

Evidence-based clinical recommendations regarding fluoride intake from reconstituted infant formula and enamel fluorosis: a report of the American Dental Association Council on Scientific Affairs.

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Abstract

BACKGROUND: This article presents evidence-based clinical recommendations regarding the intake of fluoride from reconstituted infant formula and its potential association with enamel fluorosis. The recommendations were developed by an expert panel convened by the American Dental Association (ADA) Council on Scientific Affairs (CSA). The panel addressed the following question: Is consumption of infant formula reconstituted with water that contains various concentrations of fluoride by infants from birth to age 12 months associated with an increased risk of developing enamel fluorosis in the permanent dentition?

TYPES OF STUDIES REVIEWED: A panel of experts convened by the ADA CSA, in collaboration with staff of the ADA Center for Evidence-based Dentistry (CEBD), conducted a MEDLINE search to identify systematic reviews and clinical studies published since the systematic reviews were conducted that addressed the review question.

RESULTS: CEBD staff identified one systematic review and two clinical studies. The panel reviewed this evidence to develop recommendations.

CLINICAL IMPLICATIONS: The panel suggested that when dentists advise parents and caregivers of infants who consume powdered or liquid concentrate infant formula as the main source of nutrition, they can suggest the continued use of powdered or liquid concentrate infant formulas reconstituted with optimally fluoridated drinking water while being cognizant of the potential risks of enamel fluorosis development. These recommendations are presented as a resource to be considered in the clinical decision-making process. As part of the evidence-based approach to care, these clinical recommendations should be integrated with the practitioner's professional judgment and the patient's needs and preferences.

Evidence-based clinical recommendations regarding fluoride intake from reconstituted infant formula and enamel fluorosis

A report of the American Dental Association Council on Scientific Affairs

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Many national agencies advocate breastfeeding because of its benefits to both mother and infant.¹⁻³ Healthy People 2010 (HP2010) targets for the percentage of the population initiating breastfeeding, breastfeeding infants to the age of 6 months and breastfeeding infants to the age of 12 months are 75 percent, 50 percent and 25 percent, respectively.⁴ Since 1990, national estimates of breastfeeding initiation have shown a consistent increase, and the overall national prevalence is close to reaching the HP2010 target of 75 percent.⁵ The Centers for Disease Control and Prevention (CDC), Atlanta, reported that 74 percent of mothers of children born in 2005 initiated breastfeeding in the postpartum period, with 43 percent and 22 percent of their infants continuing to be breastfed for six and 12 months, respectively.⁶ Only 12 percent of these mothers exclusively breastfed their infants through the age of 6 months.⁵ Thus, infant formula remains a major source of nutrition for many infants in the United States.^{5,7} By the time infants have reached 3 months of age, the percentage who have received any formula (61 percent) is about equal to the percentage who have received any breast milk.⁷ Exclusive use of formula is highest among infants

ABSTRACT



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Key Words. Fluoride; infant formula; fluorosis; evidence-based dentistry; clinical recommendations.

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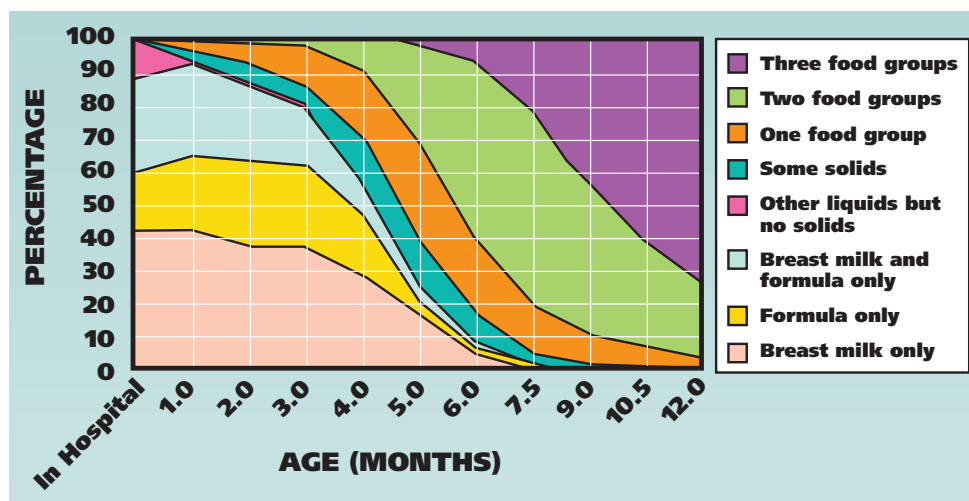


Figure. Types of foods consumed by infants, according to age. Reprinted with permission of the American Academy of Pediatrics from Grummer-Strawn and colleagues.⁷

aged between 2 and 3 months (approximately 25 percent) and then decreases to less than 5 percent by age 6 months (Figure).⁷ Whereas breastfeeding increased, the total volume of infant formula sold in the United States (measured by reconstituted ounces) decreased by 10 percent from 1994 to 2000.⁸

Among the various types of formula, across the same period, the percentage of powdered formula sold increased notably (from 43 percent to 62 percent), and concurrently the sales of liquid concentrate formula decreased (from 42 percent to 27 percent).⁸ Consistent with these changes in type of formula sold were findings from the national Infant Feeding Practices Survey II (IFPS II) that was conducted from 2005 to 2007 by the U.S. Food and Drug Administration (FDA) and CDC, in collaboration with other federal agencies. In the IFPS II, about 90 percent of mothers who participated in the survey and who fed their infants with formula reported using powder from a can throughout the infant's first year.⁹ Seven to 10 percent of these participating mothers indicated that they used liquid concentrate and 10 to 14 percent indicated that they used ready-to-feed formula.⁹ (Percentages of type of formula used do not add up to 100 percent because mothers could choose all that applied.)

INFANT FORMULAS TODAY

In the United States, other than some specialty products, most commercial infant formulas are either milk-based or soy-based products. Ready-to-feed formulas do not need to be reconstituted, but the powdered or liquid concentrate formulas require reconstitution with drinking water. Table 1 presents the mean fluoride concentra-

tion in the different types of formulas. Because powdered and liquid concentrates contain low concentrations of fluoride, the final concentration of fluoride in these formulas depends largely on the fluoride content of the water used to reconstitute them.¹⁰ Compared with the reconstituted formulas, ready-to-feed formulas contain the lower fluoride concentration.¹⁰

One can reconstitute formula with either tap or bottled drinking water. About 70 to 75 percent of the mothers who participated in the 2005-2007 IFPS II and who fed their infants with formula reported using tap water to reconstitute the formula.¹¹ The CDC reported that in 2008, 72.4 percent of the U.S. population who used public water supplies received optimally fluoridated water.¹² The optimal fluoride concentration in drinking water, as established by the U.S. Public Health Service, is 0.7 to 1.2 parts per million, a range that research has shown to be beneficial in reducing caries.¹³ In some areas, naturally occurring fluoride levels may be above or below these concentrations. Box 1 (page 82) presents information on how to learn more about the fluoride content of drinking water.¹⁴

Most bottled waters contain a less-than-optimal concentration of fluoride, and the fluoride content varies among brands.¹⁵⁻¹⁸ Bottled-water products that are marketed as "purified," "distilled," "deionized," "demineralized" or "produced through reverse osmosis" typically have concentrations of fluoride much lower than those of products marketed without these claims.¹⁹ There is no federal requirement to display the fluoride content on the bottle's label,

ABBREVIATION KEY. ADA: American Dental Association. CDC: Centers for Disease Control and Prevention. CEED: Center for Evidence-Based Dentistry (of the American Dental Association). CSA: Council on Scientific Affairs (of the American Dental Association). EPA: Environmental Protection Agency. FDA: Food and Drug Administration. HP2010: Healthy People 2010. IFPS II: Infant Feeding Practices II. IFS: Iowa Fluoride Study. MeSH: Medical Subject Headings.

unless fluoride is added specifically.¹⁹

FLUORIDE INTAKE AND ENAMEL FLUOROSIS

Ingestion of fluoride during critical periods of tooth development may result in a range of visually detectable changes in enamel opacity that are termed “enamel fluorosis,” a type of hypomineralization of the enamel.²⁰ To cause fluorosis, biological plausibility suggests, fluoride must be present at the time of enamel mineralization in sufficient quantity for a sufficient duration and in a susceptible child.²¹ The severity and distribution of fluorosis depend on the amount and duration of fluoride intake; the balance of ingested fluoride (total intake minus total excretion), which determines the fluoride concentrations throughout the body (including the fluids around and within the developing teeth); the stage of tooth development at exposure; and the child’s susceptibility to the condition.²² The excretion of fluoride occurs almost exclusively in the urine.²³ Fluoride excretion is strongly and directly related to urinary pH,²³ which, in turn, is determined by the composition of the diet.²³⁻²⁵ Sources of ingested fluoride include drinking water; foods and beverages, including infant formula; fluoride toothpaste; and prescription fluoride supplements.^{26,27}

During normal enamel maturation, the increased mineralization in the developing tooth is accompanied by the loss of matrix proteins that are secreted early in development.²⁸ Sufficiently high levels of fluoride can disrupt this process and increase enamel porosity.²⁹ When the clinician dries the teeth and inspects them carefully under direct lighting, he or she can see the milder forms of enamel fluorosis as white opacities that appear as minor striations or patches of paper-white enamel. More pronounced forms of fluorosis may manifest as enamel that is stained, pitted, lost or a combination of these because of fracture or attrition.^{22,30}

Permanent teeth, except for later-developing third molars, are susceptible to the development of enamel fluorosis in children younger than 9 years, after which time pre-eruptive enamel maturation is complete.^{26,31-35} Generally, the greater the amount of fluoride intake during tooth development, the greater the prevalence of enamel fluorosis.³³

TABLE 1

Mean (SD*) fluoride concentration (ppm†) in a range of infant formulas in the United States in 2008.‡

INFANT FORMULA TYPE	RECONSTITUTED POWDERED CONCENTRATE (ppm)§	RECONSTITUTED LIQUID CONCENTRATE (ppm)§	READY-TO-FEED
Milk-Based Formulas	1.03 (0.08)	0.64 (0.09)	0.15 (0.06)
Soy-Based Formulas	1.07 (0.09)	0.75 (0.04)	0.21 (0.10)

* SD: Standard deviation.
† ppm: Parts per million.
‡ Source: Siew and colleagues.¹⁰
§ Reconstituted with water containing 1 ppm fluoride. Note that 1 ppm = 1 milligram per liter = 1 microgram per milliliter.

SCOPE AND PURPOSE OF THE RECOMMENDATIONS

A multidisciplinary panel, comprising experts on fluoride, epidemiologists, methodologists and practitioners, reviewed the available literature to determine the risk of developing enamel fluorosis as a result of ingesting fluoride from reconstituted infant formula. The American Dental Association (ADA) Council on Scientific Affairs (CSA) convened a panel to evaluate the available scientific evidence on the topic of fluoride intake from infant formula and any association with fluorosis. Although some evidence suggests that fluoride’s caries-preventive benefit may be best achieved when a person receives both topical and pre-eruptively administered systemic fluoride,³⁶⁻³⁹ the preventive benefit derived from systemic fluoride intake specifically in the first six months of life has not been established. We should note that the panel did not review all available evidence on fluoride’s pre-eruptive caries-preventive effect. This report does not address any other health outcomes arising from exposure to infant formula.

In this report, we present a critical evaluation and summary of the relevant scientific evidence that is intended to assist the clinician in the decision-making process. This report does not represent a standard of care. The clinical recommendations presented here should be integrated with the practitioner’s professional judgment and the individual patient’s needs and preferences. This report replaces the Interim Guidance on Fluoride Intake for Infants and Young Children published by the ADA in 2006.⁴⁰

METHODS

The Council selected panelists on the basis of their expertise in the relevant subject matter. At workshops held at ADA Headquarters Nov. 10-12, 2008, and July 20-22, 2009, and in subsequent conference calls and e-mail communications, the panel evaluated the published

BOX 1

Learning more about fluoride content in drinking water.

Resources are available to help practitioners and parents learn more about the fluoride concentration in a child's primary source of drinking water.

- For those served by a public water system, the local water utility company can provide a copy of the utility's most recent Consumer Confidence Report. All public water systems are required by the U.S. Environmental Protection Agency (EPA) to publish an annual Consumer Confidence Report containing information about drinking water, including its fluoride concentration.
- For those residing in a state that participates in the Centers for Disease Control and Prevention's My Water's Fluoride program, information about a water system's fluoridation status is available online at "<http://apps.nccd.cdc.gov/MWF/Index.asp>".
- Approximately 14 percent of U.S. residents rely on private wells that are not regulated by the EPA Safe Drinking Water Act.* The EPA suggests that all wells be tested for quality once every three years, since well-water quality can change across time. Local, county or state health departments can provide information about or assistance in testing water's fluoride content if that content is unknown.

* Source: Kenny and colleagues.¹⁴

evidence and developed evidence-based clinical recommendations for the use of fluoridated water in reconstituting infant formula.

Conflict-of-interest disclosures. The panel comprised 12 people who represented a broad range of expertise. Each panelist completed a standard conflict-of-interest questionnaire.

Literature search. The panel established the following inclusion and exclusion criteria to screen for relevant articles.

Inclusion criteria. Staff members of the ADA Center for Evidence-based Dentistry (CEBD) included studies if they

- were published in English;
- were conducted in humans;
- involved the evaluation of the use of infant formula and dental fluorosis;
- involved the examination of children for fluorosis and included information on fluorosis prevalence as an outcome.

Exclusion criteria. CEBD staff members excluded studies if they

- involved evaluation of animals;
- provided information only on other fluoride exposures (for example, toothpastes and nonformula dietary sources);
- focused on primary teeth.

CEBD staff members searched MEDLINE for articles published until Sept. 9, 2008, to identify systematic reviews and current clinical studies that addressed the following clinical question: Is

consumption of infant formula reconstituted with water that contains various concentrations of fluoride by infants from birth to 12 months associated with an increased risk of developing enamel fluorosis in the permanent dentition?

Systematic reviews. The CEBD staff members limited the search to English-language articles and systematic review or meta-analysis articles and used the following search terms: "fluorosis" OR "Fluorosis, Dental" (Medical Subject Headings [MeSH] Terms) 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 behavior" OR "food analysis" OR "epidemiologic factors" OR "time factors" NOT "animals" (MeSH Terms) NOT "humans" (MeSH Terms).

This search yielded 75 articles. Two CEBD staff members (S.S. and K.A.) independently reviewed titles and abstracts and identified 20 articles for full-text review. The same reviewers read the 20 articles and excluded all of them. (For information about excluded articles along with reasons for exclusion, see Appendix 1 of the supplemental data to the online version of this article at "<http://jada.ada.org>".)

The panel considered the prepublication version of a systematic review previously commissioned by the CSA. This article subsequently was published in *The Journal of the American Dental Association*.⁴¹ On June 16, 2010, CEBD staff replicated the original search for literature published from Sept. 10, 2008, through that date but did not identify any additional reviews.

Clinical studies. CEBD staff members conducted a second search to identify clinical studies published after the last search date within the systematic review.⁴¹ They searched for clinical studies published between Sept. 1, 2007, and Sept. 8, 2008. Their initial search yielded 16 articles. Two independent reviewers (S.S. and K.A.) reviewed titles and abstracts for relevance to the clinical question. They identified five articles for full-text review, of which they selected for inclusion one clinical study by Spencer and Do.⁴² (For information about excluded articles, see Appendix 1 of the supplemental data to the online version of this article at "<http://jada.ada.org>".) After reviewing this article, the panel asked the primary author of the systematic review (P.P.H.), who also was a member of the expert panel, to incorporate this

study into the analyses performed for the systematic review and generate an updated summary estimate. (For information on the update to the systematic review, see Appendix 2 of the supplemental data to the online version of this article at “<http://jada.ada.org>”). During the panel meeting, one panel member (S.L.) also presented additional data from the Iowa Fluoride Study (IFS) for the panel’s consideration. An article containing these additional data from the IFS recently was published in JADA.²⁷ CEBD staff members updated the search on June 16, 2010, searching for relevant articles published after Sept. 9, 2008, and found 40 studies but selected none for inclusion.

Critical appraisal. The panel performed a qualitative assessment of the strengths and limitations of each study to determine the quality of the evidence. (For information about the individual studies, see Appendix 2

of the supplemental data to the online version of this article at “<http://jada.ada.org>”).

Grading the evidence and classifying the strength of the clinical recommendations.

On the basis of the included studies, the panel developed evidence statements and graded them according to a system developed by Shekelle and colleagues⁴³ (Table 2). The panel developed clinical recommendations on the basis of its interpretation of this evidence. The panelists classified clinical recommendations according to the strength of the evidence that forms the basis for the recommendation, again using a system modified from that of Shekelle and colleagues.⁴³ The classification of the recommendation directly reflects the level of scientific evidence that supports the recommendation.

Process for developing clinical recommendations. When the panel members were unable to reach a consensus in interpreting evidence into clinically relevant recommendations, they used a majority vote to make final determinations.

Review process. The panel submitted its clinical recommendations for comment to both internal and external scientific experts and organizations. (For a listing of external reviewers, see Appendix 3 of the supplemental data to the online version of this article at “<http://jada.ada.org>”). After reviewing all submitted remarks, the panel revised its recom-

TABLE 2

Shekelle system for grading evidence.*

LEVEL	CATEGORY OF EVIDENCE
Ia	Evidence from systematic review of randomized controlled trials
Ib	Evidence from at least one randomized controlled trial
IIa	Evidence from at least one controlled study without randomization
IIb	Evidence from at least one other type of quasi-experimental study, such as time series analysis or studies in which the unit of analysis is not the individual
III	Evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, cohort studies and case-control studies
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities
CLASSIFICATION	STRENGTH OF RECOMMENDATIONS
A	Directly based on category I evidence
B	Directly based on category II evidence or extrapolated from category I evidence
C	Directly based on category III evidence or extrapolated from category I or II evidence
D	Directly based on category IV evidence or extrapolated from category I, II or III evidence

* Amended with permission of BMJ Publishing Group from Shekelle and colleagues.⁴³

mendations where appropriate. The CSA approved the final clinical recommendations.

Role of the funding source. The CSA commissioned the panel’s work, which was funded by the ADA.

RESULTS

One systematic review,⁴¹ which was commissioned by the ADA, addressed the association between infant formula consumption and fluorosis. One cross-sectional study provided data in addition to those from the systematic review.⁴² One prospective study²⁷ addressed the association between fluorosis and fluoride intake from formula.

The authors of the systematic review concluded that in infants from birth to age 24 months, formula consumption can be associated with an increased risk of developing at least some detectable level of enamel fluorosis (odds ratio [OR] = 1.81; 95 percent confidence interval [CI], 1.44-2.26).⁴¹ Most of the articles included in the review provided minimal information about the extent of the participant’s exposure to infant formula, the type of infant formula the participant consumed (powdered or liquid concentrate or ready to feed), the fluoride concentration of the formula and, if the formula was reconstituted, the fluoride content of the water. Hence, the authors were unable to determine whether the increased risk was caused by fluoride intake

BOX 2

Recommendations of the expert panel regarding fluoride intake from infant formula.

The members of the American Dental Association expert panel encourages clinicians to follow the American Academy of Pediatrics guidelines for infant nutrition,* which advocate exclusive breastfeeding until the child is aged 6 months and continued breastfeeding until the child is at least 12 months of age, unless specifically contraindicated.

The panel offers the following suggestions to practitioners to use in advising parents and caregivers of infants who consume powdered or liquid concentrate infant formula as the main source of nutrition:

- Suggest the continued use of powdered or liquid concentrate infant formulas reconstituted with optimally fluoridated drinking water while being cognizant of the potential risk of enamel fluorosis development (strength of evidence: D).
- When the potential risk of enamel fluorosis development is a concern, suggest ready-to-feed formula or powdered or liquid concentrate formula reconstituted with water that either is fluoride free or has low concentrations of fluoride (strength of evidence: C).

* Source: Gartner and colleagues.⁴⁵

from the infant formula product, fluoridated drinking water or other possible sources of fluoride such as toothpastes or fluoride supplements. The authors of the review updated their analyses with the results from the cross-sectional study.⁴² The updated estimate of OR was 1.74 (95 percent CI, 1.40-2.15). (For information about the updated analyses, see Appendix 2 of the supplemental data to the online version of this article at “<http://jada.ada.org>”.)

The authors of the IFS determined the relationship between fluoride intake from reconstituted infant formula by infants between the ages of 3 and 9 months and enamel fluorosis of the permanent maxillary incisors.²⁷ The investigators used data from questionnaires completed by parents of children aged from 6 weeks to 36 months to estimate the fluoride intake from reconstituted powdered formula among infants aged 3 to 9 months, as well as the fluoride intake from other beverages (primarily reconstituted fruit juices) among infants aged 3 to 9 months and from dentifrices in children aged 16 to 36 months.²⁷ They used the Fluorosis Risk Index⁴⁴ to evaluate the fluorosis of the permanent maxillary incisors in children who were about 9 years of age. (For information about this study, see Appendix 2 of the supplemental data to the online version of this article at “<http://jada.ada.org>”.)

The panel reached the following conclusions

on the basis of available evidence. Clinicians should consider these conclusions in their totality and not as exclusive of one another.

- Consumption of infant formula may be associated with an increased risk of developing enamel fluorosis in the permanent dentition⁴¹ (level III).

- The estimated risk of enamel fluorosis related to fluoride intake from reconstituted infant formula is associated with the fluoride concentration in the drinking water²⁷ (level III).

- Factors such as multiple and often concurrent exposures to fluoride during the period of tooth development in children make it difficult to isolate an individual child’s risk of fluorosis development associated with fluoride intake from one specific exposure, such as the use of reconstituted infant formula during the first year of life^{27,41} (level III).

Box 2 presents the recommendations developed by the expert panel regarding fluoride intake from infant formula (which take into account the infant nutrition guidelines published by the American Academy of Pediatrics⁴⁵). Box 3 presents the panel’s recommendations for research, which are based in part on recommendations from CDC.²¹

DISCUSSION

On the basis of the available evidence, a majority of the panel members concluded that when advising parents and caregivers of infants from birth to age 12 months who consume reconstituted infant formula as the main source of nutrition, practitioners can suggest the continued use of powdered or liquid concentrate infant formulas reconstituted with optimally fluoridated drinking water while being cognizant of the potential risk of enamel fluorosis development. For parents and caregivers who are concerned about the potential for increasing children’s risk of developing enamel fluorosis, practitioners can suggest ready-to-feed formula or powdered or liquid concentrate formula reconstituted with water that either is fluoride free or contains only low concentrations of fluoride. Examples of such water are water that is labeled “purified,” “demineralized,” “deionized,” “distilled” or “produced through reverse-osmosis.”¹⁹ In making its recommendations based on the available evidence, the panel considered the following factors:

- amount, duration and timing of fluoride intake as they affect the prevalence of fluorosis in early-erupting permanent teeth;
- the prevalence and severity of fluorosis in children who consumed infant formula reconsti-

tuted with fluoridated community drinking water compared with the prevalence and severity in those who did not consume formula; ■ the effects of mild enamel fluorosis on oral health-related quality of life.

In general, the greater the amount of fluoride intake during tooth development in any person, the greater the prevalence of fluorosis development.³³ Bardsen,³² who conducted a meta-analysis of the literature, suggested that the duration of the fluoride exposure during the course of amelogenesis (enamel formation), rather than just during any specific or critical risk period, determines the development of fluorosis in the permanent maxillary incisors. Fluoride intake from all sources combined from birth to age 3 or 4 years can place a child at risk of developing fluorosis in early-erupting teeth.³³⁻³⁵ Fluorosis in late-erupting teeth (other than the third molars) can occur as a result of systemic exposure to fluoride until about age 8 years.^{26,32}

Infants who consume formula do so mainly during the first six months of life.⁷ During their first year of life, infants are exposed to fluoride primarily via infant formula reconstituted with fluoridated water and other beverages that contain added fluoridated water.²⁷ Before the 1994 change in the fluoride supplement schedule,⁴⁶ fluoride supplements also were prescribed for infants younger than 6 months living in communities with a water fluoride concentration of less than 0.3 ppm.⁴⁷ These exposures, along with other exposures that occur after the first year (such as use of fluoridated dentifrice; use of supplements; consumption of optimally fluoridated drinking water by itself; consumption of other beverages with water added; and consumption of selected foods, including those with substantial amounts of added water), contribute to fluorosis of the developing dentition.

Multiple and often concurrent exposures during the period of tooth development make it difficult to isolate the risk associated with fluoride intake from one specific exposure, such as the use of reconstituted infant formula during the first year of life. Children participating in the IFS ingested fluoride from many sources, including formula reconstituted with fluoridated water, other beverages with added water (mainly reconstituted juices), dietary supplements and dentifrices.²⁷ Overall, there was a statistically significant association in the IFS between substantial fluoride intake from reconstituted powdered infant formula (upper quartile of fluoride intake among the participating children) and increased fluorosis prevalence (relative risk = 1.40; 95 percent CI, 1.06-1.84,

BOX 3

Recommendations for research.

- Identify biomarkers (that is, distinct biological indicators) as an alternative to direct fluoride intake measurement to allow the clinician to estimate a person's fluoride intake and the amount of fluoride in the body.*
- Conduct descriptive and analytical epidemiologic studies to
 - estimate the total fluoride intake from all sources individually and in combination;
 - quantify the risk of developing moderate to severe fluorosis attributable to fluoride intake from consumption of reconstituted infant formula.
- Conduct metabolic studies of fluoride to determine the influence of environmental, physiological and pathological conditions on the pharmacokinetics, balance and effects of fluoride* (such as studies to determine the influence of breast milk, cow's milk-based formula and soy-based formula on the pH of urine, the associated urinary excretion and balance of fluoride, and the occurrence of dental fluorosis).

* Based in part on material in Centers for Disease Control and Prevention.²¹

$P < .02$) of the permanent maxillary incisors.

Using logistic regression to adjust for the effects of fluoride from other sources, investigators in the IFS examined the relationship between fluoride intake from reconstituted powdered infant formula, specifically, and enamel fluorosis of the permanent maxillary incisors in the children enrolled in the IFS. The authors found that an increase of 0.1 milligram of fluoride per day in average daily fluoride intake from reconstituted powdered formula in infants aged 3 to 9 months was associated with an increase in the risk of developing enamel fluorosis in the permanent maxillary incisors (OR = 1.10; 95 percent CI, 1.03-1.17, $P < .05$).²⁷ For example, according to the adjusted statistical model, children in the IFS who had median levels of fluoride intake from beverages between ages 3 and 9 months (primarily reconstituted fruit juices) and dentifrice between ages 16 and 36 months, but did not have any fluoride intake from reconstituted powdered formula between ages 3 and 9 months (that is, those who were breastfed or received ready-to-feed formula), would have a risk of 30.7 percent of developing enamel fluorosis in two or more maxillary incisors. If children consumed an average of 8 ounces of powdered formula reconstituted with water containing 1 ppm fluoride per day from age 3 months through age 9 months, in addition to the median fluoride intake from other sources, they would have a projected 35.5 percent risk of developing enamel fluorosis. If these children consumed 12 oz of reconstituted powdered infant formula daily, this risk would be

38.0 percent, whereas if they consumed 16 oz daily, the projected risk would be 40.6 percent.²⁷

In terms of prevalence, of the 600 children examined in the IFS, 178 (29.7 percent) had fluorosis on two or more maxillary incisors, 382 (63.7 percent) had no maxillary incisor fluorosis and 40 (6.7 percent) had only one affected incisor and were excluded from the analysis. The majority of fluorosis detected was mild (that is, white striations; $n = 173$, 97 percent), with only five participants having more pronounced fluorosis (that is, staining or pitting of the enamel).²⁷ According to a 2010 review of the few studies in which researchers examined oral health-related quality of life, none of those studies' results showed mild enamel fluorosis to have negative effects. Investigators in studies of the public's perceptions of enamel fluorosis have found that people generally express concern only regarding more pronounced forms of fluorosis,⁴⁸ although perceptions can change across time and can vary among different cultures.⁴⁹

CONCLUSION

Practitioners should be aware that children are exposed to multiple sources of fluoride during the tooth development period. Reducing fluoride intake from reconstituted infant formula alone will not eliminate the risk of fluorosis development. It also is important that clinicians provide advice to parents regarding the proper use of fluoridated toothpastes²¹ along with the informed prescription of fluoride supplements.⁵⁰ The panel acknowledges and encourages clinicians to follow the American Academy of Pediatrics' guidelines for infant nutrition, which advocate exclusive breastfeeding to age 6 months and continued through at least age 12 months unless specifically contraindicated.⁴⁵ Human breast milk has been shown to have consistently low levels (0.005-0.01 ppm) of fluoride.⁵¹⁻⁵³ ■

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SUPPLEMENTAL DATA

This material is an online-only supplement to the following article: Berg J, Gerweck C, Hujuel PP, et al. Evidence-based clinical recommendations regarding fluoride intake from reconstituted infant formula and enamel fluorosis: a report of the American Dental Association Council on Scientific Affairs. JADA 2011;142(1):79-87. Copyright © 2011 American Dental Association. All rights reserved.

Appendix 1 Excluded Studies

CLINICAL STUDIES	
Excluded Article	Rationale for Exclusion
Martins and colleagues¹	Evaluated children aged 19 to 39 months old; no formula exposure
Bennett and colleagues²	No relevant outcomes
Momeni and colleagues³	Not on infant formula
Hong and colleagues⁴	Total fluoride intake study
Cressey⁵	Laboratory study; patients not examined
Siew and colleagues⁶	Laboratory study; patients not examined
SYSTEMATIC REVIEWS	
Browne and colleagues⁷	Not a systematic review
Weesner⁸	Narrative discussion
Whelton and colleagues⁹	Not a systematic review; did not address clinical questions
Vitoria Miñana¹⁰	Article not in English; could not review
Levy¹¹	Not a systematic review
Warren and Levy¹²	Not a systematic review
Fomon and colleagues¹³	Not a systematic review
Mascarenhas¹⁴	Not a systematic review
Den Besten¹⁵	Not a systematic review
Rozier¹⁶	Met review criteria but did not consider infant formula
Levy and Guha-Chowdhury¹⁷	Applicable information but not a systematic review
Pendrys¹⁸	Not a systematic review
Holloway and Ellwood¹⁹	Did not address the clinical questions
Whitford²⁰	Did not address the clinical questions
Clark and colleagues²¹	Not a systematic review
Levy²²	Not a systematic review
DenBesten and Thariani²³	Did not address the clinical questions; not a systematic review
Burt²⁴	Not a systematic review
Kaminsky²⁵	Not a systematic review
Møller²⁶	Not a systematic review; did not address the clinical questions

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Appendix 2

Description of Publications Included for Evidence

HUJOEL AND COLLEAGUES¹

Infant Formula and Enamel Fluorosis: A Systematic Review

The primary aim of the authors of this systematic review was to determine if there is an association between infant formula consumption by children from birth to the age of 24 months and the risk of developing dental fluorosis, by comparing children who were fed with formula with children who were fed with breast milk or cow's milk.¹ The secondary aim was to evaluate available evidence implicating the fluoride in the infant formula as a cause of dental fluorosis.¹

The authors of the systematic review combined data from 17 studies to estimate summary odds ratios (ORs) relating infant formula use to enamel fluorosis. The authors concluded that formula consumption by children from birth to 24 months can be associated with an increased risk of developing at least some detectable level of enamel fluorosis (OR 1.81, 95 percent confidence interval [CI] 1.44-2.26).¹ The authors were unable to determine whether the increased risk was caused by fluoride intake from the infant formula product, fluoridated drinking water or other possible sources of fluoride such as toothpastes or fluoride supplements. The authors performed additional statistical analysis to assess whether the fluoride level in the water supply was associated with the increased risk of enamel fluorosis related to the use of infant formula. They conducted a meta-regression analysis that included a subset of studies that reported the level of fluoride in the drinking water supply or provided sufficient information to make assumptions about the concentration of fluoride in the water supply. In this analysis, the authors found that the estimated risk of enamel fluorosis related to the use of infant formula was

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associated with the fluoride level in the water supply (OR 1.05, 95 percent CI 1.02-1.09).¹ Table 1³⁻²¹ presents a summary of the studies included in this systematic review.

Update to systematic review: addition of Spencer and Do.² During the literature search, staff of the American Dental Association Center for Evidence-based Dentistry identified one clinical study by Spencer and Do,² published in 2008 after Hujuel and colleagues¹ had completed the search for their systematic review. After reviewing this article, the panel asked the primary author of the systematic review (P.P.H.), who sat on the panel, to incorporate the results of this study into the analyses performed for the systematic review and then generate an updated summary estimate. The OR (95 percent CI) for the Spencer and Do² study was 1.01 (0.68-1.50). The updated summary OR based on all 18 studies was 1.74 (95 percent CI, 1.40-2.15).

The panel identified the following limitations of this systematic review:

- Most of the selected studies provided minimal information about the extent of the subject's exposure to infant formula, the type of infant formula the participants consumed (whether powdered concentrate, liquid concentrate or ready-to-feed), the fluoride concentration of the formula and, if water was used for reconstitution, the fluoride content of the water.
- There was variable and limited adjustment for potential confounders among the included studies.
- This review included studies whose authors reported on infants from birth to 24 months; thus, the data include children who had been exposed to other sources of fluoride from age 12 months to 24 months.
- An Egger test²² for asymmetry of the studies confirmed publication bias. The power to detect asymmetry was limited due to the small number of included studies.