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MANATŪ HAUORA

Australian and New Zealand Nutrient Reference Values for Fluoride

Supporting Document 2

Dose response relationship between fluoride and oral health

Enquiries

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Acknowledgments

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Introduction

The assessment of fluoride and health, in infants and children up to 8 years of age, consists of two components: analysis of benefits in prevention of caries; and, analysis of hazard in terms of moderate and/or severe dental fluorosis. Some consideration has also been given to the potential hazard of skeletal fluorosis and bone fractures. However, skeletal fluorosis occurs after prolonged high exposure of fluoride, generally above 8 mg F/L in a water supply. An increased risk of bone fracture has been suggested with prolonged exposure to fluoride in water supplies above 4 mg F/L (EPA 2010). The Expert Working Group (EWG) considered that given its focus on infants and children, exposure to fluoride would not be prolonged or at levels above 4 mg F/L. Therefore the EWG considered dental caries and dental fluorosis as end-points of relevance to early-life exposure and that the dose-response relationship between fluoride and these two oral health conditions would be its focus.

Dose-response relationship between fluoride and dental caries

The dose-response relationship between the fluoride concentration in water supplies and dental caries was established by Dean and colleagues in the 21 cities study. These data were initially published in two papers (Dean et al. 1941, Dean et al 1942), but brought together at the end of the Dean et al (1942) publication and repeated in later publications (Dean 1944, 1946)[1]. Dean's research focused on the permanent dentition of early teens, 12–14 year olds. Table 1 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 score, and the percentage of examinees caries-free.

[1] Dean et al studied at least 26 cities in US; 21 cities were selected as suitable for the fluoride and dental caries research, a slightly different list of 22 cities was selected for the fluoride and fluorosis research.

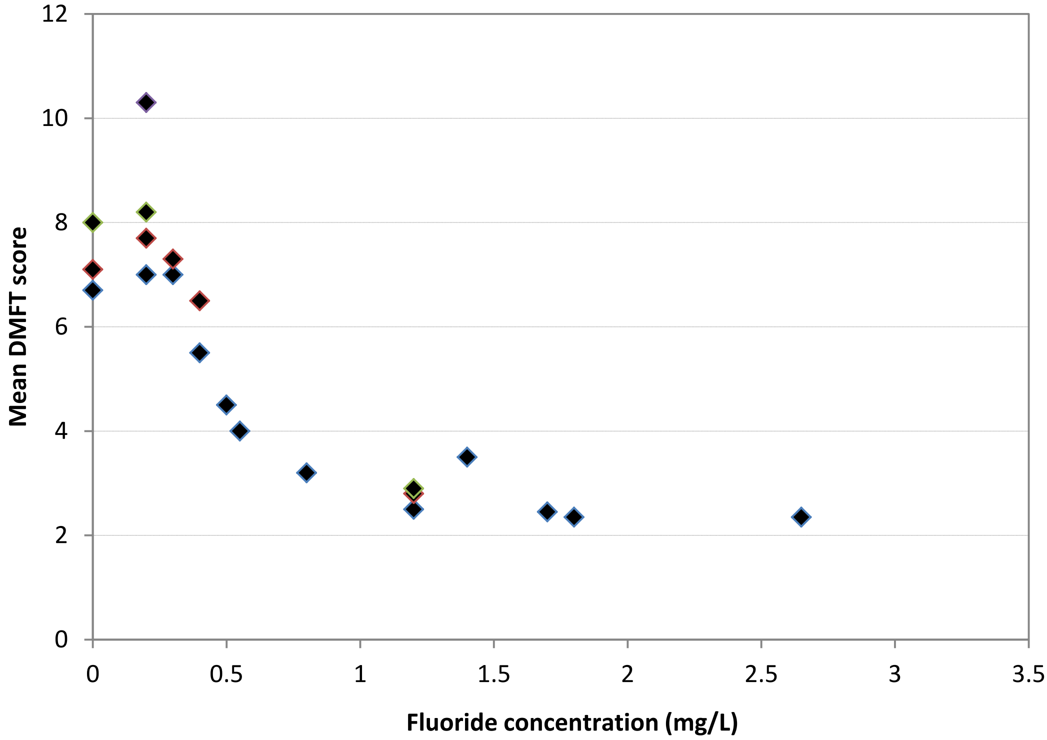
Table 1 : Mean fluoride concentration of water supplies and dental caries in US children in Dean's 21 cities study

City	No. of children	Fluoride conc. mg/L	DMFT score	Caries-free (%)
Evanston	256	0	6.73	3.7
Oak Park	329	0	7.22	4.3
Waukegan	423	0	8.10	3.1
Portsmouth	469	0.1	7.72	1.3
Quincy	330	0.1	7.06	2.4
Michigan City	236	0.1	10.37	0.0
Elkhart	278	0.1	8.23	1.4
Zanesville	459	0.2	7.33	2.6
Middletown	370	0.2	7.03	1.9
Lima	454	0.3	6.52	2.2
Marion	263	0.4	5.56	5.7
Elgin	403	0.5	4.44	11.4
Pueblo	614	0.6	4.12	10.6
Kewanee	123	0.9	3.43	17.9
Maywood	171	1.2	2.58	29.8
East Moline	152	1.2	3.03	20.4
Aurora	633	1.2	2.81	23.5
Joliet	447	1.3	3.23	18.3
Elmhurst	170	1.8	2.52	25.3
Galesburg	273	1.9	2.36	27.8
Colorado Springs	404	2.6	2.46	28.5

Adapted from: Adler 1970. Fluorides and dental health. p.325. In: Adler, Armstrong, Bell et al. Fluorides and human health. Geneva: WHO 1970.

When the mean DMF Teeth for each 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 F/L, then a plateauing of the curve by 2 mg F/L, is evident.

Figure 1: Curvilinear relationship between fluoride concentration and dental caries measured by mean DMFT score



Based on Dean's data in 21 cities of the USA (After Dean, 1954)

The interpretation of the curvilinear relationship was that near maximum prevention of dental caries was achieved when water supplies with negligible fluoride were upwardly adjusted to a concentration of above 1.0 mg F/L. However, the level of fluoride in a water supply is not just a matter of the prevention of dental caries. It also has regard to the prevention of dental fluorosis. When consideration was also given to the prevalence and severity of dental fluorosis by fluoride concentration, the optimal concentration of 1.0 mg F/L emerged.

This original research on the relationship of fluoride concentration and dental caries in children in the US 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 and Vermillion 1957). This adjustment was to vary the 'optimum' fluoride concentration of 1 mg F/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 F/L in the water supply was 0.4 – 1.7 mg/day, 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 X mean maximum daily temperature.

Using this equation with Dean's optimum fluoride concentration of 1 mg F/L for a temperate climate like Chicago with a mean maximum daily temperature of 61.6 degrees F (16.4ºC), lead to an adjustment formula for fluoride concentration levels (Adjusted F) for different climates of:

> Adjusted F 'optimum' fluoride concentration = 0.34 /(-0.038+0.0062 X 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 1962, cited in Dunning 1970, p352).

Table 2: 'Optimum' fluoride concentration of varying climates

Annual mean maximum daily Temperature (°F)	Annual mean maximum daily Temperature (°C)	Optimum fluoride concentration mg/L
50.0–53.7	10.0-12.0	1.2
53.8–58.3	12.1-14.6	1.1
58.4–63.8	14.7-17.6	1.0
63.9–70.6	17.7-21.4	0.9
70.7–79.2	21.5-26.2	0.8
79.3–90.5	26.3-32.5	0.7

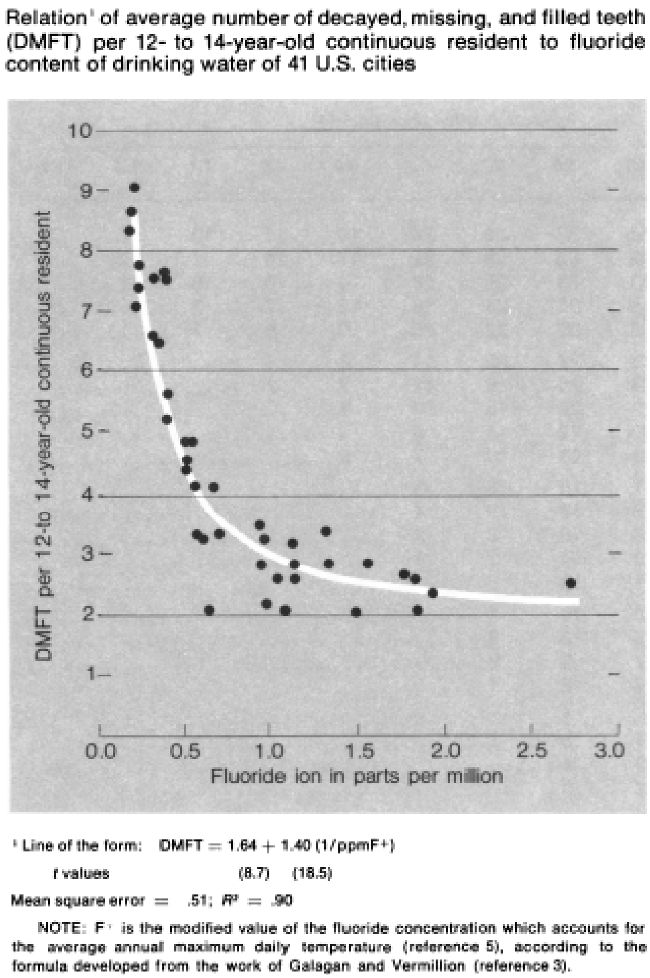
Adapted from Public Health Service 1962, cited by Dunning 1970; Fahrenheit-Celsius conversion by EWG

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 the DMFT score and took the form:

> DMFT=1.64+1.40 (1/ppm F+), where F+ was the adjusted fluoride concentration using the Galagan and Vermillion formula.

Figure 2 : Relationship between fluoride concentration adjusted for mean maximum daily temperature and DMFT in 12–14 year old children

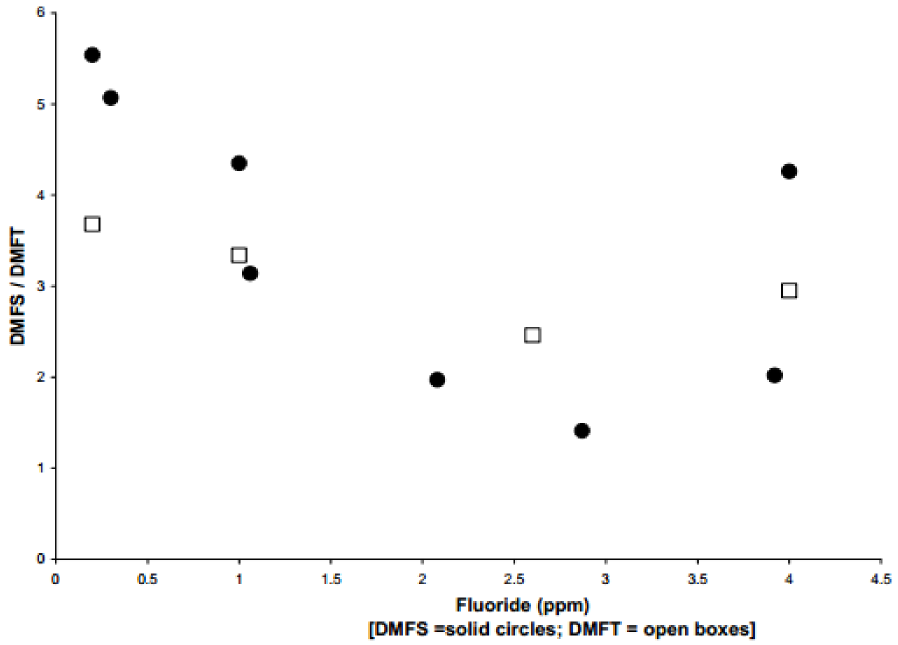


Reproduced with permission from Eklund and Striffler, Pub Health Rep 1980

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 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 2010a). These studies included the research by Driscoll et al. (1983; 1986) and Jackson et al. (1995).

Figure 3: Relationship between fluoride concentration in water supplies and dental caries (DMFT and DMFS) in children (derived from Driscoll et al. 1983, 1986 and Jackson et al. 1995)



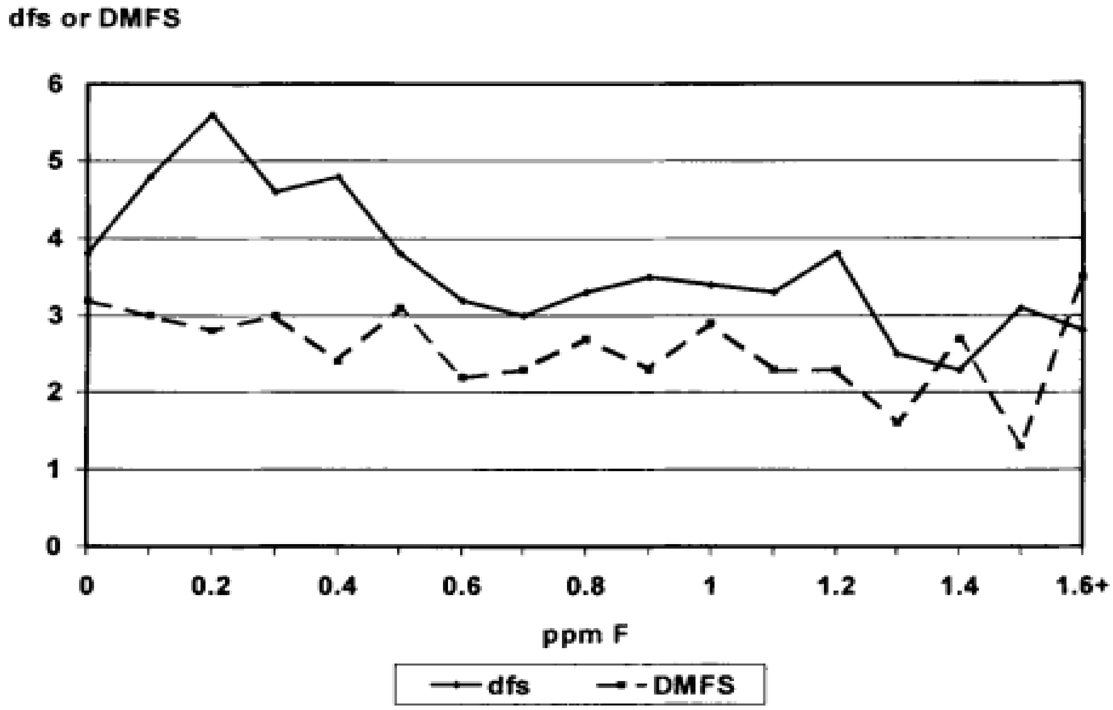
Reproduced from US EPA 2010a - no permission required

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) in more contemporary data from the US. The relationship shows a decrease in caries experience through to about 3 mg F/L, but then a levelling off, or even subsequent increase.

Recently an emphasis has been placed on the findings of Heller et al. (Heller et al. 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 F/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 F/L. There was a scarcity of data at fluoride concentration above 1.2 mg F/L.

Heller et al. went on to focus on the dose-response relationship between 0.0 and 1.6 mg F/L. Regression models for dfs and for DMFS showed a significant negative regression coefficient for fluoride (mg F/L) in the presence of several potential modifiers such as fluoride drops or tablets, school-based fluoride rinses or professionally applied fluoride treatments. However, it should be noted that there was no statistical adjustment for variations in socioeconomic contextual characteristics of sites or of the socioeconomic composition of children included in the data. A graph of the dose-response relationship across the fluoride concentration range of 0.0–1.6 mg F/L indicated a relationship, but with some fluctuation and only a little decline in caries between 0.7 and 1.2 mg F/L, 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 F/L range is presented.

Figure 4: DMFS for children aged 5–17 years, and dfs scores for children aged 5–10 years, by water fluoridation level for US school children with a history of a single residence (scores are age-and-sex-standardized to children with one residence aged 5–17 years for DMFS)



Reproduced with permission from Heller et al. J Pub Health Dent 1997.

The 'little decline' or 'plateau' of the fluoride concentration and dfs or DMFS has been cited in the US Department of Health and Human Services and EPA proposed recommendation for the elimination of the recommended optimal range for fluoride concentrations and its replacement by a single target recommended fluoride concentration of 0.7 mg F/L, in effect the lowest concentration within the old range (HHS 2011).

There are several issues surrounding 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 in the water supply, the recommended range for water fluoridation programs. Most will have had the 'optimum' fluoride concentration of 1.0 mg/L adjusted to suit their 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 School Children, 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 US also rested upon a weakened relationship between mean maximum temperature and water consumption. In theory, variation in temperature may be truncated 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 that of Galagan and Vermillion. These have included Ershow and Cantor who used the 1977–78 Nationwide Food Consumption Survey (NFCS) data to show that water 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. (1999) used the 1994–96 Continuing Survey of Food Intakes by Individuals (CSFII). They observed 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 regions of the US. Sohn et al. used NHANES III (1988–94) data to examine the relation of fluid and water consumption and mean maximum daily temperature (Sohn et al. 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 at the top end of the temperature range compared to the lower end.

Further analyses have been conducted on the relationship of fluid and water consumption and maximum temperature in the US. Whilst not published 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 leant 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 F/L reduced to a narrower range around the mid-point, 0.95 mg F/L. However the proposed target concentration of 0.7 mg F/L (EPA 2010a) is at the lower end of the existing range which reflected a judgment on reducing the risk of dental fluorosis rather than maximising the benefit of caries prevention.

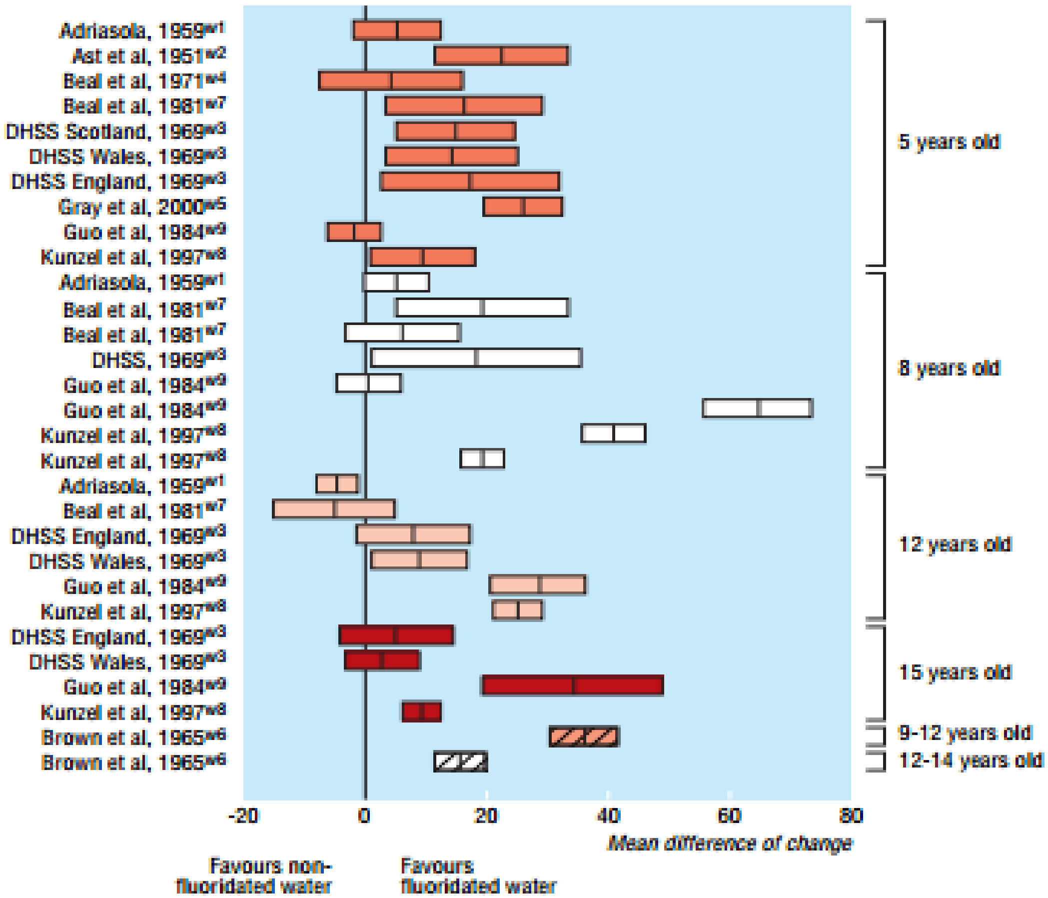
Water fluoridation and dental caries

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 1.0 mg F/L with an adjustment for mean maximum temperature. The literature in this area has 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. 2000a). It was a substantial review canvassing evidence about the effectiveness of water fluoridation up to the year 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 of sufficient quality to be included. It should be noted that while a large number of cross-sectional and ecological studies of the relationship between fluoridated water and dental caries was identified, these were not included in any aspect of the analysis of the fluoridation and dental caries.

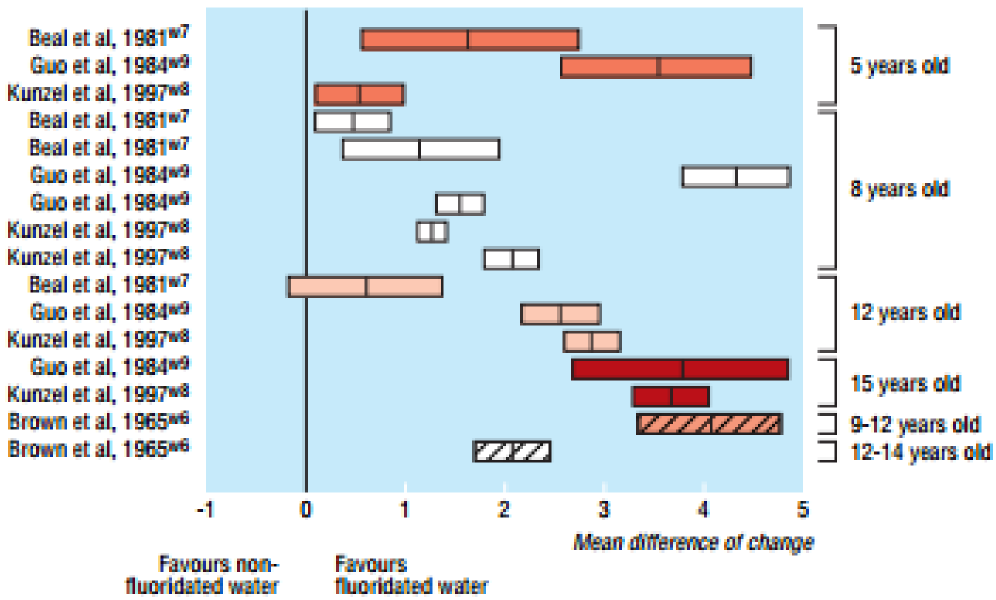
The following two figures present plots of the key findings for the preventive effect of water fluoridation on the % caries-free and the dmft/DMFT scores for children (McDonagh et al. 2000b). The median percentage change in % caries-free was 14.6% greater in fluoridated communities than non-fluoridated 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 carious 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.

Figure 5: Change in proportion caries-free (%) in fluoridated compared to non-fluoridated areas (mean and 95% CI) from the York Review (McDonagh et al. 2000b)



Reproduced with permission from McDonagh et al. BMJ 2000b

Figure 6: Change in dmft/DMFT (mean and 95% CI) in fluoridated compared to non-fluoridated areas from the York Review (McDonagh et al. 2000b)



Reproduced with permission from McDonagh et al. BMJ 2000b

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. 2000a).

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 concurrent controlled 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 versus 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.

Dose-response relationship between fluoride and dental fluorosis

Dental fluorosis has been studied since the 1930s through the seminal research of Dean and colleagues (Dean 1936; 1938;Dean, Dixon et al 1935; Dean, Elvove 1935; 1936; 1937). Dean studied the association of dental fluorosis with the fluoride concentration occurring naturally in the water supplies of some 22 cities (Dean 1942; Dean 1954). 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.

Table 3: Dose-response relationship between fluoride and prevalence and severity of dental fluorosis in populations studied by Dean 1942

Town	No.	Age (years)	F (mg/L)	Dean's Index (%) 0	Dean's Index (%) 0.5	Dean's Index (%) 1	Dean's Index (%) 2	Dean's Index (%) 3	Dean's Index (%) 4
Waukegan, IL	423	12–14	0.0	97.9	1.9	0.2	0.0	0.0	0.0
Michigan City, IN	236	12–14	0.1	97.5	2.5	0.0	0.0	0.0	0.0
Zanesville, OH	459	12–14	0.2	85.4	13.1	1.5	0.0	0.0	0.0
Lima, OH	454	12–14	0.3	84.1	13.7	2.2	0.0	0.0	0.0
Marion, OH	263	12–14	0.4	57.4	36.5	5.3	0.8	0.0	0.0
Elgin, IL	403	12–14	0.5	60.5	35.3	3.5	0.7	0.0	0.0
Pueblo, CO	614	12–14	0.6	72.3	21.2	6.2	0.3	0.0	0.0
Kewanee, IL	123	12–14	0.9	52.8	35.0	10.6	1.6	0.0	0.0
Aurora, IL	633	12–14	1.2	53.2	31.8	13.9	1.1	0.0	0.0
Joliet, IL	447	12–14	1.3	40.5	34.2	22.2	3.1	0.0	0.0
Elmhurst, IL	170	12–14	1.8	28.2	31.8	30.0	8.8	1.2	0.0
Galesburg, IL	273	12–14	1.9	25.3	27.1	40.3	6.2	1.1	0.0
Clovis, NM	138	9–11	2.2	13.0	16.0	23.9	35.4	11.0	0.7
Colorado Springs, CO	404	12–14	2.6	6.4	19.8	42.1	21.3	8.9	1.5
Plainview, TX	97	9–12	2.9	4.1	8.3	34.0	26.8	23.7	3.1
Amarillo, TX	289	9–12	3.9	3.1	6.6	15.2	28.0	33.9	13.2
Conway, SC	59	9–11	4.0	5.1	6.7	20.4	32.2	23.7	11.9
Lubbock, TX	189	9–12	4.4	1.1	1.1	12.2	21.7	46.0	17.9
Post, TX	38	~8–11	5.7	0.0	0.0	0.0	10.5	50.0	39.5
Chetopa, KS	65	~7–17	7.6	0.0	0.0	9.2	21.5	10.8	58.5
Ankeny, IA	21	~6–17	8.0	0.0	0.0	0.0	9.5	47.6	42.8
Bauxite, AK	26	14–19	14.1	0.0	0.0	3.9	3.9	38.5	53.8

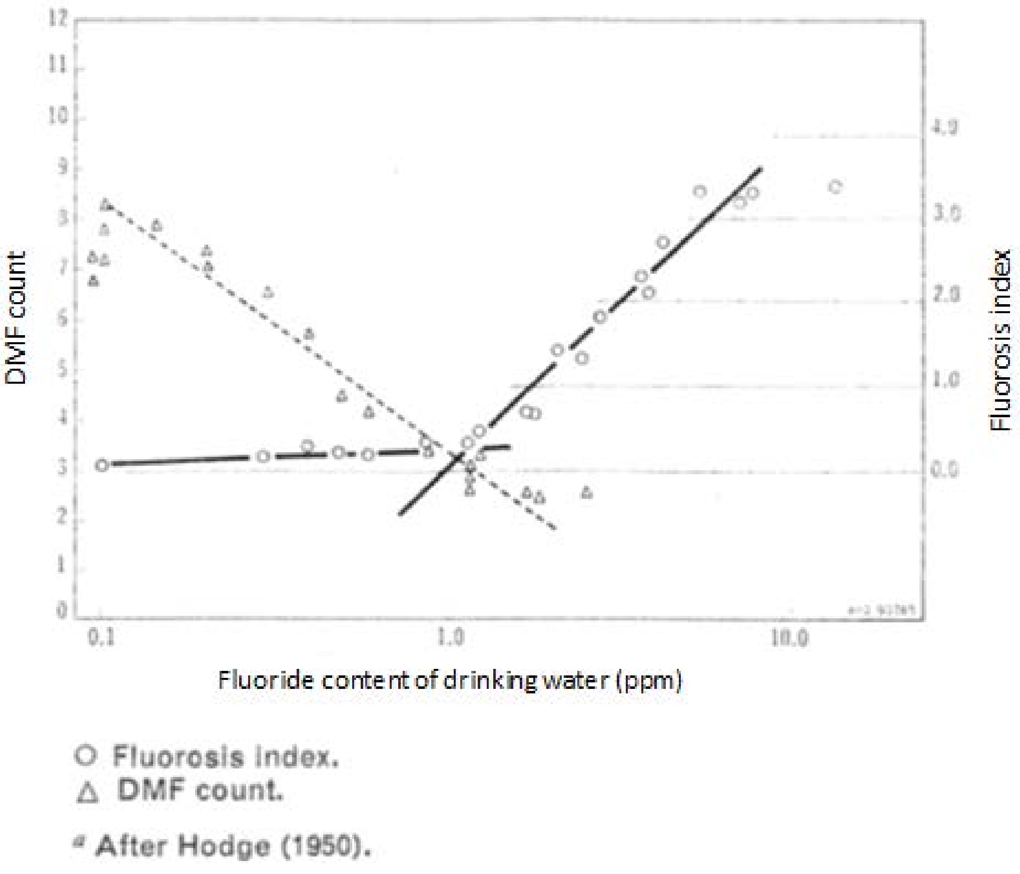
SOURCE: EPA (2010a) and modified from Dean (1942).

While Dean's data are presented as the percent distribution of the samples in the cities in the studies, there was an emphasis placed on the Community Fluorosis Index score in interpreting the prevalence and severity of fluorosis in any community.

Dean used a summary measure derived from Dean's Index, the Community Fluorosis Index (CFI), 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 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 (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.

Figure 7: Relationship between fluoride content of drinking water, caries experience and dental fluorosis[a]



Reproduced with permission for Adler Armstrong, Bell et al. Fluorides and human health. WHO 1970.

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 2010a).

A number of variations on Dean's index have emerged, including the Tooth Surface Index of Fluorosis (Horowitz et al. 1984), the Thylstrup and Fejerskov Index (Thylstrup and Fejerskov, 1978) and the Fluorosis Risk Index (Pendrys and Katz, 1989). 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 Thylstrup and Fejerskov Index and its lowest severity in the derivation of a threshold of fluoride intake at 0.03–0.4 mg F/kg bw/day (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 (Hong et al 2006).

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 change. The most common approach has been to use the concept of 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 view. 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 (Riordan 1993a and Hoskin in South Australia (Hoskin 1993) that both children and parents were able to recognise changes in tooth colour associated with dental fluorosis and that they rated fluorosed teeth less satisfactory in dental appearance. This supported an aesthetically objectionable fluorosis threshold.

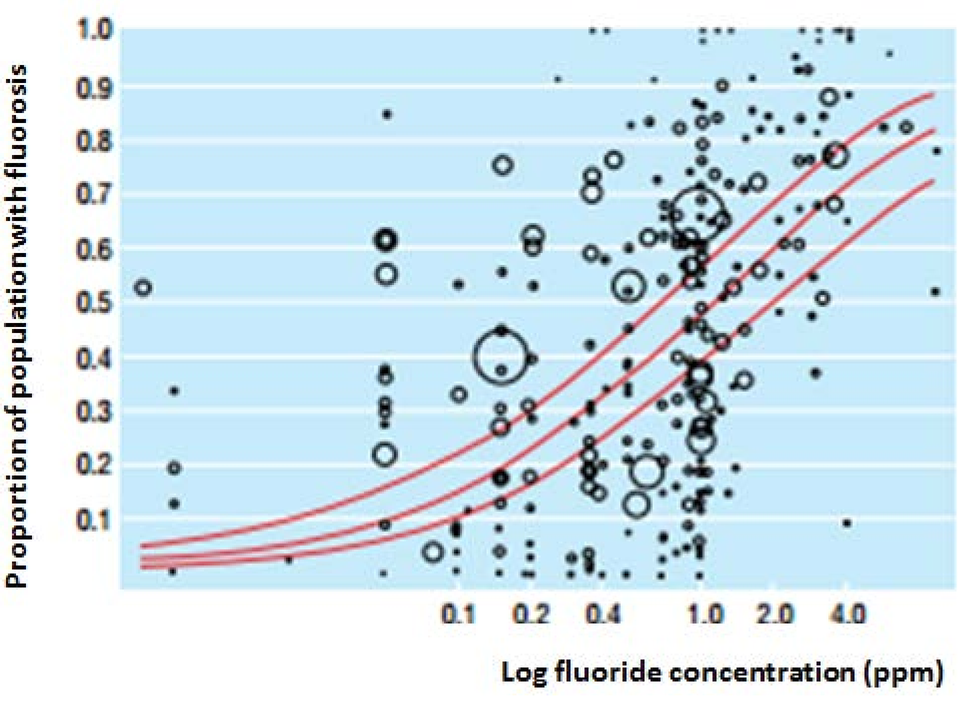
Community perceptions of aesthetics are not immutable. By the 2000 decade evidence started to emerge that while very mild, mild and even mild/moderate dental fluorosis (with the TF Index scores 1, 2 or 3) were recognised by children and parents, none was regarded as less satisfactory in dental appearance, 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 (Chankanka et al. 2010; Do and Spencer 2007). 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 to be the explanation. Further longitudinal research has shown that very mild and mild fluorosis (TF Index scores 1, 2, & 3) diminishes with time. This is possible through mineralization of porosities in enamel and possibly tooth wear. Fluorosis still present some six years later did not have a negative impact on perceptions of oral health among adolescents and young adults (Do et al., 2016). Perceptions may be dynamic, and change with time. Nair et al. (2016) have reported similar perceptions among Asian adults who only regarded severe fluorosis (TF Index 4 or 5) as aesthetically less pleasing. As a result, very mild, mild or moderate dental fluorosis is no longer regarded as a harm or an adverse effect.

The aesthetic judgement surrounding dental fluorosis was extensively discussed by the US National Academy of Science, National Research Council (NRC) 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.

In the NHS Centre for Reviews and Dissemination at the University of York University review (McDonagh et al. 2000a), two end points were included to assess potential negative effects associated with water of varying fluoride concentration. 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 Thylstrup and Fejerskov Index (Thylstrup and Fejerskov, 1978) score of 3 or more, or a Tooth Surface Index of Fluorosis (TSIF) Index (Horowitz et al. 1984) score of 2 or more.

The York review first modelled the proportion of the population with ANY fluorosis against fluoride concentration. The model is illustrated below (Figure 8).

Figure 8: 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.



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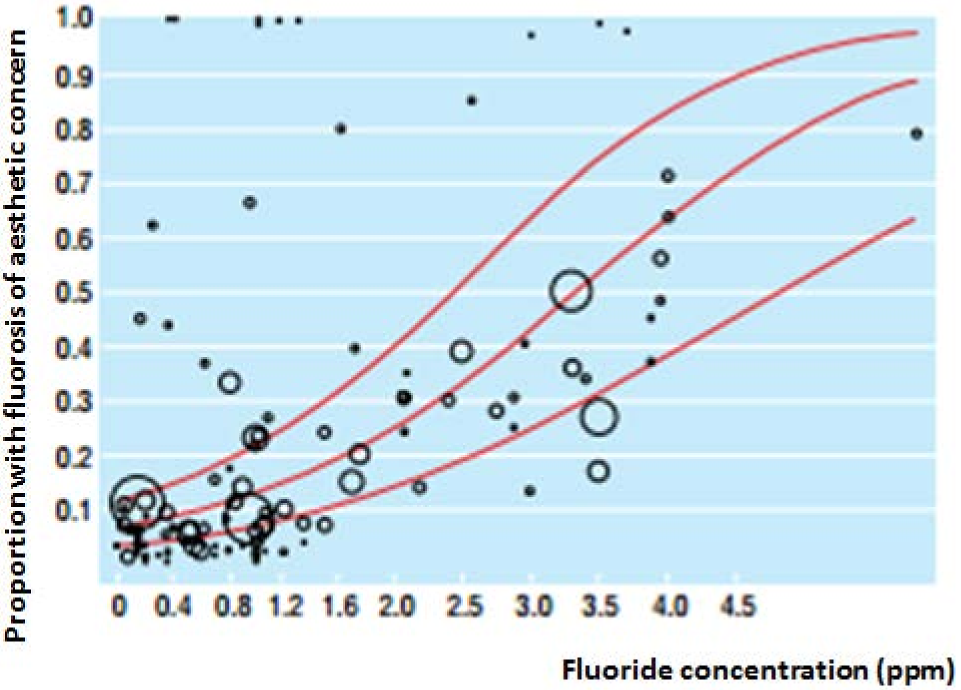
From this the estimated proportion of the population with any fluorosis was determined for a range of fluoride concentrations between 0.1 and 4 mg F/L. The proportion rose from 15 % at 0.1 mg F/L, to 48% at 1 mg F/L, and on to 61 % at 2 mg F/L and 72% at 4 mg F/L.

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 (Figure 9).

Figure 9: Proportion of population with fluorosis of aesthetic concern by water fluoride concentration (plotted on untransformed scale because of linear association between this and log (odds) of "aesthetic 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.



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The estimated proportion of fluorosis of aesthetic concern for fluoride concentrations across the range 0.1 to 4 mg F/L were 6.3%, for 0.1, 12.5% for 1, 24.7% for 2 and 63.4% for 4 mg F/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 of dental fluorosis 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 of fluoridated toothpaste by young children (Osuji et al. 1988; Pendrys and Katz 1989; Pearce 1991). In the Australian context the research by Riordan (Riordan and Banks 1991; Riordan 1993b) and by Puzio and Spencer (1993) laid 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 and likely associated with the higher prevalence of dental fluorosis than was historically expected at fluoride concentrations around 1.0 mg F/L (according to Dean's 22 cities data).

After a landmark consensus conference in Perth, Western Australia in 1993, Australian dental authorities set about reducing the level of fluoride intake from a range of sources (Dental Services 1993). These sources include 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 led to a decrease in the prevalence and severity of dental fluorosis (see Table 4) (Riordan 2002; Do and Spencer 2007). The decrease in the prevalence and severity of dental fluorosis is marked in both fluoridated and non-fluoridated areas. This attests to the role of non-water fluoride in the risk of fluorosis. The prevalence of ANY fluorosis was reduced to approximately 20–25% overall. 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 Thylstrup and Fejerskov scores of 3 or more. The distribution was also truncated, with no children observed with a Thylstrup and Fejerskov score of 4 (moderate/severe) or 5 (severe).

This substantially alters the context in which a benefit –risk evaluation of fluoride concentration in water supplies is conducted in Australia.

Table 4: Decline in the prevalence and severity of dental fluorosis (TF Index) in Australia across the 1990s and early 2000s

Western Australia

Year	Fluoridation	Prevalence (%)	*Severity (% in each group)* TF 0*	*Severity (% in each group)* TF 1	*Severity (% in each group)* TF 2	*Severity (% in each group)* TF 3	*Severity (% in each group)* TF 4	*Severity (% in each group)* TF 5
1990–91	Fluoridated	40.2	59.8	29.0	8.9	2.4	0	0
1990–91	Non-fluoridated	33.0	67.0	25.5	6.9	0.6	0	0
2000	Fluoridated	21.9	78.1	17.6	4.0	0.3	0	0
2000	Non-fluoridated	11.6	88.4	9.2	1.9	0.5	0	0

South Australia

Year	Fluoridation	Prevalence (%)	*Severity (% in each group)* TF 0*	*Severity (% in each group)* TF 1	*Severity (% in each group)* TF 2	*Severity (% in each group)* TF 3	*Severity (% in each group)* TF 4	*Severity (% in each group)* TF 5
1992/93	Fluoridated	56.7	43.3	51.7	2.8	2.2	0	0
1992/93	Non-fluoridated	29.3	70.7	28.0	0.6	0.6	0	0
2002/03	Fluoridated	29.5	70.5	16.0	11.4	2.1	0	0
2002/03	Non-fluoridated	15.0	85.0	10.1	3.7	1.2	0	0

Riordan 2002; Do and Spencer 2007

*TF0 equates to No fluorosis

Table 5 presents the latest survey information on dental fluorosis among Australian and New Zealand children. These are the findings of NSW Child Dental Health Survey 2007 (NSW CDHS 2009) and 2009 New Zealand Oral Health Survey (NZ Ministry of Health 2010).

Table 5: Prevalence and severity of dental fluorosis in Australia and New Zealand in the 2000 decade

Australia, NSW, 2007 8-12 year olds

TF Index (% in each group)	All (%)	Fluoridated area (%)	Non-fluoridated area (%)
TF 0 (No fluorosis)	75.8	74.9	83.2
TF1	14.6	14.8	13.0
TF2	6.8	7.2	3.6
TF3	2.5	2.7	0.2
TF4	0.2	0.02	0
TF5	0.04	0.04	0

New Zealand, 2009, 8-30 year olds

Dean's Index (% in each group)	All (%)	Fluoridated area (%)	Non-fluoridated area (%)
None (TF0)	55.5	54.5	56.9
Questionable	27.2	30.6	22.7
Very mild	10.2	10.2	10.3
Mild	5.1	3.0	7.8
Moderate	2.0	1.7	2.3
Severe	0.0	0.0	0.0

Centre for Oral Health Strategy NSW. The New South Wales Child Dental Health Survey 2007, NSW Department of Health 2009.

NZ Ministry of Health. Our oral health: key findings of the 2009 New Zealand Oral Health Survey. Wellington: Ministry of Health, 2010.

It should be noted that prevalence of dental fluorosis in NSW is similar to that of WA and SA earlier in the decade. Further most fluorosis observed was at the very mild or mild levels (TF 1, 2 or 3). A very low number of moderate cases of dental fluorosis were observed and just 2 cases of TF 5 or severe fluorosis. Such rare observations need a confirmatory diagnosis and case level investigation.

The NZ data are on a wider range of ages and used the Dean's Index. Dean's Questionable category makes interpretation difficult. As a rule such observations are not included in reported prevalence of fluorosis. As a result, the prevalence of dental fluorosis in NZ would appear even lower than in Australia. However, much of the difference may be due to different examination methods (air drying for the TF Index) and thresholds for an observation. No cases of severe fluorosis were observed in the 2009 NZ Oral Health Survey.

Fluoride intake in infancy and early childhood and dental fluorosis

As water fluoridation remains a risk factor for dental fluorosis and early childhood is regarded as a period of increased susceptibility, the reconstitution of infant formula powder 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 (Am Dent Assoc 2006). The ADA said that " *parents and caregivers should consider using water that has no or low levels of fluoride*". The ADA went on the 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 (2007) compared the risk of dental fluorosis (measured by the presence of fluorosis at the TF score of 1 +) associated with infant formula use in 1992–93 and 2002–03.

Table 6: Association of infant formula use and dental fluorosis in Australian children.

Time	1992/93	2002/03
Used formula (weighted %)	61.0%	57.2%
Prevalence of fluorosis (weighted %)		
Used formula	49.2%	27.4%
Not used	40.8%	23.5%
Multivariable analysis (OR)		
Used formula	1.13 (0.72–1.76)	1.05 (0.69–1.60)
Not used	1.0	1.0

Spencer and Do CDOE 2007

Infant formula use, presumably mostly reconstituted with fluoridated water (over 90% of South Australians live in fluoridated areas) was not significantly associated with dental fluorosis. However, it needs to be recognised that infant formula manufacturers had moved to reduce/eliminate fluoride from their infant formula powder marketed in Australia (Clifford et al. 2009). This contrasts with earlier research in a number of countries.

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