Infant formula and enamel fluorosis: a systematic review
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CRD summary
The review found that consumption of infant formula may be associated with increased risk of a detectable level of enamel fluorosis, related to fluoride in the water supply. Evidence of a causal relationship between fluorosis and fluoride in infant formula was weak. The authors’ cautious conclusions appeared justified given the limitations of the evidence.

Authors' objectives
To assess the risk of enamel fluorosis associated with use of infant formula compared with breast or cows’ milk and assess the extent to which any increased risk may be due to fluoride in the infant formula.

Searching
MEDLINE via PubMed, The Cochrane Library, Web of Science, Current Controlled Trials, ClinicalTrials.gov, Proquest, National Institute of Clinical Excellence and Virtual Health Library databases and websites were searched in October and November 2007. Search terms were reported. Reference lists of relevant articles were checked. There were no language restrictions.

Study selection
Controlled studies that evaluated the association between enamel fluorosis and use of infant formula and/or breastfeeding during infancy were eligible for inclusion. Fluorosis was defined (post hoc) as a detectable level of enamel fluorosis. Infant formula was defined to include both ready-to-feed formulae and those that required reconstitution with water. The comparison group of interest in the review was infants who received breast or cows’ milk. Outcomes of interest in the review were prevalence of fluorosis associated with infant formula and an association between fluorosis and exposure to fluoride in the infant formula. Studies that did not report the effect of infant formula on enamel fluorosis risk were excluded. Studies that focused exclusively on primary teeth were excluded.

Study designs varied widely and included comparisons between infants fed using different practices, in different geographical or time periods with respect to water fluoride levels and with or without fluorosis. Participants were aged from two to 17 years; most were schoolchildren. Information on infant-feeding practices was commonly obtained by interviewing mothers and/or from diet diaries. Only about half of the studies reported frequency of feeding with infant formula and none reported quantity of formula consumed. Few studies reported the format of the formula (liquid or powder, with or without reconstitution) or its fluoride content. Duration of exposure to infant formula (or other type of feeding) varied up to a maximum 24 months of age, where reported. Where fluoride content was reported it was based on historical data. A wide range of fluorosis scales and thresholds were used to detect fluorosis.

A single reviewer selected studies for inclusion. A sample of studies was assessed in duplicate to calculate reviewer agreement.

Assessment of study quality
Study validity was assessed using a modified version of the Newcastle-Ottawa Scale. Nine items were assessed for cohort studies and eight for other observational designs. Items assessed included: ascertainment of exposure and outcome; adjustment for confounders; reporting of sample size, point estimates and variability; representativeness of participants; blinding; and rates of follow-up or response.

The validity assessment was conducted by two reviewers. Disagreements were resolved by discussion.

Data extraction
Odds ratios (ORs) were extracted from each study, with 95% confidence intervals (CIs). Where studies reported mixed breast/formula feeding, different types of formula or different time intervals, data were classified as any consumption...
versus no consumption of infant formula. It was assumed that studies measured fluorosis on permanent teeth, if this was unspecified. Where necessary, the reviewers assumed that cessation/lack of breastfeeding correlated with infant formula consumption. Clustering of data in two studies was ignored. Data from two studies that reported continuous outcomes were excluded from analysis.

Data were extracted independently by two reviewers. Disagreements were resolved by discussion. Attempts were made to contact the authors of primary studies for missing data.

Methods of synthesis
Studies were combined using a random-effects model to calculate summary odds ratios and 95% CIs. Statistical heterogeneity was assessed using the $I^2$ statistic. Publication bias was assessed using Egger's test. Data were subgrouped by the fluoride concentration in the infant formula or the water supply (where data were available). Random-effects meta-regression was used to explore the impact of fluoride levels on outcomes. The impact of other study characteristics (quality, outcomes measures, dietary fluoride, socio-economic status) were explored. The effect of omitting one study at a time from analysis was checked.

Results of the review
Nineteen observational studies were included in the review (n=approximately 17,429, of whom 8,454 were analysed; range 132 to 1,346 analysed). There were one prospective and five retrospective cohort studies, six case-control studies, four cross-sectional studies and three historical-control studies. Study quality varied from 2 to 7 out of a possible 9 points (for cohort studies) and from nil to 8 points out of a possible 8 for other designs. Common weaknesses were potential for recall bias, no reported blinding of outcomes assessors, high non-response rate and failure to adjust for likely confounders (seven studies failed to adjust for any confounders).

Infant formula was significantly associated with a higher prevalence of fluorosis in the permanent dentition compared to breast or cows’ milk (OR 1.8, 95% CI 1.4 to 2.3; 17 studies) with significant heterogeneity ($I^2=66\%$). The funnel plot indicated publication bias, which was confirmed by the Egger test (p=0.002). Therefore, there were likely to be unpublished studies with negative results.

Random-effects meta-regression indicated that the odds ratio associating formula feeding with fluorosis increased by 5% for every 0.1 part per million (ppm) increase in reported levels of fluoride in the water supply (OR 1.05, 95% CI 1.02 to 1.09). The comparison group was formula-fed infants in areas with less than 0.1ppm fluoride. Meta-regression showed no significant effect of other variables tested and no single study unduly influenced the summary odds ratio.

Authors’ conclusions
Consumption of infant formula may be associated with increased risk of a detectable level of enamel fluorosis related to fluoride in the water supply. Evidence of a causal relationship between fluorosis and fluoride in infant formula was weak.

CRD commentary
The objectives of the review were clear. As the authors noted, the design and statistical methods were data-driven rather than predetermined and decisions on which data to extract were revised several times; these factors may have created bias. Relevant sources for studies were searched without language restriction. Steps were taken to minimise the risk of reviewer bias and error by having more than one reviewer undertake quality assessment and extract data. Study selection was undertaken largely by a single reviewer, which increased the risk of selection bias. Appropriate statistical techniques were used to pool the studies and assess and investigate statistical heterogeneity and publication bias. The authors suggested plausible reasons for the heterogeneity between study findings (unreported variation in infant formula intake, fluoride levels and other sources of fluoride). The review was well conducted in some respects, but the reliability of the findings was limited by the data-driven design, likely publication bias, lack of prospective studies, heterogeneity in study findings, lack of evidence on fluoride exposure and potential confounding. The authors’ cautious conclusions appeared justified given the limitations of the evidence.

Implications of the review for practice and research
Practice: The authors stated that public health officials could consider recommending that the maximum intake of fluoride advised by US Institute of Medicine should not be exceeded. Alternatively, attempts could be made to match fluoride levels in infant formula to those in breast milk. It should be mandatory to report levels of fluoride in infant formula and in bottled water.

Research: The authors did not state any implications for research.

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