secular or geographical variability in fluoride water levels.[28-30,32,42,47] In two studies, there was a secular variability in the fluoride levels[40,51] and in 10 studies, there was a geographical variability in the fluoride levels.[26,27,31,36-39,45,48,52] In none of these 10 studies did authors report having conducted statistical tests to evaluate whether the infant formula–fluorosis association depended on the level of water fluoridation. The authors of two studies stratified their results by water fluoridation[36,37] and reported a stronger, but statistically nonsignificant, association between infant formula use and fluorosis in areas with higher water fluoride levels.

Assessment of methodological quality. The methodological quality varied across studies; historical-control and cross-sectional studies generally met fewer quality criteria than did case-control and cohort studies (Table). Representativeness of the selected subjects and adjustment for at least one confounding factor were two items we commonly considered adequate in the reviewed studies. The authors of 12 studies reported analyses adjusted for at least one confounding factor,[28-32,34,38-40,42,45,48] and those of seven studies did not adjust for confounding[26,27,36,37,47,51,52] (Table). Commonly identified weaknesses were the potential for recall bias, lack of reporting of blinding of clinical examiners toward infant formula consumption, a high nonresponse rate and no adjustment for socioeconomic status and use of fluoridated products such as toothpaste (Appendix 2 in the supplemental data online [found at "http://jada.ada.org"] provides a detailed table of the study quality assessment).

Synthesis of results. The summary OR relating infant formula to fluorosis on the basis of 17 studies was 1.8 (95 percent CI 1.4-2.3) using a random-effects model (Figure 2, page 850). We did not include two studies in the forest plot or summary estimate because we could not derive an OR from the data.[26,47] There was significant heterogeneity in the magnitude of the ORs between studies (I^2 = 66 percent, $P < .0001$), suggesting that one should interpret summary odds with caution. Influence analysis indicated that the results were not influenced unduly by any single study (results not shown). We created a funnel plot that provided graphical evidence of

TABLE

Studies regarding the effects of infant formula on fluorosis.

SOURCE, YEAR, LOCATION OF STUDY	DESIGN	SETTING	SAMPLE SIZE ANALYZED	SUBJECTS' AGE (YEARS)	EXPOSED GROUP*	COMPARISON GROUP	FREQUENCY OF INFANT FORMULA USE
Ericsson and Ribelius,[47] 1970, Sweden	Cross-sectional	City (not reported)	260	8-9	EIF‡ use for nine to 12 months	No EIF for nine to 12 months	Qualitative
Forsman,[36] 1974, Sweden	Retrospective cohort	Cities	241 (~2,403)	Unclear (range from 2-35)	BF¶ for ≤ six months	BF for seven to 12 months	Not reported
Forsman,[37] 1977, Sweden	Retrospective cohort	Cities	545 (~712)	4-17	BF for < six months	BF for ≥ six months	Not reported
Walton and Messer,[26] 1981, United States	Cross-sectional	Pediatric clinic	370	2-13	BF < three months	BF for three to 36 months	Not reported
Larsen and Colleagues,[27] 1988, Greenland and Denmark	Historical-control	Schools	276 (not reported)	4-15	IF** from birth to 24 months††	Cow's milk (duration not reported)	Not reported
Osuji and Colleagues,[32] 1988, Canada	Case-control	Schools	132 (177)	8-10	IF (months not reported)	No IF from birth to 24 months	Qualitative
Pendrys and Katz,[28] 1989, United States	Case-control	Schools	544 (not reported)	11-14	IF (months not reported)	No IF from birth to 12 months	Qualitative
Riordan,[31] 1993, Australia	Retrospective cohort	Schools	350 (418)	7	BF from birth through 9 months	BF for ≥ nine months	Not reported
Clark and Colleagues,[38] 1994, Canada	Retrospective cohort	Schools	1,131 (3,126)	6-14	IF at 10-12 months	No IF at 10-12 months	Qualitative
Pendrys and Colleagues,[30] 1994, United States	Case-control	Schools	297 (not reported)	12-16	IF (months not reported)	No IF from birth to 24 months	Qualitative
Pendrys and Colleagues,[42] 1996, United States	Case-control	Schools	391 (not reported)	10-13	No BF from birth to 24 months	BF	Qualitative
Pendrys and Katz,[29] 1998, United States	Case-control	Schools	163 (not reported)	10-14	IF at 10-12 months	No IF at 10-12 months	Qualitative
Villa and Colleagues,[40] 1998, Chile	Case-control	Schools	136 (281)	10-12	IF (months not reported)	BF (months not reported)	Not reported
Brothwell and Limeback,[45] 1999, Canada	Cross-sectional	Schools	487 (1,367)	7-9	No BF	BF to age 12 months or later	Not reported
Rwenyonyi and Colleagues,[39] 1999, Uganda	Retrospective cohort	Schools	306 (491)	10-14	IF (months not reported)††	No IF from birth to 24 months††	Not reported
Burt and Colleagues,[51] 2003, United States	Historical-control	Schools	1,346 (2,844)	7-10	IF (months not reported)	EBF## from birth to 24 months	Not reported
van der Hoek and Colleagues,[48] 2003, Sri Lanka	Cross-sectional	Schools	395 (518)	14	IF from birth to 24 months††	BF	Qualitative
Hong and Colleagues,[34] 2005, United States	Prospective cohort	Hospitals	407 (1,390)	8-10	BF for < six months	BF for six to 12 months	Not reported†††
Do and Spencer,[52] 2007, Australia	Historical-control	School dental service	677 (1,401)	8-14	IF (months not reported)	No IF (months not reported)	Not reported

* The authors of most studies did not specify the type of formula; however, Larsen and colleagues[27] (1988) specified powdered milk concentrate, Pendrys and colleagues[30] (1994) specified soy-based or milk-based formula, Pendrys and Katz (1998)[29] specified ready-to-feed, liquid concentrate or powdered concentrate and Villa and colleagues[41] (1998) specified powdered milk concentrate.

† Two independent reviewers (L.G.Z., J.C.-C.) used a modification of the Newcastle-Ottawa Scale[21] to assess study quality. There were nine items for prospective and retrospective cohort studies and eight items for case-control, historical-control and cross-sectional studies.

‡ EIF: Exclusive infant formula.

§ Dean's fluorosis index.[53]

¶ BF: Breast-feeding.

\# Moller's index.[54]

TABLE (CONTINUED)

FLUORIDE CONCENTRATION IN INFANT FORMULA	FLUOROSIS OUTCOME	CONFOUNDERS	FLUORIDE LEVELS IN WATER SUPPLY	FLUORIDE AS CAUSE OF ASSOCIATION	STUDY QUALITY: NO. OF CRITERIA MET/ TOTAL NO. OF CRITERIA†
Historical estimate	Dean's fluorosis index§ score on permanent incisors and first molars (continuous)	None	Fixed	Not applicable	3/8
Not reported	Dean's fluorosis index score > 0 on permanent incisors and molars	None	Geographical variability	Not reported (visual assessment)	2/9
Historical estimate	Dean's fluorosis index score > 0 on permanent incisors and molars	None	Geographical variability	Not reported (visual assessment)	3/9
Not reported	Moller's index# on permanent incisors and molars (continuous)	None	Geographical variability	Not reported	2/8
Historical estimate	TFI‡‡ score > 0 on permanent incisors	None	Geographical variability	Not reported	0/8
Not reported	TFI score > 0, teeth NR	Mother's education, early tooth-brushing with fluoridated dentifrice	Fixed	Not applicable	7/8
Not reported	FRI§§ classification I and II ratings on permanent teeth	Fluoride supplements	Fixed	Not applicable	4/8
Not reported	TFI score > 0 on permanent incisors	Residence in fluoridated area, swallowed toothpaste, liked toothpaste	Geographical variability	Not reported	5/9
Not reported	TSIF¶¶ score > 1, teeth not reported	Residence in fluoridated area, fluoride supplements, parents' education, toothpaste use, other unspecified variables	Geographical variability	Not reported	6/9
Not reported	FRI classification I rating on permanent teeth	Toothbrushing frequency, toothpaste quantity, fluoridated supplement, age, sex, income, current town of residence, dental examiner	Fixed	Not applicable	6/8
Not reported	FRI classification I rating on permanent teeth	Fluoride supplement, toothbrushing, ethnicity, sex, income, dental examiner	Fixed	Not applicable	6/8
Not reported	FRI classification I rating on permanent teeth	Toothpaste use, fluoride supplement, water, ethnicity, age, sex, income, age at which toothbrushing began, dental examiner	Fixed	Not applicable	6/8
Not reported	Dean's fluorosis index score > 0 on permanent incisors	Birth cohorts, sex, socioeconomic status, toothbrushing, nursery school attendance, tea ingestion	Secular variability	Not reported	8/8
Not reported	TFI > 0 on permanent incisors	Home water fluoride concentration, fluoride supplement, fluoridated toothpaste, fluoridated mouthwash, income, education	Geographical variability	Not reported	5/8
Not reported	TFI score > 2 on permanent teeth	Altitude, fluoride exposure from liquids, exposure from water storage	Geographical variability	Not reported	5/9
Not reported	TFI score > 0 on permanent incisors	None	Secular variability	Not reported	6/8
Not reported	Diffuse opacities on the DDE*** Index on permanent incisors, canines, first molars and premolars	Water fluoridation, tea drinking at early age, toothpaste use, father's occupation, socioeconomic status	Geographical variability	Not reported	4/8
Not reported†††	FRI I on permanent incisors	Amoxicillin use, daily fluoride intake, otitis media	Not reported	Not reported	7/9
Not reported	TFI score > 0 on permanent incisors, canines, and first premolars	None	Geographical variability	Not reported	5/8

** IF: Infant formula.
†† The authors of this study did not report the infant's age; therefore, we assumed the child's age to be during infancy (0-24 months).
‡‡ TFI: Thylstrup and Fejerskov index.[53]
§§ FRI: Fluorosis risk index.[53]
¶¶ TSIF: Tooth Surface Index of Fluorosis.[53]
EBF: Exclusive breast-feeding.
*** DDE: Development Defects of Enamel Index.[53]
††† The authors collected this information but reported it in another publication (Van Winkle and colleagues[17]).

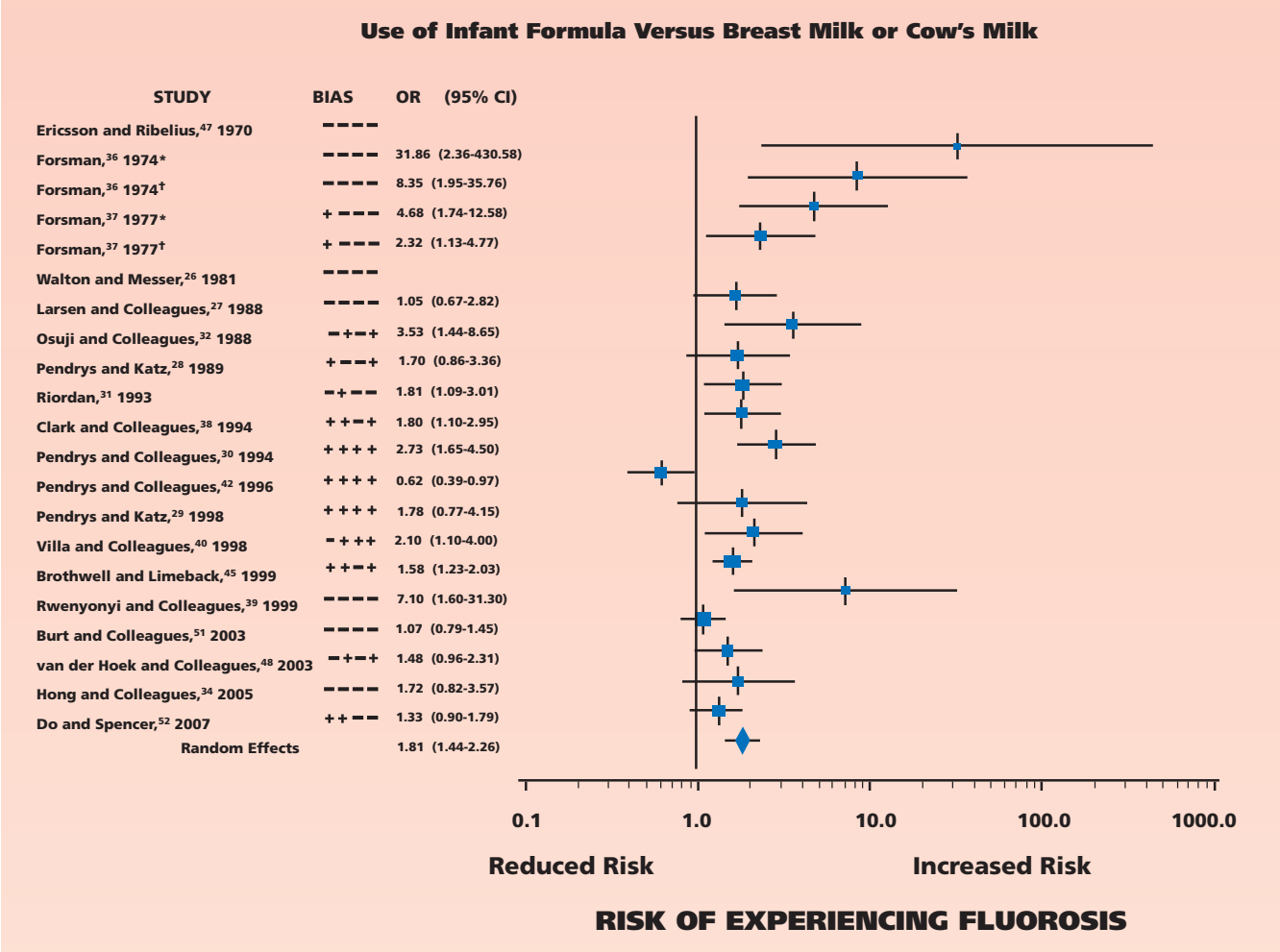

Figure 2. Forest plot of the odds ratios (ORs) relating infant formula to fluorosis. Adjustments for fluoride supplements, toothpaste, sex and socioeconomic status are summarized as present (+) or absent (-) under the column labeled "Bias." Readers should use caution in interpreting the summary estimates on the forest plot owing to the significant heterogeneity of the selected studies. CI: Confidence interval. *: Subjects exposed to fluoridated water. †: Subjects exposed to nonfluoridated water.

publication bias, which was confirmed by Egger test (P = .002) (Figure 3). A random-effects metaregression model indicated a proportionate increase in the fluorosis OR of 5 percent as the fluoride level increased by 0.1 ppm (OR 1.05, 95 percent CI 1.02-1.09) (Figure 4, page 852). To state it differently, a 1.0-ppm increase in the water supply is associated with a 67 percent increased OR for fluorosis associated with infant formula (OR 1.67, 95 percent CI 1.18 –2.36). One study in which the concentration of fluoride in the water supply was 7.5 ppm[36] had only a minor impact on the metaregression results, whether we included it in or omitted it from our analysis. When we excluded this study, we found that a 1.0-ppm increase in the water supply was associated with a 93 percent increased OR for fluorosis associated with infant formula (OR 1.93, 95 percent CI 1.09-3.45). Heterogeneity in the ORs was not substantially affected by study quality (P = .56), type of fluorosis index (P = .69 and P = .42) or adjustment for fluoride supplement use (P = .25) and socioeconomic status (P = .48).

DISCUSSION

A summary of the identified epidemiologic evidence suggests that infant formula consumption during infancy can be associated with an increased risk of developing at least some detectable level of enamel fluorosis in the permanent teeth. The size of the risk increase varied substantially across studies and may have been due in part to unreported differences in the amount, duration and frequency of infant formula

use; unreported differences in fluoride levels of infant formulas; and variability in other sources of fluoride intake. The estimated summary measure of the fluorosis risk derived from the results of the published studies likely was inflated owing to publication bias (a tendency to publish positive results preferentially, in this case regarding the link between infant formula and fluorosis, when the results are significant). None of the individual studies included a statistical assessment of whether the fluoride in the infant formula was responsible for the fluorosis. A statistical assessment across studies (a metaregression) provided weak evidence that the fluoride in the infant formula caused the increased risk of developing fluorosis; the fluorosis risk associated with use of infant formula increased significantly with the reported mean levels of fluoride in the water supply.

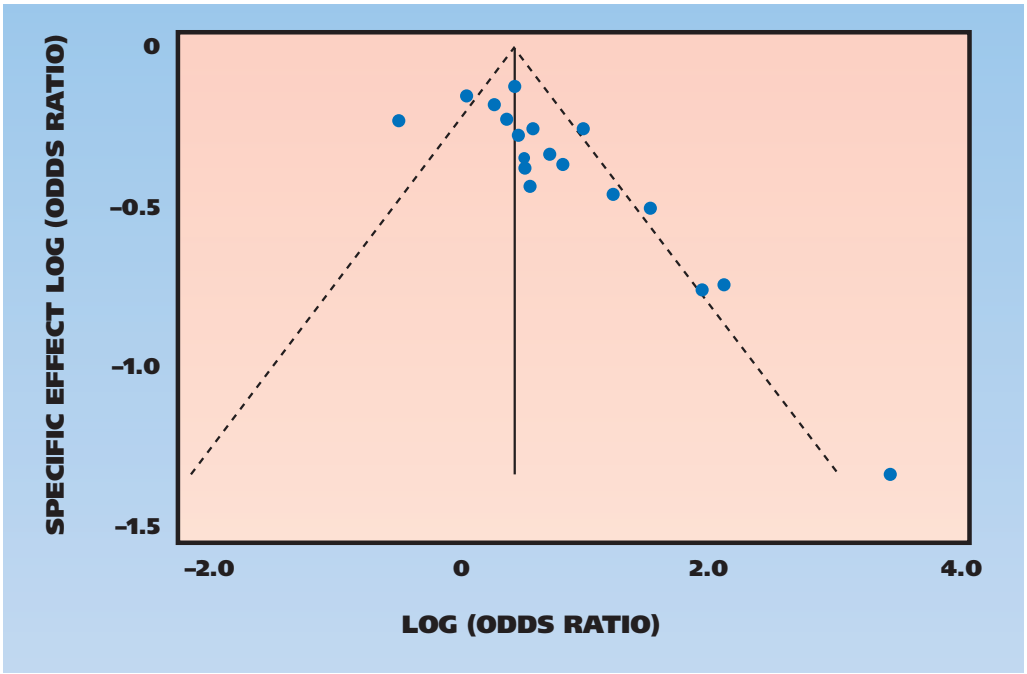

Figure 3. Funnel plot showing publication bias. The funnel plot is asymmetrical, with a sparse presence of studies on the left side of the summary estimate suggesting publication bias. As the review included only 19 studies, the power to detect asymmetry was limited.

Unpublished mean evidence may have biased the estimated mean impact of infant formula on fluorosis. The authors of about one-half of the studies reported in the materials and methods sections of their articles that they had evaluated infant feeding practices, yet they did not report the findings of this evaluation in their results sections. One of these studies[55] possibly had more subjects than the total of approximately 8,000 subjects included in this systematic review. However, its investigators did not report the effect of infant formula use because their preliminary analyses indicated a lack of a significant effect of infant formula use on fluorosis (G. Maupome, written communication, April 11, 2008). In addition, studies evaluating the effect of infant formula on fluorosis may exist; however, we could not confirm their existence in the published literature because the articles did not contain information on infant feeding practices in their materials and methods sections. Our formal statistical test of publication bias and our visual assessment of a scatter plot of the reported ORs suggest that there are likely to be other, unpublished studies with negative results. In addition, our review of the infant formula–fluorosis literature provided examples of a within-study reporting bias. In two published reports, the authors reported a risk of fluorosis associated with use of infant formula use when fluoride levels in the water supply were high, not when they were low.[39,40]

Eighteen of the 19 studies were retrospective. The amount, duration, type and frequency of infant formula use may have been difficult for those studies' participants to recall. Whereas the authors of four of the studies[28-30,42] assessed the reliability of participants' recall, in none of the studies did the investigators validate the accuracy of the mothers' responses. Recall bias may be a problem, as mothers of children with severe fluorosis may have different levels of recall regarding what may have caused "those white spots on my child's teeth" than mothers of children who have more subtle or no fluorosis. Determining the fluoride content in infant formulas or water purchased approximately a decade earlier is more challenging; participants may have for-

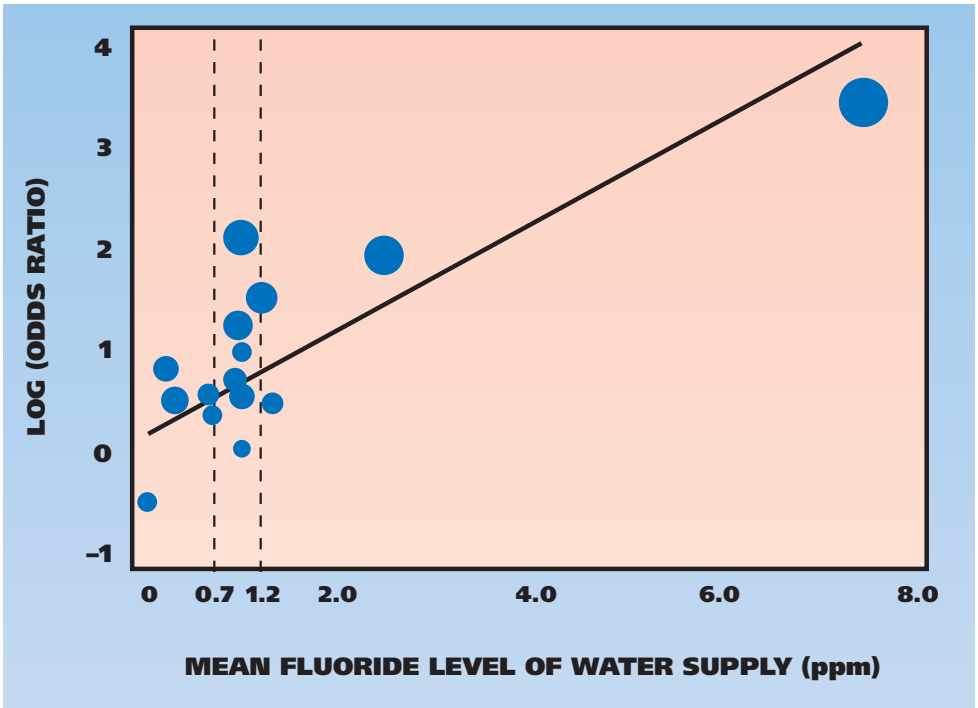

Figure 4. Scatter plot and regression of the log odds ratio for fluorosis associated with infant formula against the average fluoride level in the water supply. Compared with the consumption of infant formula in areas with 0 parts-per-million (ppm) fluoride levels in the water, the fluorosis risk associated with infant formula increased from 76 to 128 percent when the fluoride level in the water increased from 0.7 to 1.2 ppm.

gotten brand names, infant formula and water composition—even if of the same brand name or source—may have changed and historical samples may no longer be available for fluoride analysis. Misinformation about the geographical mobility of study participants may have confounded the results further. One can assume that obtaining estimates of fluoride concentrations in breast milk or cow's milk is relatively unimportant if one accepts that these concentrations remain relatively constant owing to biological pH gradients.[56] As a result, the authors of these studies generally compared a known low level of fluoride intake from breast-feeding or cow's milk with an unknown and possibly, but not necessarily, higher level of fluoride intake from formula.

The absence of information on the amount of fluoride in the infant formula may be the main reason that none of the authors of these studies assessed what proportion of the fluorosis may have been caused by the fluoride in the infant formula. An indirect method of assessing the impact of fluoride on infant formula and fluorosis would have been to evaluate how infant formula relates to fluorosis in areas with different levels of fluoride in the water supply. Authors of 12 studies[26,27,31,36-40,45,48,51,52] assessed the infant formula–fluorosis association with different fluoride concentrations in the water supply, but none of these articles included a report on whether the concentration of fluoride in the water supply played a role in this association. We assessed the effect of fluoride concentration in the water supply on the infant formula–fluorosis association across studies by using a metaregression and also within two studies that reported fluorosis risk associated with infant formula for different levels in the water supply.[36,37] The results of our meta-analysis showed that as the fluoride in the water supply increased, the reported fluorosis risk associated with infant formula consumption increased significantly.

Confounding factors may have induced spurious associations between infant formula and fluorosis. Mothers using infant formula may be more likely to use toothpaste for their infants, as was suggested in one well-conducted case-control study.[32] Socioeconomic class may relate to both infant feeding practices and use of fluoride supplements or toothpaste.[28] Breast-feeding may protect against various childhood infections such as otitis media[57] and, consequently, be associated with reduced amoxicillin use and therefore possibly reduced enamel fluorosis.[34] The presence of proteins or fats in breast milk or infant formula may decrease absorption of fluoride from other sources.[58,59] Finally, feeding patterns in infancy, including consumption of infant formula versus breast milk, may be associated with future susceptibility to infections and consequent antibiotic use, or with caries incidence and consequent fluoride use. Possibly, the habits or feeding patterns of a child as a toddler, rather than as an infant, determine fluorosis in his or her permanent dentition and, because of the correlation between tod-

dler and infant habits, infant exposures such as infant formula consumption may become correlated to fluorosis spuriously.

Weaknesses of this systematic review include the lack of an a priori design and analysis plan, the diversity of the included study designs and the lack of primary data. Whereas systematic reviews, just like original studies, should be driven by an a priori hypothesis, ours was not. We revised our decisions as to which data to abstract several times during the review process, with the goal of maximizing the types of information we could abstract. In part, the continued changes we made in analytic plans for the systematic review also reflect the lack of quality of the available evidence. Such data-driven, rather than hypothesis-driven, data abstraction may have led to biases. If we had adhered to a rigorous pretrial systematic review plan, our findings might have led to a conclusion of an absence of evidence. This may be a common challenge for researchers undertaking systematic reviews of the dental literature.[60] Our decision to include study designs ranging from cross-sectional to cohort was a weakness, as retrospective studies are inherently more susceptible to bias than are prospective cohort studies, especially when nonvalidated recall is involved. However, a systematic review of only prospective cohort studies or randomized controlled trials would have led to the identification of just one study and to the exclusion of high-quality, population-based case-control studies. Finally, some have suggested that systematic reviews should be limited to situations in which the original primary data of each study can be retrieved, analyzed and combined. Such an approach would not have been feasible for this topic.

CONCLUSIONS

Our systematic review indicated that the consumption of infant formula is, on average, associated with an increased risk of developing at least some detectable level of enamel fluorosis, that publication bias exists and that substantial heterogeneity exists in the extent to which the consumption of infant formula is associated with fluorosis. We could not determine in this systematic review whether liquid or powder infant formula with or without reconstitution affected fluorosis risk differently, as only a few studies provided such detailed information. As the fluoride concentration increased in the water supply, the risk of developing fluorosis associated with infant formula use increased. The epidemiologic evidence that it was the fluoride in the infant formula that caused the fluorosis nonetheless was weak, as we could not rule out other explanations. One interpretation of the available evidence would be that public health officials should create guidelines for infant formula consumption ensuring that the upper intake level established by the Institute of Medicine[3]—which is itself based on weak evidence—is not exceeded. Another approach would be to strive for "biological normality"[61] and to strive for fluoride levels in infant formula that are comparable with the levels observed in breast milk. For some mothers, the issue of which approach to use will be moot, as most medical public health organizations recommend breast-feeding. For mothers who opt to use infant formula, whether exclusively or in conjunction with breast milk, mandatory reporting of fluoride levels for both infant formula and bottled water would allow them to make informed decisions about how they will feed their infants and children. ■

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