Supporting Document 2: Fluoride and health

Fluoride and dental caries

The dose-response relationship between fluoride concentration in water supplies and dental caries was established by Dean and colleagues in the 21 Cities Study (Dean 1942). Dean’s research focused on the permanent dentition of early teens, 12-14 years old. The table below presents Dean’s 21 cities data ordered by mean fluoride content in mg/L and the corresponding measures of dental caries: the DMF Teeth count, first molar mortality, upper incisor proximal surface caries – each expressed per 100 examinees- and the percentage of examinees caries-free.

<table>
<thead>
<tr>
<th>City</th>
<th>Number of examinees</th>
<th>Domestic water Mean F content (mg per litre)</th>
<th>Total hardness</th>
<th>CER (DMF) count</th>
<th>First molar mortality</th>
<th>Upper incisor proximal surface caries</th>
<th>Percentage of caries-free examinees</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorado Springs</td>
<td>404</td>
<td>2.6</td>
<td>27</td>
<td>246</td>
<td>4.7</td>
<td>2.48</td>
<td>28.5</td>
</tr>
<tr>
<td>Galesburg</td>
<td>273</td>
<td>1.9</td>
<td>247</td>
<td>236</td>
<td>15.0</td>
<td>3.66</td>
<td>27.8</td>
</tr>
<tr>
<td>Elmhurst</td>
<td>170</td>
<td>1.8</td>
<td>329</td>
<td>229</td>
<td>11.8</td>
<td>4.71</td>
<td>25.3</td>
</tr>
<tr>
<td>Joliet</td>
<td>447</td>
<td>1.3</td>
<td>349</td>
<td>323</td>
<td>19.5</td>
<td>10.74</td>
<td>18.3</td>
</tr>
<tr>
<td>Aurora</td>
<td>633</td>
<td>1.2</td>
<td>329</td>
<td>261</td>
<td>14.5</td>
<td>6.16</td>
<td>23.5</td>
</tr>
<tr>
<td>East Moline</td>
<td>152</td>
<td>1.2</td>
<td>276</td>
<td>303</td>
<td>15.8</td>
<td>1.63</td>
<td>20.4</td>
</tr>
<tr>
<td>Maywood</td>
<td>171</td>
<td>1.2</td>
<td>75</td>
<td>258</td>
<td>11.7</td>
<td>4.68</td>
<td>29.8</td>
</tr>
<tr>
<td>Kewanee</td>
<td>123</td>
<td>0.9</td>
<td>445</td>
<td>343</td>
<td>29.3</td>
<td>11.38</td>
<td>17.9</td>
</tr>
<tr>
<td>Pueblo</td>
<td>614</td>
<td>0.6</td>
<td>302</td>
<td>412</td>
<td>20.2</td>
<td>3.75</td>
<td>10.6</td>
</tr>
<tr>
<td>Elgin</td>
<td>403</td>
<td>0.5</td>
<td>103</td>
<td>444</td>
<td>26.3</td>
<td>32.56</td>
<td>11.4</td>
</tr>
<tr>
<td>Marion</td>
<td>263</td>
<td>0.4</td>
<td>209</td>
<td>556</td>
<td>26.9</td>
<td>26.04</td>
<td>5.7</td>
</tr>
<tr>
<td>Lima</td>
<td>454</td>
<td>0.3</td>
<td>223</td>
<td>652</td>
<td>28.8</td>
<td>28.89</td>
<td>2.2</td>
</tr>
<tr>
<td>Middletown</td>
<td>370</td>
<td>0.2</td>
<td>329</td>
<td>703</td>
<td>65.9</td>
<td>55.41</td>
<td>1.9</td>
</tr>
<tr>
<td>Zanesville</td>
<td>459</td>
<td>0.2</td>
<td>291</td>
<td>733</td>
<td>99.8</td>
<td>88.76</td>
<td>2.6</td>
</tr>
<tr>
<td>Elkhart</td>
<td>278</td>
<td>0.1</td>
<td>220</td>
<td>823</td>
<td>34.2</td>
<td>89.21</td>
<td>1.4</td>
</tr>
<tr>
<td>Michigan City</td>
<td>236</td>
<td>0.1</td>
<td>141</td>
<td>1 037</td>
<td>80.1</td>
<td>143.64</td>
<td>0</td>
</tr>
<tr>
<td>Quincy</td>
<td>330</td>
<td>0.1</td>
<td>86</td>
<td>708</td>
<td>71.2</td>
<td>70.00</td>
<td>2.4</td>
</tr>
<tr>
<td>Portsmouth</td>
<td>469</td>
<td>0.1</td>
<td>80</td>
<td>772</td>
<td>73.8</td>
<td>82.30</td>
<td>1.3</td>
</tr>
<tr>
<td>Waukegan</td>
<td>423</td>
<td>0.1</td>
<td>134</td>
<td>810</td>
<td>79.9</td>
<td>140.19</td>
<td>3.1</td>
</tr>
<tr>
<td>Oak Park</td>
<td>399</td>
<td>0.1</td>
<td>132</td>
<td>722</td>
<td>31.0</td>
<td>70.52</td>
<td>4.3</td>
</tr>
<tr>
<td>Evanston</td>
<td>256</td>
<td>0.1</td>
<td>131</td>
<td>673</td>
<td>42.6</td>
<td>85.16</td>
<td>3.7</td>
</tr>
</tbody>
</table>

When the DMF Teeth per 100 examinees for each of the city was plotted against the fluoride concentration of the local water supplies, a curvilinear relationship with a strongly declining dental caries experience moving from negligible fluoride to 1.0 to 1.2 mg/L, then a plateauing of the curve by 2 mg/L.

FIG. 1
RELATION BETWEEN DENTAL CARIES AND FLUORIDE CONTENT OF WATER

Based on the data obtained by Dean and co-workers from the examination of the permanent teeth of 7257 schoolchildren aged 12-14 years in 21 cities of the USA. (After Dean, 1954)
This original research has been replicated in a number of countries, for instance Sweden, Denmark and England (Murray et al 1991). While the shape of the relationship is similar across the four countries, the actual level of caries activity at any fluoride concentration varies as a result of context specific patterns of other protective and risk factors for dental caries.

An adjustment of the dose-response relationship described by Dean and colleagues by mean maximum temperature was suggested by Galagan and Vermillion in 1957 to account for variation in water consumption between areas (Galagan et al 1957). This adjustment was to vary the ‘optimum’ fluoride concentration which had been regarded as 1 mg/L. The origin of the optimum fluoride intake emerged from the work of McClure in 1943. McClure estimated that the normal fluoride intake of children 1-12 years old in an area with 1.0 mg/L fluoride in the water supply was 0.4 – 1.7 mg, which provided an average intake of 0.05 mg/kg bw per day (McClure 1943). Galagan and Vermillion looked at the variation in water consumption across different temperature zones in California at different seasons. The relationship between water consumption and mean maximum daily temperature which was subsequently proposed was:
Water intake per body weight (oz/lb) = $-0.038 + 0.0062 \times \text{mean maximum daily temperature}$.

Using this equation with Dean’s optimum fluoride concentration of 1 mg/L for a temperate climate like Chicago with a mean maximum daily temperature of 61.6 degrees F, lead to an adjustment formula for fluoride concentration levels (Adjusted F) for different climates of:

$$\text{Adjusted F} = \frac{0.34}{(-0.038 + 0.0062 \times \text{mean maximum daily temperature (degrees F)})}.$$

The US Public Health Service produced a guide to the optimum fluoride concentration by mean maximum daily temperature, with estimates rounded to one decimal point (PHS 1970, also cited in Dunning 1970, p352).

<table>
<thead>
<tr>
<th>Annual average of maximum daily air temperatures$^a$</th>
<th>Recommended control limits F concentrations in parts per million</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>50.0–53.7</td>
<td>.9</td>
</tr>
<tr>
<td>53.8–58.3</td>
<td>.8</td>
</tr>
<tr>
<td>54.8–63.8</td>
<td>.8</td>
</tr>
<tr>
<td>63.9–70.6</td>
<td>.7</td>
</tr>
<tr>
<td>70.7–79.2</td>
<td>.7</td>
</tr>
<tr>
<td>79.3–90.5</td>
<td>.6</td>
</tr>
</tbody>
</table>

$^a$ Based on temperature data obtained for a minimum of 5 years.

However the adjustment slightly alters the dose-response relationship across the full range of fluoride concentrations. Eklund and Striffler examined the dose-response relationship between fluoride in water supplies and caries experience of 12-14 year old children using Dean’s 21 cities data supplemented by additional data derived from Striffler on other cities (Eklund and Striffler 1980). Eklund and Striffler had 41 data points in their analysis. They adjusted the fluoride concentration using the Galagan and Vermillion formula and fitted curvilinear relationships to the adjusted data. The best fit explained a high proportion of the variance for decayed, missing and filled teeth (DMFT) and took the form:

$$\text{DMFT}=1.64+1.40 \times (1/\text{ppm F}^+)$$

where F+ was the adjusted fluoride concentration using the Galagan and Vermillion formula.
Water fluoridation has been implemented in many countries applying the Galagan and Vermillion adjustment to the 'optimal' fluoride concentration based on mean maximum daily temperature.

The US EPA report examined selected studies more identified by the US NRC in 2006 in assessing the relationship between fluoride concentration and dental caries measured by the DMFT/DMFS score (NRC 2006, EPA 2010b). These studies included the research by Driscoll et al (1983; 1986) and Jackson et al (1995).
These data show the dose-response relationship between fluoride concentration (not adjusted for mean maximum temperature) and decayed, missing and filled teeth or surface counts (DMFT/DMFS). The relationship shows a decrease in caries experience through to about 3 mg/L, but then a levelling off or increase.

It has therefore been somewhat surprising that recent emphasis has been placed on a reinterpretation of the findings of Heller et al (Heller 1997). Heller et al used data from the 1986-87 National Survey of Oral Health of US School children (4-22 years old) in a secondary analysis. Analysis was restricted to those children for whom there was a single continuous residence. This reduced the number of children available in the analysis of caries from 40,693 to 18,755. Exposure to fluoride in water supplies was categorized into four categories <0.3, 0.3-0<0.7, 0.7-1.2, >1.2 mg/L. The initial analysis showed a dose-response for primary decayed and filled surfaces (dfs) among 5-10 year old and DMFS among 5-17 year old children at least up to 1.2 mg/L. There was a scarcity of data at fluoride concentration above 1.2 mg/L.
Heller et al. went on to focus on the dose-response relationship between 0.0 and 1.6 mg/L. Regression models for dfs and for DMFS showed a significant negative regression coefficient for ppm fluoride (F mg/L) in the presence of several potential modifiers such as fluoride drops or tablets, school-based fluoride rinses or professionally applied fluoride treatments. A graph of the dose-response relationship across the fluoride concentration range of 0.0 -1.6 mg/L indicated a relationship but with some fluctuation and what might be described as a ‘flatness’ across the 0.7-1.2 mg/L range (Heller et al. described the relationship as one of little decline in caries between 0.7 and 1.2 mg/L fluoride), the range at which water supplies in the US are recommended to fluoridate by the application of the Galagan and Vermillion formula. No specific analysis of the relationship within the 0.7-1.2 mg/L range is presented.

This ‘flatness’ has been cited in the US Department of Health and Human Services and EPA proposed recommendation for the elimination of the range and its replacement by a single target recommended fluoride concentration of 0.7 mg/L, in effect the lowest concentration within the old range (EPA 2010b).
There are several issues in drawing this interpretation of the data presented by Heller et al. First, any curvilinear relationship when broken into smaller segments will be reasonably approximated by a straight line or the little decline described by Heller et al. Second, the 1986-87 National Survey of Oral Health of US Schoolchildren was a population sample drawn from the entire USA, including adjusted fluoridation areas and areas with naturally varying fluoride levels in the local water supply. Some 50.4% of children resided in areas with 0.7-1.2 mg/L fluoride, the recommended range for water fluoridation programs. Most will have had the ‘optimum’ fluoride concentration of 1.0mg/L adjusted to suit the mean maximum daily temperature according to the Galagan and Vermillion formula. Each situation aims to produce the same ‘optimum’ prevention of dental caries given different water consumption associated with mean maximum daily temperature. To the extent that the Galagan and Vermillion formula had relevance to the two decades ahead to the 1986-87 National Survey of Oral Health of US Schoolchildren its purpose was to achieve an equivalent effect size in the prevention of dental caries.

The proposed recommendation to alter the range to a single target fluoride concentration in the USA also rested upon a weakened relationship between mean maximum temperature and water consumption. In theory much variation in temperature is ameliorated by control of the micro climate in homes, work places and cars. So this is a plausible hypothesis. However, the evidence is somewhat equivocal. There have been several analyses of the relationship since Galagan and Vermillion. These have included Ershow and Cantor who used the 1977-78 Nationwide Food Consumption Survey (NFCS) data to show that consumption was slightly greater in summer (Ershow and Cantor 1989). There were also regional differences that were larger than the seasonal pattern. Walker et al found no difference in fluid intake among children by season (Walker et al 1963). Heller et al used the 1994-96 Continuing Survey of Food Intakes by Individuals (CFSII). They found that while Galagan and Vermillion found a 60% increase in water consumption between the coldest and warmest conditions, the CSFII data showed only a 20% difference between the winter and summer months in certain region of the US. Sohn et al NHANES III (1988-94) data to examine the relation of fluid and water consumption and mean maximum daily temperature used (Sohn 2001). No significant association was found between fluid or water consumption and mean maximum daily temperature. Whist the association was not significant, water consumption was 11.6% higher across the temperature range.

Further analyses have been conducted on the relationship of fluid and water consumption and maximum temperature in the US. Whilst not published (to the best of our knowledge) they have shown an association still exists with reported water consumption and mean
maximum monthly or seasonal temperature, but not with mean maximum daily temperature which shows considerable variation (E Beltran, Personal communication, 8 August 2013).

These results lent support for the narrowing of the recommended range of optimal water concentration of fluoride in the US. In theory this would have seen the range of 0.7 – 1.2 mg/L reduced to a narrower range around the mid-point, 0.95 mg/L. However the proposed target concentration of 0.7mg/L is at the lower end of the existing range which reflected a judgment on whether the objective was maximising benefit of caries prevention or reducing the risk of dental fluorosis.

The usual relationship studied between fluoride in a water supply and dental caries is the effectiveness of the adjustment of fluoride deficient water supplies to an ‘optimum’ level, at or around 1.0 mg/L. The literature in this area have been well assessed by two recent reviews: The York review and the Rugg-Gunn and Do review.

The York review was conducted by the NHS Centre for Reviews and Dissemination at the University of York (McDonagh et al 2000). It was a substantial review canvassing evidence about the effectiveness of water fluoridation up to 2000. The York review addressed the effectiveness of water fluoridation through a systematic review and meta-analysis. They selected some 26 studies which were predominantly non-randomised controlled before and after studies and sufficient quality to be included. The following two plots of the key findings for the preventive effect of water fluoridation on the % caries-free and the dmft/DMFT scores for children.

The median percentage change in % caries-free was 14.6% greater in fluoridated communities than non-fluoridated communities, with an inter-quartile range of 5.05 to 22.1%. A median change in the number of carious teeth was 2.25 less teeth per child in the fluoridated areas than non-fluoridated areas after the implementation of water fluoridation. The inter-quartile range was 1.28 to 3.63 less teeth with caries experience.
Fig 1 Change in proportion (%) of children without caries in fluoridated compared with non-fluoridated areas (mean difference and 95% confidence interval)
The York review also addressed the consequence of the withdrawal of water fluoridation and found that "The best available evidence from studies following withdrawal of water fluoridation indicates that caries prevalence increases, approaching the level of the low fluoride group" (McDonagh et al. 2000).

Rugg-Gunn and Do updated the evidence on the effectiveness of water fluoridation in 2012 (Rugg-Gunn and Do 2012). Rugg-Gunn and Do included controlled cross-sectional studies and some ecological studies, as well as the non-randomised controlled before and after studies included in the York review, conducted after 1990. In the 30 studies on primary caries since 1990, Rugg-Gunn and Do found the modal extent of caries reduction was shared by studies with a 30-39% and 50-59% reduction in caries experience in fluoridated than non-fluoridated areas. For the permanent teeth some 53 studies were identified and the modal percent caries reduction was 40-49% in the fluoridated versus non-fluoridated comparison.

The studies included in these analyses test the association of an ‘optimal’ fluoride concentration against a negligible fluoride concentration. Just what was considered ‘optimal’
is difficult to discern in some cases. They offer supporting evidence around an association, but do not add specifically to the understanding of a dose-response relationship for the prevention of dental caries.

**Dental fluorosis**

Dental fluorosis has been studied since the 1930s through the seminal research of Dean and colleagues. Dean studied the association of dental fluorosis with the fluoride concentration occurring naturally in the water supplies of some 22 cities. The children examined were predominantly between 12-14 years old. Fluoride levels were established for each city and the presence and severity of dental fluorosis observed using Dean's Index. These data were published in several separate scientific articles in the early 1940s and combined by Dean in 1946. When combined the data identify 22 cities.

![Graph showing Dental caries and dental fluorosis related to fluoride in public water supply.](image)

*Fig. 55. Dental caries and dental fluorosis related to fluoride in public water supply. [Adapted from H. T. Dean; (1) New York Symposium (1945); (2) Int. Dent. J. 4, 311-337 (1954).]*
While Dean presented data on the percent distribution of the samples in the cities in the studies, there was also an emphasis placed on the Community Fluorosis Index score in interpreting the prevalence and severity of fluorosis in any community. As a result Dean interpreted a CFI score of <0.4 as of no public health significance (Dean 1942).

Later researchers plotted Dean’s data for the DMFT scores and CFI together further illustrating the initial emphasis placed on the CFI for the interpretation of Dean’s data.

All more recent US assessments of fluoride concentrations and dental fluorosis have returned to the data on the distribution of Dean’s Index scores rather than the interpretation of the CFI. The end point for assessments has been aesthetically objectionable fluorosis, interpreted as a Dean’s score 3 or above, or more recently severe fluorosis, a Dean’s Index score 4 (IOM 1997; EPA 2010b)

However, much research on the prevalence and severity of dental fluorosis by fluoride concentration in water supplies has been focussed on the presence of any fluorosis. In the NHS Centre for Reviews and Dissemination at the University of York University review (McDonagh et al 2000), two end points were included to assess potential negative effects associated with water fluoridation. These were ANY fluorosis, that is, any score of fluorosis with any fluorosis index, and fluorosis of ‘aesthetic concern’. Fluorosis of aesthetic concern was interpreted to be a Dean’s Index score of 2 (mild) or above, a Tooth Fluorosis Index score of 3 or more, or a TSIF Index score of 2 or more. The York review modelled the proportion of the population with ANY fluorosis against fluoride concentration. The model is illustrated below.

![Proportion of population with dental fluorosis by water fluoride concentration with 95% confidence interval for proportion. Fluoride concentration is plotted on log scale because of linear association between this and log (odds) of fluorosis. Each circle represents a study area in which the proportion of people with fluorosis is estimated—the larger the circle, the higher the precision of the estimate.](image-url)
From this the estimated proportion of the population with any fluorosis was determined for a range of fluoride concentrations between 0.1 and 4 mg/L. The Proportion rose from 15% at 0.1 mg/L, to 48% at 1mg/L, and on to 61% at 2 mg/L and 72% at 4 mg/L.

Using an end point of fluorosis of aesthetic concern the proportions were much lower. The relationship with fluoride concentration and the proportion and its confidence limits are presented in the figure below.

The estimated proportion for fluoride concentrations across the range 0.1 to 4 mg/L were 6.3%, for 0.1, 12.5% for 1, 24.7% for 2 and 63.4% for 4 mg/L. Although the proportions are much lower than when any fluorosis is used as the end point, these proportions are higher than those observed for moderate fluorosis or above using the aesthetically objectionable fluorosis definition (Dean’s Index scores 3 and 4) more commonly used in US assessments.
of the relationship between fluoride concentrations in water supplies and dental fluorosis. These variations in end point make comparisons across studies and reports difficult.

The York review does provide strong support for the dose-response relationship between fluoride in water supplies and dental fluorosis. Further it is useful in predicting the prevalence and severity of fluorosis when a fluoride deficient water supply is fluoridated.

The York review examined the prevalence and severity of dental fluorosis before and after the widespread use of fluoridated toothpaste. It found similar patterns before 1975 and after 1975. However, rather crude approaches were used to assess the use of other fluoride sources to fluoride in water supplies. The conclusion drawn was also somewhat counterintuitive. Across the 1980s there was increasing concern about the occurrence of dental fluorosis among children using fluoride supplements (drops or tablets) (Aasenden and Peebles 1974) and an increasing literature on the risk of dental fluorosis associated with the use by young children of fluoridated toothpaste (Osuji et al 1988; Pendrys and Katz 1989; Pearce 1991). In the Australian context the research by Riordan (Riordan and Banks 1991; Riordan 1993) and by Puzio (1993) lay the foundations for water fluoridation, fluoride supplements, fluoride in infant formula powder and fluoridated toothpaste (and tooth brushing practices) all being regarded as risk factors for dental fluorosis.

After a landmark consensus conference in Perth, Western Australia in 1993 Australian dental authorities set about reducing the level of fluoride in infant formula powder, restricting the use and limiting the dose regimen for the use of fluoride supplements, encouraging the availability and recommending the use of a low fluoride children’s toothpaste for those under 6 years old and providing better guidance to parents on tooth brushing practices for children (age of commencement of brushing without toothpaste, commencement of brushing with toothpaste, parental supervision, use of a smear or small pea-sized amount of toothpaste, spitting out and not swallowing toothpaste slurry, and avoiding eating or licking toothpaste straight from the tube).

There is strong evidence from research in Western Australia and South Australia that these measures collectively lead to a decrease in the prevalence and severity of dental fluorosis (Riordan 2000; Do and Spencer 2007). This substantially alters the context in which a benefit–risk evaluation of fluoride concentration in water supplies is being conducted.
With the decrease in the prevalence and severity of dental fluorosis observed in both Western Australian and South Australia, the distribution of dental fluorosis scores shifted to the left, increasing the proportion of children with no fluorosis, but also reducing the proportion with Tooth Fluosis scores of 3 or more. The distribution was also truncated, with no observed children observed with a Tooth Fluosis score of 4 (moderate/severe) or 5 (severe).

<table>
<thead>
<tr>
<th>TF score</th>
<th>F area</th>
<th>Non F area</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>TF 0</td>
<td>211 (70.5)</td>
<td>321 (85.0)</td>
<td>532 (74.3)</td>
</tr>
<tr>
<td>TF 1</td>
<td>49 (16.0)</td>
<td>39 (10.1)</td>
<td>88 (14.4)</td>
</tr>
<tr>
<td>TF 2</td>
<td>32 (11.4)</td>
<td>15 (3.7)</td>
<td>47 (9.5)</td>
</tr>
<tr>
<td>TF 3</td>
<td>7 (2.1)</td>
<td>3 (1.2)</td>
<td>10 (1.8)</td>
</tr>
</tbody>
</table>

* Chi-square, p<0.05

As water fluoridation remains a risk factor for dental flouris, the reconstitution of infant formula poweder with fluoridated water has been a particular focus of attention. This attention...
was sharpened after the American Dental Association issued an Interim Guidance on reconstituting infant formula in November 2006. The ADA said that "parents and caregivers should consider using water that has no or low levels of fluoride". The ADA went on to conduct a review of the evidence around the use of infant formula and fluorosis. Berg et al (2011) included in their evaluation of the evidence research from Australia on this issue.

Spencer and Do compared the risk of dental fluorosis (measured by the presence of fluorosis at the Tooth Fluorosis Index score of 1+) associated with infant formula use in 1992-93 and 2002-03 (Spencer and Do compared 2008):

<table>
<thead>
<tr>
<th>Time</th>
<th>992/93</th>
<th>2002/03</th>
</tr>
</thead>
<tbody>
<tr>
<td>Used formula</td>
<td>61.0%</td>
<td>57.2%</td>
</tr>
<tr>
<td>Prevalence of fluorosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Used formula</td>
<td>49.2%</td>
<td>27.4%</td>
</tr>
<tr>
<td>Not used</td>
<td>40.8%</td>
<td>ns</td>
</tr>
</tbody>
</table>

Multivariate analysis

<table>
<thead>
<tr>
<th>Used formula</th>
<th>OR 1.13 ns</th>
<th>1.05 ns</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(0.72-1.76)</td>
<td>(0.69-1.60)</td>
</tr>
</tbody>
</table>

Infant formula use, presumably mostly reconstituted with fluoridated water (over 90% of South Australians live in fluoridated areas) was not associated with dental fluorosis.

Research reviewed by Berg et al (2011). However, it needs to be recognised that infant formula manufacturers had moved to reduce/eliminate fluoride from their infant formula powder marketed in Australia. This contrasts with earlier research in a number of countries.


An area of some confusion in the interpretation of the evidence surrounding fluoride intake and dental fluorosis is the threshold of fluorosis used to define a ‘case’ in the outcome. Historically Dean and colleagues actually used a summary measure derived from Dean’s Index, the Community Fluorosis Index to define a prevalence and severity of fluorosis that was regarded as the threshold for an unacceptable level of fluorosis. The CFI is calculated for a geographic location based on the mean scores for individuals examined, where the
score for an individual is characterized by the second most severe score of all scores for the teeth examined. Dean assigned a public health significance to the CFI with scores of 0.0-0.4 being of negative public health significance, 0.4-0.6 of borderline, 0.6-1.0 being slight, 1.0-2.0 being medium, 2.0-3.0 being marked, and 3.0-4.0 being very marked. There have been criticisms of the CFI through its use of the second most severe score to characterize an individual and that the summary score is difficult to interpret. The most recent US reports on a threshold of dental fluorosis refer to the distribution of Dean's Index scores, where presumably the individual is characterized by the second most severe tooth level observation of dental fluorosis.

A number of variations on Dean's index have emerged, including the Tooth Surface Index of Fluorosis, the Tooth Fluorosis Index and the Fluorosis Risk Index. These vary in their methodology of examination of the teeth wet or dry, and the threshold for change required for scoring, particularly at the bottom and top of the range of scores. This has complicated comparisons across studies and has played itself out in some variations in the fluoride intake associated with the presence of dental fluorosis. For instance, Baelum and colleagues have used the Tooth Fluorosis Index and its lowest severity in the derivation of a threshold of fluoride intake at 0.03-0.4 mg/kg bw/d (Baelum et al 1987). Levy and colleagues used the Fluorosis Risk Index at its lowest severity involving changes to the incisal third of central incisors in their examination of fluoride intake and dental fluorosis.

However, any assessment of the benefit-risk of fluoride intake and oral health needs to define a severity of dental fluorosis that is regarded as an adverse outcome. This is not straightforward as all severities of dental fluorosis up to severe fluorosis with pitting and loss of enamel are considered as an aesthetic or cosmetic outcome. The most common approach has been to use the concept of an aesthetically objectionable fluorosis as the threshold. However, the aesthetics of dental fluorosis are subjective judgements open to change over time. There have been three phases in the way dental fluorosis has been perceived. Early on the judgement about the aesthetics of dental fluorosis was a normative or professional judgement. Low severity dental fluorosis was regarded as unlikely to be discerned by the lay public and of little aesthetic impact. Such a view was conditioned by what was considered the alternative of carious lesions and restorations to repair teeth in comparison to very mild or mild dental fluorosis. However, by the end of the 1980s it was evident from research by Riordan in Western Australia and Hoskin in South Australia that both children and parents were able to recognise changes in tooth colour associated with dental fluorosis and that they rated fluoroised teeth less satisfactory in dental appearance. This supported an aesthetically objectionable fluorosis threshold.
Community perceptions of aesthetics are not immutable. By the start of the 2000 decade evidence started to emerge that while very mild, mild and even mild/moderate dental fluorosis (with the TF Index scores 1, 2 or 3) were recognised by children and parents, none were regarded as less satisfactory in dental appearance, and furthermore, that very mild and mild fluorosis was associated with higher ratings of very good or good oral health and better oral health-related quality of life than non-fluorosed teeth. Further what might be labelled as mild/moderate dental fluorosis was judged no less satisfactory than teeth without fluorosis. Although this change has not been directly linked to community perceptions of the appeal of white teeth, this has been speculated as the explanation.

The aesthetic judgement surrounding dental fluorosis was extensively discussed by the US National Academy of Science, National Research Council committee which reviewed the EPA’s standards for fluoride in drinking water. Their majority opinion was that severe dental fluorosis should be regarded as an adverse outcome both on cosmetic and functional grounds. It was suggested that upper limits should be set to protect against severe fluorosis. However, it also noted that all previous groups examining the issue of dental fluorosis have agreed that severe and even moderate dental fluorosis should be prevented (NRC 2006, p.127-8) leaving open the selection of thresholds related to either moderate and/or severe dental fluorosis.

**Fluoride and health**

**Bone: Skeletal fluorosis - osteosclerosis, osteoporosis, osteosarcoma**

*Osteoporosis and bone fractures*

Fluoride has long been known to affect bone development by stimulating osteoblastic activity, and high doses of fluoride have often been used in the past to treat osteoporosis. Most drugs currently used to treat osteoporosis e.g. bisphosphonates, work differently by inhibiting bone resorption, and dentists have become very familiar with these drugs in recent years.

However, while high doses of fluoride increase bone mineral density, they can also alter bone crystalline structure and decrease bone elasticity and strength, particularly in non-vertebral bones. The Cochrane Collaboration now advises against fluoride as a first choice therapy for osteoporosis (ref).
A large number of studies have investigated possible associations between the levels of fluoride in drinking water and the risk of fractures of the hip and other bones. An association is biologically plausible, since very high levels of fluoride are known to affect bone function and bone strength. Half the adult intake of fluoride is retained in the bones, leading to a lifetime accumulation of fluoride, and hip fractures in elderly people are a growing public health concern.

The results of past fluoride and hip fracture studies are mixed. A Mexican study (Alarcon-Herrera et al 2001) claims a linear correlation between the severity of dental fluorosis and the frequency of bone fractures in children. However, almost all the areas surveyed had naturally occurring fluoride levels many times higher than those found in artificially fluoridated areas. The authors subjectively selected only bone fractures "that had ever occurred without apparent cause, where a bone fracture would not normally be expected to occur". They admitted that validation was a difficult task "because we depended on the subjectivity of both the interviewer and the interviewed". The authors also found that "the incidence of fractures was found to decrease at higher fluoride concentrations", but could not explain why this could be the case.

Li et al conducted a large study of bone fractures in six Chinese communities with widely varying levels of fluoride in drinking water (Li et al 2001). The study finds higher levels of both hip fractures and overall fractures in the population drinking water with fluoride levels of 4.32-7.97 parts per million, but in the population drinking water with levels of 1-1.06 parts per million fluoride (around the level used in community water fluoridation), authors also found significantly fewer overall bone fractures than the population drinking water with 0.25-0.34 parts per million, and no difference in the prevalence of hip fractures in those two populations.

The US-based National Research Council’s 2006 report Fluoride in Drinking Water: A Scientific Review of EPA’s Standards (NRC 2006) investigated possible adverse health effects of high levels of naturally occurring fluoride in drinking water. Based on generally weak studies, the National Research Council concluded that the EPA's Maximum Contaminant Level Goal of 4 parts per million fluoride (ppm or mg/L) in naturally fluoridated water is not likely to be protective against bone fractures. However, the National Research Council also stated that its conclusions regarding the potential for adverse effects from fluoride at higher levels "...do not apply at the lower water fluoride levels commonly experienced by most U.S. citizens".

A review of the scientific literature in 1999 from the Menzies Centre for Population Health Research in Tasmania (Jones et al 1999) states that "Water fluoridation both at levels aimed
at preventing dental caries and, possibly, at higher naturally occurring levels appears to have little effect on fracture risk, either protective or deleterious, at a population level".

Most early studies were ecological studies, comparing rates of hip fractures in communities with different levels of fluoride in the water supplies, but causality should always be interpreted cautiously because of the ecological fallacy, the inability to accurately account for the effects of potential confounders.

In 2000, Phipps et al. stated that previous studies finding an association between water fluoridation and hip fractures had not taken into account the potential confounding effect of other factors known to be associated with fractures, such as oestrogen use, smoking, and body weight (Phipps et al 2000). To overcome the limitations of ecological studies, Phipps et al. conducted a much stronger prospective cohort study of over 7,000 women followed for an average of seven years. The authors accounted for a broad range of potential confounders through multivariate regression techniques and actually found small, but statistically significant reductions in the risks for fractures of the hip and vertebrae.

Also in 2000, the York Review investigated 29 studies that considered a possible link between water fluoridation and bone fractures (McDonagh et al 2000). The review concludes that "Overall, the findings of studies on bone fracture effects showed small variations around the 'no effect' mark. A meta-regression of bone fracture studies also found no association with water fluoridation."

In 2007, Australia's National Health and Medical Research Council (NHMRC) conducted an extensive analysis based on York Review, but also considering more recent studies (NHMRC 2007). Their report concludes that "Water fluoridation at levels aimed at prevention of dental caries has little effect on fracture risk. Fluoridation at 0.6 to 1.1 mg/l may lower overall fracture risk compared to both no fluoridation and fluoridation at levels well above those experienced in Australia."

This consistent view has been reinforced by a recent study from Sweden published in the Journal of Dental Research (Nasman et al 2013). The Scandinavian countries maintain comprehensive electronic databases covering patient demographics and health issues and treatments for all residents. Many countries have rejected similar databases because of privacy concerns, but their use has resulted in the Scandinavian countries producing some of the best large scale epidemiological studies anywhere in the world.

The beauty of this recent study is both its strength - a retrospective cohort study - and its size. The electronic database allowed authors to follow all individuals born in Sweden between January 1, 1900 and December 31, 1919, alive and living in their municipality of
birth at the time of start of follow-up, almost half a million people in total. During this time, 60,000 hip fractures were recorded in more than 8 million person-years of follow-up, far in excess of any other study investigating fluoride and hip fractures. Drinking water fluoride exposure was stratified into 4 categories: very low, <0.3 mg/L; low, 0.3 to 0.69 mg/L; medium, 0.7 to 1.49 mg/L; and high, ≥1.5 mg/L.

Authors stated that "Overall, no association was found between fluoride exposure and hip fracture risk. We conclude that, in the fluoride range investigated, long-term fluoride exposure from drinking water seems unlikely to have any important effects on the risk of hip fracture" ((Nasman et al 2013).

While stronger studies and reviews show no increased risk of fractures from optimal levels of fluoride in drinking water, and possibly even a small protective effect, it could also be argued that "science is divided". But if the null hypothesis - that water fluoridation has no effect on the risk of hip fractures - is correct, and researchers study the association between fluoride levels and hip fractures in different settings, one would expect to see a variety of results, some showing a small protective effect, some showing a small harmful effect, and most around the middle showing no statistically significant effect. This is exactly what is seen. Evidence to date strongly supports the belief that water fluoridation has little effect on fracture risk for hips or any other bones.

**Osteosarcoma**

It has been argued that water fluoridation could increase the risk of osteosarcoma, an often-fatal bone cancer most commonly diagnosed in children and adolescents. An association between fluoride and osteosarcoma is biologically plausible, since bones readily take up much of the fluoride ingested and many children are diagnosed around the time of the pubertal growth spurt, when osteoblastic activity is particularly high.

Most concerns about fluoride and osteosarcoma are based on a single rat experiment in the early 1990s (Bucher et al 1991), a short 1992 report by Cohn (Cohn 1992), and recent PhD research from Bassin et al (Bassin 2006). In the 1991 rat experiment conducted by the National Toxicology Program in the United States by Bucher at al, osteosarcomas were observed in 1/50 male rats drinking water containing 45 parts per million (ppm) fluoride and in 3/80 male rats drinking water containing 79 ppm fluoride. These levels contrast with around 1 ppm used in community water fluoridation. Findings from animal studies are not always transferrable to humans, and this finding was described as "equivocal", or uncertain evidence of carcinogenicity. A single study of many which suggests possible significant effects should not come as a surprise. The same study found no osteosarcomas in female
rats or in mice of either sex, and no osteosarcomas in rats drinking water containing 0 ppm fluoride or 11 ppm fluoride. The US Public Health Service concluded that "...the data available at this time from these two animal studies fail to establish an association between fluoride and cancer". A subsequent similar National Toxicology Program rat study failed to find any association between high levels of fluoride in drinking water and osteosarcoma in either male or female rats (Haseman et al 1998).

The small report by Cohn relied on data from seven New Jersey counties. Over the period 1979-87, twelve cases of osteosarcoma were diagnosed among males under the age of 20 in fluoridated municipalities, compared with eight cases in non-fluoridated municipalities. The difference was statistically significant, but a causal link between fluoridation and osteosarcoma should not be automatically concluded from this relatively weak ecological study. Cohn himself stated that "No interviews were conducted, and data on individual residential history, average amount of water ingested, use of dental fluoride supplements, exposure to other carcinogens and familial cancer history were not available. In addition, the total number of cases was small. Therefore, observations should be interpreted cautiously because: 1) exposure misclassification could lead to under- or overestimation of effects, 2) unmeasured confounding by other potential causes of osteosarcomas could introduce bias leading to under- or overestimation of effects of exposure, and 3) an observed association could be due to chance." He noted that other ecological studies and stronger case-control studies had not found such an association, and concluded that "Because of the limitations of the study design and the small numbers of cases that occurred, this analysis does not imply a causal connection between fluoridation and osteosarcoma" (Cohn 1992).

The Bassin study has attracted most publicity. As a PhD student in Harvard's School of Dental Medicine, Bassin analysed data from a large case-control study, with 103 cases of osteosarcoma drawn from 11 hospitals around the United States and matching controls. A strong positive association was found in males under the age of 20, but no association for females. Authors admitted limitations to the study, including an inability to determine each individual’s uptake of fluoride by bone and the problems inherent in estimating fluoride intake for all individuals on little more than the level of fluoride in each community’s drinking water (Bassin et al 2006).

Kim et al then conducted a follow up case-control study to address some of the concerns posed by Bassin, and this study was published in the Journal of Dental Research in 2011 (Kim et al 2011). Authors analysed fluoride levels in bone taken from 137 osteosarcoma patients and 51 controls to assess if levels were higher in patients with osteosarcoma. After adjustments for age, gender, broken bones and other potential confounders associated with
osteosarcoma, the study found no significant difference in bone fluoride levels in cases and controls.

Although claims of a causal association between water fluoridation and osteosarcoma are weak, the Kim et al paper also has limitations, and some of these limitations have been addressed by Levy et al (Levy et al 2014).

Data were collected from the Iowa Fluoride Study/Iowa Bone Development Study that has followed a large birth cohort since the early 1990s (Levy et al 2014). Authors sought to determine if fluoride intake from all sources had a significant effect on various bone mineral measures. At the age of 15 (around the age when many osteosarcomas are diagnosed), 415 of these children had bone scans, and most also had a detailed dietary analysis and physical activity assessment. Data were analysed and adjusted for a large number of variables, including gender, height, weight, physical activity, calcium intake, and vitamin D intake.

Authors found that the low levels of fluoride intake associated with community water fluoridation and fluoride toothpaste resulted in consistently no greater than 3% change to the mineral content (including fluoride content) or density of the lumbar spine, proximal femur, and whole body skeleton. After adjustments for other factors known to be associated with bone outcomes, none of the weak associations with fluoride intake were statistically significant. Some of the associations were positive and some negative, strongly suggesting that the low fluoride intake associated with community water fluoridation and fluoride toothpaste has little effect on bone development in adolescents.

Particular strengths of this study are that data were taken from a well-defined cohort followed longitudinally and closely monitored for many years, and detailed measures were taken on individuals rather than relying on population data. Far fewer opportunities exist for bias and confounding than previous weaker ecological and case-control studies.

The large body of scientific evidence strongly suggests that community water fluoridation is not associated with osteosarcoma.

**Pineal gland**

Concerns about possible harmful effects of fluoride on the pineal gland are based on the findings of Luke’s 1997 PhD on the effects of fluoride on the pineal gland. The pineal gland lies near the centre of the brain, but outside the blood brain barrier that restricts the passage of fluoride into the central nervous system. The pineal gland is a mineralizing tissue containing calcium concretions called corpora arenacea (brain sand). These concretions contain hydroxyapatite crystals, and are visible on x-rays and scans. Because the pineal
gland contains hydroxyapatite, Luke hypothesized that it would also contain high fluoride levels. The first part of the PhD, published in 2001 examined the pineal glands of 11 cadavers (Luke 2001). As expected, Luke found high levels of fluoride, although the levels varied significantly (14-875 mg F/kg). She found that pineal fluoride levels are not indicators of long term fluoride exposure. Pineal fluoride was significantly associated with pineal calcium, but not with bone fluoride. Interestingly, although Luke dissected eleven cadavers, her graphs only include results for ten pineal glands.

In the second part of her research, Luke found that Mongolian gerbils exposed to high fluoride levels produced lower levels of melatonin metabolites than those exposed to low fluoride levels. A fall in melatonin levels in children may provide a trigger for the onset of puberty. However, the age at which girls reach puberty has been reducing steadily for many decades in every country in which it has been measured, with improved health and changes in nutrition being likely causes (Wysack and Frisch 1982). Earlier onset of puberty does not appear to be related to fluoride exposure, and no published research has suggested such a link.

Luke concluded her PhD by stating that "Whether or not fluoride interferes with pineal function in humans requires further investigation". Despite Luke completing her PhD in 1997, the second part of the research has yet to be published in a peer-reviewed scientific journal or studied by experts in the field. Her findings have not been repeated.

Cognitive development: IQ
A large number of studies dating back to the 1980s, almost all from China, have consistently found that children in communities with high levels of naturally occurring fluoride in drinking water have lower IQ levels than children in communities with lower levels of fluoride in drinking water. The studies are of poor quality, and few potential confounders were considered.

In 2012, Choi et al published a meta-analysis of almost all of these studies (Choi et al 2012)). Inclusion criteria were generous, despite the poor quality of the studies. The meta-analysis concluded that higher levels of fluoride in the water may reduce IQs by almost 7 points.

The results of the Chinese studies have not been confirmed in countries practising community water fluoridation. Publication bias could not be proven or disproven. The possibility exists that high levels of fluoride in drinking water in conjunction with poverty, malnutrition, associations with other contaminants e.g. lead, burning of coal indoors and inhalation of substantial amounts of coal dust, together with other confounders could have an
impact on IQ or some aspects of neurodevelopment, but these conditions are not applicable to those existing in developed nations with fluoridated water supplies.

If fluoride in drinking water adversely affected children's IQ, one would expect that Queenslanders (largely unfluoridated until recent years) would have higher IQs than Australians from other states and territories (largely fluoridated for decades). Although an imperfect proxy, NAPLAN test results in Australia do not support an association between water fluoridation and IQ.

If fluoridation lowered IQs, one would also expect to see a shift of the distribution of IQ scores to the left. A small shift may be difficult to detect for the majority of the community close to the mean value, but a significant difference would be seen at the fewer at the higher end of the IQ spectrum. In the almost 70 years in which community water fluoridation has been practised, such a finding has never been reported in the scientific, public health, or educational literature.

Since little prima facie evidence exists for a causal association between water fluoridation extremes and IQ, few studies have investigated aspects of childhood behaviour and development in communities with optimal water fluoridation. A seven-year New Zealand study compared the behaviour of children in fluoridated and non-fluoridated communities, and found "no association between exposure to fluoridated water and a large range of measures of child health and behaviour…” (Shannon et al 1986).

Delayed physical development: permanent tooth eruption

Limited evidence suggests that industrial fluoride poisoning may cause delayed eruption of permanent incisors in cattle (19). If lower levels of fluoride such as those used in community water fluoridation had a similar effect, any measured reduction in caries experience could be due to the teeth not being present in the mouth for as long and not having had as long to decay.

Komarek et al has often been quoted to support the "delayed eruption" argument (Komarek et al 2005). Their study examines caries in first permanent molar teeth in children aged 7-12, an age group with low caries experience in permanent teeth. Authors admitted that fluoride intake cannot be measured accurately, and used fluorosis levels as an indicator of total fluoride intake. They stated that "Our data suggest that ... fluoride intake delays the emergence of the permanent teeth, see Leroy et al, 2003..." But Leroy, a colleague from the same university, states that "...The present study indicates that the impact of any of the four fluoride exposure parameters (fluorosis, use of systemic fluoride supplements, age at which tooth brushing started and frequency of tooth brushing) on permanent tooth emergence was
relatively minimal. Caries experience in the primary molars had a more pronounced impact on the timing of emergence of the successors than exposure to any of the four fluoride parameters" (Leroy at al 2003).

A 1944 study by Edwin Short from the US Public Health Service found that "Public water supplies containing fluorides in concentrations of 2.6 parts per million appear to be associated with delayed permanent tooth eruption in children 12 years of age who have been continuously exposed to the water supply. Significant differences were not observed in those populations using waters containing less than 2.0 parts per million of fluoride (F)" (Short 1944). He added that "The marked difference in dental caries prevalence between populations using fluoride-free domestic waters and those using as much as 1.2-1.3 parts per million of fluorides (F) cannot be explained on the basis of differences in time of permanent tooth eruption".

Another early study found that the only teeth subject to "delayed eruption" were the permanent premolars, strongly suggesting that the "delayed eruption" was actually premature eruption of permanent premolars in non-fluoridated areas because of the more common extraction of primary molars (Jiraskova 1961).

Finally, if fluoride only delays the onset of dental caries, one would expect measures of caries experience in fluoridated areas to eventually match those in non-fluoridated areas as people age. But studies consistently show not only a significant beneficial effect of fluoridated water on childhood caries (Rugg-Gunn 2012), but also a significant beneficial effect for adults, even those from the pre-fluoride generation (Slade et al 2013). Evidence to date strongly suggests therefore that the measured benefits of water fluoridation are real and long term.

References
Refer to Section 8 References in main report.